Namita Agrawal *Editor*

Altered Metabolism: A Major Contributor of Comorbidities in Neurodegenerative Diseases

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To my father for the enthusiasm,
encouragement, advice, and support.

Preface

It is extremely gratifying to write a book on a topic like neurodegenerative diseases (NDDs) which are characterized by neuronal loss in sensory, motor, and cognitive systems. With the increase in life expectancy, the prevalence of age-related NDDs continues to rise significantly. NDDs including Alzheimer, Parkinson, Huntington's disease, and amyotrophic lateral sclerosis are prominent class of neurodegenerative diseases without a cure till date. Efforts to treat these diseases are limited due to the fact that a wide range of molecular and cellular pathologies underpin its progression leading to death. Numerous clinical and animal model studies suggest metabolism as one of the primary initiating factors of the subsequent disease-associated detrimental cascade. Therefore, managing the altered metabolism could finally prove to be an effective preventive strategy. This book encompasses a detailed understanding about altered metabolism as a major contributor of comorbidities involved in devastating neurodegenerative diseases.

The first two chapters are devoted to an overview and mechanisms underlying NDDs followed by detailed understanding about metabolic paradigm in progression of NDDs from Chaps. 3 to 12. These chapters uncover various aspects of metabolism underlying NDD progression such as glucose, lipid metabolism, protein metabolism, RNA metabolism, peripheral metabolism, gut microbiota, and signaling pathways. In Chap. 13, we have discussed about the advanced imaging techniques for evaluation and diagnosis of NDDs. Chapter 14 deals with the recent understanding about novel metabolic biomarkers and therapeutic strategies in NDDs. This book ends with one of the major concerns of NDDs, i.e., a strategy for the prevention or cure of this debilitating disease by phytochemicals by regulating metabolism. Natural compounds like phytochemicals remain to be ascertained with multiple targets and therefore, appear to be a potential and promising class of therapeutics for the treatment of NDDs with multifactorial etiology and least side effect.

This book is the passionate writing of several renowned professors and scientists from all over the world contributing in the field of NDDs for past several years. I hope as we enjoyed writing and compiling most recent information about connecting metabolism as a major cause of NDDs, the readers will also find it extremely informative.

Delhi, India Namita Agrawal

Acknowledgement

I am thankful to all the authors without whom this book would not have been possible. I am also grateful to the University of Delhi for sabbatical leave sanctioned to Prof. Namita Agrawal, which helped immensely for timely completion of this book.

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About the Editor

Namita Agrawal is currently a Professor at the Department of Zoology, University of Delhi, India. She has been addressing numerous questions related to debilitating neurodegenerative diseases for the past 25 years. She started working on neurodegenerative diseases at the Department of Development and Cell Biology, University of California, Irvine, USA. Her research group at University of Delhi is trying to comprehend the mechanistic basis of neurodegenerative diseases and its cure by using phytochemicals. Additionally, her research interests also include understanding of various aspects involved in cancer and nanomaterials.

She has published research papers in peer-reviewed journals like Science, PNAS, Journal of Cell Biology, Development, Developmental Biology, Nature Scientific Reports, PLOS One, Journal of Huntington's disease, etc. She has recently edited and wrote several chapters in a book published by Springer entitled *Toxicology of Nanoparticles: Insights from Drosophila*. Additionally, she frequently writes chapters in the books related to neurodegenerative diseases.

In addition to her dedication towards research, she has almost 15 years of experience in teaching genetics, cytogenetics, and developmental biology to postgraduate students at the Department of Zoology, University of Delhi, India.

Chapter 1
An Overview of Neurodegenerative Disorders

Parul Mittal and Namita Agrawal

Abstract Neurodegenerative diseases are late-onset devastating conditions that damage and destroy part of the nervous system, particularly the brain. The process of disease manifestation is slow but it affects many physiological activities like eating, walking, and speaking, and thereby, patients suffer enormously during the later stages of their life.

Some of the main types of neurodegenerative diseases are Alzheimer's disease, frontotemporal dementia, chronic traumatic encephalopathy, Lewy body dementia, multiple sclerosis (MS), Parkinson's disease, amyotrophic lateral sclerosis (ALS), etc. Interestingly, the clinical course, symptoms, genetic origin, and molecular processes of pathogenesis of most neurodegenerative disorders are similar. A subset of neurons is principally impacted by each neurodegenerative disease, and these disorders entail distinct ranges of molecular and clinical properties.

In the present chapter, we have discussed about multiple aspects related to key neurodegenerative diseases including their prevalence, major cause, mechanism, and symptoms. We propose that a better understanding of the mechanisms underlying neurodegenerative disease is required to develop more effective, disease-modifying treatments.

Keywords Neurodegenerative disease · Metabolism · Gut dysbiosis · Circadian rhythm

1.1 Introduction

Neurodegenerative disorders (NDDs) comprise a diverse group of neurological disorders characterized by progressive loss of neurons in the central nervous system (CNS) or peripheral nervous system (PNS) (Wilson et al. 2023). Cognitive deficits,

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dementia, trouble in understanding the language, personality issues, distress in addressing daily problems, emotional behavior, and perception are all signs of neurodegenerative illnesses. Numerous neurological disorders, including Alzheimer's, Parkinson's, Huntington's, and other neurocognitive disorders, are due to disruption in the neuronal circuits that result in neurological imbalance (Mittal et al. 2021). The prevalence of NDDs has increased, currently with an estimate of more than 30 million people with dementia, and this figure can be estimated to reach 75 million people by 2030. Dementia is impacting people worldwide and the public health importance has been described by the WHO as alarming (World Health Organization 2017).

The human brain is a complex organ consisting of billions of neurons that developed from neural stem cells. The majority of neurons are formed during infancy and drastically decrease in number by adulthood. Although neurons originate in the brain, they are found throughout the entire body. Neurons do not self-replicate or replace as they are essential for forebrain communication and are the fundamental units that make up brain and are essential for its healthy operation. Since brain is the primary controller of the body and is primarily impacted by NDDs, neurodegeneration subsequently affects many parts of the body (Mittal and Hazari 2022). An individual with NDDs has limitations with basic and complex activities of the body that include speech delivery, body posture stability, balance, urine and bowel functions, and movement.

Neurodegeneration is the primary pathophysiological alteration in many age-related diseases. Neurodegeneration is associated with progressive loss of neurons, structure and functions of neurons, dysfunction of neuronal and synaptic networks, and accumulation of different variants of proteins inside the brain along with neuronal cell death (Lamptey et al. 2022).The collapse of neural networks in brain disorders results in the breakdown of the main communication circuit, impairment of memory function, behavior, and loss of sensory and motor function along with cognitive deficits. Growing older is one of the major factors for neurological diseases, which afflict the elderly globally. The remaining risk variables may include an individual's genetic composition, environmental circumstances, or immediate environment, which may have an impact on the rate and degree of neurodegeneration.

NDDs include Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), prion disease (PrD), spinocerebellar ataxia, motor neuron disease, traumatic brain injury (TBI), spinal cord injury (SCI), chronic traumatic encephalopathy (CTE), and multiple sclerosis (MS). Alzheimer's disease and frontotemporal lobar degeneration affect cognition function, whereas Parkinson's disease and ALS affect motor neurons. In some diseases, both cognitive function and movement are impaired such as dementia with Lewy bodies and corticobasal degeneration. Out of these, AD and PD are the most prevalent NDDs. According to the Alzheimer's Disease Association report of 2022, 6.2 million people are diagnosed with Alzheimer's disease in the United States ("2023 Alzheimer's Disease Facts and Figures" 2023).

The clinical course, symptoms, genetic origin, and molecular processes of pathogenesis of most neurodegenerative disorders are similar. Neurodegeneration,

pathological protein aggregation, aberrant proteostasis, altered energy metabolism, DNA and RNA defects, cytoskeletal abnormalities, oxidative stress, neuroinflammation, and neuronal cell death are among the main characteristics of non-disruptive diseases (NDDs). A subset of neurons is principally impacted by each neurodegenerative disease, and these disorders entail distinct ranges of molecular and clinical properties.

Accumulation of particular misfolded protein deposits is the key causative factor of all NDDs. Despite similar symptoms, the different composition and distribution of the aggregated proteins define the properties of each neurodegenerative disease which make them different from each other. The deposition of aberrant proteins disrupts the normal mechanism required for protein folding and degradation resulting in disrupted protein homeostasis and excitotoxicity. Apart from aberrant protein, there is an accumulation of inclusion bodies which are relatively large electron-dense structures and they contain membrane-bound protein aggregates. The inclusion bodies are accumulated as a cause of impairment in ubiquitin-proteasomal system which is reported in ALS, FTD, HD, and PD. In PD, mutations in the PARK2 gene which encodes an E3 ubiquitin ligase can cause early onset of PD due to mutation that partially ubiquitinates the α-synuclein, and therefore, deposits of partial ubiquitinating α-synuclein are accumulated as Lewy bodies (Goedert and Spillantini 2011). Mutations in FUS and TDP-43 genes cause altered RNA processing identified in the pathogenesis of neurodegenerative disorders like ALS and FTD (Ling et al. 2013).

Neurons are highly metabolic cells and are always in need of high energy, due to which there is continuous production of energy and elimination of ROS species from the mitochondria. Any imbalance in this process can generate higher ROS species and less abundance of antioxidant molecules leading to excessive accumulation of ROS and thereby cellular damage. Higher levels of ROS can disrupt DNA and RNA processing. Mitochondrial ROS increases uptake of calcium ions with increased permeability of the membrane and release of cytochrome-C resulting in apoptosis which is observed in AD, PD, ALS, and FTD (Beal 1995). Increased ROS production is an underlying cause for mitochondrial impairment which is implicated in aging and neurodegenerative diseases. Excessive release of a neurotransmitter, glutamate, can cause excitotoxicity implicated in the development of CNS disorders. Glutamate is an important excitatory neurotransmitter and is pivotal for synaptic plasticity and transmission required for learning and memory function. There is an over-activation of the NMDA and AMPA receptors at post-synapse due to elevated glutamate levels causing neuronal death. In ALS, there is decreased expression of the gene excitatory amino acid transporter 2 (EAAT2) coding for the transporter of glutamate (Lau and Tymianski 2010).

Apart from misfolding of the proteins, aberrant RNA processing, oxidative stress, and neuroinflammation, NDDs also exhibit similar signaling pathways, organelle dysfunction, and proteostasis. The pathways regulating metabolism, aging, lifespan, and cell repair are also similar in NDDs. Certain diseases, including ALS and FTD, have gene abnormalities that can produce distinct neurodegenerative diseases in different individuals due to different mutations in a gene. This suggests

that there is a spectrum of neurons that are affected, which is a hallmark of neurodegenerative disorders. Neurons are particularly susceptible to the progression of disease due to both inherent and extrinsic causes, such as cellular stress and environmental stress (Saxena and Caroni 2011).

Anatomical data indicates that brain and gut communicate bilaterally. This intricate link is referred to as the microbiota-gut-brain axis, which involves microorganisms, gut epithelia, and the brain. Gut and brain communicate via two different pathways: the first one is a direct trans-neuronal pathway, and the second requires systemic circulation to carry blood. Microbes, for instance, can enter the brain by peripheral nerves, but certain viruses or microbial toxins can pass through intestinal epithelia and the blood-brain barrier to enter the brain through systemic circulation. Certain viruses can infiltrate the bloodstream, causing localized or systemic inflammation that can lead to neuroinflammation, a leaky blood-brain barrier, neurodegeneration, cellular atrophy, and neuronal excitotoxicity. The brain responds to these infections by either releasing hormones into the body or directly stimulating neurons (Tan et al. 2021).

1.2 Neurodegenerative Diseases: Genetics and Pathogenesis

1.2.1 Alzheimer's Disease (AD)

Alzheimer's disease (AD) is the most prevalent form of dementia affecting around 70% population worldwide. According to the reports, the number of people suffering from AD will double every 20 years and it will be around 81.1 million by 2040 ("2023 Alzheimer's Disease Facts and Figures" 2023). Memory loss, behavioral problems, difficulty in concentrating, mood swings, anxiety, and separation from family and community are some of the early indications of this illness. Alzheimer's disease is brought on by a confluence of aging factors, environmental and hereditary factors. The other possible risk factors for developing AD include a modern lifestyle which leads to obesity, hypercholesterolemia, diabetes mellitus, disturbances in sleep patterns, smoking, depression, distress, and hypotension/hypertension (Heneka et al. 2018). Longitudinal studies have claimed that stroke, smoking, and hyperhomocysteinemia are related to the subsequent risk for AD (de Bruijn and Ikram 2014). The hallmarks of AD are extracellular β-amyloid (Aβ) accumulation and intracellular neurofibrillary tangles (NFT) along with neuroinflammation in certain areas of the brain. Another prominent feature of AD pathology is a decreased level of the neurotransmitter acetylcholine due to increased activity of an enzyme acetylcholinesterase (AChE) which impairs the transmission of neurons at the synapse (Kaduszkiewicz and van den Bussche 2009). AD is currently diagnosed based on clinical symptoms, psychological testing, imaging, and disease history. The use of neuroimaging is essential for the diagnosis of AD by multimodal imaging, such as positron emission tomography (PET) and magnetic resonance imaging (MRI).

While MRI offers information on the structure and function of the brain, PET provides information on the brain's metabolism and molecular makeup.

According to the National Institute of Aging and the Alzheimer's Disease Association, there are three stages of Alzheimer's disease (AD): preclinical AD, moderate cognitive impairment (MCI), and dementia. The primary etiology of Alzheimer's disease is dementia, which is linked to abnormalities in mitochondria, oxidative stress, neuroinflammation, protein misfolding, and aggregation at the molecular level (Kim et al. 2009).

Transmembrane proteins, like APP, can pass past the membrane of a neuron and play a significant part in neuron growth, survival, and healing following injury. Two proteolytic cleavage enzymes, beta- and gamma-secretase, break down amyloid precursor protein (APP) into smaller protein fragments in Alzheimer's disease. These smaller peptide fragments, known as amyloid beta (Aβ), typically ranging from 40 to 50 amino acids in length make up amyloid plaques. These pieces produce fibrils of amyloid beta, which form clumps and accumulate as senile plaques outside of neurons. Aβ deposition increases the AChE levels around the plaques, preventing the axonal transport and leading to excitotoxicity (Nunes-Tavares et al. 2012).

Tau protein is predominantly expressed and localized by the neuronal axons and is encoded by microtubule-associated protein tau (MAPT) gene located on chromosome 17. Tau has an essential role in the homeostatic expansion and contraction of microtubule (MT) along the neuronal axon. Tau can also modify the rate of axonal transport and can control the motor proteins like dynein and kinesin. Apart from these, tau plays a role in the maturation of neurons and maintenance of cytoarchitecture. Enzymatic additions of acetylation, methylation, glycosylation, ubiquitylation, and many other modifications can modify tau protein at the post-translation level. Phosphorylation is the first and most common post-translational modification (PTM) which is linked to the development of pathogenic inclusions termed neurofibrillary tangles (NFTs). Due to this aberrant aggregation of hyperphosphorylated tau proteins, AD is also referred to as tauopathy. More than 85 possible phosphorylation sites are represented by serine, threonine, or tyrosine residues in the tau isoform which is longest expressed in the human central nervous system (2N4R isoform). Phosphorylation at Thr231, Ser262, Ser396, or Ser404 by kinases can also reduce tau's ability to support MT assembly and control MT dynamic stability in addition to MT binding. Hyperphosphorylated tau is involved in the breakdown of MT in the later stages of AD. NFT is directly correlated with the onset of cognitive impairments and a progressive reduction in dementia scores, suggesting that phosphorylated tau (p-tau) may be a neurotoxic factor in AD. However, it is still unclear how tau hyperphosphorylation causes neuronal death and aggregation. Nevertheless, several sites exhibit phosphorylation during the initial stages of the disease and may provide valuable information as prospective biomarkers (Xia et al. 2021).

Early-stage inflammation in AD has been documented, even before dementia manifests. An inflammatory reaction brought about by brain cell injury is known as neuroinflammation. Any infection, toxin production, autoimmunity, trauma, or reaction that alters neural activity can destroy cells (Werry et al. 2019).This results

in the activation of the microglia and astrocytes from the CNS, which are the primary sources of cytokines in AD. Microglia are activated through cytokines. When Aβ peptides build up, pro-inflammatory cytokines like interleukin-6 (IL-6), IL-1α, tumor necrosis factor α (TNF-α), IL-6, and granulocyte macrophage colony-stimulating factor (GM-CSF) are secreted more often, which triggers a neuroinflammatory response (Patel et al. 2005). In Alzheimer's disease, activated microglia around Aβ plaques enhance the production of pro-inflammatory cytokines such as TNF-α, IL-6, pro-IL-1β, and macrophage colony-stimulating factor (M-CSF) and macrophage inflammatory peptide (MIP-1α) (Heneka et al. 2018).

Oxidative stress is a consequence of neuroinflammation in which diffusible oxidants, such as nitric oxide (NO) and hydrogen peroxide (H_2O_2), are produced either by diffusion inside the cell from the outside or by receptor-mediated signal transduction process. Mitochondrial ROS leakage produces intracellular ROS, which is mediated by TNF-α. Another process is the creation of ROS by cytokines via NADH oxidases (NOX), which catalyzes the reduction of oxygen to superoxide anion and produces H_2O_2, which diffuses across the surrounding plasma membranes via the high-yield inducible nitric oxide synthase (iNOS) enzyme; similarly, astrocytes and microglia are also involved in the synthesis of nitric oxide in a similar manner (Hensley 2010).

The genetics of Alzheimer's disease include sporadic and familial forms. Majority of the people suffer from late-onset (i.e., more than 65 years of age) sporadic form AD, and according to the studies, the chances of getting sporadic AD are approximately 76%. The etiology of sporadic AD is complex, attributed to environmental risk factors and genetic susceptibilities of an individual. However, the inherited form is usually developed below 65 years of age and it is an autosomal dominant form. Three distinct genes—*APP*, *presenilin 1*(*PSEN1*), and *presenilin 2* (*PSEN*2)—mutate to cause AD with an early onset. The 299-amino-acid apolipoprotein E (ApoE) protein is encoded by the *APOE* gene. The expression of ApoE protein can be seen in multiple organs. ApoE protein is expressed in a variety of organs and the liver and brain have the highest expression. Microglia and astrocytes are the main non-neuronal cells expressing ApoE in the brain. Numerous single-nucleotide polymorphisms (SNPs) are dispersed throughout the human *APOE* gene. ApoE2 (cys112, cys158), ApoE3 (cys112, arg158), and ApoE4 (arg112, arg158) are the three most prevalent SNPs that cause alterations in the coding sequence and produce three common isoforms of ApoE. The structure and function of ApoE2 are significantly changed by variation in only one or two amino acid between these three main isoforms at residues 112 or 158. ApoE plays a part in the control of lipid metabolism through aiding in their transportation, delivery, and distribution across the cells through ApoE receptors and the proteins associated with lipolysis and lipid transfer. Genome-wide association studies have confirmed the leading risk factor for late-onset AD as ε4 allele of APOE (Liu et al. 2013).

APOE is involved in the transportation of cholesterol within the brain and it also mediates neuronal repair and protection. *APOE* is also contributing to the accumulation of amyloid plaques. Use of *APOE* as a biomarker for diagnosis has been limited due to its limited sensitivity and specificity. Out of the three, *APOE* e4 allele

has been known as the one linked with development of AD, whereas ApoE2 has a protective effect. As per meta-analysis studies, the chances for developing AD with homozygous carriers of the *APOE* e4 allele are almost 15-fold, whereas the odds for heterozygous carriers are threefold (Cammann et al. 2023). Mutation in any of the three genes affects the formation of beta-amyloid protein (Aß), resulting in the development of the senile plaques. The development of ApoE in AD is triggered by the buildup of amyloid plaques, and elevated ApoE levels suppress Aβ-induced neuroinflammation, potentially acting as a feedback loop. Furthermore, ApoE has anti-inflammatory qualities and regulates the innate inflammatory response. In vivo studies have shown the specific effects of ApoE isoform on neuroinflammation in human ApoE knockin mice. Studies revealed that after receiving LPS intravenously, ApoE4 knockin mice had more inflammatory reactions than ApoE3 knockin animals. These findings revealed that ApoE e4's pro-inflammatory response had a role in the pathophysiology of AD (Suppiah et al. 2019).

1.2.2 Parkinson's Disease (PD)

Parkinson's disease (PD) is the second most common prevalent neurodegenerative disorder after Alzheimer's disease, characterized by progressive abnormal aggregation of the pathogenic α-synuclein (α-syn) protein in the neuronal cell body resulting in the formation of round lamellated eosinophilic cytoplasmic inclusions known as Lewy bodies (LB) and Lewy neuritis (Braak et al. 2003). This eventually leads to the death of melanin-expressing dopaminergic neurons in the substantia nigra pars compacta (SNc) of the midbrain (DeMaagd and Philip 2015). The dopaminergic neurons of patients with motor symptoms get degenerate, which further alters the neuronal circuit required for the movement of basal ganglia (Cheng et al. 2010). Another disorder known as synucleinopathies dementia with Lewy bodies (DLB) shares overlap of symptoms with Parkinson's disease and therefore PD is also classified as synucleinopathy (Grazia Spillantini et al. 1998). This disorder is characterized by dementia and visual hallucinations in the beginning and further development of PD motor symptoms (Arnaoutoglou et al. 2019). In PD, there are four cardinal motor symptoms which are postural instability, bradykinesia, muscular rigidity, and resting tremors (Jankovic 2008). The non-motor symptoms of PD include loss of smell, depression, dementia, and gastrointestinal (GI) dysfunction such as abnormal salivation, constipation, defecatory dysfunction, nausea, and dysphagia (Parashar and Udayabanu 2017).

The incidence of Parkinson's disease is 1.5 times higher in men than in women and it increases with age ranging more than 65 years but around 4% are diagnosed with PD below age 50. There are multiple environmental and genetic factors contributing to PD development. The environmental factors include exposure to pesticides, dairy products, depression, traumatic brain injury, anxiety, mitochondrial poisons such as MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), and aging (Gardner et al. 2015; Langston 2017; Vázquez-Vélez et al. 2021). Exposure to

metals such as carbon monoxide can affect the nigrostriatal region which can cause PD. Exposure to chemicals like paraquat can increase the chances of PD by almost threefold. Rotenone is an organic pesticide and a lipophilic mitochondrial toxin. On exposure, rotenone can inhibit the mitochondrial complex 1, increasing the production of ROS and decreasing the production of ATP leading to mitochondrial dysfunction (Pang et al. 2019).

The genetic factors responsible for developing PD are autosomal dominant genes—*SNCA*, *LRRK2*, *VPS35*, *CHCHD2*—and autosomal recessive genes such as *Parkin, PINK1,DJ-1*, *ATP13A2*, *FBXO7*, and *PLA2G6* (Shulman et al. 2011). All these genes are responsible for impairment of metabolic pathways in dopaminergic neurons and this induces neurotoxicity. *SNCA* (*PARK1/4*) is a five-exon gene present on chromosome 4 (4q22.1) and encodes for 14-kDA protein α-syn which is widely expressed in the brain. SNCA is one of the genes included in synuclein family exclusively expressed in vertebrates. The α-syn protein is involved in the release of neurotransmitters, formation of SNARE complex, synaptic plasticity, and presynaptic vesicle trafficking of the lipids.

The second most potential genetic factor attributing to sporadic PD includes mutations in *LRRK2*. *LRRK2* accounts for 29% of familial PD in Ashkenazi Jewish individuals and 70% of PD in North Africans. *LRRK2* gene accounts for approximately 1% of Parkinson's disease and this gene encodes for 253-kDa protein, leucine-rich repeat kinase2 which has multiple domains expressed in the lungs, kidneys, immune system, and the brain. One domain of *LRRK2* has kinase activity, whereas the other domain has GTPase activity carried out by a complex of Ras proteins (ROC)/C-terminal of Ras (COR). Variants in *LRRK2* (*PARK8*) can also be a factor for autosomal dominant PD and the age for onset of disease can vary for different *LRRK2* pathogenic variants. According to recent reports, *LRRK2* kinase activity is elevated in brains of sporadic PD patients (Di Maio et al. 2018). Another gene *VPS35* (*PARK17*) codes for vacuolar protein sorting 35 and is involved as the core protein in the retromer required for retrograde sorting of proteins from the endosome towards the cell membrane and trans-Golgi network (Vilariño-Güell et al. 2011).

The first gene linked with autosomal recessive (AR) Parkinson's disease and early-onset PD (EOPD) was found to be *Parkin* (*PARK2*). *Parkin* codes for E3 ubiquitin ligase and has diverse roles such as being important for the regulation of mitochondrial biogenesis; it can influence mitophagy, mitochondrial fusion, and mitochondrial transport through ubiquitylation. Its loss of function can predominantly affect ubiquitin-proteasomal function (Shimura et al. 2000). Another gene causing AR PD is PTEN-induced kinase (*PINK1*), accounting for 4% of early-onset cases of PD. *PINK1* is involved in the maintenance of calcium homeostasis in mitochondria. During mitochondrial dysfunction, there is an interaction of the two genes. *PINK1* recruits *Parkin* to the mitochondrial membrane required for quality control of mitochondria and mitophagy (Dugger and Dickson 2017). Thus, mitochondrial dysfunction can cause Parkinson's disease.

1.2.3 Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is characterized by progressive degeneration of selectively upper and lower motor neurons in the brain and spinal cord and upper motor neurons in the motor cortex region (Robberecht and Philips 2013). The upper motor neurons are the neurons projecting from the cortex to the spinal cord and the brainstem, whereas the lower motor neurons project from the spinal cord or brainstem to the muscle. This leads to weakness, fasciculations, spasticity, and muscle atrophy. ALS is also known as motor neuron disease (MND). Apart from motor neurons, it also has non-motor symptoms such as defecation disorder, fatigue, pain, cognitive and behavioral changes, sialorrhea, and sleep disorders. These non-motor symptoms reduce the life quality of an individual more than those showing motor symptoms of ALS (Hirayama et al. 2023). Post-arousal of first symptom of ALS, the mean survival expectancy of an individual is only 3 to 5 years. ALS is the most common neurodegenerative disorder occurring in young and middle-aged people (Gotkine et al. 2020). It affects 1 to 2 individuals per 100,000 every year. The prevalence of males affected with ALS is higher than females. The onset of the disease usually occurs during the 50–60 years of age. The diagnosis time is 9–15 months post-onset of symptoms. In ALS, it usually affects the limbs first, i.e., spinal onset, whereas in some patients, there is bulbar onset which involves difficulty in speech (dysarthria) and difficulty in swallowing problems (dysphagia).

Two categories of ALS are clinically similar. The categories include sporadic ALS (SALS) and familial ALS (FALS). Familial ALS is autosomal dominant and is predominantly hereditary; in rare cases it can be autosomal recessive. Mutation in certain sets of genes involved in FALS such as superoxide dismutase 1 (*SOD1*), ubiquitin 2 (*UBQLN2*), valosin-containing protein (*VCP*), TAR DNA-binding protein 43 (*TDP43*), optineurin (*OPTN*), and charged multivesicular body protein 2b (*CHMP2B*) has been implicated in the pathophysiology of ALS.

Superoxide dismutase 1 (*SOD1)* is an enzyme consisting of 153 amino acids and is involved in free radical scavenging. Mutations in *SOD1* underlie about 20% of familial ALS. An effect of mutant *SOD1* has been observed on protein degradation in the in vitro as well as in vivo models of rodents and humans. There is misfolding of mutant *SOD1* which becomes the target for ubiquitylation. Additionally, mutant *SOD1* has a toxic effect on cell's degradation machinery, due to which two major pathways—proteasome and autophagy—get impaired (Basso et al. 2006).

In ALS, axonal connections fail during the retraction of the axons and denervation of the lower motor neurons resulting in cell death. The excitatory amino acid transporter 2 (EAAT2) is impaired in ALS, an astroglial protein and main synaptic glutamate reuptake transporter resulting in excessive glutamate stimulation at synapses and toxicity of motor neurons. Degeneration of prefrontal and temporal cortex neurons leads to frontal executive dysfunction and concomitant frontotemporal dementia in around 15% of patients. This is termed ALS with frontotemporal lobe degeneration (FTLD) and they both cover opposite ends of the spectrum of a disease (Robberecht and Philips 2013). Another hallmark of ALS is aggregation and

accumulation of ubiquitylated proteins or inclusions in the motor neurons. The reason behind the mechanism of formation of these inclusions has not been understood yet. The aggregated proteins result in secondary respiratory deficiencies that further increase oxidative stress. The other functions impaired in ALS are DNA repair, nuclear export, vesicular transport, axon dysfunction, neuronal hyperexcitability, and glial dysfunction (Hardiman et al. 2017).

Aggregated proteins are the mutant proteins occurring as oligomeric complex precursors involved in disturbing the homeostasis of normal protein and aberrant RNA metabolism and induce cellular stress. In most types of ALS, *TDP43* is the main constituent of these inclusions. Mutations in *TARDBP* are a rare cause of ALS. Mutations in chromosome 9 open reading frame 72 (*C90RF72*) and *TARDBP* which encodes *TDP43* and *FUS* disturb normal RNA processing, yielding disrupted assembled proteins and toxic RNA species (Bendotti et al. 2012). The aggregates of different mutated proteins such as *SOD1*, *UBQLN2*, and others interfere with several cellular functions such as protein degradation, ER stress, Golgi and mitochondrial failure, failure of cytoskeletal architecture, intracellular transport, and stress (Basso et al. 2006). Motor neurons are more susceptible to TDP43 and this triggers NF-KB-mediated pathogenic pathways (Huang et al. 2012).

In 97% of cases, patients of ALS have TDP43 proteinopathy with the depletion of TDP43 in the nucleus and cytoplasmic aggregates with skein-like morphology in motor neurons. Mutations in *CHCHD10* can lead to mitochondrial dysfunction (Genin et al. 2016). Based on research publications, it is clear that ALS is a multisystem disease caused by a disrupted synaptic network.

1.2.4 Polyglutamine Diseases

Nine monogenic neurodegenerative disorders with comparable etiologies are grouped under the umbrella term "polyglutamine diseases." Polyglutamine diseases are characterized by CAG triplet repeat expansion in a specific gene producing a pathogenic protein. Expansion of CAG trinucleotide repeat region in the disease-affected gene results in an extended stretch of glutamine (Q) residues in the corresponding protein, which sets off downstream amendments like increased DNA damage, intracellular aggresomes, transcriptional dysregulation, and proteasomal dysregulation. They exhibit neuropathological accumulation of disease protein aggregates, primarily in neurons. The age of disease onset is influenced by the length of the CAG repeat in many illnesses, with longer CAG repeat tracts linked to earlier disease manifestation and greater severity of the illness, indicating a direct correlation between polyQ length and degree of toxicity. The predominant toxic characteristics of the disease-causing proteins—which, when exhibiting a polyQ expansion, interact differently with different protein partners and are susceptible to aggregate—are believed to be the main cause of the underlying mechanisms involved in polyQ diseases (McLoughlin et al. 2020). In several of these disorders, CAG repeat also expands both somatically during the course of an individual's

lifetime and through germline meiotically (between generations). Except for SBMA, which is X-linked and sex-limited, all polyQ diseases are autosomal dominant disorders. Nonetheless, some pathological symptoms are unique to a given disease and most likely indicate the gene of interest's expression profile or the interactome of cognate protein. These archetypal protein-folding abnormalities include dentatorubral-pallidoluysian atrophy (DRPLA); numerous spinocerebellar ataxias (SCAs) such as SCA1, SCA2, SCA3, SCA6, SCA7, and SCA17; Huntington disease (HD); and spinal and bulbar muscular atrophy ataxias X-linked type 1 (SBMA also known as SMAX1) (Lieberman et al. 2019). Except for SCA6 with the shorter disease repeat which results in cytoplasmic aggregates that do not exhibit ubiquitin expression, all of them exhibit accumulation of the mutant protein in sizable intranuclear inclusions (Zoghbi and Orr 2000).

Proteolytic cleavage is the initial step in the development of polyglutamine disorders, producing a toxic fragment. The expansion of a polyglutamine tract permits a change into a unique conformation which can be harmful in several ways. The peptide can self-associate to generate toxic oligomers or it can be toxic as a monomer. The oligomers eventually settle in macromolecular intracellular inclusions after assembling into bigger aggregated species. The primary harmful consequences of the misfolded protein could involve modifications in transcription, metabolism, or the breakdown of the proteasome or stress response mechanisms (Shao and Diamond 2007).

1.2.5 Spinocerebellar Ataxia (SCA3)

Among the polyQ diseases, SCA3 seemed to be the most prevalent dominantly inherited type of ataxia, affecting between 1 in 50,000 and 100,000 individuals. In SCA3, the CAG repeat expansion resides in exon 10 of the *ATXN3* gene. A wide range of progressive motor impairments is seen in individuals with SCA3, such as oculomotor abnormalities, impaired balance, limb incoordination, dystonia, stiffness, dysarthria, dysphagia, and significant cerebellar ataxia with aberrant gait (McLoughlin et al. 2020). Failure in brainstem-associated functions typically results in mortality within 10 to 15 years from the onset of symptoms, albeit the severity and rate of deterioration vary among patients (Lieberman et al. 2018). Neuronal dysfunction and neuronal cell death in somatosensory and motor nuclei encompassing the brainstem, cerebellum, midbrain, spinal cord, striatum, and thalamus cause progressive motor impairment in SCA3 (Rüb et al. 2013). Enlargement of the fourth ventricle, which results from atrophy of neurons in the basilar pons and deep cerebellar nuclei, as well as loss of pontocerebellar fibers and spinocerebellar tracts, is a significant gross morphological characteristic in individuals with SCA3. Significant loss of dopaminergic neurons in the substantia nigra and vestibular nuclei is seen in post-mortem SCA3 disease brains. Degeneration of motor neurons in the globus pallidus, red nucleus, subthalamic nucleus, cranial nerve nuclei, and some thalamic nuclei is another effect of SCA3. Dorsal nuclei, dorsal root ganglia,

and anterior horn can all experience spinal cord atrophy. In contrast to the majority of other SCAs, SCA3 mostly spares the cerebellar cortex, including Purkinje cells, and olivary nuclei.

Vulnerable brain areas in SCA3 have ubiquitinated protein aggregates or inclusions including the mutant polyQ-expanded ATXN3 (Fu et al. 2018). Although smaller neuronal cytoplasmic inclusions (NCIs) and distal axonal aggregates also occur, neuronal nuclear inclusions (NNI) account for the majority of aggregates. ATXN3 NNI stains positively for various other proteins, which is similar to aggregates in other polyQ diseases. These proteins involve heat shock factor proteins, proteasomal subunits, transcription factors, autophagy-associated chaperones like p62, other polyQ proteins, and non-expanded wildtype ATXN3. SCA3 is a deadly, incurable disease even though its genetic etiology has been known for decades. Advances in the understanding of diseases and possible treatments are being achieved.

However, there is still much to learn about how brain malfunction and cell death brought on by the CAG expansion in the ATXN3 gene appear as a distinctive clinical condition (McLoughlin et al. 2020).

1.2.6 Huntington's Disease (HD)

The expansion of the CAG repeats in exon 1 of the *HTT* gene is the cause of Huntington's disease (HD), which is characterized by increasing chorea, behavioral, and cognitive symptoms (Bunting et al. 2022). HD is an autosomal dominant neurodegenerative disorder affecting approximately 5 out of 100,000 individuals in Western countries. In HD, cortical pyramidal neurons and striatal GABAergic projection neurons are most vulnerable to degeneration. In 1993, the genetic mutation responsible for HD was identified. In the polyglutamine (polyQ) tract close to the Htt gene's N terminus, there are typically 19–35 CAG repeats (MacDonald et al. 1993). This number rises to more than 36 repetitions in disease conditions. When the CAG repeat length is 42 or greater, complete penetration is observed. The onset of the disease can vary from early infancy to old age, with a mean duration of 15–20 years. HD symptoms typically appear at the age of 40 or 50. HD's etiology is still not entirely understood. Excitotoxicity, oxidative stress, poor energy metabolism, aberrant protein accumulation, transcription dysregulation, and aberrant protein interactions are some of the processes involved in the pathophysiology of HD (Tabrizi et al. 2020). Currently, there is no medication available to either prevent the onset or slow down the progression of HD due to insufficient understanding of its pathophysiology.

Clinical symptoms manifest quickly after commencement and consist of three distinct motor symptoms, with hyperkinesia giving way to hypokinesia. Patients first exhibit modest involuntary movements and psychological changes. The first motor symptom is usually irregularities in eye movement. Orofacial dyskinesias, which affects the head, neck, trunk, and arms, then gradually develops into chorea.

The mobility disorder worsens with the course of the disease. The intensity might range from moderate, sporadic hyperbole in gesture and expression, fidgeting hands, an unsteady, dance-like walk, to a constant stream of incapacitating, violent motions. Almost every kind of movement problem can be observed, including dystonia, rigidity, myoclonus, and athetosis, despite chorea being the most common. The degree and frequency of choreiform movements may decrease as the disease worsens; the initial hyperkinetic state gradually gives way to a more hypokinetic one where bradykinesia, stiffness, and dystonia predominate (Bunting et al. 2022). Psychosocial problems and cognitive deficiencies are associated with the movement condition. Dementia and issues with executive functioning are examples of cognitive impairment. Apathy and sadness are the most typical signs of psychiatric disorders, although they can also take the form of substance misuse, psychosis, paranoia, and obsessive-compulsive disorder. Loss of weight is another prevalent aspect of the illness. The patients eventually lose their independence and become dependent on continuous care; they typically pass away 17 years after the disease first manifests. Aspiration pneumonia owing to dysphagia and consequences from falls or chronic illnesses are the usual causes of death (Ferrante et al. 1985).

At death, HD brains weigh substantially less than healthy brains. The caudate and putamen regions in the basal ganglia exhibit significant atrophy, and this is a highly noticeable neuropathological characteristic of HD. Furthermore, gliosis in the striatum along with the loss of neurons is observed in HD. According to Vonsattel et al., the pathophysiology of HD ranges from grade 0 (no alterations) to grade 4, depending on the extent of striatal atrophy (reduction of the caudate and putamen to a tissue rim) (Vonsattel et al. 1985). Numerous neuronal subtypes, including interneurons and medium spiny projection neurons, make up the striatum. The latter group consists of big aspiny cholinergic neurons, neuronal nitric oxide synthase (nNOS)-positive neurons, and medium-sized aspiny reduced nicotinamide adenine dinucleotide phosphate (NADPH) diaphorase-positive neurons. In the early stages, HD mostly affects GABAergic medium-sized spiny neurons, sparing the other subpopulations of striatal neurons. While the striatum is most severely impacted by HD, other areas including the cortex, thalamus, superior olive, zona reticulata of the substantia nigra, lateral tuberal nucleus of the hypothalamus, and deep cerebellar nuclei may also experience neuronal loss (Cicchetti and Parent 1996). As a result, the striatal alterations show a comparatively specific susceptibility to cell death.

The development of cytoplasmic aggregates and intranuclear inclusions (NII) in neurons in susceptible brain regions is the hallmark of Huntington's disease (HD). Htt is a 348-kDa multidomain protein with a polymorphic glutamine/proline-rich domain at its amino terminus. Animal models of HD and human post-mortem brain tissues have revealed the localization of mHtt in the form of aggregates. Small N-terminal Htt fragments typically form the inclusions and aggregates, which are co-localized with other cellular proteins involved in protein breakdown, vesicle trafficking, and proteolysis. It is still uncertain if these aggregates are accidental, protective, or harmful. The cleavage of both mHtt and wHtt has been linked to caspases and calpain (Wellington et al. 1998). Small N-terminal fragments are produced and

accumulate as a result of caspase cleaving Htt; these fragments have the potential to create cytoplasmic aggregates and NII.

1.2.7 Frontotemporal Dementia (FTD)

Frontotemporal dementia is characterized by selective deterioration of frontal and temporal lobes typically resulting in altered behavior, difficulty in speaking, and symptoms related to mental health. Up to 20% of cases of presenile dementia are caused by frontotemporal dementia, which is the most prevalent type of primary degenerative dementia after Alzheimer's disease that affects adults in their middle years. Although the disorder can manifest before the age of 30 and in older adults, it most frequently manifests between the ages of 45 and 65. The rate of incidence is the same in men and women. The sickness lasted between 2 and 20 years, with an average of 8 years. About half of the cases had a family history of dementia (Snowden et al. 2002).

The clinical manifestations of FTD are referred to as the behavioral variant (bvFTD), the semantic and non-fluent variants of primary progressive aphasia (svPPA and nfvPPA), the right lobe variant (rtvFTD), and FTD linked with motor neuron disease (FTD-MND). Two tau-deposition-associated neurodegenerative illnesses, cortico-basal syndrome (CBS) and progressive supranuclear palsy (PSP) may also be associated with frontotemporal dementia (FTD) and may exhibit symptoms of frontal lobe dysfunction along their clinical course.

While AD affects posterior cingulate regions and spares the ACC, frontotemporal lobar degeneration (FTLD) affects the pregenual anterior cingulate cortex (ACC), spreading back to the midcingulate cortex (Robberecht and Philips 2013). Behavioral variant (bv) FTLD is best distinguished by impairments in the ACC and frontal insula from AD. It has been demonstrated that layer Vb of those regions contains large bipolar spindle-shaped von Economo neurons (VENs), which constitute an early target in bvFTLD but not AD. After accounting for surrounding layer 5 neuron loss in bvFTLD, a 69% decrease in VENs was discovered. This VEN selectivity was observed in patients who had the illness at an early stage. Late-stage AD (Braak stage VI) did not exhibit any selective loss of ACC VENs, in contrast to bvFTLD. There are still no tangles in VENs39. One uncommon cause is Pick's disease (Snowden et al. 2002).

1.3 Selective Neuronal Vulnerability in NDDs

In neurodegenerative disorders, "selective vulnerability" refers to subpopulations of neurons that are more prone to abnormal function or death in response to particular pathological states or injuries that occur in different brain regions and cause a systemic breakdown over time. Neuronal cells in neurodegenerative diseases are

always under stress from a variety of external sources and their internal metabolic processes. Neurons are the most vulnerable cells due to neurodegeneration since they are unable to recover after injury and must continue to meet the metabolic needs for long axonal projections and neurotransmission (Mattson and Magnus 2006). Due to their high energy requirements and reliance on axonal transport, bigger neurons are prominently more susceptible to environmental contaminants. Their myelinated axons also reach farther, making them even more difficult to work with. It is hypothesized that certain neurons have unique pathogenic mechanisms that make them more vulnerable than others. In general, neurons are the developed cells of the neuroblast, which form at 8 weeks of embryonic life from neuroectoderm. All of a person's neurons share the same genes, but each neuron's distinct function ultimately dictates how the gene is expressed. At this stage, some neurons are more vulnerable to anoxia and oxidative stress, and the variables that cause selective susceptibility include the type of neuron and their neuronal environment (Wang and Michaelis 2010).

It is even more difficult for larger neurons with myelinated axons to extend longer distances due to high energy demand, and being reliant on axonal transport, they cover a large surface area, making them highly prone to environmental toxins. According to the hypothesis, some neurons are more susceptible than others due to their specific pathological processes. In general, neurons are the differentiated cells of the neuroblast which arise from neuroectoderm at 8 weeks of the fetal life. In an individual, all the neurons have the same genes but it is the gene expression that determines the final fate of any neuron by determining its specific function. The kind of neuron and its neuronal surroundings are the elements that lead to selective susceptibility at this stage, where some neurons are more vulnerable to oxidative stress and anoxia. Different neurons and brain regions are impacted by each neurodegenerative disease, and the subcellular targets of these illnesses include autophagy, proteostasis, oxidative stress, ER stress, and neuroinflammation (Saxena and Caroni 2011).

Neurons that are susceptible to a given NDD have pathways specific to it that impact important homeostatic processes in that neuronal population, which is why these neurons are selectively vulnerable. For example, in Parkinson's disease, the dopaminergic neurons are the vulnerable neurons highly susceptible to reactive oxygen species (ROS)-induced injury. The neurons in the substantia nigra are rich in iron and copper metals and low in antioxidant molecules such as glutathione making them capable of catalyzing ROS formation, thereby increasing the susceptibility of these neurons. The reduced mitochondrial function and elevated levels of cytosolic calcium further silence and degenerate the vulnerable neurons.

In Alzheimer's disease, the vulnerable neurons lost in the early stage of the disease mainly include large pyramidal neurons in layer II of the entorhinal cortex (EC II), the cornu ammonis area 1 (CA1) region of the hippocampus, the subiculum, the noradrenergic neurons in the locus coeruleus, and the corticopetal cholinergic neurons in the basal forebrain (BF) (Whitehouse et al. 1982). In ALS, motor neurons require an efficient axonal transport system, strong cytoskeleton and neuronal filament. These motor neurons are high in metabolism and they are very sensitive to

energy demands. According to post-mortem studies of ALS patients, motor neurons with large axonal diameters are the most vulnerable neurons for degeneration. In Huntington's disease, the neurons expressing D2 type of dopamine receptors, neurotensin or met-enkephalin, are vulnerable (Table 1.1).

1.4 Disrupted Food Intake and Gut Dysbiosis in NDDs

Apart from genetics, environment and lifestyle are also risk factors contributing to the initiation of NDDs. Diet can influence the progression of brain pathology and cognitive deficits in neurodegenerative disorders. It has been reported that a diet containing a low intake of fiber and alcohol consumption, rich in refined carbohydrates, and a high amount of saturated or trans-fat can adversely affect cognitive function in humans. Diet can affect the composition of the microbiome present in human gut. Different nutrients are absorbed from the diet which will favor or disfavor different functions of certain gut microbiota (Frausto et al. 2021). The gut microbiome plays an important role in the regulation of bidirectional signaling of gut-brain axis. Dietary changes can alter the composition of microbiome which can lead to gut dysbiosis and affects gut-brain axis along with bidirectional communications which contribute to the neuroinflammation and pathogenesis of several CNS disorders such as Alzheimer's disease, Parkinson's disease, and others (Burokas et al. 2015).

Carbohydrates, fats, and proteins are the main food components of a human diet. Short-chain fatty acids (SCFAs), secondary bile acids, and micronutrients (vitamins) are the major metabolites produced by bacterial fermentation in the gut. Organic acid is released as a byproduct of carbohydrate fermentation which is used by the bacteria residing in the gut as an energy source. The metabolites enter the blood circulation either by passive or active transport to the gastrointestinal tract endothelia and then they enter into the blood circulation (Conlon and Bird 2015). Gut dysbiosis is associated with a decreased abundance of SCFAs which is further associated with inflammation and disruption of gut epithelia (Hirschberg et al. 2019). There is a vicious circle in which alterations in diet cause an imbalance in gut

Table 1.1 Table depicting selectively vulnerable cells and protein aggregates involved in neurodegenerative disorders (Fu et al. 2018)

Disease	Vulnerable neuron	Aggregated protein
Alzheimer's disease	Cholinergic neurons in BF, pyramidal neurons in EC II, and HP-CA1; noradrenergic neurons in LC	Aβ 42, tau
Parkinson's disease	Dopaminergic neurons	α-Synuclein
Huntington's disease	GABAinergic neurons	Huntingtin
Frontotemporal dementia	Frontotemporal cortical neurons	Tau, TDP-43, SOD1, FUS, DPRs
Amyotrophic lateral sclerosis	Upper and lower motor neurons	TDP-43, SOD1, FUS, DPRs

microbiota which in turn will disrupt the cellular metabolic processes in the human body shown in Fig. 1.1 (Morris et al. 2017).

Environmental factors such as physical activity, psychological stress, biological stress, and diet can be the etiology of AD development. Out of all these risk features, diet is a critical factor for cognition and neuroinflammation. Human diet is a combination of different nutrients which makes the impact of nutrients complex in AD. It has been reported in an animal model that a diet composed of elevated levels of saturated and trans-fat can increase the hippocampal oxidative stress and deposition of cerebrovascular amyloid deposits and possibly induce neuroinflammation and cognitive impairment as well (Pistollato et al. 2016). This implies that there is a negative effect of saturated and trans-fat on AD pathology. Additional clinical studies have shown that a diet with high sugar/carbohydrates and fat can impair memory functions (Martínez Leo and Segura Campos 2020). As per Framingham Heart Studies, drinks such as soft drinks and fruit juices high in carbohydrate levels are involved in decreasing the hippocampal volume and cognitive functions in a dose-dependent manner. Thus, consumption of refined carbohydrates in large quantities can enhance memory dysfunction, induce neuroinflammation, and impair hippocampal neurogenesis and plasticity. There is an increased AD prevalence in those who consume meat and meat products, whereas there is a lower risk of AD or dementia for those consuming plant-based protein (Romanenko et al. 2021).

Microorganisms play a very important role in human body for various aspects such as metabolism of bile acids, sterols and drugs, synthesis of vitamins B and K, fermentation of undigested carbohydrates, and production of short-chain fatty acids

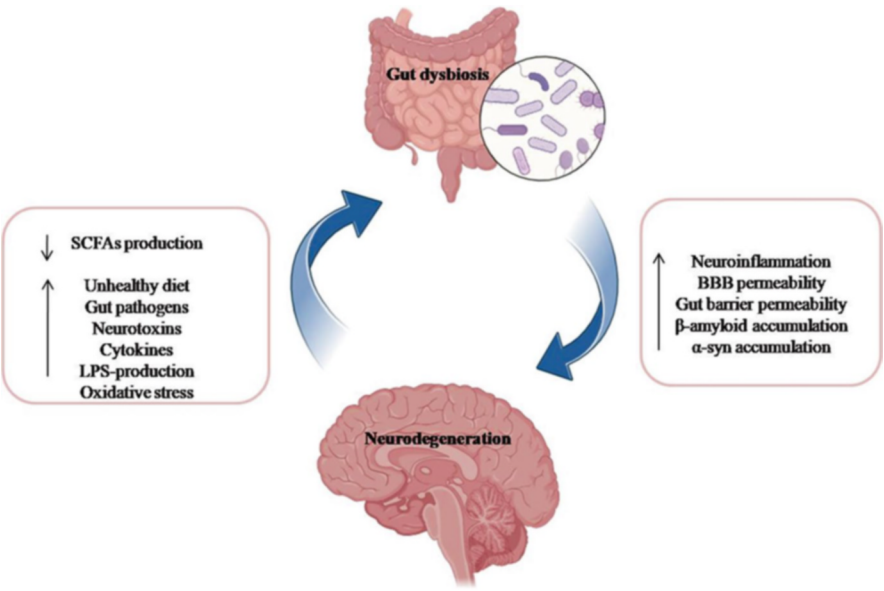

Fig. 1.1 The role of gut dysbiosis in the pathogenesis of neurodegenerative disorders

(SCFA). Apart from these, they also protect human gut from foreign pathogens. Human gut is the generating site for microbiota post-birth. Gut microbiota is the presence of symbiotic association of different microorganisms like viruses, algae, fungi, bacteria, and archaea in the GI tract of humans. Bacteroidota and Firmicutes are the two most prominent phyla of microbiota present in human gut. Two types of gut flora have been identified and named as essential or beneficial flora as well as housekeepers of the gut and the other one is opportunistic bacteria which cause infection (Roy Sarkar and Banerjee 2019). Essential flora comprises *Lactobacillus* species (*L. plantarum*, *L. rhamnosus*, *L. acidophilus*, etc.), *Propionibacterium*, *Enterococcus*, *Peptostreptococcus*, and *Bifidobacterium* (*B. bifidum*), whereas the opportunistic bacteria is consisting of Clostridia, *Bacteroides*, Actinobacteria, Bacilli, *Peptococcus, Streptococcus, Staphylococcus, Enterobacteriaceae*, yeasts, etc. Any imbalance between these two groups of bacteria can cause gut dysbiosis resulting in various gastrointestinal diseases such as ulcerative colitis, colorectal cancer, Crohn's disease, metabolic diseases, and irritable bowel syndrome (IBS). These GI disorders augment pro-inflammatory cytokines, T helper cells, lipopolysaccharides, and monocytes which will increase intestinal and BBB permeability through microbiota-gut-brain axis (Burokas et al. 2015).

There is an intricate link between gut dysbiosis and neurodegenerative disorders. Changes in the composition of gut microbiome activate the pro-inflammatory cytokines which increase the permeability of intestine and lead to insulin resistance which can be a risk factor for development of brain disorders such as AD (Bekkering et al. 2013). There is an intimidating relationship between the gut epithelia and human brain termed as gut-brain axis. The central nervous system and the enteric nervous system are comprised of two terminal nodes for communication: sensory nerves and the autonomic nervous system (ANS). The connection between these nodes is mediated by the hypothalamic-pituitary-adrenal (HPA) axis. The CNS communicates bidirectionally with the enteric nervous system (ENS also known as the "little brain of the gut"), gut muscle layer, and mucosa layer of the intestine through afferent and efferent autonomic pathways (ANS) (Carabotti et al. 2015). The gut involves the sympathetic and parasympathetic nervous systems for its communication. The brain modulates several aspects such as immunity, gut motility, permeability, and mucus secretion. Several risk factors can influence the development of microflora in gut such as diet, sanitation level, gestational age, and exposure to antibiotics. Microflora is also associated with NDDs as it is involved in the synthesis of neuroactive molecules and metabolites which can modulate the pathogenesis of NDDs (Quigley 2017).

In NDDs, gut bacteria activate the immune system through a defective gut barrier, impairing the blood-brain barrier, which further increases neuroinflammation and neural injury and leads to degeneration. Defective intestinal barrier alters the microglial properties and activates reactive microglia which releases a high concentration of pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-6, and TNF-α and produces reactive oxygen species (ROS) as well as high amounts of nitric oxide (NO). Activated microglia also produce neurotoxic reactive astrocytes (Heneka et al. 2018).This impairs the microbiota-gut brain axis pathway which

results in deposition of beta-amyloid plaques in Alzheimer's disease and misfolding and aggregation of α-synuclein protein in Parkinson's disease. It has been reported that certain gut bacteria such as *Escherichia* and *Shigella* are involved in the production of pro-inflammatory cytokines, LPSs, amyloids, and modulation of certain signaling pathways involved in neuroinflammation and deposition of beta-amyloids in the brain (Friedland 2015).

According to published reports, an imbalance in the gut microbiota has a pivotal role in aggravation of PD. A highly oxidized (aerobic) gut environment can lead to neuroinflammation which can develop into PD. *Helicobacter pylori* has been associated with impaired absorption of levodopa and disease severity leading to progression of Parkinson's disease (Martínez Leo and Segura Campos 2020). Lipopolysaccharides (LPS) and neurotoxins produce local inflammation and oxidative stress in the intestine initiating the deposition of α-synuclein (α-syn) leading to the microglial activation, neuronal death, and subsequent activation of TLRs. The dysbiosis product, LPS, and BMAA damage the intestinal tight junction and junction protein (ZO-1) which leads to muscle weakness and decrease in muscle size. This enhances neuroinflammation, neurodegeneration, and death of brain and spinal cord motor neurons leading to ALS. As per statistics records, the mean life expectancy of ALS patients is 3–5 years, but 10% of ALS patients live for more than 8 years due to many factors that can affect the survival rate of patients such as age, gender, diet, location of lesion, and environment. Insufficient nutrients and exuberant metabolism negatively affect the neuromuscular status. Alterations in levels of LPS and BMAA can disrupt the BBB and can contribute to the pathogenesis of ALS (Roy Sarkar and Banerjee 2019).

Internal dysbiosis is known to be brought by psychological and physical stress, and this change in the microbiota's composition may either directly or indirectly encourage the emergence of an inflammatory state in the central nervous system, which in turn can cause emotional disorders. Dementia is highly correlated with a low *Bacteroides* abundance and a high number of other bacteria. Studies have also demonstrated that propionate causes behavior similar to those of autism spectrum disorder (ASD). Therefore, a poor metabolism of propionic acid is associated with the typical aberration in neurodevelopment observed in persons with autism, and this may be related to a change in the gut microbiota that produces propionate. Clostridium has also been the subject of much research in ASD because of its propensity to produce toxins and propionate, which can exacerbate the disease symptoms. Patients with schizophrenia have larger proportions of Firmicutes as compared to healthy people, who likewise have high amounts of Bacteroidetes and Actinobacteria. When compared to control, the gut microbiota of schizophrenia patients also contained higher concentrations of *Clostridium* and *Megasphaera*. This finding is consistent with the knowledge that *Clostridium* produces a variety of neurotoxins, such as phenylalanine derivative, which affects the central nervous system in a manner similar to autism. *Megasphaera* is linked to inflammation and cognitive delays. Several studies have reflected the importance of the dysregulated tryptophan metabolism in the pathogenesis of the disease. Due to the dysregulation of the metabolic pathway, the levels of the byproduct kynurenic acid, an

N-methyl-D-aspartate receptor antagonist, increase leading to cognitive deficits, synaptic impairment, and memory loss accelerating the progression of several neuropathologies. However, the role of kynurenic acid in schizophrenia is not fully elucidated, but few reports suggest intestinal microbiome may have a role in influencing the plasma levels of tryptophan (Almeida et al. 2020).

1.5 Disruption in Circadian Rhythmicity in Neurodegenerative Disorders

Another characteristic of neurodegenerative disorder includes disruption of sleep patterns and circadian rhythmicity occurring in the early course of NDDs such as Parkinson's disease, Alzheimer's disease, and Huntington's disease. Clock genes regulate several genes and biochemical mechanisms and their alteration contributes to neurodegeneration.

Circadian rhythm acts as biological timekeepers that perpetuate life from a mere second to the full Gregorian year. It plays a crucial role in sustaining living organisms. Circadian rhythm coordinates with multiple cellular processes with the predictable 24-h cycle of light and dark on Earth (Bell-Pedersen et al. 2005). For example, the daily patterns of sleeping and waking up, blood pressure, heart rate, and rise and fall of core body temperature, all are mediated by the circadian clock. There is release of a variety of hormones mainly melatonin from the pineal gland which is under the control of circadian clock in the human body. Mammalian circadian rhythms can affect several aspects and can bring changes in host physiological, biochemical, and behavioral processes (Arendt 2012).

Light is the external stimulus which activates intrinsically photosensitive ganglion cells of the retina (ipRGCs). This in turn innervates the suprachiasmatic nucleus (SCN) residing dorsal to the optic chiasm, entraining mammals to the 24-hour day cycle. The SCN acts as the central pacemaker and regulates circadian clock in the human body. The retinohypothalamic tract provides input to the SCN about exposure to daily light to synchronize the endogenous clock to the external environment (Welsh et al. 2009). In response, the SCN sends signals through diffusion and synapse to other organs such as the lungs, heart, liver, adrenal glands, and various regions of the brain. The coordination of the SCN throughout the body is very crucial for good health and well-being (McFadden et al. 2014). Efferent projections from the SCN innervate structures such as the pineal gland and produce melatonin during the night for induction of sleep. Through a series of genes regulating their own transcription and translation for 24 h, by negative feedback loops are controlled at cellular level for the circadian clock. The heterodimers of the transcription factors BMAL1 and CLOCK are involved in driving the expression of various genes, *Cryptochrome* (*Cry1*/*Cry2*) and *Period* (*Per1*/*Per2*) genes, *REV-ERBα*, and the nuclear receptors retinoid-related orphan receptor (*RORα*) and several downstream genes also termed as clock-controlled genes (CCGs). The Per and

Cry proteins dimerize and are involved in the inhibition of transcriptional activity of BMAL1. The activity of PER-CRY dimmers is regulated by casein kinase 1 at post-transcriptional level. This cycle of gene expression of clock takes place in 24 h in mammalians (Wilking et al. 2013). In addition, these genes (clock genes) also serve as transcriptional factors for other genes regulating different functions such as metabolism, immune response, cell division, and oxidative processes (Duffield 2003).

Disrupted sleep patterns are highly evident in a number of diseases such as cancer, depression, metabolic disorders, bipolar diseases, and other CNS-related disorders. Disruption of circadian rhythms or fluctuations in 24-h cycle can contribute to the onset of characteristic cognitive and motor symptoms in neurodegenerative disorders (Mattis and Sehgal 2016). Mutations in *BMAL1* and *PERIOD* genes can impair cognitive functions and can shorten the lifespan in *Drosophila* and mice (Kondratov et al. 2006; Krishnan et al. 2009). There is an increased risk of PD associated with single-nucleotide polymorphism in BMAL1 and PER1 (Sharma et al. 2020). In PD patients, the SCN activity is reduced which disrupts the sleep-wake cycle and results in the elimination of the rhythmic secretion of melatonin or other hormones which are related to clock gene (Shkodina et al. 2022). In AD, *presenilin-2* gene regulates the formation of amyloids and is linked to familial early onset. This *presenilin-2* gene is expressed in SCN and its expression has been regulated by dimers of CLOCK-BMAL1 at the transcriptional and post-transcriptional level (Hood and Amir 2017). The alteration in expression of circadian clock genes such as mPer2 and mBmal1 disrupts sleep pattern which further exacerbates the symptoms of Huntington's disease such as depression, memory impairment, and aggression (Canever et al. 2023). Loss of sleep accelerates the progression of the disease. In HD, patients experience disturbed nocturnal sleep with prolonged sleep-onset latency, increased wakefulness, and fragmented and irregular sleep stages due to the disruption of circadian rhythm (Faragó et al. 2019).The studies suggest that the circadian rhythm can contribute to neurodegeneration by regulating cellular responses to oxidative stress by rhythmic release of hormone melatonin, an effective free radical scavenger (Wilking et al. 2013). Disruption of molecular clock can disrupt metabolism and DNA replication processes. Oxidative stress can further cause mitochondrial dysfunction, neuronal damage, and cell death. Thus, clock genes regulate the expression of genes involved in the pathogenesis of neurodegenerative disorders such as AD, PD, and HD.

1.6 Conclusion

Determining the abnormal protein interactions in the afflicted cells will be a key task in figuring out the pathophysiology of neurodegenerative diseases. Understanding the aberrant cellular protein transport, protein interactions, and protein aggregation is a necessary step in this process. Alzheimer's disease and prion diseases are characterized by the homodimerization of protein fragments into b-pleated sheets; disorders involving abnormally high numbers of CAG repeats are

associated with defects in glutamine, ubiquitin, and proteasome processing. Alzheimer's disease is caused by the pathogenic interaction of apolipoprotein E with beta-amyloid, tau; Parkinson's disease, diffuse Lewy body disease, and multiple system atrophy may be influenced by the passive or active role of a-synuclein. These defects in the cells can cause apoptosis, which kills the neurons. High metabolic load in the neurons of the affected regions of the brain makes them highly susceptible to superoxide species, further leading to improper folding of α-syn proteins (Rietdijk et al. 2017). Neurodegenerative disorders have been shown to exhibit links with multiple factors such as dietary changes and anomalies associated with the gut microbiome and circadian rhythm which can mark the onset of the disease. Dietary changes have a direct influence on the composition of the gut microbiota which in turn has been associated with neuropathogenesis of CNS disorders. The current lifestyle and dietary patterns are the major factors increasing the risk of developing not only metabolic diseases but also the development of NDDs. Any disruption in a balanced diet can lead to gut dysbiosis and it generates pro-inflammatory cytokines and bacterial metabolites which can disrupt the intestinal barrier and blood-brain barrier leading to elevated systemic circulation of microbes, neuroinflammation, and neurodegeneration. This can facilitate the pathogenesis of several neurodegenerative disorders like AD, PD, MS, and ALS. Thus, gut microbiota and healthy nutrients play a significant role in controlling gut-brain axis function. Due to the disruption of circadian rhythm, there is a high degradation of SCN and central endogenous circadian timekeeper observed in AD patients. PD and HD patients have also experienced similar disruptions in the expression of clock genes. Delineating these abnormalities further should offer an opportunity to find the treatments that block or prevent these distressing diseases.

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Chapter 2
Mechanism Underlying Major Neurodegenerative Disorders

Anjalika Chongtham and Namita Agrawal

Abstract Neurodegenerative disorders (NDDs) are brain-associated late-onset disorders, and due to increase in its prevalence, significant efforts have been made to uncover the underlying molecular and cellular pathogenic mechanisms. Even though NDDs uniquely affect specific neuronal subpopulations, the accumulation of distinct protein is known to cause neuronal loss. Additionally, with the advent of new techniques, progressive neuronal loss, synaptic dysfunction, altered calcium homeostasis, aberrant neural activity, and impairment in large-scale neural circuits are also well-documented features of NDDs.

In the present chapter, we provide a comprehensive insight into the common pathogenic mechanisms underlying debilitating neurodegenerative diseases. We have discussed about the abnormal protein dynamics with misfolding, defective degradation, proteosomal dysfunction, and aggregation.

Keywords Metabolism · Neurodegenerative diseases · Protein aggregation · Autophagy

2.1 Introduction

The proper functioning of cells and organisms relies on the precise activity of an extensive network of thousands of proteins. The functionality of a protein is determined by its stable three-dimensional structure, a folded conformation determined by its amino acid sequence. Chaperone proteins play a crucial role in overseeing the folding of proteins, minimizing errors, and eliminating malfunctioning proteins. Despite this regulatory mechanism, accumulating evidence suggests that protein

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misfolding and aggregation may be a primary contributor to various neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and related polyglutamine disorders including several forms of spinocerebellar ataxia (SCA); transmissible spongiform encephalopathies (TSEs), which include several human and animal diseases; and amyotrophic lateral sclerosis (ALS). Despite the apparent differences in clinical symptoms and disease progression, these disorders share some noteworthy commonalities. Most neurodegenerative diseases can manifest both sporadically and through inherited origins. Additionally, they typically appear later in life, often after the fourth or fifth decade. A shared pathology among these conditions involves neuronal loss and synaptic abnormalities, linking them at a molecular level despite their varied clinical presentations. Another common event considered a fundamental cause of these diseases is the progressive accumulation of misfolded protein aggregates in highly ordered structures, commonly known as amyloid. While the specific protein aggregates implicated in various neurodegenerative diseases may differ, the process of protein misfolding, its intermediate stages, end products, and key features exhibit striking similarities. This chapter explores several important mechanisms governing protein misfolding and aggregation in neurodegenerative diseases. It underscores the pivotal role played by protein quality control and degradation systems in preserving cellular proteostasis, emphasizing their dysfunction as a contributing factor to neurodegeneration. Finally, the chapter discusses the toxic effects of misfolded proteins, elucidating their adverse impact on neuronal function and survival in various neurodegenerative disorders (NDDs).

2.2 Protein Misfolding and Aggregation in NDDs: An Overview of Contributing Factors

A common hallmark feature of conformational disorders is the ability of a specific protein to fold into a stable alternative conformation. This alternative conformation frequently results in protein aggregation and accumulation in tissues as fibrillar deposits. Aggregates of phosphorylated tau, a microtubule-associated protein, in neurofibrillary tangles and neuropil threads in conjunction with amyloid-β (Aβ) deposits, are characteristic of sporadic AD. This tau-related pathology extends to a subset of cases of frontotemporal lobar degeneration (FTLD), specifically classified as FTLD-tau, and in other rare tauopathies. Moreover, intranuclear deposits of polyglutamine (polyQ)-expanded huntingtin (Htt) protein are a defining characteristic of HD. Furthermore, α-synuclein accumulation in Lewy bodies and neurites serves as the pathological signatures of sporadic PD, PD with dementia, and dementia with Lewy bodies. Finally, almost all cases of ALS and a specific subgroup of FTLD (FTLD-TDP) are characterized by aggregates composed of TAR DNA-binding protein 43 (TDP-43). Although these deposits share certain morphological, structural, and staining characteristics, it is probable that distinct biochemical or biological features exist among different protein deposits. This variability is likely influenced

by whether the aggregates accumulate intra- or extracellularly. Amyloid is a generic term encompassing protein aggregates that share a common structural motif known as the cross-β sheet, characterized by specific tinctorial properties such as binding to Congo red and thioflavin S. Amyloid structures also exhibit higher resistance to proteolytic degradation and present a fibrillar appearance under electron microscopy, featuring straight, unbranched fibrils that are approximately 10 nanometers wide. Initially, these large protein deposits were considered the primary neurotoxic species in the brain. However, recent evidence suggests that smaller, soluble misfolded oligomers, precursors to these fibrillar aggregates, are the real culprits of neurodegeneration (Soto and Pritzkow 2018). Misfolded oligomers constitute a heterogeneous group of species, spanning from dimers to larger protofibrillar structures, possibly composed of hundreds of monomers. This dynamic oligomeric ensemble exists in equilibrium with monomers and fibrils. Furthermore, certain oligomers act as on-pathway intermediates in the formation of amyloid fibrils, while others may represent terminal off-pathway products with the potential for high toxicity (Soto and Pritzkow 2018) (Fig. 2.1).

Protein folding is a complex process involving numerous intermediate states and rate-limiting steps influenced by local structural features and hydrophobic collapse. However, not all folding intermediates contribute to the formation of the final, functional protein structure. In fact, some intermediates can misfold by forming

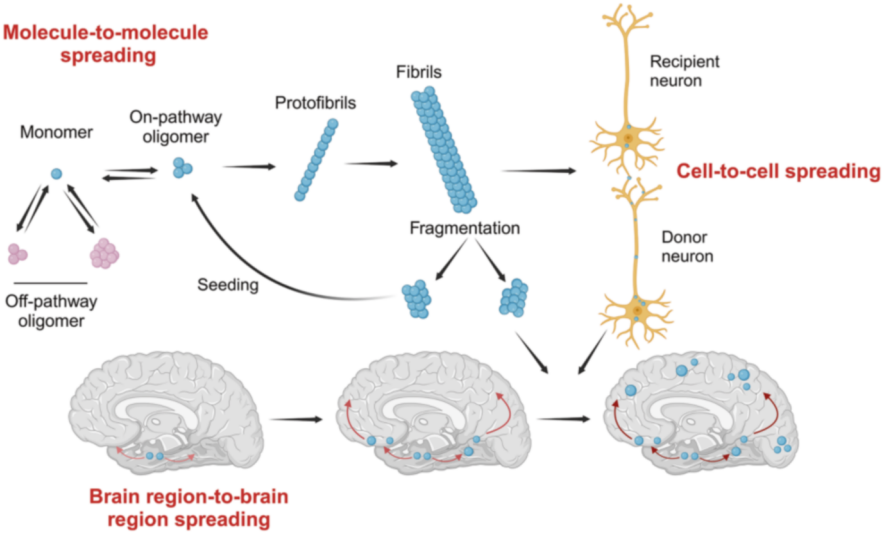

Fig. 2.1 The prion-like mechanism underscores the pathological transmission of misfolded proteins. Misfolded monomers aggregate, giving rise to both on-pathway and off-pathway oligomers. On-pathway oligomers have a propensity to evolve into protofibrils and, ultimately, fibrils, whereas off-pathway oligomers lack the capability to form amyloid fibrils. The propagation of protein misfolding plays a pivotal role in the pathogenesis of neurodegenerative diseases, occurring at various levels—from molecule-to-molecule interactions to cell-to-cell transmission, and even across different brain regions

non-native interactions, thereby deviating from their original native folding trajectory. When these misfolded proteins encounter each other, they can interact and eventually form aggregates. Gaining insights into the mechanisms of protein misfolding and aggregation is essential for the development of novel therapies and diagnostic tools for neurodegenerative diseases. Achieving this requires a comprehensive understanding of the factors influencing both processes. Several mechanisms contribute to protein misfolding and aggregation associated with neurodegenerative diseases, some of which are discussed in the following subsections.

2.2.1 Genetic and Environmental Factors

Several genetic and environmental factors have been implicated in protein misfolding and aggregation in neurodegenerative diseases. The destabilization of the native protein conformation is a primary mechanism by which mutations lead to conformational changes and disease states, favoring protein misfolding and aggregation. For example, HD is caused by a mutation in the huntingtin gene, resulting in an abnormal expansion (greater than ~35 repeats) of a polyQ tract within the first exon of Htt (The Huntington's Disease Collaborative Research Group 1993). This expansion of the polyQ tract is correlated with the aggregation of Htt, a multifaceted process involving various aggregate species, such as oligomers, amorphous aggregates, fibrils, and annular structures. Although early-onset Alzheimer's disease (EOAD) constitutes only 1–2% of Alzheimer's cases compared to late-onset Alzheimer's disease (LOAD), it is notably more complex genetically, involving an interplay of genetic, epigenetic, and environmental factors. The catalytic subunit of γ-secretase, presenilin 1 (PSEN1), produces Aβ peptides of varying lengths, and mutations in PSEN1 tend to elevate the Aβ42/Aβ40 ratio in EOAD. These mutations may alter the distribution of Aβ isoforms, favoring the production of the more toxic Aβ42, known for its increased susceptibility to aggregation. Mutations in the SNCA gene, encoding α-synuclein (αSyn), are the primary cause of early-onset familial Parkinson's disease (FPD). Five missense mutations have been identified to date: A30P, E46K, H50Q, G51D, and A53T. Mutations in the SNCA gene, increased oxidative stress, and various environmental stressors can all induce or exacerbate αSyn aggregation and associated toxicity (Stephens et al. 2019). Supporting this notion, elevated SNCA gene dosage and autosomal dominant mutations in the gene both lead to early-onset PD. The transition of αSyn to pathological fibrillar aggregates, the main constituents of Lewy bodies, necessitates disruptions in homeostasis and protein folding pathways.

Several environmental factors, including alterations in metal ions, pH changes, oxidative stress, and macromolecular crowding, can catalyze protein misfolding and aggregation. Many of these alterations are closely associated with aging, aligning with the typical late onset of neurodegenerative diseases. Conformational alterations in disease-associated proteins (Aβ, tau, and αSyn) play a central role in the

pathogenesis of neurodegenerative diseases. Specifically, the conformational changes and oligomerization of Aβ are pivotal in the process of Aβ-induced neurodegeneration. Trace elements such as Al3+, Zn2+, Cu2+, Mn2+, and Fe2+ act as accelerating factors in protein conformational changes; notably, they have the capacity to enhance Aβ oligomerization (Kawahara et al. 2017). Aβ (1–42) peptides exhibit a higher efficiency in forming large and complex fibrillar structures under acidic conditions compared to neutral pH. Moreover, Aβ aggregates induce substantial apoptotic death in PC12 cells, particularly at pH 5.8. This underscores the evidence that Aβ present in acidic organelles is more prone to forming neurotoxic fibrils compared to neutral cellular compartments. Compelling evidence supports a bidirectional relationship between oxidative stress and protein aggregation since aggregation-prone conformers, such as Aβ, exacerbate the production of reactive oxygen species (ROS), which, in turn, promotes aggregation (Butterfield and Boyd-Kimball 2019). While the detailed mechanisms of how oxidative stress induces protein aggregation are currently limited, in silico studies on the prion protein offer intriguing insights. These studies propose potential pathways wherein ROS may directly or indirectly induce the formation of β-sheets—a structure predisposed to aggregation. In the first case, the destabilization of the prion's physiological α-fold form is attributed to the direct oxidation of methionine residues by ROS. On the other hand, in the second case, ROS generated through copper reduction initiates the cleavage of the prion's N-terminus. Subsequently, the remaining copper facilitates β-sheet formation by chelating with neighboring histidine residues. However, further validation is required, and the applicability of these findings to other disarranged proteins remains a subject of exploration. Macromolecular crowding agents exert their influence by steric reduction of configurational entropy in proteins, employing an excluded volume mechanism. Furthermore, the impacts on protein conformation can result from the nonspecific interactions of proteins with crowding agents through various forces, including van der Waals forces, hydrophilic/hydrophobic effects, and electrostatic interactions. Macromolecular crowding exerts a profound influence on the aggregation of amyloid-forming proteins (Löwe et al. 2020). The extent of amyloid formation can be significantly altered in a crowded environment compared to aggregation in bulk solution. This effect is modulated by various factors, including the concentration of the crowding agent and the nature of its interactions with the aggregating protein. For example, α-synuclein aggregation is accelerated by various crowders, including polyethylene glycol (PEG), dextran, Ficoll, lysozyme, and bovine serum albumin, with larger macromolecular crowders promoting protein aggregation more rapidly than smaller crowders.

2.2.2 Seeding–Nucleation Mechanism

Kinetic studies have revealed that the aggregation of proteins such as Aβ, PrP, Htt, αSyn, and others implicated in systemic amyloidosis adheres to a seeding/nucleation mechanism. The seeding–nucleation model provides a comprehensive

framework for understanding the mechanism of protein misfolding and aggregation. This process unfolds with a slow and thermodynamically unfavorable nucleation phase, followed by a rapid elongation stage. Within the nucleation phase, the rate-determining step is the formation of protein oligomers that act as a stable seed or nucleus to direct further growth of aggregates. Nucleation-dependent polymerization is characterized by a slow lag phase, during which a series of energetically unfavorable interactions culminates in the formation of an oligomeric nucleus. This stable nucleus then acts as a template for the rapid growth of larger polymers. Large polymers have the capacity to undergo fragmentation, a process not well-understood in vivo, leading to the generation of additional seeds that facilitate the propagation of the reaction. A notable characteristic of the seeding–nucleation model is the ability of preformed seeds to significantly accelerate the aggregation process by recruiting the soluble normal protein into the expanding aggregate. From a biophysical perspective, the process of protein misfolding and aggregation involves a structural reorganization, transforming the protein into a series of β-strands. These strands are stabilized by hydrogen bonding and hydrophobic interactions, creating exposed "sticky" ends that attract molecules of the folded or partially unfolded protein. This attraction forces the protein to misfold to fit into the cross-β polymeric structure. While the primary scaffold of misfolded aggregates shares similarity, individual molecules can adopt diverse structures, giving rise to the possibility of conformational strains. In the pathway from the native monomeric protein to the fully aggregated fibrillar structure in vitro, at least two intermediates have been identified, primarily through studies of Aβ. The first category comprises soluble, low-molecular-weight oligomers ranging from dimers to decamers. These intermediates have been observed in test-tube experiments, in the conditioned medium of cells constitutively secreting Aβ, as well as in human cerebrospinal fluid and brain homogenate (Levine 1995; Kuo et al. 1996; Lambert et al. 1998; Walsh et al. 2002). The structural and biochemical characterization of these intermediates has posed challenges due to their transient and unstable nature. The second category of intermediates consists of short, flexible, rod-like structures known as protofibrils. Protofibrils are unbranched polymers characterized by a width of 3–6 nm and a length of up to 100 nm. Kinetic studies have revealed that these structures are metastable intermediates that elongate through the coalescence of smaller protofibrils, with the rate depending on factors such as Aβ concentration, temperature, ionic strength, and pH. Protofibrils exist in a dynamic equilibrium with oligomeric Aβ and serve as the immediate precursor to amyloid-like fibrils. Studies on secondary structure reveal that protofibrils possess a high β-sheet content and exhibit binding capabilities with amyloid-specific dyes such as Congo red and thioflavin T. Additionally, protofibrils have been identified in the aggregation process of αSyn This evidence suggests the coexistence of these intermediates, the monomeric protein, and the fibrillar aggregates in a dynamic equilibrium.

2.3 Impaired Cellular Protein Quality Control System and Clearance Mechanisms in NDDs

Cellular functions, including maintaining cell viability, rely on protein homeostasis or proteostasis. Maintaining cellular protein homeostasis is particularly crucial for long-lived post-mitotic cells like neurons. Proteostasis is closely linked to the identification and removal of unwanted proteins, ensuring protein quality control. Unsolicited, damaged, misfolded, and aggregated proteins are primarily degraded by the ubiquitin–proteasome system (UPS) and the lysosome-dependent autophagic process (Auzmendi-Iriarte and Matheu 2021). In UPS, ubiquitinated substrates are unfolded into nascent polypeptide chains and cleaved into smaller peptides, which are then transported through the proteasome's narrow catalytic chamber for degradation. UPS serves as the initial defense mechanism for the degradation of soluble misfolded proteins. Macroautophagy and chaperone-mediated autophagy (CMA) are two major subtypes of autophagy that mediate the selective removal of misfolded proteins. Macroautophagy is characterized by the formation of double-membrane vesicles called autophagosomes, which fuse with lysosomes to degrade their contents. In contrast to macroautophagy, CMA does not require the formation of vacuoles and selectively degrades individual proteins. Despite their distinct mechanisms, macroautophagy and CMA are connected during the autophagy–lysosomal degradation process, particularly in neurological disorders. Macroautophagy acts as a compensatory mechanism to eliminate malfunctioning proteins from the cytoplasm when CMA is impaired, and vice versa. In the following sections, we summarize current knowledge concerning the biological mechanisms involved in UPS and autophagy and highlight their roles in neurodegenerative diseases (Fig. 2.2).

2.3.1 Dysfunction of the Ubiquitin–Proteasome System in NDDs

Ubiquitin, an evolutionarily conserved 76-amino acid protein, is covalently attached to target proteins for degradation by the UPS. This essential process accounts for the degradation of approximately 80% of intracellular proteins in eukaryotes. The presence of ubiquitin in intracellular inclusions, such as amyloid plaques and neurofibrillary tangles in AD, Lewy bodies in PD, and intranuclear inclusions in polyglutamine repeat disorders, has been observed in various neurodegenerative diseases. The UPS targets misfolded proteins and a vast array of short-lived proteins residing in various cellular compartments, including the cytoplasm, nucleus, and ER. The UPS-mediated degradation of misfolded proteins commences when chaperones and ubiquitin ligases detect abnormalities in protein folding, such as exposed hydrophobic residues and aberrant disulfide bonds.

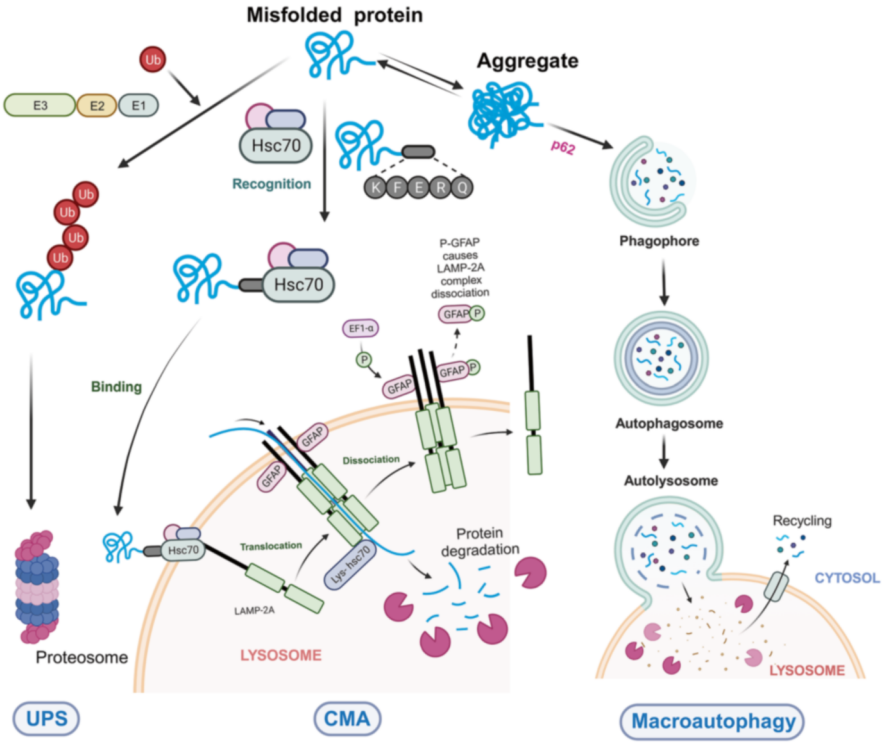

Fig. 2.2 Proteolytic pathways involved in the degradation of misfolded proteins. Initially recognized by molecular chaperones, misfolded proteins are directed to the UPS, CMA, or macroautophagy based on their misfolding nature, size, and solubility. Soluble and monomeric misfolded proteins are predominantly processed by the UPS and CMA. In CMA, substrates bearing the KFERQ motif are identified and bound by Hsc70 in conjunction with chaperones. These substrates are then transported to the LAMP2 complex on the lysosomal membrane, translocated to the lumen, and enzymatically broken down into amino acids by lysosomal hydrolases. However, misfolded proteins prone to aggregation are directed toward macroautophagy. Molecular chaperones like Hsc70 recognize misfolded protein substrates for macroautophagy, ubiquitin ligases add ubiquitin moieties, and the substrates are delivered to the autophagic adaptor p62. This process results in the formation of p62 protein bodies. The targeted protein aggregates, bound to p62, are subsequently transported to autophagic membranes for lysosomal degradation through interaction with LC3 on the autophagic membrane

Protein ubiquitination involves the sequential action of three specialized enzymes: E1 (ubiquitin-activating enzyme), E2 (ubiquitin-conjugating enzyme), and E3 (ubiquitin–protein ligase). The process commences with the ATP-dependent attachment of a single ubiquitin moiety to an active-site cysteine residue within E1 via a thioester bond. Subsequently, this activated ubiquitin is transferred to E2. Finally, E2, in collaboration with a specific E3 ligase, transfers the ubiquitin chain onto the intended substrate protein, marking it for degradation by the 26S proteasome. E3 ligases, the key determinants of ubiquitination specificity, fall into three

main classes based on their unique domains: RING (really interesting new gene)- or U-box domain-containing E3 ligases, HECT (homologous to E6AP C-terminus) domain-containing E3 ligases, and RBR (RING-between-RING) domain-containing E3 ligases. RING E3 ligases directly transfer ubiquitin from E2 ligases to substrates by binding both enzymes. HECT E3 ligases, on the other hand, harbor a conserved cysteine residue that serves as an initial ubiquitin acceptor. Activated ubiquitin is transferred from E2 ligases to the HECT domain before being conjugated to the substrate by the E3 ligase. Unlike RING E3 ligases, RBR E3 ligases possess two RING domains (RING1 and RING2) separated by an in-between-RING (IBR) domain. Functionally, RBR E3 ligases mirror HECT E3 ligases, as both catalyze the initial transfer of ubiquitin from E2 ligases to a catalytic cysteine residue on E3 ligases and subsequently from E3 ligases to substrates. The fate of a ubiquitin-linked protein is determined by the specific lysine residue to which the ubiquitin moiety is attached. Lys48-linked polyubiquitin chains typically target proteins for degradation via the proteasome, whereas other lysine-linked polyubiquitin chains play diverse roles in cellular processes such as NFκB signaling, mitophagy, and cell cycle regulation. When a ubiquitin chain of four or more ubiquitin moieties is attached to Lys48 of a protein, it serves as a signal for degradation by the 26S proteasome which consists of a proteolytic 20S core particle capped at both ends by a 19S regulatory particle. The 19S particle binds and unfolds the polyubiquitinated protein substrate, feeding the unfolded polypeptide chain into the narrow chamber of the 20S particle. Simultaneously, the 19S particle removes the ubiquitin moieties from the substrate to recycle ubiquitin. Within the 20S particle, the substrates are cleaved into small peptides by three distinct proteolytic subunits: β5, β2, and β1, exhibiting chymotrypsin-like, trypsin-like, and caspase-like peptidase activities.

The downregulation of the UPS is a significant factor contributing to the pathogenesis of several neurodegenerative diseases, including AD, PD, ALS, HD, and prion diseases. Aging is a major risk factor contributing to reduced UPS activity in degenerating brains. Proteasomal activity decreases with age, leading to impaired misfolded protein degradation and promoting the accumulation of pathological protein aggregates. Furthermore, the presence of aggregated proteins can impede the activity of UPS components, including the proteasome. For instance, the accumulation of ubiquitinated and aggregated tau in AD can directly impair proteasomal degradation by obstructing the gate of the 19S catalytic particle and hindering substrate access.

2.3.2 Dysfunction of the Autophagy–Lysosome System in NDDs

Autophagy is a cellular mechanism that involves the lysosomal degradation of cytoplasmic components. In neurodegenerative diseases, autophagy is essential for the removal of aggregated forms of pathogenic proteins, such as tau in AD, α-synuclein

in PD, and Htt in HD (Park et al. 2020). Autophagy is classified into three main types: microautophagy, CMA, and macroautophagy, each distinguished by the mechanism by which cellular components are delivered to the lysosome. Microautophagy involves the direct engulfment of cytoplasmic components by lysosomal or endosomal membranes. Unlike microautophagy, CMA specifically targets misfolded proteins that carry the KFERQ motif. This pentapeptide motif, found in about 30% of cytosolic proteins, is normally buried within the protein's structure but becomes exposed upon misfolding or partial unfolding. The chaperone Hsc70, along with its cochaperones, recognize this exposed motif. The substrates are then delivered to the CMA adaptor (lysosomal membrane-associated protein 2A (LAMP-2A) on the lysosomal membrane, where they are unfolded, translocated into the lysosomal lumen, and degraded. In neurons that are undergoing degeneration, CMA becomes constitutively active to compensate for a decline in macroautophagy.

In macroautophagy, cytoplasmic components, including misfolded proteins are enclosed within double-membraned structures called autophagosomes and subsequently digested by lysosomal enzymes. The selective targeting of misfolded proteins to autophagosomes relies on specific adaptors such as the p62/SQSTM-1/sequestosome. P62 possesses a UBA domain that interacts with polyubiquitin chains attached to misfolded proteins and a PB1 domain that promotes self-aggregation, forming condensed cargo–p62 complexes. These complexes are delivered to autophagosomes through the interaction of p62 with light chain 3II (LC3-II) present on the autophagosome surface. When misfolded or damaged proteins exceed the cellular capacity for direct delivery to autophagosomes, they are temporarily stored in the aggresome—an intracellular inclusion located near the nucleus. This process, known as aggrephagy, relies on histone deacetylase 6 (HDAC6) in collaboration with molecular chaperones. HDAC6 binds freely floating ubiquitinated aggregates and transports them along with microtubules to a location near the nucleus. This strategic sequestration minimizes the toxicity of these aggregates until they are eventually degraded by either the UPS or macroautophagy. Key components of aggresomes include ubiquitinated proteins, along with specific regulatory proteins like p62, ALFY, and NBR1. The survival of neurons is critically dependent on the efficient clearance of misfolded proteins through autophagy, as they lack the ability to dilute cellular toxins through cell division. This process is inherently challenging in neurons due to their unique elongated structure, which extends into dendrites and axons. Misfolded proteins generated in these distal regions must be packaged into autophagosomes and undergo a long retrograde journey back to the cell body, where lysosomes are concentrated. As autophagosomes undergo retrograde transportation toward the cell body, they frequently merge with late endosomes originating in neurites, leading to the creation of amphisomes. This process is challenging and highly complex, with its overall efficiency susceptible to adverse effects from various factors, including aging and genetic mutations. In aged neurons, besides the inherent decline in autophagic activity, the functionality of autophagic components may suffer due to interactions with protein aggregates. In conditions like frontotemporal lobar dementia with Ub-positive inclusions and PD,

tau and αSyn, respectively, exhibit heightened affinity for LAMP-2A. This heightened affinity results in a congestion scenario, disrupting the smooth translocation of cargo across the lysosomal membrane. Another risk factor contributing to the dysregulation of autophagy in aged neurons is a genetic mutation in an autophagy regulator, such as p62. Mutations in the p62 gene are linked to both familial and sporadic forms of ALS, where p62-positive inclusions accumulate in affected neurons.

Given the central role of protein misfolding in the pathogenesis of neurodegenerative diseases, it is crucial to comprehend how protein quality control pathways respond to disease-associated misfolded proteins and determine their impact on the proteostasis network. In the following sections, we will focus on the dysregulation of the protein quality control system and clearance mechanisms in AD, PD, HD, and ALS.

2.3.3 Protein Quality Control in AD

In AD, the UPS plays a role in downregulating amyloid precursor protein (APP) and Aβ at different stages of processing, extending from the endoplasmic reticulum (ER) lumen to the plasma membrane (Liu et al. 2022). The initial UPS degradation event takes place as a nascent APP polypeptide is cotranslationally translocated into the ER lumen, leading to the cleavage of its signal peptide. Following this, a properly folded mature APP protein progresses into the Golgi secretory pathway. However, terminally misfolded APP undergoes ER-associated degradation, a process involving substrate unfolding, ubiquitination, retrotranslocation across the ER membrane, and subsequent degradation by the proteasome. The targeting by ER-associated degradation is facilitated by the E3 Ub ligases HRD1 and FBXO. Alternatively, proteasomal degradation can take place upon APP's arrival at the Golgi apparatus, where APP undergoes ubiquitination through a K63 linkage by E3 ligases stimulated by ubiquilin-1. This leads to the retention of APP without proteasomal degradation. At the plasma membrane, APP can be internalized into endosomes and enter the endosome–Golgi pathway, where APP is cleaved, giving rise to Aβ. The intracellular Aβ generated is susceptible to misfolding and is subject to UPS-dependent protein quality control. This quality control involves the E3 ligase CHIP, which facilitates the ubiquitination of misfolded proteins, targeting them for proteasomal degradation. Unlike APP, Ub-conjugated Aβ in affected neurons is not efficiently degraded by the proteasome. The degradation of Aβ involves autophagy; however, autophagy itself is compromised in the brains of AD patients. This impairment manifests as an overabundance of autophagosomes and other autophagic vacuoles in affected neurons, creating a reservoir of cytotoxic Aβ peptides. The excessive accumulation of immature autophagic vacuoles is attributed to factors such as increased synthesis of autophagic core components, impaired retrograde transportation of autophagosomes, and disrupted fusion with lysosomes. Collectively, these impairments in proteasomal degradation and autophagy contribute to the accumulation of Aβ (Liu et al. 2022).

The primary defense against tau accumulation in AD is the E3 ligase CHIP, which facilitates the ubiquitination of tau, particularly in its phosphorylated form. This process involves a collaboration between CHIP, Hsp70, and Hsp90. While an in vitro study demonstrated that the E2 enzyme Ube2w can also mediate E3-independent ubiquitination of tau (Scaglione et al. 2013), ubiquitinated tau remains resistant to proteasomal degradation and accumulates as detergent-resistant aggregates, contributing to neurofibrillary tangle formation. Interestingly, CHIP appears to co-localize with its substrate and other ubiquitinated proteins within neurofibrillary tangles during the process of targeting tau to the proteasome. Additionally, overexpression of the molecular chaperone Hsp70 has been shown to enhance UPS-dependent clearance of tau (Petrucelli et al. 2004). Given the inefficiency of UPS-dependent tau degradation, autophagy plays a pivotal role in AD pathogenesis, particularly in the formation of amyloid plaques and tau aggregates (Jiang and Bhaskar 2020).

2.3.4 Protein Quality Control in PD

Lewy bodies (LBs), pathological hallmarks of both sporadic and familial PD, encompass over 90 proteins, including α-synuclein, DJ-1, LRRK2, Parkin, and PINK-1. Additionally, LBs contain mitochondria-related proteins and components of the UPS and autophagy, particularly those implicated in aggresome formation. Remarkably, many of the proteins in LBs play roles in protein quality control, and major causative mutations in familial PD are linked to genes involved in the UPS or autophagic pathways. These include α-synuclein, PINK-1, the Ub ligase Parkin, UCH-L1, PARK7, and LRRK2/PRAK8 (Leitão et al. 2021). In PD, the accumulation of misfolded αSyn, primarily in its monomeric and non-fibrillar forms, is considered more toxic than the formation of fibrillar aggregates. Interestingly, the presence of LBs may represent a cellular protective response aimed at sequestering and isolating the harmful alpha-synuclein molecules (Leitão et al. 2021). Besides mutations in ubiquitin ligases, rare mutations in the deubiquitinating enzyme UCH-L1 have been linked to familial, early-onset PD. These mutations in UCH-L1 result in reduced deubiquitinating activity, leading to the accumulation of α-synuclein in presynaptic terminals. Moreover, UCH-L1 can act as an E3 ligase, mediating K63-linked ubiquitination in its dimer form. Although soluble αSyn is efficiently degraded by the proteasome, filamentous αSyn directly interacts with the proteasomal 20S core, decreasing its proteolytic activity. The consistent association of proteasome misregulation with PD pathology in the substantia nigra provides compelling evidence for its role in disease pathogenesis.

Two specific PD-linked mutations, A30P and A53T, exhibit an unusually high affinity for the CMA adaptor LAMP-2A. This abnormal interaction hinders the efficient delivery of these mutant proteins to the lysosomal lumen, the site of degradation in the CMA pathway. Consequently, a traffic jam occurs within the CMA system, triggering a compensatory response in the form of macroautophagy.

Degradation of CMA-targeted αSyn within the lysosomal lumen is mediated by cathepsin D, a primary lysosomal protease. While monomeric or soluble oligomeric αSyn is degraded by both the UPS and CMA, aggregated αSyn is specifically targeted for lysosomal degradation via macroautophagy. Macroautophagy plays a crucial role in αSyn degradation, as evidenced by its accumulation in the lysosomes of neurons and the impaired lysosomal targeting of PD-linked mutant αSyn under macroautophagy inhibition (Hou et al. 2020). However, treating cells with rapamycin, a drug that inhibits mTOR and activates macroautophagy, enhanced the degradation of both wild-type and mutant α-synuclein (Tofaris et al. 2011).

2.3.5 Protein Quality Control in HD

Despite the critical role of mutant Htt (mHtt) in HD pathogenesis, the mechanisms governing its cellular clearance remain largely elusive. This obscurity is likely attributed to mHtt's inherent resistance to degradation by known proteolytic pathways, such as the UPS, CMA, and macroautophagy. Moreover, mHtt has been shown to impede the function of proteolytic machinery, even during its degradation process. Despite being tagged with ubiquitin, mHtt exhibits poor degradation by the proteasome, leading to the enrichment of ubiquitinated mHtt in the inclusions found in the brains of HD patients and mice. This accumulation of mHtt inclusions is not attributed to direct proteasomal inhibition but rather stems from a broader disruption of protein quality control mechanisms, exacerbated by the sequestration of molecular chaperones. The expansion of polyglutamine repeats in mHtt impedes its translocation across the lysosomal membrane. This delay arises from the increased affinity of mHtt for Hsc70 and LAMP-2A, which diverts mHtt away from the lysosomal degradation pathway. The impaired delivery of initially targeted mHtt to the lysosome creates a bottleneck in CMA-mediated degradation, triggering a secondary disruption in proteostasis. This failure to effectively degrade mHtt leads to the deposition of perinuclear and intranuclear inclusions in the neurons of HD patients.

The core components of macroautophagy, including LC3, exhibit consistent upregulation across various HD mouse models and in both neuronal and non-neuronal cells of HD patients. In HD, macroautophagy is accompanied by the excessive formation of cargo-free autophagic vacuoles, suggesting a disruption in cargo delivery to these vacuoles (Croce and Yamamoto 2019). The decline in autophagic flux leads to the accumulation of macroautophagy components, including p62, LC3-II, mTOR, and Beclin-1, in the striatum of HD transgenic mice (Lee et al. 2012). The sequestration of autophagic regulators, such as mTOR, within mHtt inclusions contributes to the increased production of autophagic core components observed in HD. This dysregulation, characterized by the accumulation of cargo-free autophagosomes, stems from impaired cargo delivery to autophagosomes and is exacerbated by Htt-mediated inhibition of macroautophagy in an age-dependent manner (Pircs et al. 2022).

2.3.6 *Protein Quality Control in Amyotrophic Lateral Sclerosis (ALS)*

Mutations in ALS genes can affect key components of protein quality control, including dynein, dynactin, p62, Ubqln2, and Optineurin, which play crucial roles in autophagosome transport and degradation. Other ALS mutations produce proteins with aberrant folding, including SOD1, TDP-43, and FUS/TLS. Initially targeted for degradation by the UPS, misfolded SOD1 and TDP-43 mutants often evade proteasomal degradation due to their aggregation propensity. Consequently, a subset of these mutants is diverted to autophagy. In familial ALS mutant mice and the postmortem spinal cord of sporadic ALS patients, mutant proteins that resist degradation by the UPS and autophagy form intracellular inclusions containing Ub and Ub ligases (Ciechanover and Kwon 2015). Insoluble aggregates typically emerge in the brainstem and spinal cord at symptom onset and progressively accumulate throughout the late stages of ALS. Autophagy is frequently dysregulated in the spinal cord of sporadic ALS patients and is characterized by the elevated accumulation of autophagosomes (Chua et al. 2022). This dysregulation can be partly attributed to the sequestration of various protein quality control components such as proteasomal subunits, ubiquitin ligases like Dorfin, molecular chaperones HSP70 and HSP40, and the motor protein dynein, which is crucial for cargo delivery to the aggresome. ALS proteins, in their monomeric or oligomeric forms, can directly obstruct both proteasomal activity and autophagic flux. This disruption of proteolytic pathways, in turn, promotes the accumulation of ALS protein aggregates, further exacerbating the dysfunction of proteasomal and autophagic mechanisms. This vicious cycle between misfolded proteins and proteolytic pathways accelerates the formation of insoluble inclusions and ultimately leads to the death of affected motor neurons.

2.4 Protein Toxicity and Its Implication in Neurodegenerative Disorders (NDDs)

Neurodegenerative diseases are becoming increasingly prevalent due to the rising average life expectancy. Patients with these debilitating conditions suffer from severe neurological impairments, such as memory loss and motor dysfunction, for which there is no cure. A hallmark of neurodegenerative diseases is the presence of protein toxicity. In this context, protein toxicity is defined as the pathological cascade of events triggered by the accumulation, oligomerization, and/or multimerization of disease-associated toxic proteins (Wilson et al. 2023). In neurodegenerative diseases, protein toxicity within affected neurons can cause cellular defects, including transcriptional alterations, mitochondrial dysfunction, and a compromised protein/RNA quality control system. These cellular impairments collectively play a pivotal role in initiating and driving the progression of neurodegenerative diseases.

While cell death represents the ultimate outcome of the disease process, it is often preceded by neurological deficits in both animal models and patients. Importantly, these cellular defects are not exclusive to specific neurodegenerative diseases and are commonly observed across various disease states. Given the pivotal role of protein toxicity in neurodegenerative disease pathogenesis, enhancing our understanding of protein toxicity mechanisms is essential for developing rational and effective therapies for these debilitating conditions. The following sections will explore the underlying mechanisms of protein toxicity across different subcellular compartments in neurodegenerative diseases, including AD, PD, HD, ALS, and FTD, among others.

2.4.1 Proteotoxicity in the Nucleus

Nuclear inclusions (NIs) composed of toxic proteins in neurons are a hallmark of a broad range of neurodegenerative diseases. Despite increasing evidence suggesting a central role for nuclear dysfunction in the pathogenesis of several neurodegenerative diseases, the precise role of neuronal intranuclear inclusion bodies in disease progression remains a subject of debate. One prevailing view proposes that microscopically visible NIs are not inherently toxic but rather serve as self-protective structures or incidental byproducts of the pathogenic process. This view suggests that the more soluble protofibrillar or oligomeric aggregates, as opposed to the more mature fibrillar aggregates formed within the nucleus, are responsible for the toxic effects observed in affected neurons. Although the precise role of nuclear inclusion bodies (NIBs) in neurodegenerative diseases remains under debate, nuclear dysfunction is a prevalent feature in these disorders. This includes transcriptional alterations and impaired nucleocytoplasmic transport, both of which can contribute to disease progression (Bitetto and Di Fonzo 2020). The nuclear accumulation of disease-associated toxic proteins is particularly evident in polyQ diseases such as HD, dentatorubral–pallidoluysian atrophy (DRPLA), spinal bulbar muscular atrophy (SBMA), and the spinocerebellar ataxias (SCAs) caused by CAG (Q) repeat expansion mutations within the genes responsible for each disorder. These mutations cause the disease-associated proteins, which often exhibit nuclear mislocalization, to have an increased tendency to aggregate and interact with various target proteins. For example, ataxin-3, a cytoplasmic de-ubiquitinase protein, shifts to the nucleus upon expansion mutation in SCA3. Similarly, nuclear aggregation of mHtt was observed in animal models of HD (Pouladi et al. 2013). However, nuclear accumulation of mutant polyQ proteins is not always directly linked to disease pathogenesis. In SCA2, nuclear localization of the SCA2 protein is not essential for disease development in mice or humans (Huynh et al. 2000). The presence of various transcription factors, including cAMP response element-binding protein (CREB)-binding protein (CBP), TATA-binding protein (TBP), nuclear corepressor (NCoR), and RE1-silencing transcription factor/neuron-restrictive silencer factor (REST/NRSF), within polyQ nuclear inclusions (NIs) suggests that polyQ proteins

may induce transcriptional dysregulation through a sequestration mechanism. Evidence suggests that mHtt and ataxin-3 proteins can directly interact with histone acetyltransferases (HATs) like CBP and p300/CBP-associated factor (P/CAF), potentially disrupting histone acetylation in neurons (Steffan et al. 2001). However, the extent of histone acetylation reduction by mHtt remains controversial. Additionally, direct epigenetic modifications to DNA have been observed in HD. Studies have reported DNA hypomethylation in CpG-poor regions in HD cell cultures (Ng et al. 2013), decreased levels of 7-methylguanine (7mG) in mouse and human HD patient samples due to mHtt (Thomas et al. 2013), and a direct interaction between mHtt and methyl-CpG-binding protein 2 (MeCP2), which enables mHtt to bind directly to methylated DNA regions (Jaenisch and Bird 2003).

Transcriptional and epigenetic alterations play a significant role in the diverse range of neuronal phenotypes observed in polyQ diseases, spanning from early neuropathic features to late-stage neuronal cell death. Recent studies have demonstrated that polyQ proteins induce early changes in dendrite morphology by disrupting RNA granule formation and transcriptional cascades regulating the ER-to-Golgi (COPII) pathway (Kweon et al. 2017). Additionally, treatment with histone-deacetyltransferase (HDAC) inhibitors (sodium butyrate, 4-phenylbutyric acid sodium salt, and suberoylanilide hydroxamic acid) has shown promise in ameliorating neurotoxicity in HD and DRPLA mouse models (Ferrante et al. 2003; Hockly et al. 2003; Gardian et al. 2005). These findings underscore the critical contribution of transcriptional and epigenetic alterations in a subset of polyQ diseases. In addition to transcriptional and epigenetic alterations, nucleocytoplasmic transport defects have emerged as a prominent nuclear dysfunction observed in neurodegenerative diseases such as ALS/FTD, HD, and AD. The underlying mechanisms of nucleocytoplasmic transport disruption encompass the sequestration of nuclear pore complex (NPC) components by toxic RNA or proteins and direct blockage of nuclear pores by toxic disease proteins.

2.4.2 Proteotoxicity in the Cytoplasm

Many disease-related proteins exhibit a propensity to accumulate in the cytoplasm, where the pool of potential target molecules differs significantly from that of the nucleus. Notably, the cytoplasm, rather than the nucleus, houses the majority of protein quality control machinery. Additionally, the cytoskeleton is considerably more complex in the cytoplasm compared to the nucleus. Consequently, due to this physical proximity, cytoplasmic protein toxicity can directly impact both the protein quality control system and cargo transport through cytoskeletal disruption. Studies have shown that beta-sheet-rich prion aggregates and tau aggregates in AD can directly impede the 20S and 19S proteasome particles, respectively, thereby impairing UPS-mediated protein degradation (Deriziotis et al. 2011; Tai et al. 2012). Furthermore, genetic mutations in key UPS components, like the E3 ligase Parkin, the deubiquitinating enzyme UCH-L1, and the ATPase VCP, are known to trigger neurodegeneration (Dantuma and Bott 2014).

A previous study revealed that α-synuclein aggregates in PD bind to LAMP-2A with exceptional affinity, creating a "traffic jam" that disrupts cargo movement across the lysosomal membrane and inhibits CMA. Notably, specific mutations in LRRK2, another PD-linked protein, enhance its binding to the lysosomal membrane, facilitating the accumulation of α-synuclein and other CMA substrates (Orenstein et al. 2013). Furthermore, PD-associated mutations in UCHL1, a deubiquitinating enzyme, also impede the CMA process (Kabuta et al. 2008). These compelling findings suggest that CMA plays a central role in degrading PD-associated proteins and that disrupting this pathway contributes significantly to α-synuclein accumulation, a key driver of PD pathology. In HD, two distinct mechanisms impair autophagic clearance of toxic proteins. First, mHtt proteins exhibit an unconventional conformation that hinders their recognition by autophagic vacuoles, leading to reduced macroautophagy activity (Fu et al. 2017). Second, despite the compensatory induction of autophagy in response to proteasomal dysfunction, it appears insufficient to overcome the overwhelming burden of ubiquitinated protein aggregates in HD (Croce and Yamamoto 2019).

Cytoskeletal protein aggregates, including neuronal intermediate filament (IF) proteins and the microtubule-associated protein tau (MAPT), serve as neuropathological hallmarks of numerous neurodegenerative diseases. Notably, tau-associated microtubule defects are central to a group of diseases known as "tauopathies," while altered F-actin structures have been implicated in both polyQ diseases and AD. The formation of ADF/cofilin–actin filament bundles (rods) can occlude neurites and impede vesicle transport, further contributing to neurodegeneration. Beyond these structural alterations, the accumulation of toxic disease proteins directly disrupts axonal transport, a vital process for neuronal health (Berth and Lloyd 2023). Notably, defective axonal transport precedes neurodegeneration in various SOD1 animal models of ALS, highlighting its early and critical role in disease pathogenesis. Similarly, animal models of HD exhibit abnormalities in both anterograde and retrograde axonal transport, underscoring the widespread impact of protein aggregation on neuronal communication (Gunawardena et al. 2003; Gauthier et al. 2004).

Cytoplasmic protein toxicity manifests in a diverse range of neuronal phenotypes that often overlap across neurodegenerative diseases. This suggests the potential for therapeutic strategies aimed at neutralizing cytoplasmic protein toxicity, provided the proteins remain localized. However, the journey for these toxic proteins doesn't end in the cytoplasm. They can be transported to other organelles, such as the nucleus, stress granules, and mitochondria, complicating efforts to address their detrimental effects. This underscores the crucial need to delve deeper into protein toxicity within each organelle where these proteins tend to accumulate.

2.4.3 Proteotoxicity in Mitochondria

Extracellular amyloid beta aggregation is a defining pathological hallmark of AD, where accompanying mitochondrial dysfunction has long been observed. However, the precise mechanistic link between these two hallmarks remained elusive until

2004. Lustbader et al.'s study revealed that amyloid beta can directly target mitochondria, binding to the aptly named amyloid beta-binding alcohol dehydrogenase (ABAD) and triggering mitochondrial toxicity (Lustbader et al. 2004). Moreover, amyloid beta has been shown to interact with cyclophilin D (CypD), a crucial component of the mitochondrial permeability transition pore (mPTP). This interaction sensitizes the mPTP to opening, a phenomenon observed in both AD patients and mAPP mice brains (Du et al. 2008), potentially contributing to neuronal demise. APP, the precursor protein to amyloid beta, also exhibits mitochondrial toxicity in both AD models and patients. This toxicity appears to stem from physical interactions between APP and amyloid beta with various mitochondrial proteins. These interactions trigger a cascade of detrimental effects, including oxidative stress, reduced ATP production, mitochondrial membrane depolarization, and increased mPTP sensitivity, all hallmarks of the mitochondrial dysfunction observed in AD. Further supporting this crucial link, a previous study demonstrated that promoting mitochondrial proteostasis significantly reduced amyloid beta toxicity, highlighting the central role of mitochondrial dysfunction in AD pathogenesis (Sorrentino et al. 2017).

Over two decades ago, researchers first recognized an energy deficit linked to mitochondrial dysfunction in HD. Beyond disrupting the nuclear transcription of genes crucial for mitochondrial biogenesis and function, mHtt can directly interact with mitochondrial proteins, further compromising their activity. Notably, the N-terminal fragment of mHtt localizes to mitochondria (Orr et al. 2008) and disrupts the mitochondrial import process via its interaction with the TIM23 complex. These detrimental interactions disrupt calcium regulation, sensitize mPTP to opening, depolarize the mitochondrial membrane, and ultimately cause neuronal loss (Orr et al. 2008; Yano et al. 2014). Numerous genetic mutations associated with PD lead to mitochondrial dysfunction. αSyn, the central protein component of Lewy bodies, a hallmark of PD and related Lewy body diseases, exhibits a strong affinity for negatively charged lipids, including those in mitochondrial membranes (Rostovtseva et al. 2015). This affinity allows αSyn to interact with various mitochondrial proteins, such as the voltage-dependent anion channel (VDAC) in its monomeric form and TOM20 in its oligomeric form. These interactions disrupt the crucial exchange of ATP/ADP between mitochondria and the cytosol, hindering energy production and impairing the import of essential mitochondrial proteins, both of which significantly compromise mitochondrial function. Although ALS and FTD present distinct clinical symptoms, they share intriguing overlaps in their underlying causes. Both diseases are characterized by the pathological hallmark of cytoplasmic TDP-43 mislocalization, but the precise mechanism by which cytoplasmic TDP-43 exerts its toxic effects remains elusive. A previous study proposes a novel mode of toxicity by revealing that TDP-43 possesses internal mitochondrial targeting signals. Notably, this mitochondrial targeting is significantly enhanced in ALS and FTD patients, leading to disruption of oxidative phosphorylation. Specifically, TDP-43 binds to mitochondria-encoded ND3 and ND6 mRNA, effectively halting their translation and compromising mitochondrial function. Intriguingly, arginine-rich dipeptide repeats DPRs (poly-GR repeats) generated by

the hexanucleotide expansion mutation in C9ORF72, another key genetic cause of ALS/FTD, have also been shown to target mitochondria. Once inside, these DPRs interact with mitochondrial ribosomal proteins, disrupting their function and triggering mitochondrial dysfunction. These compelling findings add to the growing body of evidence implicating mitochondria as a potential primary driver of neurodegeneration in ALS/FTD.

2.4.4 Proteotoxicity in Stress Granules

In response to cellular stress displayed by degenerating neurons, multiple cellular responses are activated to mitigate the impact. One crucial process initiated under such conditions is the formation of stress granules (SGs). When stress is induced, cap-dependent translational processes are halted, causing messenger ribonucleoproteins (mRNPs) to disengage from ribosomes and coalesce. The electrostatic interaction of RNA-binding proteins (RBPs) in these mRNPs, facilitated by low complexity domains (LCDs), leads to liquid–liquid phase separation (LLPS), resulting in SG formation. Simultaneously, chaperones like HSP70 are up-regulated through m6A-mediated cap-independent translation to alleviate stress by promoting the refolding or degradation of misfolded proteins. Once the stress is resolved, chaperones, along with autophagy, play a key role in disassembling SGs.

In ALS and FTD, SGs become infiltrated by disease-related proteins, hijacking the normal stress response. Many ALS genes encode proteins that are integral to SGs, such as Profilin-1, hnRNPA1/A2, FUS, TIA1, and TDP-43, with several overlapping with FTD. Elevated cytoplasmic levels or mutations within the LCDs of these proteins appear to promote initial LLPS, leading to the formation of SGs that persist beyond physiological needs. These stabilized SGs may then evolve into pathological fibrils, exacerbating disease progression. Additionally, SOD1 aggregation around SGs and valosin-containing protein VCP's SUMOylation-dependent SG infiltration highlight non-LCD pathways in ALS and FTD. The connection between HD and SG pathology remains a topic of debate. One study suggests that mHtt forms stress bodies that are distinct from SGs (Nath et al. 2015). Another study indicates that both normal and mHtt can interact with SG-associated proteins like Caprin-1 and G3BP1 but the size and number of SGs were significantly larger in striatal precursor cells expressing mHtt compared to those expressing normal Htt (Ratovitski et al. 2012). Emerging evidence suggests that instead of mHtt directly localizing to SGs and causing their dysfunction, SG-associated factors may be misdirected to mutant Htt inclusions (Riguet et al. 2021). Despite the well-established association between SG pathology and neurodegeneration, the precise mechanisms by which pathological SGs drive neurodegeneration remain elusive. Several studies have demonstrated that SG formation can disrupt intracellular signaling by sequestering crucial signaling molecules, such as the mammalian target of rapamycin (mTORC1) (Takahara and Maeda 2012; Wippich et al. 2013; Mahboubi and Stochaj 2017). This suggests that chronic disruption of intracellular signaling may be one of

the mechanisms by which pathological SGs contribute to neurodegeneration. Therefore, unraveling the mechanistic link between pathological SGs and neurodegeneration should be a central focus of future research.

2.4.5 Propagation of Disease-Associated Proteins

A defining feature of neurodegenerative diseases is the progressive deposition of specific protein aggregates in the brain, with a regional distribution unique to each disease. Extensive evidence from in vitro and in vivo studies indicates that intercellular transmission of protein aggregates within synaptically connected brain networks represents a key pathogenic mechanism underlying neurodegeneration. For instance, the postmortem examination of PD patients' brains has revealed a stereotypical progression of pathogenic inclusions, originating in the autonomic nervous system and dorsal motor and anterior olfactory nuclei and gradually extending to encompass the substantia nigra, basal forebrain, locus coeruleus, hippocampus, neocortex, and basal ganglia. Similarly, in AD patients' brains, tau inclusions initially appear in the transentorhinal cortex and subsequently spread to the hippocampal formation and neocortex (Braak and Braak 1991). These findings support the hypothesis that the expansion of affected brain regions is mediated by a "prion-like" intercellular transmission of aggregates rather than a cell-autonomous accumulation of neuronal aggregates. Lending further credence to this hypothesis, clinical studies have demonstrated that healthy embryonic mesencephalic neurons grafted into the striatum of patients with advanced PD developed scattered α-synuclein- and ubiquitin-positive inclusions many years after transplantation. The introduction of either patient-derived fibroblasts or pluripotent stem cells harboring mHtt into the brains of neonatal wild-type mice resulted in cell-to-cell propagation of the mutant protein, a progressive loss of host cells, and behavioral deficits reminiscent of HD (Jeon et al. 2016). These findings suggest that bioactive aggregates can indeed transfer between diseased and healthy cells in both humans and animals.

More compelling evidence supporting the intercellular mobility of aggregates has emerged from studies utilizing either intracerebral administration of exogenous aggregates isolated from diseased humans and animals or ectopic overexpression of α-synuclein and tau in a neuronal population to investigate the potential for aggregates to propagate through the brain connectome. For instance, an intracerebral injection of brain extracts derived from symptomatic P301S tau transgenic mice was found to induce neurofibrillary tangles in presymptomatic mice not only at the injection site but also in distant brain regions (Desplats et al. 2009). Furthermore, accumulating evidence indicates that peripherally introduced aggregates can induce the accumulation of misfolded proteins in the central nervous system (CNS). For example, a previous study demonstrated that α-synuclein fibrils injected into the olfactory bulb of wild-type mice propagate transneuronally to distant brain areas, leading to progressive olfactory deficits (Rey et al. 2016). Similarly, mHtt ectopically expressed in sensory receptor neurons of *Drosophila* can propagate

transcellularly to neuronal and glial cells in the brain (Pearce et al. 2015). Furthermore, systemic administration of aggregates, including repeated tail vein injections of α-synuclein fibrils and intraperitoneal inoculation of tau extracts or amyloid beta seeds, resulted in the accumulation of aggregates in the brain (Peelaerts et al. 2015).

2.5 Conclusion

Protein misfolding and aggregation are a defining feature of numerous neurodegenerative diseases, posing a significant challenge to neuronal health and, ultimately, cognitive function. While significant advancements have been made in understanding how molecular pathways are disrupted by proteotoxicity, leading to cell death in neurodegenerative diseases, our knowledge of the underlying causes remains incomplete. This chapter explores how disease arises from the inability of neural cells to maintain proteome stability through proper protein folding and degradation. Although shared features like misfolding, aggregation, protein propagation, and proteostasis impairment are implicated across neurodegenerative diseases, including AD, PD, HD, and ALS, the proteins and genetic basis driving these pathologies appear to be unique to each disease. Unraveling the interplay of proteins and their interactions within and between these diseases is crucial for further progress. Understanding the complex association between protein structure, cellular clearance systems, and disease progression holds immense potential for developing effective therapeutic strategies. Although significant progress has been made in deciphering the molecular underpinnings of these diseases, the path to effective treatment remains challenging. Future research efforts must focus on deciphering the precise triggers and propagation mechanisms of protein misfolding, developing targeted molecules to stabilize or refold proteins, and enhancing the efficiency of cellular clearance pathways. This multifaceted approach holds great promise for the development of transformative treatments, marking a significant step toward addressing the complexities of neurodegenerative diseases.

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Chapter 3
Involvement of Metabolic Paradigm in Progression of Neurodegenerative Diseases

Nidhi Krishna Shrivastava and Mallikarjun N. Shakarad

Abstract Neurodegenerative diseases (NDDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS) are relatively common and devastating neurological disorders. Despite of the significant increase in number of patients all over the world, these diseases are characterized by the lack of true disease-modifying therapy that can reverse or halt disease progression. Recent studies indicated that metabolic alterations have been observed in neurons and glia of these diseases, suggestive of an alternative target to protect against disease onset and progression. Oxidative stress associated with disrupted glucose metabolism is an expected end state of most of the NDDs. Clinically, brain hypometabolism associated with the oxidative stress is considered as an early biomarker for most NDDs and stopping it could prove to be an effective preventive strategy.

In the present chapter, we have presented recent understanding related to the involvement of metabolic paradigm in NDD onset and progression.

Keywords Neurodegenerative diseases · Metabolism · Energy deficit · Cachexia

3.1 Introduction

The increased longevity of human population is primarily responsible for the rising occurrence of neurodegenerative illnesses affecting the central nervous system (CNS) (Swenson et al. 2019). This group of diseases includes multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral

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sclerosis (ALS), and other associated disorders. A number of pharmaceutical treatments have been created to address disease symptoms, but none of the aforementioned disorders currently have an effective medication to stop the condition from progressing, nor is a cure in sight. It is of concern that, despite having a list of identified mutations that raise the risk of neurodegenerative illnesses, we are still unable to predict the occurrence, timing, and underlying causes of these disorders. It seems that there is still a piece of the puzzle that is hidden or barely noticeable. It appears that we need to change our method in order to make major progress in the treatment of neurodegeneration. This includes determining the elements that either directly or indirectly contribute to the onset and progression of neurodegenerative diseases. In the last 20 years, scientists all over the world have been investigating a new theoretical framework in which they take a metaposition approach to study various diseases, changing the emphasis from individual symptoms or the existence of mutated proteins to a systemic understanding of the disease as a whole. There is a general resistance to question an established paradigm, yet there seems to be a rising recognition that the etiology of neurodegenerative illnesses has to be reexamined. There are currently no effective medications that can stop or reverse the progression of neurodegenerative diseases such as AD, PD, MS, and ALS. Reevaluating the current paradigms of how to target these disorders is imperative, given the unfulfilled medical need. It is possible to explain the common pathogenic characteristics of neurodegenerative disorders by taking a systemic neurometabolic approach (Swenson et al. 2019).

The brain uses 20% of the body's oxygen and 25% of its glucose even though it makes up only 2% of the body's mass. Interestingly, not all cells use the same amount of energy; microglia, astrocytes, and oligodendrocytes use 20–30%, while neurons use 70–80% of the total energy. The brain uses glucose as its primary energy source, but under conditions of starvation, it can also use other substrates. Age-related impairments in the brain's glucose metabolism are exacerbated in ND and neuroinflammatory (NID) illnesses; in particular, dysregulated oxidative metabolism, amino acid metabolism, and other general brain metabolism alterations have been linked to ND. However, these assessments have been performed in isolated cells that have experienced mechanical or enzymatic stress, which probably alters their metabolic status. Cellular responses of isolated cells in-vitro might not mimic the in-vivo responses. This emphasizes the necessity for methods that can identify in situ cell-specific metabolic alterations (Camandola and Mattson 2017).

Different cellular compositions and functions in brain areas translate into distinct metabolic requirements. Therefore, the condition and severity of a disease may be significantly affected by metabolic disturbances in particular areas. Current "metabolic imaging" modalities, including positron emission tomography (PET), magnetic resonance spectroscopy (MRS), and magnetic resonance imaging (MRI), have shed light on the regional modifications in metabolic processing that take place both before and during NDs (Wang et al. 2023).

In this chapter we have discussed the understanding of brain metabolism in NDD and the new paradigm, indicating that modifications in brain metabolism could be a therapeutic target for ND treatment (Fig. 3.1).

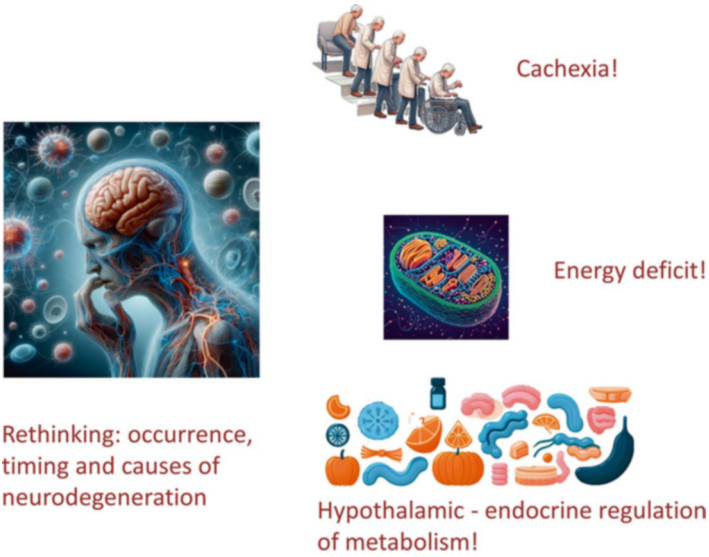

Fig. 3.1 Figure showing the outline of the chapter. (Individual pictures generated using MS Copilot)

3.2 Cachexia in Neurodegenerative Conditions: The Key Phenotypic Indicator of Metabolic Disruption

Cachexia is a multifaceted metabolic disorder linked to underlying life-threatening conditions such as cancer, severe heart and lung failure, end-stage renal disease, and others. Its primary characteristics include anorexia and decreased muscle and fat mass. Cachexia affects between 10% and 40% of people with long-term illnesses such as cancer, heart failure, chronic obstructive pulmonary disease, HIV, renal failure, and hepatic failure. Due to the combination of sarcopenia, malnourishment, and inactivity, which becomes more common as people age, elderly people are especially susceptible to cachexia (Minaglia et al. 2019). Severe wasting is typically the initial symptom of cachexia, and it is often linked to myolysis, systemic inflammation, and insulin resistance (IR). The European Society for Clinical Nutrition and Metabolism's Special Interest Group on "cachexia-anorexia in chronic wasting diseases" has put up a consensus definition to distinguish between sarcopenia and cachexia. Accordingly, a diagnosis of cachexia is based on a set of core criteria, namely, the existence of an underlying chronic condition, an unintentional weight reduction of >5% of the average body weight during the last 6 months, and anorexia which is characterized by restriction of food intake leading to decrease in body weight. Further, sarcopenia is characterized by muscle failure, caused by harmful alterations in the muscles that develop over the course of a lifetime. It is linked to an increased risk of negative consequences like falls, fractures, physical impairment, and death.

In the context of an underlying illness, cachexia is understood to be a multifactorial syndrome defined by an abrupt loss of body weight (muscle and fat mass) and accelerated protein catabolism. Cachexia is a highly relevant clinical disease since it raises morbidity and death. Systemic inflammation, heightened muscle proteolysis, and compromised lipid, protein, and glucose metabolism are major causes of cachexia (Ferrer et al. 2023).

Lean body mass, which is primarily made up of skeletal muscles, and subcutaneous fat mass have been related to dementia risk in a number of studies. Nonetheless, erratic results have been noted. The idea that the many components of body composition are highly correlated—in that, modifications to one frequently affect modifications to other components—is an intriguing one. Therefore, the dementia risk was not dictated by the actual number of body composition components, but rather by their interplay. A growing body of research has highlighted the significance of fat-to-muscle mass ratio (FMR) in predicting dementia. It is yet unknown, though, if FMR—which combines the opposing effects of muscle and fat—is linked to dementia risk apart from total obesity (Wang et al. 2022).

Numerous epidemiological research have looked at the relationships between muscle and fat mass separately and the chance of having dementia, but the results haven't always been reliable. A low lean mass, particularly appendicular lean mass, was found to be associated with an increased risk of dementia in a longitudinal study of 344 older adults (mean age, 78 years; 62.2% women) with a median follow-up period of 6 years (Cui et al. 2020). However, no significant difference was found in another cross-sectional study including 3025 women aged 75 years and older, which is consistent with the recent findings (Abellan van Kan et al. 2013; Wang et al. 2022). The age, gene/environment susceptibility study, which included 169 individuals (mean age, 76 years; 57.1% women), found that women who had higher levels of subcutaneous fat mass in their thighs and abdomen had a lower risk of developing dementia when fat mass was taken into account (Spauwen et al. 2017). Similarly, a United Kingdom Biobank-based study with 400,000 people in the age range 37–73 years and a median follow-up of 8.1 years found a monotonic inverse relationship between dementia risk and fat mass in both sexes (Cao et al. 2020). Though these studies were limited to an older population with considerably smaller sample sizes, some reported a favorable link between fat mass and dementia risk, while others found no association (Cui et al. 2020). Nevertheless, the protective evidence is not consistently strong. The explanations for these seemingly disparate causes of the observed variations are unclear, but in order to detect an elevated risk of dementia, a large prospective study with approximately 500,000 people may be required. Further, it is essential to take both muscle and fat mass into account, in order to minimize the discrepancies.

According to a study that was significantly larger than earlier research, higher FMR was linked to a lower risk of dementia from all causes in older persons (Wang et al. 2022). A number of biological theories have been put out to explain the correlations that have been found. Above all, adipokines' role in mediating the endocrine properties of adipose tissue may provide insights into the connection to dementia (Kiliaan et al. 2014). For instance, the protein hormone leptin, which is

mostly released by adipose tissue, may permeate the cerebrospinal fluid and central nervous system, influencing the hippocampus' role in learning and memory (Harvey et al. 2006), and has been linked to a lower risk of dementia in later life. However, leptin did not appear to have a protective effect against dementia in midlife in a study of middle-aged women with up to 32 years of follow-up. This could be because leptin is a short-term rather than a long-term indicator of body composition, which is consistent with the so-called obesity paradox (Gustafson et al. 2012). There is evidence that individuals with comparatively high body fat may consume more vitamin E and D, which may have an impact on cognition through modulating neurotrophic expression or reducing the harmful effects of beta-amyloid (Devore et al. 2010). It has been noted that leg subcutaneous fat has a particular protective role linked to long-chain fatty acid storage, shielding against the negative consequences of ectopic fat accumulation (Manolopoulos et al. 2010).

It has been reported that the inverse FMR-AD connection was significant only in men with respect to dementia subtypes (Wang et al. 2022). The basis of this link is unclear despite some data suggesting a sex-specific effect on the obesity-related risk of AD. Inflammation and sex hormone appeared to be implicated. Men with lower BMI than women, for instance, had a higher risk of AD among those genetically predisposed to the disease. This difference in risk may be attributed to testosterone's discovery as a preclinical risk factor for AD and its correlation with male adipogenesis suppression (Moody et al. 2021). Further, research indicates that women are more likely to be obese than males, and that women also have a stronger correlation between inflammation and the risk of AD (Moser and Pike 2016). Furthermore, there was no statistically significant correlation between FMR and vascular dementia (VD) in men or women when VD was taken into account as the outcome. The nonsignificant result for this outcome need not be interpreted as the absence of a relationship because of the comparatively smaller case numbers for VD in this study and the fact that the HR point estimates actually dropped among men and women (Wang et al. 2022).

3.3 Energy Deficit in NDDs

In a number of neurodegenerative illnesses, such as PD, AD, HD, and others, bioenergetic failure has been proposed as the cause of neuronal death. Energy failure, however, has never been shown to happen in these diseases in dying neurons or even in intact neurons in various disease models. The practically overwhelming evidence that mitochondria are altered in various ways in all of these conditions—from genetic, animal, and human studies—and the possibility that many of these alterations could lead to bioenergetic failure lend credence to this argument. Nevertheless, it is yet unknown if this truly happens in the impacted neurons. Further, mitochondria not only produces adenosine triphosphate (ATP) but also produces reactive oxygen species (ROS), buffer calcium, control apoptotic pathways, lipid biosynthesis, and neurotransmitter metabolism. Any amendment to these functions may also

lead to neurodegeneration. Therefore, while suggestive, a change in mitochondrial function alone does not always translate into an energy deficit. One of the main problems was that most of the methods, tools, and model systems employed for investigation lack the required resolution to make a definitive connection. The creation of new approaches that get around some of these obstacles may shed light on the early alterations in mitochondria that happens during dementia and how they impact bioenergetic function (Pathak et al. 2013). Majority of the groundbreaking research in energy metabolism and neurodegenerative diseases (NDDs) has concentrated on changes in glucose catabolism through glycolysis and the generation of reducing equivalents in the tricarboxylic acid cycle (TCA), which supplies the respiratory chain and ultimately uses the protonic force in mitochondria to produce ATP. According to the working theory, NDDs are linked to disruptions in ATP production, and dysfunction and neurodegeneration in NDDs may be triggered in part by reduction in ATP bioavailability. Studies using primary cultures of neurons revealed that subtoxic blockade of energy production significantly stimulated neuronal death, also known as "excitotoxicity" (caused by excessive glutamate release, overstimulation of ionotropic glutamate receptors, and Ca2+ overload), and there was a renewed interest in this hypothesis (Novelli et al. 1988). The theory of "indirect excitotoxicity," which postulates that partial energy deficits might cause gradual cell death, was developed in response to similar observations in animal models (Beal 1992). In the 1980s, positron emission tomography (PET) was used to monitor the locoregional consumption of glucose using the positron emitter [18F]-fluorodeoxyglucose (FDG), leading to the observation of abnormalities in energy metabolism in NDs in in-vivo condition. The striatum in HD patients and some regions of the cerebral cortex (i.e., the parietotemporal, frontal, and posterior cingulate cortices) in AD patients showed the most notable decrease. These changes in metabolism have frequently been explained as the result of decreased synaptic activity and/or neuronal death (Bonvento et al. 2017; Dienel 2019). The "mitochondrial" concept has benefited from research in recent decades due to the growing body of knowledge about mitochondrial physiology and its direct role in neurological diseases. In fact, complicated disorders exhibiting neurological symptoms are caused by point mutations or minor deletions in the mitochondrial DNA (Wallace et al. 1995). The "apoptosis" era in the early 1990s aided in the identification of critical roles played by mitochondria in regulating cell viability. Remarkably, research revealed that sometimes energy is indeed needed even for cell death. If there is enough ATP present, the apoptosome (Apaf1-caspase9-cytochrome c) is activated (Li et al. 1997). On the other hand, the reduction of proton force and disruption of the mitochondrial membrane potential occur when apoptotic pathways are triggered. The hypothesis that mitochondria and energy abnormalities may play a major role in nondiagnostic neuropathy is further supported by the release of cytochrome c, which ultimately disrupts electron flow in the respiratory chain leading to increased generation of reactive oxygen species (ROS) (Lin and Beal 2006). Circumstantial evidence for a potential participation of mitochondria is also provided by the fact that the likelihood of developing NDDs increases with age. As oxidative stress and mitochondrial dysfunction are typical in normal aging, caution

should be exercised while attributing these changes to NDDs alone. One of the strongest claims is that the human brain has a cumulative, age-dependent buildup of molecular indicators of oxidative stress in its nuclear and mitochondrial DNA, which results in very specific abnormalities in the expression of genes involved in energy metabolism. The alterations associated with proteostasis, DNA repair, and autophagy, in addition to others, might make neurons and astrocytes more susceptible to pathogenic processes in the aging brain (Lu et al. 2004).

Because of the intricacy of current metabolic pathways and their cellular and subcellular compartmentalization, there are very few techniques available to evaluate energy metabolism in patients. Due to their poor sensitivity (both in space and time), current clinical approaches are blind to majority of cellular processes and focus only on highly concentrated brain metabolites. As such, our understanding of energy transitions in NDDs is probably oversimplified. In order to eventually apply novel techniques in the therapeutic context, we must expand our understanding of brain energy metabolism in health and disease through studies carried out in cell and animal models. Recent years have seen emergence of novel strategies that may be more effective in addressing the issues of cell specificity, energy metabolism dynamics, and compartmentalization (Law et al. 2022).

3.4 Hypothalamic-Endocrine Regulation of Metabolism in NDDs

Apart from conventional symptoms, NDDs include additional symptoms and indicators that include mood swings, changed behavior, weight loss, and endocrine disruptions. It is interesting to note that a lot of these characteristics might result from harm to the hypothalamus, a tiny brain region that acts as a hub for integration between the environment and the central nervous system (CNS). The hypothalamus coordinates information from the central nervous system and the peripheral nervous system (PNS), controlling fundamental bodily processes such as reproduction, feeding, circadian rhythm regulation, and sleep-wake cycles. There are several nuclei in the hypothalamus, and each one has a different purpose. It is situated symmetrically on both sides of the third ventricle, on the ventral side of the brain, which is a part of the central nervous system. The role of hypothalamic neurons in the regulation of energy balance is exquisitely complex, and there are major nuclei and neuronal populations involved in the regulation of energy balance (Vercruysse et al. 2018). Depending on the metabolic state, the hypothalamus is essential for integrating various peripheral or central inputs into a coherent response (Timper and Brüning 2017). The hypothalamus coordinates behavioral responses, such as modified food intake and food-seeking behavior, optimizes energy utilization through behavioral adaptations, and altered energy expenditure in settings of altered energy supply (e.g., fasting, postprandial state). There are numerous peripheral cues that enable the hypothalamus to detect the metabolic state appropriately. Three

peripheral hormones stand out in particular: ghrelin, insulin, and leptin. Key anorexigenic hormones include insulin and leptin, which are produced by the endocrine pancreas and adipocytes upon replenishment of adipose reserves, respectively. The stomach produces the hormone ghrelin, which promotes hunger. The majority of the other peripheral hormones that regulate metabolism send signals to the hypothalamus. Additionally, hypothalamic neurons can change metabolic balance by sensing changes in nutrients like glucose or fatty acids.

The primary site of peripheral cue integration is the arcuate nucleus, also known as the infundibular nucleus in humans, which is situated in the medial region of the hypothalamus, closest to the third ventricle. In fact, pro-opiomelanocortin (POMC) and agouti-related peptide (AgRP) neurons are the two main neuronal populations on which leptin, insulin, and ghrelin directly act. Leptin, insulin, and ghrelin inhibit AgRP neurons, which co-express AgRP, neuropeptide Y (NPY), and GABA. Ghrelin activates AgRP neurons and by their activation eating and weight gain increase (Morton et al. 2014). Leptin and insulin stimulate POMC neurons, which co-express POMC, cocaine, and amphetamine regulated transcript (CART). A number of neuropeptides are produced when POMC is cleaved, one of which is α-melanocyte-stimulating hormone (α-MSH), which is primarily in charge of the anorexigenic impact brought on by POMC neuron activation. AgRP opposes endogenous agonistic effect of α-MSH on melanocortin MC3 and MC4 receptors. Through effects on food intake and energy expenditure, the integration of melanocortin tone in projection neurons targeted by POMC and AgRP neurons results in the management of energy balance. The paraventricular nucleus (PVN), the lateral hypothalamic area (LHA), the dorsomedial hypothalamus (DM), and the ventromedial hypothalamus (VMH) are the principal sites of projection of POMC and AgRP neurons. Due to the coordinated action of multiple neuropeptides, including oxytocin, vasopressin, corticotropin-releasing hormone (CRH), and thyrotropin-releasing hormone (TRH), the PVN, which is situated at the border of the third ventricle, is a major anorexigenic center. Melanin-concentrating hormone (MCH) and orexin (ORX)/hypocretin neurons are the two main neuronal types that are thought to play a large role in hunger in the LHA, which is the outermost region of the hypothalamus (Berthoud and Münzberg 2011; Schwartz et al. 2000). Increased food intake is mediated by both MCH and ORX neurons, although their regulation of sleep-wake cycles is antagonistic (Berthoud and Münzberg 2011; Brown et al. 2015). ARC projections also target VMH and DM. Brain-derived neurotrophic factor (BDNF) and its receptor TrkB are highly expressed in the ventral midline hippocampus (VMH), which is thought to be a satiety region. These two factors are genetically linked to human obesity (Yeo and Heisler 2012).

It is important to remember that hypothalamus is not only extra-hypothalamic region that controls energy balance. Several brainstem nuclei, such as the nucleus tractus solitarius and raphe nuclei, or telencephalic structures, such as the ventral tegmental area and several cortical areas, are also involved in this intricate function. Several studies in recent years have reported changes in the structure and/or function of the hypothalamus nuclei in NDDs and they have started to unravel the functional implications for the progression of the disease.

3.4.1 Alzheimer's Disease (AD)

Hypothalamic atrophy has been reported in a number of neuroimaging investigations in AD patients. In their separate cohorts, Callen et al. (2001) and Loskutova et al. (2010) reported 10% and 12% decrease in hypothalamus volume, respectively. Early AD clinical phases were characterized by this type of hypothalamic atrophy. AD patients' hypothalamus frequently exhibits classic AD pathology, such as amyloid plaques and neurofibrillary tangles (NFTs). According to reports, amyloid plaques and NFTs have been seen in a number of hypothalamic nuclei, including the supraoptic nucleus, paraventricular nucleus (PVN), lateral hypothalamic area (LHA), suprachiasmatic nucleus (SCN), and tuberomammillary nucleus (Ishii and Iadecola 2015).

According to reports, there is a 40–50% reduction in ORX neurons at the cellular level in the lateral hypothalamic area (LHA). The CSF of AD patients consistently had somewhat lower levels of ORX (Fronczek et al. 2012). There have also been reports of SCN degradation in AD (Harper et al. 2008). This is in accordance with the fragmentation of sleep that highlights AD (Lim et al. 2014). Worldwide, dysfunctions of the hypothalamic-pituitary-adrenal (HPA), hypothalamic-pituitary-thyroid (HPT), and hypothalamic-pituitary-gonadal (HPG) axes have been reported in patients with AD and may contribute to the pathophysiological development of the disease. Although disruptions in any of these systems could potentially encourage modifications in energy homeostasis, the subsequent section will concentrate on specific metabolic indices, particularly management of body weight and its correlation with glucose homeostasis (Ishii and Iadecola 2015).

3.4.2 Huntington's Disease (HD)

An established clinical characteristic of HD is weight loss, especially in its later phases. Higher energy metabolism could be one explanation for weight reduction, given there is no evidence linking it to greater motor activity (Süssmuth et al. 2015). Indeed, patients in the mild-to-moderate and early stages of the disease show higher basal/resting energy expenditure and increased total energy expenditure (TEE). Moreover, carriers of presymptomatic HD mutations eat more calories (Mochel et al. 2007), maybe to offset their higher metabolism.

Interestingly, energy expenditure evaluated by indirect calorimetry in HD patients has been reported to increase further following insulin stimulation, contrary to what has been observed in control participants (Aziz et al. 2010). Insulin is known to stimulate sympathetic nervous system, which is a key regulator of the resting metabolic rate, via acting on the ventromedial hypothalamus (VMH). In reality, people with HD have an overactive sympathetic nervous system (Bellosta Diago et al. 2017). Therefore, the finding that insulin stimulation has greater effect on energy metabolism in HD patients implies that hyperactivity of the sympathetic

nervous system may play a role in the altered energy metabolism of the HD system. However, the causes of hyperactive sympathetic nervous system in HD patients are yet unknown.

Changes in energy homeostasis could play a significant role in HD's pathogenic process. According to numerous reports, patients with HD who had a higher BMI at the beginning of their symptoms actually experienced a slower course of the disease. According to Duan et al. (2014), there is a chance that the underlying cellular and molecular mechanisms of the altered metabolism in HD will offer new targets for therapeutic approaches aimed at improvement of the condition.

Several investigations have looked into whether peripheral metabolic variables are different in HD. A few recent studies have not been able to identify any altered metabolic markers in HD patients, despite previous reports showing reduced levels of leptin, increased levels of ghrelin, and insulin resistance. As of now, there isn't a distinct metabolic signature in the blood that can account for HD's altered energy metabolism (Nambron et al. 2016). However, studies in *Drosophila* model have reported metabolic changes at transcriptional level, thus highlighting the potential of using metabolic paradigm in disease treatment (Singh and Agrawal 2021).

3.4.3 Amyotrophic Lateral Sclerosis (ALS)

About one-third of the ALS patients evaluated have pathological TDP-43 inclusions in their hypothalamus (Cykowski et al. 2014). In a case study of 30 ALS patients, the density and existence of inclusions did not correlate with the length of the disease. Further, regardless of whether the patients had hypothalamic inclusions or not, their BMIs were comparable. On the other hand, a lower BMI was linked to aggregates in the LHA. An MRI study with 251 ALS cases that had 19 symptomatic, 32 carriers of presymptomatic mutations, and 112 healthy controls reported that compared to controls, ALS patients and presymptomatic gene carriers had a pronounced hypothalamic atrophy of almost 22%. The shrinkage was dispersed throughout the anterior and posterior hypothalamus and was unrelated to the clinical development of ALS patients' disease or brain atrophy. Nonetheless, the anterior section of the hypothalamus' atrophy mapped with the age at onset, and the hypothalamus' atrophy was linked to BMI, particularly in familial instances of ALS. Hence, a premotor symptom is suggested by the hypothalamus' region-specific degenerative process. Further, a lower hypothalamic volume is related with an earlier onset of the disease, suggesting the potential involvement of the hypothalamus in both the development of the disease and the weight issues linked to ALS (Gorges 2017). Proof of hypothalamic dysfunction in ALS patients and animal models was found by Dupuis et al. (2012) after a post hoc review of clinical samples from patients using the antidiabetic drug pioglitazone. It has been demonstrated that pioglitazone, which has well-established peripheral effects, increases food intake via inhibiting hypothalamic MCH neurons. In fact, pioglitazone caused 3–5 kg increase in body weight in adults. Pioglitazone did not cause individuals to gain weight, despite the fact that it had all

of the anticipated peripheral effects in ALS patients. When compared to wild-type mice, pioglitazone treatment did not consistently improve food intake in Sod1 (G86R) animals. Several faults in POMC and AgRP neurons could be a result of intrinsic defects in the hypothalamic MCH neurons (Vercruysse et al. 2018). The question of whether these changes represent a pertinent therapeutic target is still unanswered.

3.5 Interrelationship Between Neuronal Activity and Metabolic Regulation in NDDs

To sustain optimal cellular and systemic function, regulation of the supply of tissue metabolites and cellular energy metabolism is crucial. In the central nervous system (CNS), where energy use is extremely dynamic, this regulation is particularly important. Increased energy consumption in the brain is driven by higher neuronal activity, which in turn improves neuronal function through compensatory metabolic and vascular changes (Roy and Sherrington 1890). The brain's response to physiological events is largely determined by three key cellular components: (1) neurons, which use electrical processing to determine cerebral physiological activity; (2) astrocytes and other glial cells, which directly collaborate with blood vessels to regulate energy needs and maintain the extracellular environment; and (3) blood vessels, which transport nutrients like glucose and oxygen to the brain and eliminate waste products like CO_2 and heat. These three components work together to support every facet of metabolic activity, creating a cohesive and effective metabolic unit. There is a connection between neural activity, astrocytic reactions to this activity, and energy balance. Changes in the nervous system's energy homeostasis occur with aging and growth, as well as with the nervous system's adaptation to pathological circumstances like hypoglycemia or ischemia. Increased metabolism, or the production of ATP, is necessary for the activation of neurons. This metabolism first causes depletion of substrate and then triggers a number of signals that improve astrocytic activity, local blood flow, and substrate supply. Significant heat is also produced during the production of energy, especially in mitochondria, and during the process of ATP hydrolysis. In addition to improving local substrate delivery, the localized spikes in blood flow that are observed after neuronal activation also serve as a heat sink to aid in brain cooling and the elimination of waste byproducts.

Typically, motor activity or sensory or cognitive stimuli elicit neural activation. In response to the strong incoming synaptic input, stimulation activates neurons in specific brain regions, which usually causes a series of action potentials to fire. Further, during the rapid-eye movement (REM) stage of sleep, which is linked to the production of dreams and the consolidation of learning and memory, there may also be sporadic spikes in neural activity. In-vitro arrangements can also be used to induce neural activation through the use of brief electrical stimulation pulses that excite presynaptic terminals and axons. This results in postsynaptic action

potentials and, frequently, a compound evoked potential response that combines synaptic and action potentials. Although the timing and density of this stimulation can be changed, it usually lasts between 5 and 30 seconds to momentarily "activate" neurons by providing them with a strong incoming synaptic input. Depending on the configuration and method, the energy requirements linked to neuronal activity produce a series of metabolic events that can be monitored in a variety of ways. Extracellular K+, Ca2+, oxygen, and metabolic imaging markers like FAD or NADH are frequently measured. For instance, the thalamus and brainstem's glucose metabolism is increased by stimulation of the trigeminal nerve or whiskers. While neural activity returns to baseline during recovery, metabolic demands may still exist, and delayed blood flow enhancement may still occur. For instance, astrocytic metabolism continues, extracellular lactate rises, local blood flow is elevated, and short-term intermediate molecules within the mitochondria are depleted. NADH is briefly enhanced due to ongoing TCA cycle dehydrogenase activity and lactate uptake. Neuronal activation eventually winds down, resulting in a decline in metabolism and O_2 consumption that eventually trends down to basal levels. Pumps then restore membrane potentials, stabilizing NADH and other mitochondrial intermediates, and local blood flow finally declines to maintain levels. NADH levels eventually return to their initial levels (Shetty et al. 2012). Precise synaptic function and regulated synapse stability and elimination are necessary for neuronal network function. Presynaptic vesicle dynamics, cytoskeletal modifications, neurotransmitter, calcium fluctuations, and postsynaptic signaling all influence synaptic function. Maintaining calcium homeostasis and ionic balance, including through membrane pumps that reset ion gradients during neural signaling, is essential for synaptic function and involves strict management of mitochondrial function and energy supply. In order for synaptic function to be properly maintained, energy is also needed for the removal and replenishment of constituents. These processes include autophagy, mitochondrial homeostasis, lipid and RNA metabolism, proteostasis, and carefully regulated and coordinated axonal transport. Moreover, astrocytes and microglia are crucial for maintaining energy and neurotransmitter balance, as well as for removing and stabilizing synapses.

Numerous reviews emphasize the data from genetics, preclinical studies, and patient-derived studies suggest synapse failure and dysfunction play a critical role in NDDs. Excessive glutamate excitotoxicity results in an excessive Ca2+ influx that kills neurons. Elevated calcium levels result in energy depletion due to mitochondrial dysfunction and the activation of enzymes like calpains. These processes lead to the breakdown of proteins and lipids, disruption of physiological processes, and, eventually, death of cells. It has also been suggested that glutamate-mediated excitotoxicity and neural hyper-excitability are significant factors in the etiology of ALS and might also have a role in the neurodegenerative processes associated with other NDDs. Moreover, it is noteworthy that a number of proteins that aggregate in NDDs play physiological role at the synapse and/or that associated pathological forms cause synaptic failure or dysfunction. These findings emphasize the interdependence of NDD hallmarks, such as tau in AD, APP/Aβ and PD's α-synuclein, and tauopathies. Further, it is known that a number of genes associated with normal

synaptic function—such as C9orf72121 in ALS/FTD and SNCA, SYNJ1, DNAJC6, and DNAJC13 in PD—are altered in some other NDDs as well. Therefore, a complex pattern of dysregulated neurotransmission in the brain is likely to be seen in NDDs due to a combination of hypo- and hyperactive synapses. Before neurodegeneration, synaptic failure and dysfunction have been identified in NDDs. For example, in AD, synapse loss and synaptic failure occurred prior to neuronal death, and several brain regions also exhibited hyper-excitability. In PD, synaptic dysfunction precedes dopaminergic neuron loss at the outset of symptoms, and axonal and synaptic degradation occurs before neuronal loss. It has also been discovered that in HD, symptoms and synaptic abnormalities occur prior to explicit neuronal death, and in ALS, there is a disconnect between motor neurons and muscle prior to death of motor neurons. The expression of pathogenic proteins, including APP, tau, α-synuclein, Htt, and various ALS/FTD genes, induces synaptic and neuronal network dysfunction in preclinical models and is spatially and temporally associated with early protein aggregates, particularly oligomeric aggregates, providing more evidence for the involvement of synaptic defects in NDDs. Different NDD proteins can aggregate within synapses at the pre- or postsynaptic specialization, and this is linked to negative consequences for synaptic function (Wilson et al. 2023).

As previously mentioned, the operation of and interaction with the fundamental physiological processes linked to the characteristics of NDD are necessary for proper synaptic and neural network function. Therefore, abnormal energy metabolism, oxidative stress, (local) protein synthesis by axonal transported RNA, protein and organelle disintegration, cytoskeletal dynamics, and neuronal death are all strongly associated with both synaptic dysfunction and excitotoxicity. Conversely, depending on how resilient and vulnerable the neuron is, the synapse may function as a cell-autonomous trigger of cell malfunction and death. In addition, damage to synapses could be caused by non-cell autonomous processes. For instance, misfolded protein propagation at the synapse, improper synaptic pruning, and altered microglial/astrocytic interactions—all of these are crucial for synaptic function, and all can result from microglial activation (Wilson et al. 2023).

3.6 Conclusion

Age-dependent yet rapid disease progression is a feature of NDDs. These illnesses are all characterized by the buildup of oxidative reaction products that cause extensive protein and lipid damage. At several levels, including cognitive and motor deterioration and problems in molecular signaling such as altered insulin signaling, these neurodegenerative illnesses mimic advanced aging. Remarkably, neurodegenerative pathology coexists with a metabolic dysfunction phenotype in all NDDs. Although aberrant protein aggregates, like mutant htt or Aβ plaques, can cause harm to the hypothalamus and contribute to energy dysregulation, the entire process cannot be fully explained by hypothalamic pathology alone. A more comprehensive and reliable hypothesis that explains the altered metabolism along with the neuronal

damage in these diseases outlines a broken link between the central nervous system (CNS) and peripheral organs that control energy regulation via changes in insulin, ghrelin, leptin, and GLP-1 signaling. There is growing evidence that effective therapies for NDDs should ideally address issues related to the entire body instead of just the central nervous system. Multiple endocrinological factors are expected to play a combinatorial role in enabling the pathophysiology of AD, HD, and PD; and hence, research that aims to comprehend the collective impacts of various hormones, rather than simply the individual, are urgently needed.

Recent research, both experimental and clinical, suggests that metabolic disruption is a common co-occurring feature in many NDDs, which may aggravate neurological symptoms. Therefore, it makes sense that metabolic pathways should be included as potential treatment targets for the most prevalent neurodegenerative diseases. It is significant to note that many animal studies are complicated by a number of factors, such as diet and housing, which can increase the risk of metabolic dysfunction in these subjects and make it difficult to determine whether the metabolic phenotype is related to the course of the disease or the animal's lifestyle.

Studying the combinatorial effects of metabolic hormones and neuronal signaling molecules in whole animal models rather than isolated cell cultures will help us better understand disease processes and provide care for patients. It will also help us identify and characterize the potential that metabolic factors hold for treating a variety of neurodegenerative diseases.

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Chapter 4
Glial Cell Metabolism and Neurodegenerative Diseases: The Current Perspective

Jaldhi, Himanshi Yadav, and Shashank Kumar Maurya

Abstract Glial cells play an important role in the maintenance of brain homeostasis. Microglia have an active role in immunological surveillance, immune response, synaptic plasticity, and neurogenesis. Astrocytes feed and nourish neurons with metabolites and growth factors. Oligodendrocytes also provide metabolic support and neurotrophic factors and produce myelin. Further, metabolic changes in glial cells have been reported in neurodegenerative diseases. Metabolic reprogramming has also been reported in glial cells to exacerbate neurodegeneration. Therefore, targeting glial metabolism could be a possible intervention in the management of NDDs. In the present chapter, we have provided comprehensive details about neurodegenerative disease-specific metabolic alterations in glial cells. Further, effort has been made to provide possible therapeutic targets to regulate metabolic changes in glial cells to maintain brain homeostasis.

Keywords Neurodegenerative diseases · Microglia · Astrocytes · Oligodendrocytes · Metabolism

4.1 Introduction

Neurodegenerative diseases (NDDs) are characterised by various features such as neuronal loss, neuronal dysfunction, impaired protein clearance, oxidative stress, mitochondrial dysfunction, neuroinflammation, and cell death, where cellular metabolic activities play a major role. Glial cells are the primary immunological component of the central nervous system (CNS) that undergo phenotypic alterations and

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influence various pathologies. The neuroglial population consists of three primary populations, i.e. oligodendrocytes, microglia, and astrocytes. These cells have distinct roles and can be identified by specific molecular markers (Huang et al. 2023). Glial cells, such as astrocytes and microglia, play important roles in delivering nutrients and antioxidants to neurons along with eliminating viruses and cell debris from the brain. Glia also aid in maintaining neuronal signalling and defining synaptic connections; however, they do not actively participate in synaptic exchanges or electrical signalling.

The metabolic machinery of glial cells is highly plastic and is rapidly reprogrammed in a context-dependent manner. This metabolic reprogramming maintains homeostasis in the CNS. Several studies have shown that cellular metabolic pathways highly affect morphological and functional variability of glial cells including microglia as well as astrocytes (Peruzzotti-Jametti et al. 2021). Glial cells undergo metabolic reprogramming to tackle acute challenges and resolve detrimental processes. However, in the case of chronic inflammation, continuous metabolic reprogramming impedes essential immune functions and exacerbates neurodegenerative processes (Le Douce et al. 2020) as is evident in Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD).

All these neurodegenerative diseases are not identical; however, change in metabolism due to disruption of mitochondrial function is a common link which indicates that these organelles act as a critical link. Mitochondria are the epicentre of various cellular functions and metabolic pathways that include regulation of intracellular calcium signalling, lipid synthesis, reactive oxygen species (ROS) signalling, and cell death. The survival of cells in healthy as well as diseased condition depends critically on how mitochondria will react to stress. Deficits in mitochondrial biogenesis could be a factor in the development of mitochondrial dysfunction in neurodegenerative diseases, including Friedreich ataxia, AD, PD, and HD. As mitochondria are important for neuronal functioning, any changes in morphology or function can have serious effects on neurons (Napolitano et al. 2021). There has not been much focus on how dysfunctional mitochondria affect glial cell activity in neurodegenerative disorders and how they consequently affect neuronal homeostasis. However, recent research has shown the ability of glial cells to maintain mitochondrial health (Clemente-Suárez et al. 2023).

Neuroinflammation is described as an inflammatory response that occurs in the brain or spinal cord. This inflammation is caused by the release of cytokines, chemokines, ROS, and secondary messengers by the resident CNS glia (microglia and astrocytes). Microglia are innate immune cells that provide the principal immunological surveillance and macrophage-like functions of the CNS, including generation of cytokines and chemokines. These reactions are crucial for coordinated communication between the immune system and brain. Infections or diseases cause microglia to become 'activated' and operate as inflammatory cellular mediators. Activated microglia rapidly modify their transcriptional profile and release pro-inflammatory cytokines and chemokines. Microglia undergo dynamic alterations during physiological and pathological situations, as evidenced by a change in shape

from ramified (resting) to amoeboid (active) form (Nimmerjahn et al. 2005). Rather than the advantageous domestic tasks performed by quiescent and mildly active microglia, hyperactivation of microglia leads to an excessive generation of inflammatory mediators (Polazzi and Contestabile 2003). When microglia consistently release inflammatory mediators at amounts that are detrimental to neurons and frequently result in neurodegeneration when combined, this condition is referred to as overactivation (Frank-Cannon et al. 2009). Microglia assume reactive states as a result of overactivation, marked by notable morphological and phenotypic alterations combined with increased expression of the pro-inflammatory cytokines TNF-α, IL-6, IL-1β, and NO (Wolf et al. 2017). The hyperactive state of microglia intensifies loss of neurons and synapses and fosters a persistent neuroinflammatory milieu. Fundamentally, these immune mediators can function as scavengers to manage regular neuronal turnover and assist in removing necrotic cell debris; yet, chronically activated microglia in neurodegenerative illnesses may worsen condition by secreting an excessive amount of these cytotoxic substances (Subhramanyam et al. 2019).

Astrocytes are the most prevalent type of glia cells in the central nervous system (CNS). Astrocytes, like microglia, maintain homeostasis and feed neurons with metabolites and growth factors. Furthermore, astrocytes play an important part in synapse formation and synaptic plasticity and influence extracellular balance of ions, fluid, and free radical elimination at the blood-brain barrier activities (Sofroniew 2009). Like microglia, astrocytes are also active participants in neuroinflammation, and their reactions can be useful or detrimental to tissue regeneration, depending on the stimuli presented by the inflamed environment. Under pathological situations, astrocytes undergo morphological and functional alterations that include cell enlargement and excessive release of neurotoxic substances, which are known as reactive astrocytes.

Oligodendrocytes are another major important glial cell that provides neurons trophic and metabolic support. Their primary function is to produce myelin, which permits action potentials to spread. Similar to microglia and astrocytes, abnormalities cause oligodendrocytes to undergo substantial alterations in their morphological, functional, and metabolic composition. It has been shown that oligodendrocytes in neurodegenerative conditions exhibit several disruptions in intrinsic metabolic processes (Afridi and Suk 2023).

Glia possess complete machinery to utilise major biomolecules such as carbohydrates, amino acids, and fatty acids (FAs) to generate ATP. However, the main source by which glia synthesise ATP is glucose and it provides neurons with essential metabolic precursors. Reprogramming of these metabolic hubs and production of pro-inflammatory signals is the major factor in driving neuroinflammation-mediated neurodegeneration (Afridi and Suk 2023). Therefore, modifying glial metabolic reprogramming poses as a potential strategy to treat neurodegenerative disorders (NDDs).

4.2 Altered Glial Metabolism in Neurodegenerative Disorders

The metabolic mechanism of glial cells is remarkably malleable. To meet their metabolic needs, they can metabolise a range of metabolic precursors, such as proteins, lipids, and carbohydrates (Bernier et al. 2020). Metabolic reprogramming is a critical mechanism that glial cells use to maintain CNS homeostasis. Glial cells are functionally and structurally heterogenous cells; the metabolic pathways for adenosine triphosphate (ATP) production also vary among these cells. Numerous abnormalities in glial metabolic pathways linked to neuroinflammatory and neurodegenerative disorders show that tight regulation of the intricate interactions between inflammation and metabolism is necessary to maintain basic function of glial cells (Afridi and Suk 2023). In this section, we will be discussing the metabolic activities of microglia, astrocytes, and oligodendrocytes about their role in neurodegenerative diseases.

Microglia, the first line of immunological defence in the CNS, constantly assess their surroundings and interact with neurons, astrocytes, oligodendrocytes, and immune cells that infiltrate them. They play important roles in the homeostatic brain, including synapse pruning, damage repair, phagocytosis, support for other glial cells, and communication homeostasis maintenance. Microglial activation is observed in the pathogenesis of neurodegenerative disease (Gao et al. 2023). Microglia have dual function: they exert protective effect by phagocytosing and eliminating pathogenic protein aggregates; at the same time they can be detrimental when they uptake excessive protein aggregates. This can cause impairment to the microglial phagocytic ability, neuroinflammation, and ultimately neurodegeneration (Gao et al. 2023).

Microglial activity depends significantly on glucose metabolism. When microglia are in a quiescent state, they derive the majority of their energy from oxidative phosphorylation (OXPHOS) and shift to glycolysis when the brain microenvironment is under stress (Kelly and O'Neill 2015). However, since increased glucose intake by glycolytic microglia is associated with neuroinflammation, persistently elevated glycolysis is more harmful in chronic neurodegenerative diseases. Increased glycolysis has an impact on ATP synthesis also, which impairs microglia function. The glycolysis, pentose phosphate pathway (PPP), and the tricarboxylic acid (TCA) cycle are the primary metabolic processes implicated in glucose metabolism (Afridi et al. 2022). PPP is crucial for microglial activation, polarisation, and function. The oxidative phase and the non-oxidative phase are the two phases of the PPP, which splits off from glycolysis. The non-oxidative phase produces ribose-5-phosphate (R5P), a precursor for nucleotide synthesis, whereas the oxidative phase produces NADPH, which is necessary for preserving cellular redox equilibrium and biosynthetic reactions. The function of the PPP in microglial activation and function has been demonstrated by recent studies. The rate-limiting enzyme of the PPP's oxidative phase, glucose-6-phosphate dehydrogenase (G6PD), was upregulated in microglia upon LPS stimulation. Moreover, nitric oxide (NO) and pro-inflammatory

cytokine production were decreased by blocking G6PD, suggesting that the PPP is involved in controlling neuroinflammation.

Glycolysis is a crucial metabolic mechanism involved in microglial activation and polarisation during neuroinflammation. This fundamental metabolic process breaks down glucose to create ATP, which provides cells with quick energy. Two ATP and two NADH molecules are synthesised for every glucose molecule after a series of metabolic events to convert glucose to pyruvate (Ghosh et al. 2018). Pro-inflammatory microglia exhibit elevated glucose uptake and increased expression of glycolytic enzymes during neuroinflammation. The metabolic switch to glycolysis is critical for microglial state and function, allowing for rapid ATP generation regardless of its relative inefficiency (Lauro and Limatola 2020). During glycolysis, disrupting pyruvate entrance into the TCA cycle causes an increase in nitric oxide (NO) and interleukin (IL)-1β. NO irreversibly inhibits the electron transport chain and pyruvate dehydrogenase, limiting cell growth. The TCA cycle, also known as the Krebs cycle or citric acid cycle, is a major system of metabolism that produces energy by oxidising acetyl-CoA derived from carbohydrates, lipids, and proteins. The TCA cycle in microglial cells is critical for energy production, redox equilibrium, and important chemical manufacturing. When elevated, intracellular succinate, the TCA cycle intermediate, protects primary microglia by preventing them from adopting a pro-inflammatory phenotype (Tannahill et al. 2013). Deficiency in TCA cycle enzymes increases reactive oxygen species (ROS), hastening neurodegeneration (Klivenyi et al. 2004). Microglial mitochondrial dysfunction has been found as a major contributor to neuroinflammation in neurological disorders such as AD (Li et al. 2022). Microglial activation and subsequent neuroinflammation in AD are preceded by mitochondrial dysfunction, which includes mitochondrial DNA (mtDNA) damage, metabolic abnormalities, and quality control (QC) issues (Li et al. 2022). Furthermore, components of the mitochondrial complex, translocator protein (TSPO) and hexokinase-2 (HK), play important roles in microglial respiratory-glycolytic metabolism and phagocytosis (Fairley et al. 2023). Oxidative phosphorylation (OXPHOS) is the primary source of ATP synthesis in healthy microglia. However, microglia switch to glycolysis in the event of mitochondrial dysfunction. The pro-inflammatory phenotype, which is shown by increased production of pro-inflammatory cytokines and ROS, is evident as a result of this metabolic change. In contrast, the anti-inflammatory phenotype is more reliant on OXPHOS and is linked to anti-inflammatory and tissue repair actions. During mitochondrial failure, elevated ROS levels can stabilise HIF-1α, which in turn causes the overexpression of glucose transporters and glycolytic enzymes (Chandel et al. 1998). This metabolic reprogramming sustains a pro-inflammatory state that aids in neurodegenerative processes while meeting the energy needs of activated microglia (Miao et al. 2023). Fatty acids are essential components of cellular metabolism and are characterised by their chain length and saturation level. They are critical for energy production, signalling, and regulating microglial activity (Ebert et al. 2003). Fatty acid metabolism, including fatty acid oxidation (FAO), accounts for roughly 20% of the total energy requirement in the brain (Ebert et al. 2003). Microglia have recently been discovered to express FAO-related proteins, including acyl-CoA synthetases (ACSs)

and lipoprotein lipase (LPL). Activated microglia have increased energy demands, which can be partially supplied by fatty acid consumption. Increased fatty acid metabolism can also lead to ROS generation and consequent cellular oxidative stress, both of which are pathogenic hallmarks of many neurological disorders (Nadjar 2018). Thus, fatty acids play an important role in microglial activation and function, which makes them potential therapeutic targets in neurodegenerative disorders. Modulating microglial activity requires a balance between saturated and unsaturated fatty acids, where unsaturated fatty acids usually promote an anti-inflammatory phenotype and saturated fatty acids induce an inflammatory phenotype (Miao et al. 2023).

Astrocytes constitute majority of glia in the brain, and they nourish neurons trophically and metabolically throughout their lives. They can modulate neurotransmission by releasing ions that are essential for neuronal electrical activity or by supplying metabolic precursors needed for the manufacture of neurotransmitters. Astrocytes are also essential for neurogenesis, synaptogenesis, and the preservation of synaptic plasticity. In addition, astrocytes possess immunological capabilities and react to any stimuli that may jeopardise brain homeostasis, and when the brain tissue is strained, they alter morphologically and transcriptionally in a stimulus-dependent manner (Beard et al. 2022). Astrocytes are essential for the central nervous system's survival and function. These cells provide metabolic and structural support for neural circuits. Astrocytes can also undergo ketogenesis, which, in addition to offering an alternate source of energy metabolism, may help to prevent the accumulation of non-esterified fatty acids and the synthesis of pro-apoptotic ceramide. They are also a fundamental regulator of neuronal metabolism and act as an anatomical link between circulation and brain circuits. Neural activity is involved in the coordination and interplay of all these events. Consequently, astrocytes support neurons by providing substrates for biosynthesis, energy metabolism, and neurotransmission in addition to handling waste. The glycogen accumulates in astrocytes in the adult brain. Glycogenolysis and lactate production in astrocytes are essential for long-term memory development. Thus, impaired astrocyte metabolic processes might cause neuronal dysfunction and eventually contribute to neurodegeneration (Oksanen et al. 2019). As metabolic reprogramming is the only process that controls phenotypic change, reactive astrocytes can be identified from homeostatic astrocytes by analysing their metabolic profiles (Beard et al. 2022).

According to Yan et al. (2013), astrocytic metabolic dysfunction may contribute to amyloid-beta (Aβ) formation in AD. In the AD model, astrocytes failed to clear lipid droplets which makes neurons more susceptible to degeneration. Degenerating brain regions in Parkinson's disease (PD), like the substantia nigra, contain relatively less astrocytes than other brain regions. This could make dopaminergic neurons more vulnerable to changes in metabolism and energy. Glucose deprivation enhances α-synuclein aggregation, but increased lactate supply inhibits it. This suggests that astrocytic metabolic dysregulation plays a role in PD pathogenesis. In PD astrocytes, mitochondrial metabolism is disrupted, resulting in increased histocompatibility complex I and II expression (Russ et al. 2021). In mouse HD models, astrocytes exhibit higher Ca^{2+}-dependent exocytotic glutamate release, which is

associated with increased glutamate production due to overexpression of astrocytic pyruvate carboxylase. Metabolomics investigations on motoneurons and astrocytes expressing mutant human SOD1 demonstrated that menadione-induced oxidative stress disrupted the TCA cycle and glutamate metabolism (Veyrat-Durebex et al. 2016). Crucially, hypermetabolism—which may result from aberrant astrocytic mitochondrial metabolism—has been connected to ALS in humans (Cistaro et al. 2012). This hypermetabolism is also shown in pre-symptomatic SOD1 mutant animal models, suggesting that it may be a crucial factor in the early pathogenesis of the illness (Ferraiuolo et al. 2011). Higher Ca^{2+}-dependent exocytotic glutamate release is shown in astrocytes in mice HD models, and this is linked to increased glutamate synthesis as a result of astrocytic pyruvate carboxylase overexpression. Metabolomic investigations on motoneurons and astrocytes expressing mutant human SOD1 demonstrated that menadione-induced oxidative stress disrupted the TCA cycle and glutamate metabolism (Veyrat-Durebex et al. 2016). Importantly, ALS in humans has been linked to hypermetabolism, possibly due to abnormal astrocytic mitochondrial metabolism (Cistaro et al. 2012), which is present in pre-symptomatic SOD1 mutant mouse models and may thus play a key role in early disease pathogenesis (Ferraiuolo et al. 2011).

Demyelination and axonal degeneration are associated with metabolic alterations in oligodendrocytes. AD significantly impairs oligodendrocytes' OXPHOS, glycolysis, and ketolysis, three adenosine triphosphate-generating processes. Furthermore, aged and AD mice have different pathways involved in myelin production. NLRP3 signalling has been demonstrated to be elevated in oligodendrocytes with defects in the glycolytic pathway (Zhang et al. 2020). Furthermore, AD-like pathology could be initiated in oligodendrocytes by changes in their lipid metabolic pathways. According to Ferrari Bardile et al. (2019), oligodendrocytes in HD also showed a decrease in cholesterol production pathways. These modifications resulted in increased neurodegeneration and behavioural abnormalities in animal model of HD.

4.3 Cellular Machinery Underlying Disrupted Glial Metabolism in NDDs

Neurodegenerative processes are being fuelled by aberrant glial activation (Cragnolini et al. 2019). According to Rodríguez-Gómez et al. (2020), microglia are sensitive to a variety of inflammatory stimuli, such as cytokines, interferons (IFN), lipopolysaccharide (LPS), microbial-associated molecular patterns (MAMPs), and damage-associated molecular patterns (DAMPs) (Rodríguez-Gómez et al. 2020). Microglia undergo a quick transformation from their homeostatic condition to a variety of different phenotypes in response to stimuli, such as lipid droplet-accumulating microglia (LDAM), disease-associated microglia (DAM), and microglial neurodegenerative phenotype (MGnD) (Afridi et al. 2020). In microglia,

altered mitochondrial dynamics also enhance inflammatory signalling. ATP homeostasis maintenance requires oxidation of amino acids, fatty acids, and monosaccharides. The energy transfer is received in the form of electrons by FAD and NAD+; however, some are immediately converted to ATP. Re-oxidation of the reduced electron transporters is essential for the molecular oxidation process to continue. This is mediated by the OXPHOS system in the mitochondria or the cytosolic enzyme lactate dehydrogenase (LDH). The dual activity of the OXPHOS system guarantees greater energy utilisation. The maintenance of mitochondrial functionality is important in the brain, and changes in the ability of the OXPHOS system to mediate oxidative phosphorylation are compromised in neurodegenerative diseases. This results in altered metabolic pathways and their activity, as well as intracellular aggregate accumulation, apoptosis, excitotoxicity, and mitochondrial dysfunction (Afridi and Suk 2023).

In case of challenges due to microenvironment alteration, microglia switch to glycolysis from OXPHOS. This is done to compensate for the ongoing changes and to regulate immune functions. In neurodegenerative disorders, the constantly elevated glycolysis is detrimental and increased uptake of glucose negatively affects microglial ATP production which leads to impaired functioning of immune processes. One of the numerous mechanisms by which heightened glycolysis can affect immune function includes lactate level changes. Lactate is a by-product of glycolytic metabolism involved in histone lactylation. In the case of AD, increased glycolysis leads to a surge in intracellular lactate levels, leading to positive feedback and accelerating the glycolytic rate through histone lactylation (Pan et al. 2022). Moreover, an increase in glycolysis exacerbates NLR family pyrin domain-containing 3 (NLRP3)-associated inflammation and AD pathology. Elevated levels of hexokinase-2 and 6-phosphofructo-2-kinase/fructose-2,6-biphosphate 3 (PFKFB3) have also been reported to drive microglial cells into an energy-deficient state leading to impaired phagocytosis, leading to increased amyloid-beta deposition, neuroinflammation, and impaired cognition (Piers et al. 2020). According to Joshi et al. (2018), stimulation with mutant proteins promotes mitochondrial fission 1 protein (FIS1) and dynamin-related protein-1 (Drp1) boosting neuroinflammatory responses in microglia (Joshi et al. 2018) via numerous pathways such as NF-κB and MAPK link neuroinflammatory signalling and mitochondrial dynamics. In BV-2 murine microglial cells activated with LPS, Drp-1-induced fission boosted the formation of reactive oxygen species (ROS) and accelerated the release of pro-inflammatory cytokines through NF-κB and NLRP3 signalling (Park et al. 2016).

Through the inflammatory activation of reactive astrocytes and microglia, elevated neuroinflammation plays a crucial role in the pathophysiology of ALS (Liu and Wang 2017). Moreover, both in vitro and in vivo models of Parkinson's disease have also shown microglial metabolic reprogramming and subsequent inflammatory activation (Kam et al. 2020). Leucine-rich repeat kinase 2 (LRRK2) mutations are one of the recognised genetic risk factors for the advancement of PD (Nguyen et al. 2020). Since LRRK2 controls dynamics of the mitochondria, mutations in this gene are linked to an increase in the fragmentation of mitochondria via phosphorylating Drp-1.

Sphingolipid, phosphatidylcholine, and glycerol levels have also been found to increase in mouse microglial cells exposed to lipopolysaccharides (LPS) (Blank et al. 2022). A phospholipid called lysophosphatidic acid (LPA) is known to cause microglia to exhibit an inflammatory phenotype (Plastira et al. 2019). When exposed to LPA, BV-2 microglial cells released more lactate into the media, which is a typical indicator of enhanced glycolysis. The production of aromatic amino acids such as phenylalanine, tyrosine, and tryptophan as well as alanine and glycine is also enhanced by LPA exposure. In microglia, LPA also boosted lipogenesis, which enhanced the production of phospholipids, free FA, cholesteryl esters, diacylglycerols, and triacylglycerols (Joshi et al. 2019).

In inflammatory microglia, indoleamine 2,3-dioxygenase (IDO) activity is also elevated (Wang et al. 2010). Higher tryptophan breakdown as a result of elevated IDO activity produces the neurotoxic metabolite quinolinic acid. IDO expression has been found to increase in mouse primary microglial cells exposed to lipopolysaccharide (LPS) (Koshiguchi et al. 2017). Along with progression in neurodegeneration, increased IDO activity is also associated with AD (Widner et al. 2000). Human microglial cells exposed to Aβ also exhibit enhanced IDO activity, which results in a buildup of neurotoxic quinolinic acid production (Guillemin et al. 2003). Further, plaque-associated microglia isolated from human samples have also been found to have consistently elevated expression of genes regulated by hypoxia-inducible factor 1 (HIF-1α), such as aldolase A (ALDOA), LDHA, and PKM encoding for the glycolytic enzymes (Grubman et al. 2021). Reduced transcription of genes related to mitochondria and enhanced activation of HIF-1 signalling pathways have been observed by Aβ plaque-associated microglia, or AβAM (March-Diaz et al. 2021). Microglial quiescence with reduced mitochondrial respiration and proliferation is the outcome of increased HIF-1 signalling in AβAM (March-Diaz et al. 2021). Thus, elevated HIF-1 signalling inhibits the microglial metabolism, which decreases their coverage of Aβ and enhances the neuropathology associated with Aβ plaque.

The ability of astrocytes to control neuronal metabolism and neurovascular coupling is essential for using brain energy for neuronal function. Glutamate is specifically absorbed by astrocytes at synapses in response to neuronal activity. This process initiates astrocytic aerobic glycolysis, which in turn causes glucose intake and lactate release. The main features of ageing are decreased mitochondrial oxidative phosphorylation in neurons and reduced aerobic glycolysis in astrocytes, and notwithstanding their limited capacity to control glycolysis and prevent the buildup of oxidative stress, neurons are primarily dependent on mitochondrial oxidative phosphorylation. They are therefore more vulnerable to age-related mitochondrial malfunction. Astrocyte dysfunction has detrimental effects on neurons, increasing their susceptibility to degeneration and causing normal ageing to give way to neurodegeneration. The availability of metabolic substrates and the expression of metabolic pathways are restricted with ageing, and these factors are strongly linked to aberrant energy metabolism, inappropriate astrocyte glutamate circulation, and modifications in neurovascular coupling. A major contributing factor to ageing is

also the decline in astrocyte count and the compromised lactate shuttle, which supports fewer neurons (Ahadiat and Hosseinian 2023).

In AD, PD, HD, and ALS, astrocytes have been found to show extensive changes in their metabolic pathways controlling the synthesis or breakdown of carbohydrates and fatty acids. Elevated rates of glycolysis in neurotoxic astrocytes lead to neurodegeneration by impairing the supply of metabolites to neurons and inducing inflammatory signals. Astrocytes showed impairment in mitochondrial OXPHOS, which resulted in increased formation of reactive oxygen species (Afridi et al. 2022). In addition to depriving neurons of energy, impairments in astrocytic glycolysis stop the production of several glycolytic intermediates, which are necessary for the synthesis of other macromolecules (Mulica et al. 2021). A non-essential amino acid called L-serine is necessary for the synthesis of certain bioactive macromolecules.

The process of making L-serine entails the sequential phosphorylation of 3PG by several enzymes, one of which is 3-phosphoglycerate dehydrogenase (PHGDH), which catalyses the initial step in the process. In 3xTg-AD mice, astrocytic reduction in PHGDH leads to reduced long-term potentiation and cognitive performance, as well as low D-serine availability in the brain. Furthermore, in AD, astrocytes are reported to perform poorly in removing lipid droplets, which increases the susceptibility of neurons to degeneration. This suggests that the neurodegeneration seen in AD is directly related to astrocytic altered metabolism (Le Douce et al. 2020).

Joshi et al. (2019) showed decreased ATP levels and increased production of ROS in the mitochondria of mouse primary astrocytes isolated from SOD1-G93A mice, a mouse model of ALS. This suggests that inflammatory neurodegeneration driven by A1 astrocytes has a role in metabolic failure (Joshi et al. 2019).

Through the production of neurotoxic mediators and decreased clearance of α-synuclein, reactive astrocytes worsen neurodegeneration in Parkinson's disease (PD). Moreover, astrocytes from Parkinson's disease patients with the G2019S mutation in the LRRK2 gene have shown impaired mitochondrial respiration. According to Sonninen et al. in 2020, they also displayed elevated expression of GFAP and Lcn2, along with mitochondrial abnormalities. Significant changes in mitochondrial metabolic pathways, including uncoupled mitochondrial respiration and decreased baseline respiration, are observed in human astrocytes exposed to α-synuclein fibrils (Russ et al. 2021).

In the case of HD, primary astrocytes from HD mouse model R6/2 mice exhibit metabolic impairment. The decreased ATP levels and increased production of ROS in the mitochondria are linked to inflammatory neurodegeneration mediated by A1 astrocytes (Joshi et al. 2019). Reduced glutamine synthesis has also been found in striatal astrocytes in HD mouse model which have an altered TCA cycle (Skotte et al. 2018). In the mouse model of HD, neurotoxicity is exacerbated by compromised metabolism and disrupted glutamine glutamate cycle in astrocytes (Skotte et al. 2018).

Major histocompatibility complexes I and II are expressed more often in PD astrocytes due to changes in mitochondrial metabolism (Farmer et al. 2020). Similar observations have also been reported in ALS, wherein inflamed astrocytes had

severe mitochondrial impairments along with elevated inflammatory signalling (Reid and Kuipers 2021). Studies conducted on mice have also demonstrated that stimulating cortical astrocytes in the brain with inflammatory cytokines enhances glucose use, which is then metabolised by the tricarboxylic acid cycle (TCA) and pentose phosphate pathway (PPP), leading to a decrease in glycogen level. LPS-exposed mouse primary cortical astrocytes have been found to show transiently different metabolic patterns. Additionally, chronic LPS administration enhances OXPHOS and decreases both GLUT1 expression and glycolytic rates; however, acute LPS treatment of astrocytes increases glycolysis (Robb et al. 2020). Metabolic changes in the microglia are accompanied by transient changes in cytokine expression due to LPS stimulation (Robb et al. 2020).

In AD and PD, there is disruption in metabolic connection between astrocytes and neurons, which causes cerebral hypoperfusion and blood-brain barrier integrity deterioration, which may affect the ability of the lymphatic system to operate. In AD, the neurovascular connection is compromised. Reduced glucose metabolism is a corollary of cerebral hypoperfusion that will cross-talk with downstream pathways like the astrocyte-neuron lactate shuttle (ANLS). In response to elevated oxidative stress, neuronal PPP is activated in AD and late PD. A second aggravating factor of oxidative stress is the interruption of glutathione *S* transferase (GSH) flow from astrocytes to neurons. The AD-related ApoE4 isoform impedes the transport of neuronal peroxidation FA to astrocytes, where they are oxidised by FAO, resulting in the buildup of hazardous FA. Due to ineffective glutamate elimination from the synaptic cleft, which results in excitotoxicity-induced neuronal death, the Glu/GLn cycle is compromised in both situations (Mulica et al. 2021). Under pathological circumstances, oligodendrocytes experience significant structural, functional, and metabolic alterations similar to those of microglia and astrocytes. Numerous changes in the innate metabolic pathways such as altered glycolysis have been documented in neurodegenerative illnesses which cause demyelination and axonal. Transient alterations in cytokine expression are assumed to accompany the metabolic changes, specifically elevated TNF-α in the acute phase and elevated IL-6 and IL-10 expression in the chronic phase after LPS stimulation. One possible explanation for reactive astrocytes developing tolerance during the chronic phase could be a widespread impairment in energy metabolism, which would lead to a decrease in pro-inflammatory cytokine levels (Robb et al. 2020).

Bioactive lipids known as ceramides have been linked to neurodegenerative and neuroinflammatory disease pathology (Ayub et al. 2021). Numerous demyelinating illnesses have been connected to increased lactosylceramide (LacCer) synthesis in inflammatory astrocytes (Mayo et al. 2014). Recent research has revealed that LacCer uses metabolic reprogramming to control astrocyte-driven neurotoxicity. Increased NF-κB signalling results from LacCer's stimulation of the CARD domain in the mitochondrial antiviral signalling protein (MAVS) and the C2 domain in cytosolic phospholipase A2 (cPLA2)(Yu et al. 2021).

The metabolic pathways of oligodendrocytes alternate between glycolysis and OXPHOS at various stages of myelination. Following myelination, glycolysis becomes the primary metabolic function of oligodendrocytes, which supplies

glycolytic products as energy substrates to maintain myelinated axons (Fünfschilling et al. 2012). According to recent research, oligodendrocytes that have sustained CNS damage also become transcriptionally activated to promote remyelination. In order to undergo remyelination, the OPC migrates in the direction of the demyelinated axons and quickly matures into an oligodendrocyte (Moyon et al. 2015). Upregulation of lipid and protein synthesis genes necessary for myelin production indicates that oligodendrocytes are transcriptionally activated. In addition, these processes are linked to an increase in pathways that produce energy to meet the ATP requirements of remyelination. FA production by oligodendrocytes appears to be a need for remyelination in an animal model of demyelinating disorders, and ablation of oligodendroglial FASN led to defective remyelination (Dimas et al. 2019). Numerous genes involved in the synthesis of cholesterol, including 3-hydroxy-3-methylglutaryl-CoA synthase 1 (Hmgcs1), farnesyl diphosphate synthase (Fdps), and farnesyl diphosphate farnesyltransferase 1 (Fdft1), are expressed less often in oligodendrocytes with demyelinating diseases (Voskuhl et al. 2019).

Further, oligodendrocytic glycolysis was reported to be reduced in AD (Zhang et al. 2020). In the early stages of AD, mature oligodendrocytes undergo NLRP3-dependent gasdermin D-associated inflammatory damage, which results in axonal degeneration and demyelination. Mitochondrial disruptions in mature oligodendrocytes during the early stages of AD caused Drp-1 to become hyperactivated, which in turn raised NLRP3 activation and ultimately resulted in axonal degeneration and demyelination. When oligodendrocytes were treated with oligomeric Aβ1-42, lactate production and extracellular acidification rates (ECAR) were reduced, highlighting the critical role that oligodendrocyte glycolytic deficiencies play in the onset and progression of AD (Mitew et al. 2010). According to Takahashi and Suzuki (2012), one of the myelin-specific alterations in AD is the loss of lipid components such as glycosphingolipids (Takahashi and Suzuki 2012). Adult mice developed AD-like disease when cerebroside sulfotransferase (CST), which catalyses the last reaction of sulfatide biosynthesis, was deleted in an oligodendroglial-specific manner. In addition to inducing transcriptional alterations in microglia and astrocytes that resulted in their inflammatory activation, the loss of CST in oligodendrocytes raised the expression of ApoE4, implying that oligodendroglial lipid changes are a potent precursor to the pathophysiology of AD (Qiu et al. 2021). In HD, oligodendrocytes also showed reduced cholesterol production pathways, which resulted in increased behavioural abnormalities and neurodegeneration in HD (Ferrari Bardile et al. 2023). The R6/2 mouse model of HD has also shown to exhibit impairment in the cholesterol pathway, supporting the notion that oligodendroglial cells contribute to white matter abnormalities in the disease (Valenza et al. 2007). The reduction of lipogenic pathways and changes in myelin production in oligodendrocytes occur before neurodegeneration and behavioural abnormalities in animal models of HD (Ferrari Bardile et al. 2019).

Neurodegeneration is exacerbated when inflammatory microglia emit neurotoxic chemicals and activated astrocytes are unable to sustain neurons metabolically (Franklin et al. 2021). Furthermore, because of their decreased capacity for phagocytic activity, neurotoxic glial cells in the deteriorating brain are unable to remove

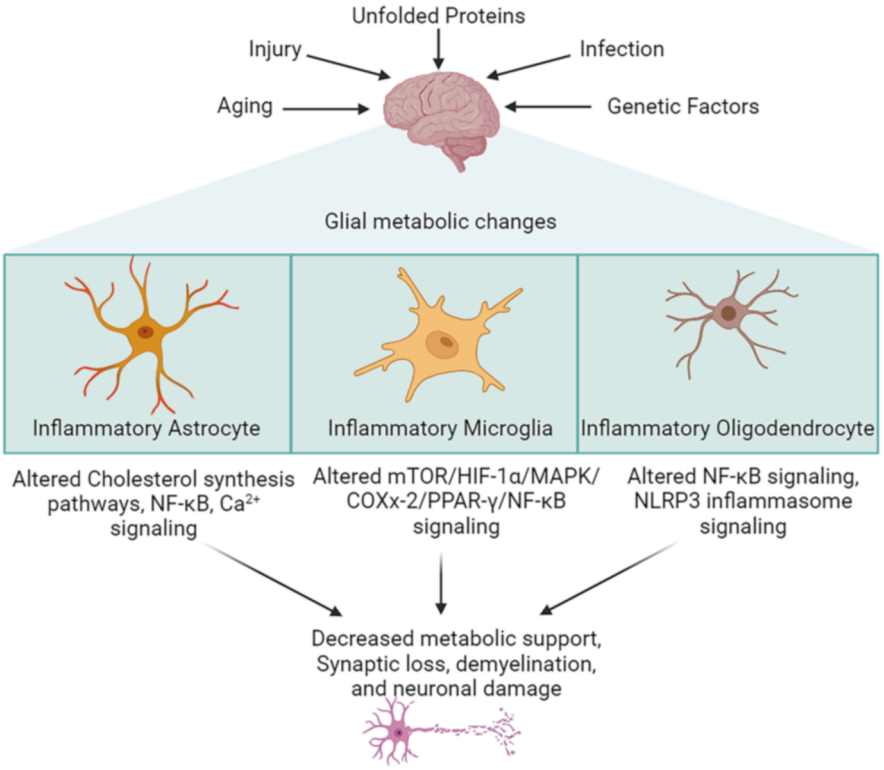

Fig. 4.1 Schematic diagram representing dysfunctional glial metabolism leads to neurodegenerative diseases

dead cells, protein clumps, or myelin debris (Baik et al. 2019). It is known that glial-specific metabolic changes lead to neurodegeneration. Notably, a lot of research has been done recently on the metabolic changes that drive astrocytic and microglial polarisation towards neurotoxic phenotypes (Fig. 4.1).

4.4 Glial-Induced Neuroinflammation and Its Impact on Brain Homeostasis

Microglia can release a wide range of cytotoxic substances in response to environmental toxicants and disease proteins including inflammatory prostaglandins, superoxide, NO, and TNF-α (Lull and Block 2010). In order to support development, preserve homeostasis, aid in tissue repair, and contribute to the pathogenesis of illnesses, microglia interact with almost every type of brain cell. An important factor in the development of neuroinflammation is the interaction between activated microglia and astrocytes. By upregulating the expression of cytokines and

chemokines, particularly by stimulating nuclear factor-κB (NF-κB) signalling, microglia can amplify the inflammatory activation of astrocytes (Kirkley et al. 2017). Extracellular vesicles are mediators in the interaction between astrocytes and microglia. Astrocyte-derived ATP causes neighbouring microglia to release IL-1β and produce EVs, which sets off a neuroinflammatory response (Bianco et al. 2005). Reactive astrocytes have elevated expression of prominent markers such as glial fibrillary acidic protein (GFAP). Activated astrocytes, like activated microglia, produce inflammatory cytokines like IL-1β, IL-6, and TNF-α, leading to impaired neuronal functioning. The permeability and maintenance of the blood-brain barrier (BBB) are facilitated by astrocytes. They also have an impact on immune cell activation and trafficking regulation. In response to danger signals, astrocytes are immunological-competent cells that can secrete cytokines and chemokines, which trigger adaptive immune defence, and the overactivation of astrocytes causes damage to neurons and dysfunction of the blood-brain barrier (Farina et al. 2007). Astrogliosis is a common factor in many neurodegenerative conditions, including AD and HD, and it may be necessary for the progression of many other neurodegenerative disorders (Fig. 4.2).

In AD, microglia that surround plaques exhibit an activated phenotype. Apart from generating pro-inflammatory mediators like cytokines, microglia have also been observed to cause harm to neurons that were previously exposed to modest levels of Aβ42 (Bate et al. 2004). Elevated levels of ATP, ROS, and Aβ drive the activation of microglia in AD, which is associated with neuroinflammation. This activation could downregulate TREM2 and activate P2X7R. P2X7R activation would increase calcium influx, which would in turn trigger the release of inflammatory cytokines from activated microglia. Decreases in TREM2 would hinder microglia's ability to phagocytose Aβ, increasing the Aβ brain parenchymal burden in AD. Activation of microglia is linked with the activation of NF-κB and NLRP3 inflammasomes, which leads to the secretion of pro-inflammatory cytokines IL-1β

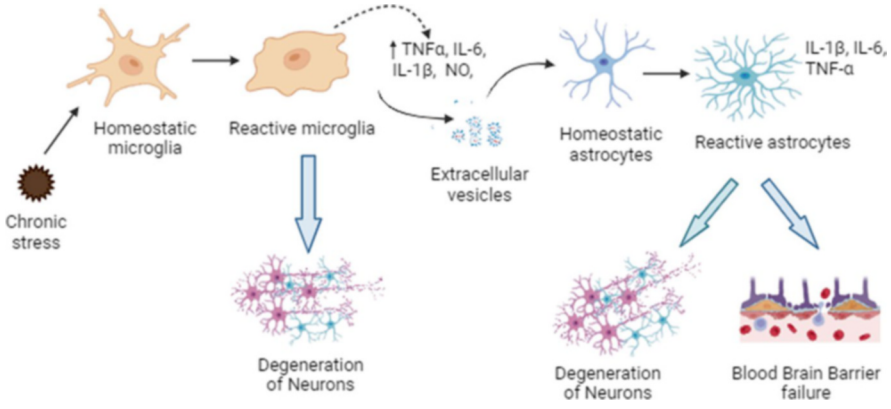

Fig. 4.2 Overactivation of microglia, release of pro-inflammatory cytokines, and activation of astrocytes that results in degeneration of neurons and failure of the blood-brain barrier are shown

and IL-18 and activation of caspase-1 (Al-Ghraiybah et al. 2022). The pro-inflammatory microglia increase phosphorylation of tau and exacerbate tau pathology (Lee et al. 2010). In AD, endothelium RAGE and LRP1 expression are upregulated and downregulated, respectively. This results in decreased LRP1-mediated Aβ clearance and increased RAGE-mediated Aβ influx into the brain, feeding the vicious cycle of Aβ accumulation in the brain, astrocyte activation, and BBB dysfunction. Activated astrocytes produce inflammatory cytokines such as IL-1β, IL-6, and TNF-α, leading to impaired neuronal functioning (González-Reyes et al. 2017). Astrocytes may experience malfunction due to incompletely degraded Aβ deposits. This can result in detrimental apoptotic signalling in neurons. Additionally, astrocytes can deposit Aβ in pro-inflammatory settings, aggravating AD difficulties (Fakhoury 2018). Reactive astrocytes activate NLRP3 inflammasomes and NF-κB pathways, resulting in the production of cytokines and inflammatory markers like ROS, RAGE, COX, and MMP9 which leads to blood-brain barrier dysfunction. Furthermore, pro-inflammatory cytokine release would rise with TLR4 and TLR6 activation via binding to CD36, resulting in neuroinflammation and disruption of the blood-brain barrier. Glutamate dysregulation and synaptic degeneration have been connected to pro-inflammatory reactive astrocyte phenotypes (Liddelow and Barres 2017; Oksanen et al. 2019). Reactive astrocytes produce ROS and inflammatory markers like COX and NOS, which would disrupt the BBB-endothelium (blood-brain barrier). Increased pro-inflammatory mediators and MMP9 activation may result from BBB failure, cytoskeleton reorganisation, downregulation of tight junction proteins, activation of NLRP3 inflammasomes and NF-κB pathways, and other factors (Spampinato et al. 2017). Experiments have revealed that inhibiting astrogliosis can enhance the buildup of β-amyloid plaques and promote inflammatory signalling (Frost and Li 2017)

Moreover, progressive loss of dopaminergic neurons in the substantia nigra pars compacta is a hallmark of Parkinson's disease. The death of these neurons is linked to a glial response mostly made up of reactive astrocytes and activated microglial cells. The neuroinflammatory response triggered by α-syn is regulated by microglia and astrocytes. Neurons that aggregate α-syn release exosomes that carry the protein out of cells and cause microglia and astrocytes to become inflamed. These exosomes specifically target microglia (Gordon et al. 2018). A variety of inflammatory mediators, including TNF-α, IL-6, NOS2, COX2, and ROS, are produced by activated microglia in PD, and an excess of these mediators can cause DA neurons to continuously and permanently die (Subhramanyam et al. 2019). It has been reported that α-syn stimulates microglia to trigger a neuroinflammatory response, suppresses autophagy, and ultimately leads to neurotoxicity in PD (Zhang et al. 2022). α-Syn also reduces the expression of microglial glucocorticoid receptors (GR) by sensitising the TLR4-dependent inflammatory response. GR in microglia increases TLR9 translocation to endolysosomes and stimulates TLR9 cleavage, both of which result in the production of pro-inflammatory genes (Kwon and Koh 2020). Then, microglia encourage neuronal death by secreting cytokines. TNF-α, C1q, and IL-1α are produced by reactive microglia, and these substances cause the neurotoxic A1 astrocyte phenotypic conversion.

After becoming stimulated, A1 astrocytes cease to perform vital roles like promoting neuroinflammation and preserving neuronal survival, which aids in the development of neurodegenerative diseases (Yun et al. 2018). Astrocytes in PD are intimately associated with inflammation, defects in macroautophagy, and MHC-II controlling Th1/Th2 cytokine production triggered by α-syn. Astrocytes are involved in inhibiting the accumulation and spread of α-syn accumulation in dopaminergic neurons. Nonetheless, astrocytes may be stimulated into the A1 reactive state in the later stages of PD, which is extremely cytotoxic to neurons and oligodendrocytes as opposed to phagocytic (Cheng et al. 2022).

In the HD brain, neuroinflammation is characterised by the reactive morphology of microglia and astrocytes. Microglia and astrocytes contribute to neuronal death in HD. The reactive gliosis found in HD may lead to both neuronal and pericyte mortality around cerebral blood vessels (Palpagama et al. 2019). Stimulating chemicals that cause PU1 upregulation, CCAT binding, and NF-κB signalling activate microglia. Reactive astrocytes and activated microglia release reactive oxygen species (ROS) and neurotoxic compounds such as quinolinic acid, which can trigger chemical reactions that result in the death of neurons. Additionally, stimulatory chemicals cause reactive astrogliosis, which increases the production of pro-inflammatory cytokines, glutamate excitotoxicity, and neuron hyperexcitability (Palpagama et al. 2019). Prolonged inflammatory mediator generation by activated microglia leads to chronic inflammation and is associated with further tissue damage (Ellrichmann et al. 2013). Reactive microglia are found in HD brain tissue in the globus pallidus, cortex, and neostriatum. The degree of neuronal loss was directly correlated with the amount of active microglia in the striatum and cortex, and microglia were tightly linked to pyramidal neurons, indicating that the degenerating neurons may be the source of neuroinflammatory alterations. As the disease progressed, there was higher loss of striatal neurons and increased microglial activation (Sapp et al. 2001). In the brain of HD, reactive astrogliosis is also reported. In the brain during HD, the number of astrocytes increased. Reactive astrocytes were absent from grade 0 HD brains, and reactive astrocytosis is only shown after commencement of neurodegeneration, even though microglial density and activation were seen before the development of symptoms and neuropathological alterations. The gradient of striatal neurodegeneration in the HD striatum is connected with an increasing number of GFAP positive reactive astrocytes (Vonsattel et al. 1985). In addition to neuronal death reactive astrocytosis in HD may also hasten the disease's course by causing pericyte death along the cerebral blood vessels (Hsiao et al. 2013). HD brain astrocytes also exhibit a variety of anomalies in their electrical characteristics. These have been demonstrated to alter the release of glutamate and adenosine triphosphate (ATP), which influences neuronal signalling, and they probably affect their capacity to maintain ion homeostasis (Xiong et al. 2018). Notably, there is a correlation between the severity of the disease and the levels of reactive astrocytosis and microglial activation. In addition to neuronal death and reactive astrocytosis, HD may also hasten the disease's course by causing pericyte death along the cerebral blood vessels (Hsiao et al. 2013). Reactive astrocytes may have

varying degrees of expression for signalling molecules, transcription factors, and chemokines or cytokines and accelerate neurodegeneration.

In the case of multiple sclerosis (MS), which is typically diagnosed as an autoimmune disease, it is linked to lesions in the CNS's white and grey matter that have higher than normal numbers of activated microglia and ROS and pro-inflammatory cytokines released by microglia (Liu et al. 2006). Astrocytes and myeloid cells like microglia frequently change into reactive subtypes with larger cell bodies and retracted processes under inflammatory-demyelinating circumstances. The progressive degeneration of neurons from a healthy state to a degenerated state with axonal degeneration and synapse loss followed by retrograde injury and damage to neuronal cell bodies is mirrored by changes in the morphology and function of glial cell types, such as complement secretion and activation, antigen presentation via MHC classes I and II, cytokine production, and complement factor release (Schirmer et al. 2021).

4.5 Targeting Glial Cell Metabolism as a Potential Strategy to Treat NDDs

Microglia are primarily involved in immunosurveillance, phagocytosis, and removal of misfolded proteins and pathogens. An insult or chronic stress, such as NDs, leads to the transformation of homeostatic microglia to reactive ones, resulting in the production of reactive oxygen species pro-inflammatory cytokines and proteases and a concomitant shift from oxidative phosphorylation (OXPHOS) to glycolysis. Microglia increase the glucose uptake to compensate for the persistent changes in gene expression and other immune functions. These hyperglycolytic microglia are positively correlated with neuroinflammation and metabolic and mitochondrial dysfunction. Several unwanted by-products of increased glycolysis lead to the impairment of homeostatic immune functions of microglia (Maurya et al. 2022). Hence, the primary therapeutic approach against NDDs has been reprogramming microglia metabolism by interfering with glycolysis or enhancing OXPHOS and modulation of FA metabolism.

Triggering receptor expressed on myeloid cells 2 (TREM2) is a microglia-surface receptor, which recognises apoptotic cells, phospholipids, and lipoproteins, and is involved in autophagy and phagocytosis. TREM2-deficient mice show abnormal mammalian target of rapamycin (mTOR) signalling, leading to defective ATP production and bioenergetics. Dietary administration of cyclocreatine to TREM2-deficient 5xFAD mice alleviated metabolic abnormality by ATP production from phosphorylation of cyclocreatine by creatine kinase bypassing the TREM2-mTOR axis. It also reduced autophagy and alleviated neurite dystrophy (Ulland et al. 2017). Clock 1 (Clk1) is a mitochondrial hydroxylase required for the synthesis of ubiquinone which is an indispensable part of the mitochondrial electron transport chain. Clk1-deficient mice show enhanced aerobic glycolysis and reduced mitochondrial

electron transport leading to reduced oxygen consumption and ATP production and hypersensitivity to LPS-induced neuroinflammation due to increased HIF-1α expression by mTOR activation and ROS production. Clk1-deficient mice also show exacerbated DA neuron loss in the MPTP-induced mice model. Hence, modulation of Clk1 activity can act as a potential therapeutic intervention in anti-PD therapies (Gu et al. 2017). Transient receptor potential vanilloid type 1 (TRPV1) is a ubiquitous non-selective cation channel involved in nociception, synaptic transmission, GABA crosstalk, and microglia-neuron communication. They have also been implicated in the regulation of M1-M2 activation states of microglia, neuroinflammation, and neuropathic pain. Agonism of TRPV1 with capsaicin rescued impaired OXPHOS, aerobic glycolysis, and immune responses in Aβ-challenged primary microglia by boosting the AKT/mTOR pathway. Stimulation of TRPV1 also reprogrammed OXPHOS, reduced the pro-inflammatory cytokine production and microgliosis, and enhanced microglial autophagy of Aβ plaques in APP/PS1 mice (Lu et al. 2021). Peroxisome proliferator-activated receptor-γ (PPARγ) along with its coactivator PGC1α is involved in microglial metabolic switch during neuroinflammation by mTOR-dependent FA uptake and lipid metabolism reprogramming. They have been shown to reprogram microglia towards beneficial function. Honokiol, a neuroprotective compound from *Magnolia officinalis*, has been shown to increase PPARγ and PGC1α expression in microglia and reverses the switch from OXPHOS to aerobic glycolysis during oxidative stress in BV2 microglia (Li et al. 2021). Prostaglandin E_2 (PGE_2) is a downstream product of the cyclooxygenase 2 (COX-2) pathway and has established involvement in driving age-associated neuroinflammation. On interacting with its receptor EP2, PGE_2 induces an energy-deficient state by reducing mitochondrial respiration and sequestration of glucose into glycogen. Administration of EP2 inhibitor, benzoxazepine 52, to 7-month-old mice resulted in increased glycolysis and tricarboxylic acid (TCA) cycle and reduction in glycogen synthesis and restoration of mitochondrial respiration in microglia. It also restored levels of pro- and anti-inflammatory cytokines in plasma and hippocampus in old mice to levels comparable to young mice (Fox et al. 2015). Succinate dehydrogenase (SDH) is a part of the complex II of the mitochondrial electron transport chain and also participates in TCA cycle by catalysing the oxidation of succinate to fumarate. During LPS challenge or neuroinflammation, microglia shift from OXPHOS to glycolysis, leading to succinate accumulation; as a result, increased oxidation of succinate by SDH results in overproduction of mitochondrial ROS. Inhibition of SDH by dimethyl malonate (DMM) has been shown to control LPS-induced metabolic rewiring, mitochondrial dysfunction, and pro-inflammatory cytokine production. SDH inhibition also downregulates HIF-1α recruitment which induces glycolysis and cytokine production. In 6-month 5xTg-AD mice, DMM administration dampened cortical expression of TNF-α and IL-1β, normalised the iNOS/Arg1 ratio facilitating M2 phenotype of microglia, and abrogated neuroinflammation (Sangineto et al. 2023). Apolipoprotein E (ApoE) is a class of lipid-binding protein involved in the transport and metabolism of lipids and cholesterol. Low-density lipoprotein receptor (LDLR) is a metabolic receptor of apoE involved in its endocytosis and degradation in lysosomes. ApoE has been established as a risk

variant for AD and is involved in Aβ deposition and exacerbation of the disease. Microglial LDLR overexpression leads to a deficiency of apoE and leads to reduced activation and neuroinflammation. Microglia with apoE deficiency downregulate genes involved in glycolysis such as enolase 2 (Eno2), glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and lactate dehydrogenase A (LDHA) and mTOR signalling such as mitogen-activated protein kinase kinase 2 (MAP2K2), solute carrier family 3 member 2 (SLC3A2), and late endosomal/lysosomal adaptor, MAPK and mTOR activator 4 (LAMTOR4). Selective knockout of apoE or overexpression of LDLR has the potential to reprogram microglial metabolism to homeostatic conditions (Shi et al. 2021). Lactate dehydrogenase A (LDHA) is a cytosolic enzyme which catalyses the conversion of pyruvate to lactate. The function of LDHA in neoplastic tissues is well established. In gliomas, it has been shown to regulate the Warburg effect and push glia towards increased glycolysis by removing the final product, pyruvate. miR-200b has been shown to directly target 3′ UTR of LDHA mRNA, reducing the expression of LDHA. By repressing LDHA, miR-200b reduced glycolysis and lactate levels and alleviated metabolic distress in U87 and U251 glioma cell lines (Hu et al. 2016). Aldose reductase (AR), an aldo-keto reductase, catalyses the first step of the polyol pathway and converts glucose to sorbitol. Acceleration of the polyol pathway has been seen in inflammatory diseases such as ulcerative colitis, sepsis, and airway inflammation, leading to oxidative stress. AR induces inflammatory responses through ROS-PKC-mediated NF-κB and MAPK pathways. Inhibition of AR using Sorbinil and Zopolrestat in Aβ-induced BV2 microglial cells downregulates expression of pro-inflammatory cytokines and inhibits ROS-PKC and JNK/p38/ERK pathways (Song et al. 2017). Ca^{2+}-dependent K^+ channels (KCa3.1) and voltage-gated K^+ channels ($K_v1.3$) are involved in microglial polarisation during activation, by maintaining a negative membrane potential by K^+ efflux. KCa3.1, being voltage-independent, opens under the influence of small amounts of Ca^{2+}. $K_v1.3$ being voltage-gated assists in maintaining the negative membrane potential and leads to increased Ca^{2+} influx. This Ca^{2+} influx is implicated in mitochondrial dysfunction, microglial proliferation, migration, and NO production. Targeting KCa3.1 and $K_v1.3$ has been shown to prevent neurotoxicity in the MCAO ischaemia mice model and reduces neuroinflammation and Aβ plaque load (Fumagalli et al. 2018).

Astrocytes constitute the largest population among glia and are primarily involved in providing trophic and metabolic support to neurons. Astrocytes also regulate energy homeostasis and immune functions and maintain BBB. As opposed to microglia, the primary bioenergetic process in astrocytes is glycolysis and relies less on OXPHOS as they express low levels of pyruvate dehydrogenase (PDH). This leads to less conversion of pyruvate to acetyl-CoA and progression into TCA cycle. Due to this, astrocytes produce lactate using pyruvate by LDH and export it using monocarboxylate transporter 4 (MCT4). This lactate acts as a metabolic substrate for neurons and oligodendrocytes. Astrocytes also abundantly express genes for unsaturated FA oxidation and hence are efficient in FA oxidation and can direct FA into TCA cycle (Brandebura et al. 2023). Redirecting astrocyte metabolism from detrimental to favourable has been preliminarily achieved by targeting several

proteins involved in as well as regulating glycolysis, OXPHOS, and FA metabolism. Glutathione (GSH) is a tripeptide (γ-l-glutamyl-L-cysteinyl-glycine), synthesised in the cytosol and then transported to mitochondria, nucleus, and endoplasmic reticulum. Mitochondria being the major source of ROS production and mtDNA being susceptible to oxidation, GSH acts as an antioxidant by oxidation of the redox-active thiol (-SH) group and subsequent conversion to oxidised glutathione (GSSG). The GSH/GSSG ratio is the primary indicator of oxidative stress and mitochondrial dysfunction; a decrease in this ratio indicates increased production of ROS. The ketogenic diet (high-fat, low-carbohydrate) has been shown to directly enhance mitochondrial GSH levels by upregulating the rate-limiting enzyme in GSH biosynthesis, glutamate cysteine ligase (GCL). Ketoacids have also been shown to increase GSH/GSSG ratio and reduce H_2O_2 production in mitochondria (Jarrett et al. 2008). Glucagon-like peptide 1 (GLP-1) is a pleiotropic hormone secreted by L-cells in the gut and performs a myriad of metabolic functions like glucose-dependent stimulation of insulin secretion, gastric emptying, and regulation of food intake. GLP-1 is also involved in neuroprotection by being anti-inflammatory and anti-apoptotic. Administration of liraglutide, a GLP-1 agonist, increased aerobic glycolysis in cortices of 5xFAD mice as well as in $A\beta_{1-42}$-induced primary astrocytes by upregulating hexokinase 1 (HK1), pyruvate kinase M2 (PKM2), and Akt phosphorylation. This leads to increased trophic support to neurons by astrocytes. GLP-1 also reduced oxidative stress and memory impairments in 5xFAD mice. A reversal in metabolic reprogramming was also seen after administration of GLP-1 antagonist, 2-deoxyglucose (2-DG) (Zheng et al. 2021). c-Abl is a non-receptor tyrosine kinase and an oncogene which has been involved in mitochondrial distress, ROS production and astrogliosis in neuroinflammation, and neurodegeneration. Nilotinib, a selective c-Abl inhibitor, improved bioenergetic dynamics by enhancing ATP production and expression of NADH dehydrogenase beta sub-complex subunit 8 (complex I), cytochrome *b*-*c*1 subunit 2 (complex III), cytochrome *c* oxidase subunit 1 (complex IV), and ATP synthase subunit alpha (complex V), eventually enhancing OXPHOS in 3xTg-AD mice astroglia by NF-κB-dependent pathway (Adlimoghaddam et al. 2021).

Pyruvate dehydrogenase (PDH) is a constituent enzyme of supramolecular pyruvate dehydrogenase complex (PDC) along with dihydrolipoamide acetyltransferase (E2) and dihydrolipoamide dehydrogenase (E3). It is expressed in lesser magnitude in astrocytes and is involved in oxidative decarboxylation of pyruvate to acetyl-CoA which links glycolysis to the TCA cycle. In $SOD1^{G93A}$ mutant rats and derived astrocytes, PDH undergoes prolonged phosphorylation by PDH kinase (PDK), rendering it inactive. Inhibition of PDK by dichloroacetate (DCA) resulted in the betterment of mitochondrial dysfunction and oxidative stress and reduced the $SOD1^{G93A}$ mutant astrocyte-induced toxicity to motor neurons. DCA also enhanced motor function and survival of $SOD1^{G93A}$ mutant mice (Miquel et al. 2012). α-Amino-3-hydroxy-5--methyl-4-isoxazole propionic acid receptor (AMPAR) is a fast ionotropic excitatory glutamatergic receptor involved in synaptic plasticity and transmission and long-term potentiation (LTP). Astrocytes supply lactate to glutamatergic neurons, hence directly influencing synaptic plasticity. CX546 is a cognitive-enhancing drug which modulates AMPAR activity. Administration of CX546 with AMPA has resulted in

glutamate-dependent enhancement of glucose utilisation and lactate production without changing oxygen levels in a concentration-dependent manner in cortical, cerebellar, and hippocampal astrocytes of mice. This enhancement of aerobic glycolysis by dual effect CX546 and AMPA is due to increased Na^+ influx in astrocytes due to reduced AMPAR desensitisation by CX546, which eventually leads to increased glutamate co-transport with Na^+ and a concomitant increase in Na^+/K^+ ATPase activity. This increase in intracellular Na^+ and glutamate levels leads to boosting glucose utilisation and lactate production (Pellerin and Magistretti 2005). Cytosolic phospholipase A2 (cPLA2) is a Ca^{2+}-dependent enzyme which hydrolyses membrane-bound phospholipids to produce lysophospholipids such as arachidonic acid which contribute to neuroinflammatory pathways mediated by COX-2 and lipoxygenase (LOX) in CNS injury such as SCI and TBI. Mitochondrial antiviral signalling (MAVS) protein is a mitochondrial outer membrane-bound protein. It is essential in anti-viral combat by enhancing NF-κB expression which leads to secretion of pro-inflammatory cytokines. Normally, MAVS is bound to HK2 leading to its activated state which drives glycolysis and lactate production by resting astrocytes, an activity essential for neurons. However, a sphingolipid lactosylceramide (LacCer) activates cPLA2 which in turn displaces HK2 from the MAVS-HK2 complex and forms cPLA2-MAVS complex. Formation of this complex leads to an inflammatory cascade by activation of NF-κB mediated pathways in experimental acute encephalomyelitis (EAE) and multiple sclerosis (MS) mice models. Miglustat, an approved drug for type 1 Gaucher disease and Niemann-Pick disease type C, inhibits the synthesis of GlcCer, a precursor of LacCer. Administration of miglustat to non-obese diabetes-induced EAE (NOD EAE) mice model resulted in reduced infiltration of inflammatory monocytes in CNS, axonal loss, and demyelination (Chao et al. 2019).

Oligodendrocytes are the myelinating glia in CNS which insulate neurons and provide them with trophic support. Due to such specialised and energetically expensive functions of myelin production, they require a constant source of ATP, amino acids, and acetyl-CoA for converting them into FAs. Therefore, they rely primarily on aerobic glycolysis for rapid ATP production. Oligodendrocytes also take up lactate produced by astrocytes via MCT1, followed by conversion to pyruvate, mitochondrial shuttling, acetyl-CoA production, and eventually lipid biosynthesis (Rosko et al. 2019). Although oligodendrocyte metabolic dysfunction has been rarely reported in many NDs, demyelinating disorders such as MS have been related to lipid metabolism in oligodendrocytes. Therefore, targeting lipid metabolism has been linked to oligodendrocyte precursor cell (OPC) differentiation. Sterol 14α-demethylase cytochrome P450 (CYP51) is an enzyme involved in the sterol biosynthetic pathway which converts lanosterol to a demethylated product and eventually cholesterol in animals. Inhibition of CYP51 by imidazole halts the cholesterol biosynthetic pathway and leads to the accumulation of sterol intermediates. Among these intermediates, only 8,9-unsaturated sterols have been shown to robustly enhance myelin basic protein-positive (MBP^+) oligodendrocytes from mouse epiblast stem cell-derived OPCs. Imidazole also penetrates the BBB and promotes remyelination in mouse models of remyelination (Hubler et al. 2018). Bazedoxifene (BZA) is a selective oestrogen receptor, which has also been shown

to improve MBP+ OPC differentiation to oligodendrocytes and remyelination in primary rat OPCs and lysolecithin-induced focal demyelination mice models. However, BZA function was shown to be independent of ERα and ERβ but showed effect through emopamil-binding protein (EBP) which is a 3-β-hydroxysteroid-Δ8,Δ7-isomerase involved in cholesterol biosynthesis. Similar to imidazole, this inhibition also resulted in the accumulation of 8,9-unsaturated sterols which in turn promoted OPC differentiation (Rankin et al. 2019). Acetyl-CoA carboxylase 1 (ACC1) and acetyl-CoA carboxylase 2 (ACC2) are the enzymes involved in lipid metabolism and catalyse the first step of conversion of acetyl-CoA to malonyl CoA in FA biosynthetic pathway. ACCs are primarily expressed in oligodendrocytes in the CNS which require them for myelin synthesis. Biotin (vitamin B_7) acts as a cofactor for ACC function. High doses of MD1003, a high-dose pharmaceutical-grade biotin, have been shown to enhance myelin synthesis by targeting ACCs in oligodendrocytes via upregulation of FA metabolism (Sedel et al. 2016). Pyruvate carboxylase (PC), propionyl-CoA carboxylase (PCC), and 3-methylcrotonyl-CoA carboxylase (MCC) are the catalytic enzymes involved in anaplerotic reactions which feed to the TCA cycle. PC catalyses the conversion of pyruvate to oxaloacetate, PCC converts propionyl CoA to methylmalonyl CoA which is then converted to succinyl-CoA, and MCC is involved in leucine catabolism and eventually leads to the formation of acetyl-CoA. Therefore, these carboxylases are directly involved in maintaining ATP flux by regulating TCA cycle. These carboxylases also contain biotin as the cofactor and therefore high doses of MD1003 can induce activation of these enzymes which in turn leads to enhanced ATP production which is beneficial for mitigation of degenerating and demyelinating neurons in in vivo and in vitro models of progressive MS (Sedel et al. 2016, Fig. 4.3).

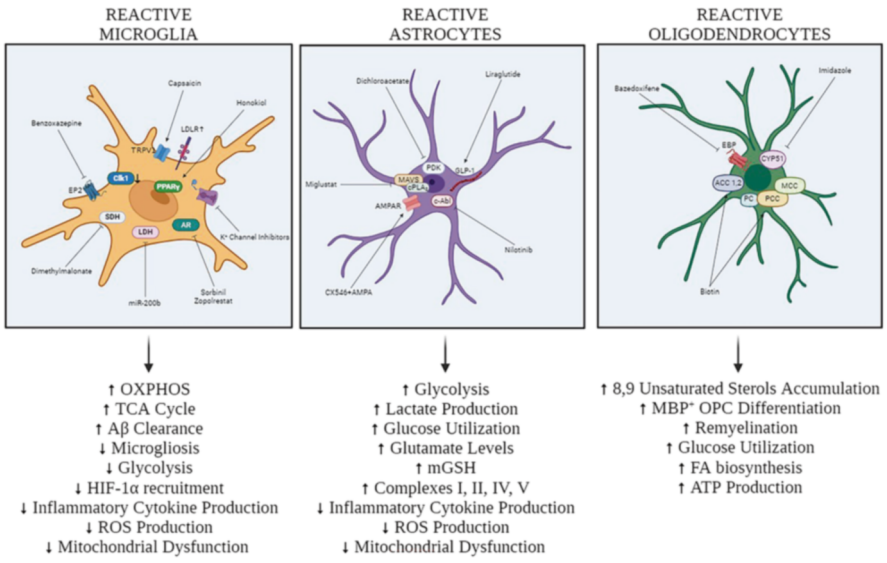

Fig. 4.3 Possible therapeutic targeting of glial cell metabolism as a potential strategy in the management of NDDs is presented

4.6 Conclusion

Glial cells play an essential role in maintaining brain homeostasis. Dysregulated glial cellular machinery as a consequence of altered metabolism leads to the development and progression of NDDs. Recent studies have indicated glial metabolism targeting as a potential intervention in the management of NDDs. However, understanding complex glial-neuron crosstalk and identification of potent metabolic drug targets to regulate glial functions can provide a better way for the management of NDDs.

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Chapter 5
Altered Glucose Homeostasis in Neurological Disorders

Nidhi Krishna Shrivastava and Mallikarjun N. Shakarad

Abstract Glucose is the major circulating energy source for the adult brain. Therefore, dysfunction in glucose metabolism disturbs normal functioning of neurons and it has been observed in several neurodegenerative disorders (NDDs). A major focus in the field of neurodegeneration is about understanding the mechanisms underlying glucose metabolism, and the regulation of the process during disease onset and progression relieves the neurons from degenerative stress leading to suppression of disease.

In this chapter, we highlight the alteration in glucose homeostasis in major neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Huntington's disease, etc. We suggest that maintaining glucose metabolism can be a potential therapeutic target for the management of neurological disorders.

Keywords Neurodegenerative diseases · Glucose homeostasis · Metabolism

5.1 Introduction

Brain and systemic metabolic abnormalities can both contribute to the onset of neurological disease because brain and systemic metabolic disorders operate in concert to regulate glucose metabolism. Numerous lines of evidence connect late-life neurodegenerative disorders to metabolic imbalance. Interestingly, risk factors for obesity, diabetes, and neurodegenerative disorders (especially Alzheimer's disease (AD) and Parkinson's disease (PD))—like inactivity and high calorie intake—all overlap. Research efforts have shifted significantly to understand the mechanisms of

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metabolic adaption during disease development, with the hope that addressing these processes could alleviate degenerative stress on neurons. Although additional research is necessary, treatments based on insulin administration, anti-diabetic medication use, or some type of dietary modification has demonstrated promise as therapeutic approaches for neurodegenerative diseases (NDDs) in their early stages of progression. In this chapter, we focus on the relationship between glucose absorption and metabolism, which results in diabetic-like circumstances, and many fatal downstream pathways, which cause neuronal cell death and therefore cognitive deficits (Fig. 5.1).

The brain uses glucose as its main energy source, which accounts for 20% of total body glucose consumption (Jais et al. 2016; Zhang et al. 2014). Ketone bodies (acetoacetate and hydroxybutyrate), lactate, fatty acids, and amino acids (valine, glutamine, leucine, isoleucine) are additional fuel sources for the brain that are primarily used under conditions of low glucose availability, such as fasting, starvation, and prolonged exercise (Bowman et al. 2019; Camandola and Mattson 2017; Qi et al. 2020; Schönfeld and Reiser 2017). Adenosine triphosphate (ATP) can be produced by brain glucose metabolism to carry out complex neurological functions, such as neuronal signaling (action potentials, synaptic transmission, glutamate cycling, etc.), which uses 70% of the brain's energy, and non-signaling activities (resting potentials, axonal transport, mitochondrial proton leak, oligonucleotide turnover, actin cytoskeleton remodeling, etc.), that uses 30% of the ATP. Additionally,

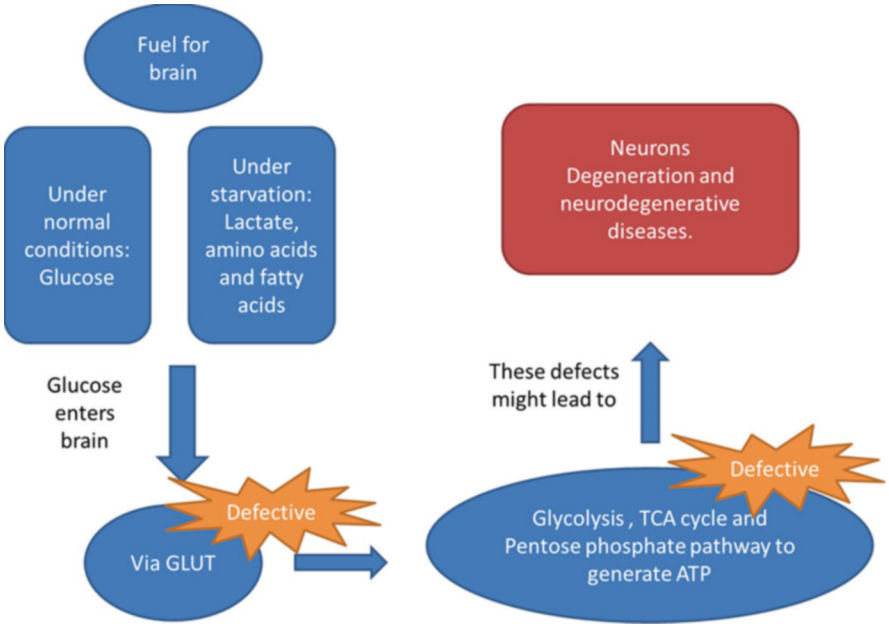

Fig. 5.1 Schematic representation of the importance of glucose metabolism in regulating neuronal health and brain pathologies

the carbon in the structure of glucose can be transferred to metabolites like pyruvate and glyceraldehyde-3-phosphate, which aid in the production of nucleic acids, fatty acids, and amino acids (Dienel 2019). Further, the regulation of oxidative stress (NADH/NAD+ and NADP+/NADPH) is also influenced by glucose metabolism (Dienel 2019; Yu et al. 2018). Furthermore, it has been demonstrated that glucose metabolites and enzymes involved in metabolism, such as glyceraldehyde-3-phosphate dehydrogenase, acetyl-CoA, and hexokinase, can directly affect cellular signaling and functional control (Sivanand et al. 2018). For instance, lactate functions as a messenger, influencing a number of molecular targets (such as the ATP-sensitive potassium channel (K^+ ATP), the acid-sensing ion channel, the NADH/NAD+ ratio, etc.). Additionally, the inflammatory cascade can be suppressed by the decreased ratio of NADH and NAD+ brought on by glucose metabolism in microglia (Shen et al. 2017). As a result, glucose metabolites not only contribute to the synthesis of macromolecules and ATP, but also regulate a variety of neuronal and glial cell processes. It has been shown that serum glucose levels can be up to five times higher than levels in the brain. The family of specialized glucose transporters (GLUTs) regulates the admission of glucose into the brain by facilitated diffusion (Hwang et al. 2018). The blood–brain barrier's vascular endothelial cells (GLUT1), neurons (GLUT3, 4, 6, 8), astrocytes (GLUT1, 2), and microglia (GLUT1, 3, 4, 5, 6, 8, 9, 10, 12, and 13) all play a role in the transfer of glucose to brain cells from the blood (Zhang et al. 2014), and for glucose metabolism in the brain, GLUT-mediated glucose regulation is crucial. The cortex and striatum are also somewhat involved in the maintenance of blood glucose homeostasis together with the hypothalamus and pituitary (Zhang et al. 2021). Additionally, the cerebral cortex, hippocampus, hypothalamus, thalamus, choroid plexus, and cerebellum all have high levels of insulin receptor expression (Dakic et al. 2023). As a result, the brain is crucial in controlling peripheral glucose metabolism. The downregulation of GLUT1 expression in vascular endothelial cells, in turn, can reduce brain glucose uptake due to systemic metabolic disorders brought on by high-fat diets. Vascular endothelial growth factor can be produced in order to counteract this reaction, preventing obesity-related neurodegeneration (Jais et al. 2016).

5.2 Disrupted Glucose Metabolism in NDDs

5.2.1 Insulin Resistance: A Risk Factor for Neurodegenerative Disorder

Every therapeutic trial based on the amyloid theory has failed or has produced extremely small, insignificant changes that have little practical implications. Neurodegenerative diseases that progress over time, like AD and PD, are intricate systems involving several physiological and pathological processes affecting various cell types and organs. Such syndromes are unlikely to have a mono-causal

explanation, and treating them successfully will not result from one. In order to identify more effective treatment approaches, it is necessary to revisit and examine the underlying pathology and physiology of these conditions (Hölscher 2020). Preclinical research has demonstrated that altered insulin signaling and a variety of downstream consequences are present in animal models of AD and PD, which contributes to the disease. The discovery in recent years that insulin signaling is also desensitized in the brains of AD and PD patients is a significant one. Similar to what is seen peripherally in diabetes, brain tissue from patients showed inactivation of the insulin and insulin-like growth factor 1 (IGF-1) receptor, as well as the insulin receptor substrates 1 and 2 (IRS1/2) and important second messenger kinases like Akt and mTOR. One report actually referred to AD as "type 3 diabetes" (González et al. 2022). Nevertheless, elevated insulin and glucose levels cause insulin desensitization in diabetes, and insulin desensitization in AD patients' brains has been seen in non-diabetic individuals as well. Given that insulin is necessary for the development and maintenance of neurons, it is likely that insulin desensitization would eventually increase the risk of harm to neurons. Because the brain does not produce new neurons (cortical neurogenesis is minimal), damage to neurons can build up over time and eventually manifest as neurodegeneration (de la Monte 2017).

The idea that enhancing insulin signaling may be advantageous and potentially alleviate the pathology was first supported by the finding that patients with AD and PD had impaired insulin signaling in their brains. A number of significant clinical investigations have been carried out by Suzanne Craft's research group and associates to explore this notion in mild cognitive impairment (MCI)/AD patients. The group used a technique wherein insulin is applied to non-diabetic individuals in order to investigate whether enhancing insulin signaling has any positive benefits in the brain. Insulin administered intravenously would not be safe because it reduces blood sugar levels. As a result, nasal application method was used. In this manner, peripheral insulin levels in the blood rise relatively slowly while insulin enters the brain by absorption via the nasal epithelium (Dhuria et al. 2010). Verbal memory recall was enhanced by insulin therapy, but peripheral blood glucose levels remained unchanged. The memory-impaired non-apolipoprotein E epsilon 4 (APOEε4) carriers showed greater improvements in memory than did the memory-impaired APOEε4 carriers and the control participants. It was interesting to note that after receiving insulin, APOEε4 carriers with memory impairment had worse recall. These encouraging findings show that intranasal insulin does, in fact, enhance memory. Additionally, the data showed that the effectiveness of insulin treatment is influenced by the APOEε4 allele. In a different trial including AD/MCI patients, insulin therapy enhanced verbal memory recall in memory-impaired non-APOEε4 carriers. Conversely, APOEε4 carriers with memory impairments displayed a decline in verbal memory. These findings supported the earlier pilot study and provided additional evidence that APOE influences insulin, which has an impact in a complex interaction. In contrast to the clinical trials testing drugs that lower amyloid levels in the brain, these clinical trials with occasionally even small patient numbers and brief exposure to insulin treatment consistently showed improvements, proving that this type of treatment does affect important mechanisms underlying the pathology

of AD. Despite the positive outcomes of the insulin research, insulin is not the best medication to be developed as a primary treatment for AD and PD. In the clinic, insulin is used to treat T2DM. Unfortunately, the long-term prognosis for insulin treatment in diabetes is poor because increased insulin levels exacerbate insulin desensitization to the point that insulin loses its effectiveness (Craft et al. 2017). Due to the detrimental attribute of insulin, researchers investigating new pharmacological treatments for diabetes have shifted their focus from insulin analogs to newer peptide hormones with comparable effects, specifically the incretin hormones (GLP-1 and GIP). Further, GLP-1 analogues can be safely administered to AD or PD patients who are not diabetic since they have no effect on blood glucose levels in normoglycemic individuals. The relatively modest negative effects include nausea and appetite loss. Clinical trials are currently ongoing, testing the drugs lixisenatide (clinical trial identifier NCT03439943), liraglutide (NCT02953665), or semaglutide (NCT03659682) in PD patients, underscoring the rising importance of this drug discovery field (de la Monte 2017).

Recent findings demonstrate that enhancing insulin signaling in AD or PD patients' brains has a definite disease-modifying impact. Patients with AD and PD not only have significant reduction in symptoms like attention, memory problems, or other cognitive impairments but improvements in motor coordination in PD patients that persist longer than the period of pharmacological treatment. An analysis of the biochemical changes in the brain using the exosome technique proved that insulin signaling in the brain had indeed been re-sensitized, providing proof of concept that the insulin hypothesis does affect disease progression and has the potential to be a disease-modifying treatment that can halt the progression. 18FDG-PET and fMRI brain scans demonstrated a lasting improvement in brain activity and energy utilization (Hölscher 2020). However, larger clinical trials and testing of newer, more powerful medications are required to create effective therapies for PD and AD.

5.2.2 Alzheimer's Disease (AD)

The respiratory quotient of the brain, which is almost 1, shows that the primary substrate for the brain's oxidative metabolism is carbohydrates. Glucose transit and intracellular oxidative catabolism are the two primary functions of cerebral glucose metabolism. Reduced brain glucose metabolism is seen in AD patients. It has been shown that higher proteostasis and improved glucose absorption and consumption have neuroprotective effects (Duran-Aniotz and Hetz 2016). Further, dysregulated glycolytic enzymes reduce glucose utilization and, alternatively, by increasing the protein glycosylation process, induce age-related neurodegeneration (Hipkiss 2019; Yan et al. 2020). Additionally, the expression of the crucial glucose transporters, GLUTs, is reduced in the aging brain, which results in a reduction in cerebral glucose uptake.

Early phases of neurological illnesses, stroke, and more subtly in AD and PD all involve disturbances of glucose metabolism. In the brain of AD patients and AD

mouse models, glucose utilization is reduced, particularly in the brain regions most affected by the disease. According to different researches, disrupted cerebral insulin action or poor glucose metabolism may be to blame for the loss of neurons in AD (Camandola and Mattson 2017). It has been shown that in AD and type 2 diabetes mellitus (T2DM), a decrease in glucose absorption slows the glucose catabolic process and lowers levels of the antioxidant pyruvate (Zilberter and Zilberter 2017). Additionally, it has been shown that the buildup of Aβ plaques impairs mitochondrial redox potential, which in turn causes oxidative stress and protein misfolding-related stress (ER stress). Alternatively, ROS buildup enhances aberrant tau phosphorylation via glycogen synthase kinase 3 (GSK3) (Llanos-González et al. 2019) and boosts the apoptotic signal-regulating kinase 1 (ASK1)–p38 MAPK axis in AD brain aging (Hasegawa et al. 2018). In T2DM, unutilized glucose builds up because the insulin receptor is insensitive, which leads to hyperglycemia and a number of cytotoxic consequences. T2DM frequently results in hyperglycemic protein misfolding (Mukherjee et al. 2015), and misfolded protein deposits made up of Aβ and tau result in defective proteostasis in AD (Hetz and Saxena 2017). In postmortem AD brains, the unfolded/misfolded protein response (UPR) was active (González et al. 2022). Additionally, the deficiency in de novo protein synthesis and memory loss in AD transgenic mice can be reversed by suppressing the ER stress-related proteins PERK and eIF2a (Yang et al. 2016).

More than 99.6% of earlier clinical trials that focused on the Aβ cascade failed to make it through the clinical approval phases. It is doubtful that future treatments for AD will include existing methods that target tau and Aβ. There is an urgent need for additional therapies that are both accessible and effective. For the purpose of creating therapeutic strategies, researchers must re-examine various important pathways involved in AD. However, when taking into account the results of metabolic analysis, we discover that changes in glucose metabolism could be a plausible target for development of new medication candidates for the treatment of AD.

5.2.3 Parkinson's Disease (PD)

At every stage of the disease course, patients with PD have impairments in regional and systemic glucose metabolism. These impairments are linked to the occurrence, progression, and unique symptoms of PD that has impact on every physiological process involved in glucose metabolism, including glucose uptake, glycolysis, the tricarboxylic acid cycle, oxidative phosphorylation, and the pentose phosphate shunt pathway. Several mechanisms, including insulin resistance, oxidative stress, aberrant glycation, blood–brain barrier dysfunction, and hyperglycemia-induced damage, may be responsible for these abnormalities. These mechanisms may then result in excessive methylglyoxal and reactive oxygen species production, neuroinflammation, abnormal protein aggregate formation, mitochondrial dysfunction, and decreased dopamine, which in turn may lead to insufficient energy supply,

neurotransmitter dysregulation, α-synuclein aggregation and phosphorylation, and loss of dopaminergic neurons (Dai et al. 2023).

About 50–80% of PD patients consistently have impaired glucose tolerance (Sandyk 1993). It was reported that 10.02% (95% confidential interval (CI) 7.88–12.16) of PD patients had diabetes (Komici et al. 2021). Even in the early stages of PD, brain neurons show poor glucose metabolism (Dunn et al. 2014). Patients with early-stage PD have glucose hypermetabolism in the bilateral pallidum, SN, unilateral caudate, and shell nuclei and hypometabolism in the cortex. Regardless of levodopa administration or medication discontinuance, patients with advanced PD showed reduced glucose absorption in the parietal, frontal, and temporal cortex as well as in the caudate nucleus. Individuals with less advanced PD were shown to have glucose hypermetabolism in prefrontal areas; patients with more advanced PD did not exhibit this finding, suggesting that the impairment of frontal glucose metabolism worsens as PD progresses (Dai et al. 2023; Szturm et al. 2021). Distinct subtypes of PD patients exhibit impairments in distinct brain areas related to glucose metabolism. When compared to PD patients with dominant tremor, the ventral striatum of akinetic-rigid individuals showed worse dopamine uptake and worse glucose hypometabolism. Treatment-related impairment in brain glucose metabolism was observed in PD patients. An hour after levodopa is administered, there is a reduction in overall brain glucose consumption; however, this reduction fails to persist after levodopa has been discontinued. Further, following levodopa administration, there is a considerable reduction in glucose uptake in the thalamus and ventral/orbital frontal cortex. Deep brain stimulation on bilateral subthalamus nuclei (STN) may lead to a decrease in glucose metabolism in the orbitofrontal cortex and parahippocampal gyrus and an increase in the pallidum, superior brainstem, dorsolateral prefrontal cortex, and posterior parieto-occipital cortex. Abnormal glucose metabolism may potentially be a sign of cognitive impairment in people with PD. When compared to patients without cognitive loss, people with moderate cognitive impairment have more severe glucose hypometabolism in the temporoparietal region during the early stages of PD. Furthermore, patients with PD share a pattern of glucose hypometabolism similar to that of patients with AD, which manifests in the posterior cingulate cortex, lateral parietal, lateral temporal, and lateral frontal binding areas, but patients with PD show greater involvement of the visual cortex, and non-demented PD patients show widespread cortical glucose hypometabolism without selective temporoparietal defects. It is noteworthy that there are similarities in the patterns of glucose hypometabolism in the bilateral inferior frontal, medial frontal, and right parietal lobes between individuals with PD and Lewy body dementia (LBD). But, PD and LBD can be differentiated from each other, due to specific features of the impaired glucose metabolism in PD patients, such as hypermetabolism in the anterior cingulate and lateral temporal cortex (Dai et al. 2023).

Further investigations are necessary to understand if the regional glucose absorption deficit seen in PD patients' brains represents changes in brain activity connected to the disease or is simply a pathophysiological feature of the disease.

5.2.4 Huntington's Disease (HD)

HD is largely thought to be an uncommon neurological ailment, but like other neuro-syndromes AD or PD, it has been connected to changes in glucose metabolism and diabetes (Montojo et al. 2017). Even before the genetic era, a link between HD and carbohydrate intolerance was suggested, albeit with inconsistent findings. Once the CAG expansion in exon 1 of the HTT gene was identified as the disease's etiology, the diagnosis improved, and models for conducting precise investigations on glucose metabolism were developed.

Patients with HD experience significant weight loss even with continued calorie consumption. This was the evidence that changes in energy metabolism contributed to the etiology of HD. Using *Drosophila* model of HD, altered lipid metabolism has been shown to be associated with HD (Aditi et al. 2016), and further this was associated with changes in mitochondrial membrane potential and calcium derangement (Singh and Agrawal 2021). Several evidences suggest that the impaired brain glucose absorption, specifically by neurons, is a contributing factor to the energy metabolic impairment observed in HD patients. It has been demonstrated that embryonic cortical neurons in mice models significantly absorb less glucose than WT neurons. There has been a significant decrease in the amount of GLUT1 and GLUT3 in the membranes of post-mortem samples of the caudate and cortex brain regions in patients with advanced HD stages when compared to non-HD controls. In grade 3 HD caudate, for example, GLUT1 and GLUT3 concentrations were, respectively, three and four times lower than in non-HD controls. However, at earlier stages (grade 1), there was no significant difference in GLUT1 and GLUT3 membrane concentration compared with non-diseased controls. Before the onset of disease symptoms, HD mutation carriers have been demonstrated to undergo a number of changes. PET scans and MRIs of adults have shown reduced absorption of glucose or 18-Fluoro-2-deoxy-d-glucose and increasing white matter atrophy, particularly in the caudate nuclei. Pre-manifest HD patients also displayed thalamic hypermetabolism as a compensatory response to a steady decline in the caudate's intake of glucose, as well as a metabolic drop in the striatum, frontal, and temporal lobes, albeit to varying degrees. The decline in glucose metabolism is especially marked and progresses in the caudate nucleus in all HD participants. This reduction in glucose metabolism probably affects symptoms when it falls below a threshold (Montojo et al. 2017).

5.2.5 Amyotrophic Lateral Sclerosis (ALS)

In both human and animal models of ALS, there is a decrease in glucose consumption along with functional alterations in the brain regions linked with it, such as the motor, frontal, and occipital cortex, as well as spinal cords (Tefera et al. 2021). It is interesting to note that at the mid-symptomatic stage of the disease, glucose uptake

in the peripheral tissues involved in glucose disposal, specifically skeletal muscles, adipose tissue, and liver, was also seen to be elevated via a mechanism unrelated to insulin levels in SOD1^{G93A} mice (McDonald et al. 2021). It is conceivable that the increase in glucose uptake in an effort to preserve glucose availability is caused by modifications in metabolic balance. Studies on ALS skeletal muscles during the early pre-symptomatic stage have shown a selective loss of glycolytic fibers and a metabolic shift towards an oxidative metabolism. Pure oxidative MHC I isoform was preserved at the disease onset stage of SOD1^{G93A} mice, and their glycolytic skeletal muscle demonstrated a significant decrease in the activity of phosphofructokinase, a crucial enzyme involved in glucose metabolism, in tandem with an increase in mitochondrial mass and expression of oxidative/intermediate myosin heavy chain (MHC) IIa isoform (Palamiuc et al. 2015; Scaricamazza et al. 2020). In the face of impaired glycolytic activity, this change is probably an adaptive response to maintain the functional needs by enlisting the remaining motor units. Nevertheless, in the glycolytic muscles of SOD1^{G93A} animals, the rate of ATP synthesis, mitochondrial activity, and other complex activities were markedly impaired, indicating that glucose metabolism is downregulated in the early stages of the disease. Interestingly, given that mitochondria play a crucial role in energy homeostasis, these findings of defects in their metabolism in skeletal muscle may be responsible for early pathological events in ALS. Further, these findings were only observed in the spinal cord at the symptomatic stage of the disease (Scaricamazza et al. 2020). Alternatively, higher dependency and capability of lipid mobilization revealed in the early phase of sickness in SOD1^{G93A} mice indicate a shift from glucose metabolism to lipid metabolism to compensate for mitochondrial malfunction and defective glucose utilization. As the disease worsens, the substantial deficits in glucose oxidation aggravate this metabolic shift even further (Palamiuc et al. 2015; Scaricamazza et al. 2020). Moreover, increased lipogenesis and lipophagy were demonstrated by C9orf72-deficient mice embryonic fibroblasts and induced pluripotent stem cell-derived motor neurons from C9orf72-linked ALS patients, emphasizing the dysregulated lipid metabolism in ALS (Liu et al. 2018).

5.2.6 Prion Disease

Pathogenic prions PrPSc are the cause of transmissible sporadic encephalopathies (TSEs), also referred to as prion diseases, as they cause degeneration of brain neurons. Even while normal cellular prion protein (PrPC) function(s) is disrupted by PrPSc to cause neurotoxicity, little is known about the mechanisms behind prion disorders. As of now, there is no medication to combat TSEs. Arnould et al. (2021) demonstrated that a contributing factor to neurodegeneration in prion diseases is the dysregulation of PrPC regulatory function towards glucose metabolism. PrPSc-induced overactivation of pyruvate dehydrogenase kinase 4 (PDK4) and downstream reduction in mitochondrial pyruvate dehydrogenase (PDH) activity promote a metabolic shift from pro-oxidant fatty acid β-oxidation to glucose oxidative

degradation, which contributes to prion pathogenesis in the brains of infected mice. By restoring normal glucose metabolism, pharmacological suppression of PDK4 prolongs the life span of mice infected with prion infections.

5.3 Impaired Central Nervous System Glucose Homeostasis in NDDs

5.3.1 Alzheimer's Disease (AD)

A number of genetic risk factors have been identified, with apolipoprotein E (APOE) ε4 allele demonstrating the highest risk, despite the fact that many cases occur exceptionally. The stated odds ratio for AD for heterozygous APOE4 carriers is 3, while the odds ratio for homozygous APOE4 carriers is 12. Additionally, sex-dependent variations in APOE4 effects on metabolism have been discovered in recent research. Male APOE4 carriers showed no discernible difference in cerebral glucose metabolism compared to non-carriers, but female carriers had greater cerebral glucose metabolism (Jiang et al. 2020). The literature suggests that this may be caused by an interaction between APOE4, estrogen receptors, and estradiol. However, clinical investigations have shown conflicting findings, thus necessitating additional research in order to provide clarity (Belloy et al. 2019). In mice models of AD, it has been discovered that microglia and astrocytes convert to glycolysis, generating more lactate and displaying reduced TCA cycle activity (Aldana 2019). This appears to be at odds with results from fluorodeoxyglucose positron emission tomography (FDG-PET) investigations, which indicate that AD and PD patients' brains show signs of glucose hypometabolism. Relative hypoglycemia, however, could be a sign of systemic metabolic abnormalities, which are increasingly linked to an increased risk of AD. Further, because FDG and glucose compete with one another for the binding of hexokinase, blood glucose levels can also impact FDG-PET readings (Sarikaya et al. 2019). Due to comparatively lower glucose levels in hypoglycemia, FDG will bind hexokinase more easily and with less competition. Similarly, for increased relative competition, FDG will bind its target less readily in hyperglycemia. This should be taken into account when designing new studies and interpreting data since it confounds FDG-PET findings in neurodegenerative diseases (Cleland et al. 2021).

According to one hypothesis, AD brain inflammation-cells use up enough glucose to cover for neuronal metabolic deficiencies. In a rodent model of AD, for instance, metabolic tracer investigations have demonstrated that AD neurons display reduced expression of important mitochondrial enzymes and less tricarboxylic acid cycle (TCA cycle) activity (Nilsen et al. 2014), which results in poorly sustained ionic gradients and neuronal dysfunction. Furthermore, the inability to maintain neurotransmitter homeostasis results from the loss of astrocytic TCA cycle activity, which cuts off the neuronal supply of neurotransmitters. Further,

demonstrating the necessity to comprehend this series of events in a temporal and spatial framework is the connection between neurons and astrocytes, both of which show metabolic changes in AD. This interaction results in a cascade of events that culminates in neuronal death and cognitive decline (Nilsen et al. 2014) .

5.3.2 Parkinson's Disease (PD)

Similar to AD, studies using PET and magnetic resonance imaging have discovered glucose hypometabolism in PD patients (Edison et al. 2013). In familial types of PD, mutations in genes encoding α-synuclein, Parkin, PTEN-induced kinase 1 (PINK1), leucine-rich repeat kinase 2 (LRRK2), and DJ-1 have been found together with decreased levels of PPP enzymes in PD patients (Dunn et al. 2014). The pentose phosphate pathway (PPP, a metabolic pathway parallel to glycolysis) converts glucose-6-phosphate into pentoses and generates ribose-5-phosphate and NADPH, thereby governing anabolic biosynthesis and redox homeostasis. While PPP enzyme levels are not harmful in and of themselves, they hinder the cells' capacity to produce pentoses, which are essential for ATP synthesis and DNA repair. Gene mutations associated with familial PD have been linked to mitochondrial malfunction, which prevents OXPHOS and forces cells to rely on glycolysis for ATP synthesis (Dunn et al. 2014). Neurons primarily depend on mitochondrial respiration to supply their energy needs, whereas astrocytes are less dependent on OXPHOS. As a result, decreased oxidative metabolism in neurons will impede neural processes and advance PD. Microglial activation has been proposed as a result of amyloid accumulation, which is also observed in PD (Edison et al. 2013). Numerous investigations have demonstrated that PD patients have higher levels of microglial activation, which may aggravate neurodegeneration in PD brains (Aldana 2019). The increase of translocator protein—a marker linked to microglial activation in patients with Parkinson's disease dementia (PDD) and PD—was measured using [(11)C](R)PK11195-PET and found to be significantly elevated in PD patients and even more pronounced in PDD cases (Edison et al. 2013). However, Edison et al. (2013) also discovered that microglial activation was an early event in the neuropathogenesis of PD and was unrelated to amyloid pathology. Additionally, they discovered that PD patients had concurrent decreases in glucose metabolism, which lends credence to the theory that disease pathogenesis may be driven by metabolic permutation (Edison et al. 2013). These activated microglia produce reactive species that harm neurons and are thought to have a major role in the pathophysiology of PD (Aldana 2019). Additionally, it has been proposed that increased extracellular glutamate emission from activated microglia may contribute to neuronal injury because it impairs mitochondrial respiration in neurons and prevents them from producing enough ATP. This series of events culminates in cell death, underscoring the significance of metabolic cross talk between brain cells in the pathogenesis of PD.

5.4 Brain–Body Control of Glucose Homeostasis

In healthy humans, homeostatic processes control food intake and energy expenditure to preserve energy balance. There is ample evidence to suggest that the brain, and specifically the hypothalamus, is principally in charge of controlling energy balance (Roh et al. 2016). By detecting variations in the plasma levels of important metabolic hormones and nutrients, the brain keeps track of changes in the body's energy state. In response to altering metabolic conditions, the brain's specialized neural networks regulate adaptive adjustments in food intake and energy expenditure (MacDonald et al. 2021).

The ensuing identification of glucose-sensing neurons in the hypothalamus (Anand et al. 1964) and the proof of their functions in preserving normal glucose levels have lend credence to the idea of central regulation of glucose metabolism during the last several decades. To control glucose homeostasis, a specific subset of neurons in the brain detects nutrients (glucose and fatty acids) and hormones (insulin and leptin). The brainstem and hypothalamus are the main locations where these metabolic signals converge. Neurons in the brain areas that regulate glucose metabolism have excitability that varies in response to changes in the amount of glucose present in the extracellular fluid. The hypothalamic nuclei and brainstem, which are also crucial regions in the regulation of energy balance, include these glucose-sensing neurons. Two subgroups of glucose-sensing neurons can be distinguished. A rise in extracellular glucose levels excites neurons that are glucose-excited. Conversely, a decrease in the levels of extracellular glucose activates glucose-inhibited neurons. While glucose-inhibited neurons are dispersed across the LH, ARC, and PVN, glucose-excited neurons are primarily found in the VMH, ARC, and PVN. The dorsal motor nucleus of the vagus, area postrema, and the NTS are all included in the brainstem's dorsal vagal complex, which is the location to both types of neurons (Chambers et al. 2023; Yoon and Diano 2021).

5.4.1 Peripheral Signals That Influence How the Brain Controls Glucose Metabolism

5.4.1.1 Insulin

In the last 10 years, it has been established that insulin acts on the brain to maintain glucose homeostasis. Insulin modulates hepatic glucose metabolism via its action on the brain. By injecting insulin receptor antisense oligonucleotides into the intracerebroventricle (ICV), it has been demonstrated that during hyperinsulinemic clamp trials in rats, insulin-mediated regulation of hepatic glucose production (HGP) was compromised by central insulin action inhibition. Additionally, insulin infusion into the cerebroventricle inhibited HGP independent of insulin levels in circulation. Furthermore, insulin's capacity to suppress synthesis of glucose was

reduced by central delivery of insulin antibodies or inhibitors of insulin's downstream signaling. Insulin activities in hypothalamic neurons are mediated by the ATP-sensitive potassium (K^+ATP) channel. Insulin delivered centrally and peripherally both decrease glucose production when neuronal K^+ATP channels are activated by intracellular delivery of a K^+ATP channel activator (diazoxide). On the other hand, glucose production is not reduced when insulin is infused with a K^+ATP blocker (sulfonylurea). Furthermore, mice deficient in the K^+ATP channel's sulfonylurea receptor component SUR1 exhibit a reduced reaction to central insulin activity. Since hepatic vagotomy prevents central insulin activities, it suggests that vagal efferent fibers make up the brain–liver axis of insulin actions. It is interesting to note that ICV insulin infusion raises hepatic IL-6 production, which in turn activates hepatic STAT3 signaling. In the liver, activated STAT3 suppresses production of gluconeogenic genes and FoxO1 activity. All neuronal K^+ATP channel–vagus nerve–hepatic IL6/STAT3 signaling mediates central insulin effects; however, the specific mechanisms are still unknown (Roh et al. 2016).

5.4.1.2 Leptin

An essential function of leptin is to regulate the metabolism of glucose; not only does obesity result from a deficiency of leptin (ob/ob mice) or its functioning receptor (db/db mice), but it also causes metabolic disruption, which includes insulin resistance and diabetes. In ob/ob mice, leptin therapy enhances glucose homeostasis. Interestingly, acute leptin administration in ob/ob mice via systemic and central pathways improves glucose metabolism without affecting dietary consumption or obesity levels. Leptin-treated ob/ob mice consistently show a significant drop in insulin and blood glucose levels. In lipodystrophy mice, leptin therapy reduces hyperglycemia and insulin resistance without affecting food consumption. Therefore, leptin controls glucose homeostasis without affecting anorexia. One important area where leptin regulates glucose metabolism is the hypothalamus. In the model of lipodystrophy mice, insulin-converting enzyme (ICV) injection of leptin corrects insulin resistance and restores defective insulin signaling in the liver. On the other hand, identical dose of leptin injected peripherally produced no comparable results. Acute ICV injection of leptin inhibits glycogenolysis and decreases hepatic insulin resistance brought on by high-fat diets. Leptin receptor-null mice that have had their leptin signaling restored by viral gene therapy exhibit a significant improvement in hyperinsulinemia and a return to normal blood glucose levels, along with a slight drop in body weight and food consumption. These findings show that the preservation of glucose homeostasis depends on leptin signaling in the ARC. The hypothalamic STAT3 and PI3K signaling pathways underlie the regulation of glucose metabolism by leptin. Similar to db/db mice, s/s mice with a mutant leptin receptor show significant hepatic insulin resistance due to their inability to activate STAT3. The significance of leptin-induced STAT3 signaling is confirmed by the elimination of leptin's HGP-suppressive action when leptin-induced STAT3 activation in the hypothalamus is blocked. On the other hand, leptin sensitivity and

glucose metabolism are improved by hypothalamic ablation of suppressor of cytokine signaling 3, a negative regulator of STAT3 signaling. In contrast, insulin sensitivity is enhanced by restoration of leptin receptors in the ARC of leptin-receptor-deficient fa^k/fa^k rats; however, this effect is mitigated by ICV infusion of PI3K inhibitor. Rats with constitutively active Aktin fa^k/fa^k consistently exhibit ARC expression, which is consistent with the effect of restored hypothalamic leptin signaling (Roh et al. 2016).

5.4.1.3 Glucose

A key component of glucose regulation is hypothalamic glucose sensing. Pancreatic β-cells and hypothalamus neurons both use similar glucose-sensing systems. In order for glucose to be signaled in glucose-excited neurons, glucose must first be absorbed by the type 2 glucose transporter. This is followed by an increase in the cellular ATP/ADP ratio, intramitochondrial glucose oxidation, and glucose phosphorylation by glucokinase. This triggers the release of neurotransmitters and increases neuronal activity by closing ATP-sensitive K^+ATP channels, depolarizing the membrane potential, and allowing Ca^{2+} to enter through voltage-dependent calcium channels. It has been shown that the hypothalamus type 2 glucose transporter, glucokinase, and K^+ATP channels are involved in the detection of hypoglycemia and the subsequent production of counter-regulatory hormones. It is unclear how glucose inhibits neuronal activity in neurons that are glucose-inhibited. A plausible explanation is that glucose elevates the ATP/ADP ratio, hence inducing hyperpolarizing currents and stimulating the Na^+/K^+-ATPase pump. Alternatively, the activation of ATP-dependent Cl^- channels by glucose may cause the plasma membrane to become hyperpolarized.

When 2-deoxy-D-glucose is injected into the ventricle muscle hypothalamus (VMH), it raises the levels of catecholamines and glucagon in the plasma. On the other hand, hypoglycemia-related counter-regulatory hormonal reactions are suppressed by intra-VMH glucose infusion. Additionally, during hypoglycemia, the brainstem is implicated in the release of counter-regulatory hormones and glucoprivic feeding. Feeding and glucose responses, as observed in hypoglycemia, are induced by injecting 5-thio-D-glucose, another glucose anti-metabolite, into the NTS and the basolateral medulla. These regions contain A1/C1 catecholaminergic neurons that extend to the hypothalamic PVN and ARC. Similarly, immunotoxins that destroy catecholaminergic neurons in the hindbrain prevent feeding and blood glucose responses that are triggered by 2-deoxy-D-glucose (Roh et al. 2016).

5.4.1.4 Fatty Acid

Long-chain fatty acid (LCFA) controls peripheral glucose metabolism and notifies the brain when nutrients are available (Obici et al. 2002). Hepatic glucose production (HGP) is suppressed by ICV injection of oleic acid during baseline insulin

clamping. The inhibitory effect of oleic acid on glucose production is reduced by ICV delivery of a K^+ATP channel blocker, suggesting that brain K^+ATP channels are involved in this process. Endogenous glucose synthesis is suppressed when hypothalamic neurons have elevated LCFA-CoA levels. HGP is elevated by pharmacological suppression of hypothalamic esterification of fatty acids or surgical excision of the vagus nerve's hepatic branch. Thus, by a process involving the esterification of LCFAs to LCFA-CoAs, open K^+ATP channels, and vagal outflow to the liver, hypothalamic lipid sensing controls glucose homeostasis (Roh et al. 2016).

5.5 Regulatory Cascade of Neuronal Loss and Glucose Metabolism

Although there have been substantial advancements in our understanding of the triggers for many neurodegenerative disorders, no novel disease-modifying therapy is shown to be significantly beneficial for people suffering from these debilitating disorders to date. Given that the majority of neurodegenerative disorders manifest gradually, have a late onset, and appear to display prodromal stages that are long and generally asymptomatic, it is plausible that drugs that optimally target the triggers of these disorders may not yield significant benefits when started in a symptomatic patient. When administered prophylactically or during the prodromal phase, such therapies might be effective, but in the case of a symptomatic patient, there might be too much damage to the neural networks for them to be restored to functionality by lowering or even removing the primary stressor. It is obvious that avoiding neuronal death and dysfunction will have a significant positive therapeutic impact because functional neuronal demise and overt neuronal death are most likely the primary elements that underlie the functional impairment. Unfortunately, all neurodegenerative illnesses have neuronal death pathways that despite several efforts are not fully understood and thereby impede disease treatment. Most importantly, our fundamental research efforts should be redirected to pinpoint the specific steps in each neurodegenerative disease's pathological cascade that ultimately results in neuronal death and, if at all feasible, establish the order in which these events occur within extremely complicated cascade. The next step is to decide which of these can be the focus of our investigation. Lastly, innovative treatments should be created that obstruct these processes and show that they are clinically beneficial when used either by itself or in conjunction with treatments that aim to eliminate the causes of these devastating illnesses.

The regulation of cell death and glucose metabolism are evolutionarily related and this link is tightly regulated in a similar way in variety of cell types, supporting the idea that co-regulated metabolic and apoptotic pathways play a universal role. These cell types can use comparable processes to adapt to substrate deprivation and increase survival. It has been shown that hexokinase II (HKII), a hypoxia-regulated HK isoform in the brain, regulates neuronal survival based on the metabolic status.

The extent to which HKII suppresses or prevents apoptosis in various cell types is dependent on its binding status to mitochondria, as well as the availability of glucose. Moreover, HKII's ability to phosphorylate glucose plays a role in determining the cell's metabolic status. Further, HKII's antiapoptotic effect is triggered by a molecular interaction with PEA15/PED (phosphoprotein abundant in diabetes and astrocytes). In the event of oxidative stress followed by hypoxia, HKII activation prevents neuronal cell death. But in the absence of glucose, HKII causes a rise in the death of neuronal cells, acting as a molecular switch that controls neuronal survival based on the state of metabolism. Crucially, this impact is mediated via HKII's ability to phosphorylate glucose and its connection with PEA15. It has also been shown that, in some circumstances, GAPDH and other glycolytic cascade enzymes can prevent cell death. But it has also been proposed that GAPDH mediates the process of neuronal apoptosis following DNA damage. Hence, pro- and antiapoptotic actions of glycolytic enzymes can be seen in the context-dependent regulation of neuronal cell death. It does not seem that glucose-metabolizing enzymes control apoptosis in a one-way fashion. For instance, in liver and pancreatic β-cells, the Bcl-2 family member BAD interacts with GK (glucokinase also referred to as hexokinase IV) to regulate apoptosis in response to variations in glucose levels. Whether GK regulates neuronal survival in some glucose-sensing neuronal populations based on their metabolic state is yet unknown. Additionally, it has been proposed that BclXL, an antiapoptotic member of the Bcl-2 family, increases the metabolic efficiency of neurons by reducing a proton leak across the inner mitochondrial membrane and within the F_1F_O ATPase.

Autophagy and mechanisms leading to cell death are tightly associated with disrupted metabolism. In fact, autophagy is regulated by GAPDH and several participants in the apoptotic cascades. It is yet unknown if these processes are governed by co-regulated apoptotic/autophagic pathways such as those mediated by the Bcl-2 family or (dysfunctional) glucose sensing through glycolytic enzymes. Therefore, it is believed that a wide range of disorders has pathophysiological roots in disrupted signaling via these pathways.

5.6 Conclusion

There is a tight relationship between brain physiology, function, and glucose metabolism. The primary energy substrate in circulation for the adult brain is glucose. Due to the high energy requirements of brain cells, glucose undergoes active oxidation to create ATP, where it works in concert with mitochondria in metabolic pathways. As is frequently seen in neurodegenerative diseases, abnormal glucose metabolism invariably impairs neurons' ability to function normally. The intricate regulation of biochemical, cellular, and systemic pathways has been reported before omics technology era, and now recently after omics, many aspects of this regulation are still debatable or unclear. The study of cellular, subcellular, and even biochemical mechanisms in the cell or in vivo will be possible with previously unheard-of

temporal and spatial precision due to the development of innovative and sophisticated biochemical or genetic tools, screening techniques, imaging technologies, and systems analyses. Apart from examining distinct biochemical or cellular pathways and their regulation of intracellular signaling cascades (like programmed cell death), peripheral homeostasis, or brain activity, forthcoming challenges encompass piecing together the fragmented information to create a comprehensive image of the collaboration among various systems and cell types. An in-depth understanding of these mechanisms will provide insight into the pathophysiology of a variety of distinct brain diseases which in turn is likely to facilitate the development of new disease management and treatment approaches.

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Chapter 6
Lipid Metabolism: Key Determinant in Neurodegenerative Diseases

Mansi Yadav, Jassika Gupta, and Namita Agrawal

Abstract One of the major and necessary events in the normal development of the central nervous system is the proper formation of myelin sheath which is influenced by dietary lipids. Lipids play a pivotal role in normal and physiological function of the brain. There are eight different classes of lipids that form the central nervous system. To understand the link between lipids and neurodegenerative diseases, the role of these different classes of lipids at different stages of the disease has been a focus of researchers and clinicians. A newly emerged discipline that studies pathways and network of cellular lipids by mass spectroscopy is lipidomics. Currently, there is no cure for the CNS disorders and it affects the quality of the patient's life. With the advent of lipidomics, a better understanding about the cellular lipids might pave path towards diagnosis and treatment of neurodegeneration. Neurodegenerative diseases involve dysregulated lipid metabolism and oxidative stress; therefore, targeting lipid metabolism by drugs can provide a new perspective for treatment of the disease and, thereby, improvement of the patient's quality of life.

Keywords Neurodegenerative diseases · Lipid metabolism · Carbohydrate metabolism · Mitochondrial metabolism

6.1 Introduction

Lipids are pivotal organic compounds playing a role in vital functions of the body such as maintaining the structural integrity of living cells as they are one of the membrane components, signalling molecules and help in channelling energy, thereby ensuring the proper functioning. These hydrophobic, nonpolar macromolecules are divided into two broad categories: simple and complex lipids, where triglycerides and steryl esters fall into the former group, whereas phospholipids and glycolipids in the latter. Mammalian cells comprise glycerolipids, sphingolipids,

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triacylglycerol (TAG), phospholipids and sterols constituting the lipid pool, and each of these are assigned different roles based on their structure (Harayama and Riezman 2018). The building blocks of lipids are fatty acids that include carboxylic acid and hydrocarbon acyl chain in the structure. Fatty acids (FAs) contribute to the diversity of lipids with the variation in the length of the hydrocarbon chain and degree of saturation which is defined as the presence of double bonds in the hydrocarbon acyl chain. FAs are normally synthesised using acetyl-CoA, a process that requires ATP, biotin, Mg^{++} and Mn^{++}. Intermediate fatty acid biosynthesis is inhibited by glucagon and epinephrine and stimulated by insulin. The intermediates in fatty acid biosynthesis are attached to acyl carrier protein (ACP).

Lipid metabolism involves anabolism and catabolism pathways of the lipids leading to the synthesis of different types of functional lipids required to sustain metabolic homeostasis and degradation to fulfil the energy demands of tissues. In mammals, the liver and pancreas are the two main organs that are associated with lipid homeostasis and the liver serves as the leading reservoir of the lipids (Natesan and Kim 2021)**.** Pivotal organelles with respect to lipid synthesis are the endoplasmic reticulum (ER), Golgi apparatus and mitochondria, owing to their bilayer and presence of the compartments which offers the desirable area and space required for accommodating and assembling the lipid machinery. Endoplasmic reticulum is responsible for synthesising the majority of the lipid pool and maintains close contact with other organelles of the cells for transport purposes. These close contact sites are generally where lipids are exchanged between the organelles with the help of lipid transfer proteins. The lipids can be synthesised at any leaflet of the bilayer; in particular, the macromolecules which are synthesised at the leaflet facing the lumen of the organelle are not accessible to lipid transfer protein; therefore, they have to be moved from one leaflet to the other facing the cytosol. This inter-leaflet movement requires transporters like scramblases, flippases and floppases which help in moving the lipid from one leaflet to another with or without ATP consumption (Chiapparino et al. 2016). Lipid metabolism starts in the intestine; the ingested triacylglycerol is broken down with the help of pancreatic lipase and bile salts into free fatty acids (fFAs) which enable them to cross the membrane. These fFAs are reconstituted into TAGs and are packed in a vesicle along with the cholesterol called chylomicrons. The chylomicrons transport the fat and cholesterol in the circulatory system from where they are absorbed by the liver and adipose tissue and can be stored in the form of lipid droplets. On the other hand, lipolysis occurs via the breakdown of these TAGs into fatty acids and glycerol in the cytoplasm. The glycerol then enters into the glycolysis cycle yielding ATP and pyruvate as end products. The fatty acid molecules generated from TAG enter into the beta-oxidation pathway where they are first converted into fatty acyl-CoA and a molecule of carnitine is attached to transport into the mitochondria. The acyl-CoA is converted into acetyl-CoA which enters into the Krebs cycle yielding energy (Cockcroft 2021). Therefore, triglycerides are a fundamental source for fulfilling energy demands as one fat molecule has many carbons resulting in the production of a significantly higher number of ATP molecules as compared to carbohydrates or proteins.

Neurodegenerative disorders (NDDs) are a group of ailments caused due to the loss of a particular subset of neurons in the brain. The underlying cause is faulty protein synthesis which leads to consecutive malfunctions in the brain and a targeted set of neuronal death. NDDs comprise Alzheimer's disease (AD), Parkinson's disease (PD), Lewy body disease, amyotrophic lateral sclerosis, Huntington's disease (HD) and many more. Out of all these, the prevalence of AD and PD is significantly higher worldwide than the rest of neurodegenerative diseases. Nearly a million Americans are living with Parkinson's and the count goes around six times higher for Alzheimer's, thereby making them the most common neuronal diseases (Lamptey et al. 2022). The primary manifestations of these diseases are cognitive decline, dementia, motor dysfunctions, psychological abnormalities, mitochondrial dysfunction, inflammation, etc., whereas the secondary manifestations are altered lipid dynamics and peripheral comorbidities (Cleland et al. 2021). Despite the breakthrough research findings in the field of NDDs, the struggle to find the root cause to drive the disease to their terminal stages is not clear yet. The research of many decades has positively shifted the perspective of considering these disorders not only as neuron-mediated death but a complex of many associated ailments, and one such strong correlation is between metabolic changes/dysfunction along with altered lipid and neurodegenerative diseases.

Elevated or reduced levels of lipids and accumulation of unwanted lipids are linked to innumerable disorders (Xiao et al. 2021). The brain requires a constant supply of metabolites to feed the ATP-generating pathways to avoid any malfunction. To meet this soaring energy demand, in addition to glycolysis, oxidative pathways of ATP production are employed in astrocytes using fatty acids as substrates (Ebert et al. 2003). There exists enormous literature linking the progression of NDDs with increased peroxidation of fatty acids and ROS production (Cleland et al. 2021)**.**

In order to comprehend the link between lipids and progression of the NDDs, a better understanding of the role and fate of lipid metabolism in the disease is mandatory. In the present chapter, an insight into cholesterol metabolism, mitochondrial dysfunction, protein aggregation and autophagy with respect to lipid dynamics has been discussed. Additionally, the chapter deals with the advancement in the field of lipidomics and how crucial it can be to map lipid-lipid interaction and trace the changes in lipid metabolism during the progression of NDDs.

6.2 Dysregulated Lipid Metabolism in NDDs

Altered lipid metabolism has been insinuated in the progression and pathogenesis of neurodegenerative diseases. Lipids are fundamental components in maintaining cell structure and changing membrane dynamics and are central for the well-being of cell organelles. Any kind of disturbance or disruption in lipid homeostasis can have a profound effect on neurons affecting neuronal signalling and overall cellular health. The lipid pool of the CNS is composed of sphingolipids, cholesterol, fatty

acids and glycerophospholipids and is primarily involved in the biogenesis of lipid raft, myelin sheath, synaptogenesis, neuronal plasticity, cellular signalling and structural integrity. The role of lipids, particularly sphingolipids and cholesterol, is cardinal for the normal development and functionality of the central nervous system. These lipids, notably abundant in myelin, have been extensively documented (Giussani 2021; Kishimoto et al. 1969).

Sphingolipids are the precursor of several lipid metabolites and the simplest of those metabolites are ceramides and sphingosine, whereas sphingomyelin and glycosphingolipids are the complex ones. This class of lipids is involved in regulating synaptic stability and transmission, crucial signalling pathways, apoptosis, mitochondrial function, immune responses and metabolism and also functions as secondary messengers (Bollinger et al. 2005). The versatility of these lipids and their metabolites highlights the possible ways in which lipid metabolism contributes to the overall health and dynamic functions of the central nervous system (Fig. 6.1).

For the past few decades, researchers have been actively assaying the role of sphingolipids in AD pathogenesis. Several studies and post-mortem examinations of AD patients have reported elevated levels of ceramide in the CSF cortical regions of the brains (He et al. 2010). Concurrently, with the elevated levels of the ceramides, investigations revealed reduced levels of sulphatide in the same brain regions. Sulphatides, a type of glycosphingolipids, are important components of myelin, and their reduction may contribute to the disruption of myelin integrity and function as observed in AD. There exists a discrepancy in the ceramide levels in the brain regions of AD patients. Alteration in the ceramide levels has been reported in astrocytes and white matter of the brain, whereas there is no change in the grey matter ceramides which indicates the difference in lipid metabolism of astrocytes and

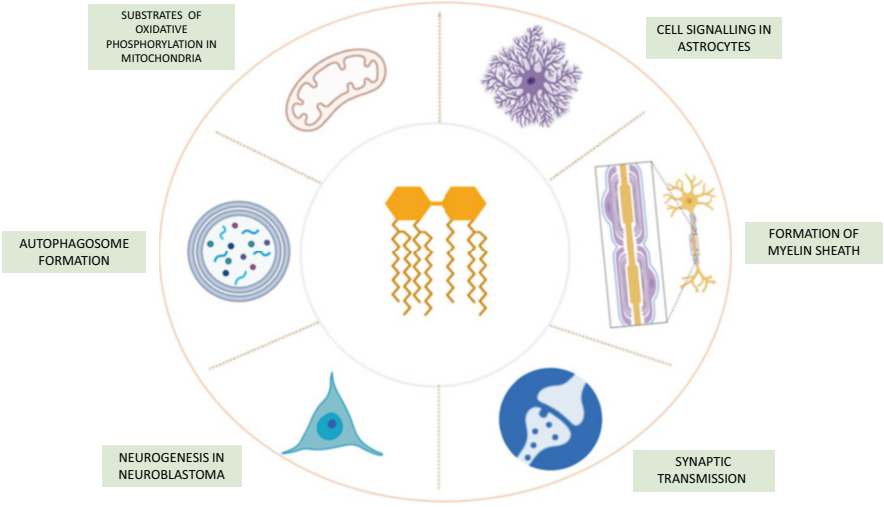

Fig. 6.1 An illustration depicting the role of lipids in the proper functioning of the human brain

neurons (Han et al. 2002; Hejazi et al. 2011). The ceramide accumulation caused by hydrolysis of sphingomyelin further promotes the amyloid precursor protein processing via β-secretase stabilisation (Puglielli et al. 2003). The involvement of sphingolipid dysregulated metabolism in the progression of Parkinson's disease has been first reported in the Gaucher disease (GD) associated with faulty GBA gene. The non-pathogenic form of GD, type 1 GD, is generally associated with the development of PD (Bultron et al. 2010). Ceramide expression has been reported to be inconsistent in the brain of PD patients as some of the regions such as the frontal cortex are associated with elevated ceramide level, whereas no change has been reported in the substantia nigra. This variation in the ceramides has been reported to be directly proportional to the α-synuclein accumulation. Type 1 GD-implicated glucosylceramide (GlcCer) accumulation leads to the breakdown of α-synuclein tetramers in their monomeric form, resulting in aggregation and at the same time contributing to cellular toxicity (Kim et al. 2018). Amyotrophic lateral sclerosis (ALS), a motor neuron disease, is also connected with sphingolipid alterations. Abnormalities in sphingolipid and cholesterol metabolism have been observed in the spinal cords of ALS patients and the mice models of ALS. These anomalies are characterised by heightened levels of sphingomyelin, ceramides and cholesterol esters. In the ALS mice model, lipid variation occurs before the onset of clinical symptoms. Additionally, increased oxidative stress is observed in ALS patients along with lipid changes (Cutler et al. 2002). In Friedreich's ataxia (FRDA), iron accumulation has also been linked with sphingolipids, particularly changes in the ceramide level. In the fruit fly model of FRDA and in the FRDA patients, ceramide levels are reported to be high but how the impaired mitochondrial dysfunction has been correlated with the increased ceramide level is not fully understood (Navarro et al. 2010). The breakdown of lipid metabolism homeostasis is closely linked to compromised energy metabolism, mitochondrial dysfunction and impaired calcium signalling. This deterioration has been demonstrated to directly result from mutant huntingtin (mHtt) expression in a *Drosophila* model of Huntington's disease (Burtscher et al. 2023). Research suggests that the mutant huntingtin protein (mHtt) directly influences sphingolipid metabolism. Several mechanisms have been proposed to explain these alterations observed in HD. One such mechanism involves disruption of enzymes involved in sphingolipid synthesis and metabolism, leading to abnormal accumulation or depletion of specific sphingolipid species, especially sphingosine-1-phosphate, a precursor to ceramide (Di Pardo et al. 2017).

Unravelling PUFA- and MUFA-related implications has also been one of the hotspot areas of research in neurodegenerative disorders. Polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids (MUFAs) are types of lipids (fats) that are essential components of cell membranes, including those in the brain. These fatty acids cannot be produced by the human body and must be obtained from dietary sources. Omega-3 and omega-6 fatty acids are examples of PUFAs, while oleic acid is an example of a common MUFA. Increased concentrations of unbound fatty acids, along with their metabolic by-products such as acyl-carnitines and acyl-CoA, have neurotoxic effects and can trigger mitochondrial uncoupling and disturbances in cellular energy production (Schönfeld and Reiser 2017). Changes in brain

fatty acid metabolism in neurodegenerative diseases are also indicated by disruptions in the levels of free fatty acids.

Several research reports of AD suggested that individuals exhibit lower levels of unsaturated fatty acids, including omega-3 PUFAs and a MUFA (oleic acid), both in the brain (including the cortex, middle frontal gyrus and inferior temporal gyrus) and in plasma, compared to cognitively normal controls. These changes contribute to an overall reduction in the unsaturation index (Cunnane et al. 2012). DHA (docosahexaenoic acid) is an omega-3 fatty acid that is positively correlated with cognitive function and down-regulated in AD patients. Unlike DHA, arachidonic acid (AA) belonging to omega-6 fatty acid family characterised by their pro-inflammatory qualities are up-regulated in AD. This suggests and correlates with the oxidative and inflammatory state of CSF in AD patients (Belkouch et al. 2016). Dysregulation of fatty acid metabolism may contribute to the pathogenesis of Parkinson's disease as well. PUFA-associated alterations have been reported in PD, such as omega-3 and omega-6 PUFAs, in the plasma, brain tissue, or cerebrospinal fluid of individuals with Parkinson's disease compared to healthy controls (Yoo et al. 2021). The exact mechanisms underlying the variation of PUFAs and MUFAs in Parkinson's disease are not fully understood. On the contrary, there is less prevailing literature suggesting the role of MUFA and PUFA in the pathogenesis of other neurodegenerative diseases. Moreover, MUFA and PUFA are involved in modulating inflammatory responses and oxidative stress, which are prominent features of NDDs. Imbalances in these fatty acids may exacerbate oxidative damage and inflammation, further contributing to disease progression. Moreover, further research is needed to fully understand the role of altered lipid metabolism in NDDs; accumulating evidence till date suggests that dysregulation of sphingolipids along with the free fatty acid composition in the brain may contribute to the aetiology of these debilitating diseases. Therefore, understanding the role of these fatty acids could provide insights into the mechanism of neurodegenerative disease progression and pathogenesis that would potentially identify novel therapeutic targets aimed at restoring lipid homeostasis and mitigating neurodegeneration.

6.3 Cholesterol Metabolism in NDDs

Sterol lipids play a critical role in maintaining optimal brain function and health. There are several forms of sterol lipids synthesised in the body; cholesterol stands out as the primary and most abundant form across all mammalian species. Implicated in numerous neurological processes, including the formation and maintenance of cell membrane and structure and permeability, facilitation of molecules across the membrane, synthesis of the myelin sheath and neuronal signalling pathways highlights the fundamental role of cholesterol.

Cholesterol synthesis occurs in the endoplasmic reticulum (ER) of all nucleated cells. The liver is considered the primary site for cholesterol synthesis; however, substantial amounts are also produced by the brain, intestine and adrenal glands

(Blom et al. 2011). Cholesterol synthesis progresses through the mevalonate pathway, consisting of a complex cascade of over 20 enzymatic reactions. The pathway initiates with the acetyl-CoA converted into 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) with the aid of enzymes and then into mevalonate. Conversion of HMG-CoA into mevalonate is a crucial rate-limiting and irreversible step catalysed via HMG-CoA reductase. Mevalonate undergoes a six-enzyme process to produce squalene, further metabolised into lanosterol, the first cyclic intermediate. The pathways then branch into the Kandutsch-Russell or Bloch pathways, dictated by the hydrocarbon chain's properties, before merging again to yield cholesterol. Subsequently, cholesterol serves as a precursor for bile acids, steroid hormones, or vitamin D synthesis (Bloch 1965).

Cholesterol metabolism serves as a central axis in the complex mechanisms underlying neurodegenerative diseases, impacting a multitude of cellular processes crucial for neuronal function and survival. Chaos in cholesterol equilibrium has been associated with NDDs like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Niemann-Pick type C disease (NPC) as well as acute neuronal injuries like trauma or stroke. The required cholesterol in the brain is synthesised de novo as the plasma lipoproteins do not cross the intact blood-brain barrier; therefore, the cholesterol synthesis is independent of the peripheral circulation. The brain has its own transport network via the lipoproteins. Astrocytes in the brain carry out the synthesis of cholesterol as well as apolipoprotein E (ApoE) which together with phospholipids synthesises brain lipoproteins (Boyles et al. 1985). ApoE carry out the uptake and transport of the cholesterol and phospholipids via ApoE receptor between the regions of the brain. It is important to understand that cholesterol has a very long half-life in the brain around 5 years; therefore, continuous synthesis is not required (Dietschy and Turley 2001). Cholesterol by itself is not able to cross the blood-brain barrier but its conversion to 24-hydroxycholesterol is the major mechanism followed by the cells to eliminate the excess cholesterol from the brain. The conversion is mediated by CPY46 enzyme and is crucial for maintaining cholesterol homeostasis (Russell et al. 2009).

The pathogenicity of AD is caused when the generated C terminal of APP protein is further cleaved by γ-secretase, leading to the formation of Aβ peptides containing 40–42 amino acids. There is some experimental evidence suggesting a potential association between alterations in brain cholesterol metabolism and the development of AD, but a direct relationship has not been firmly established (Umeda et al. 2012). Studies indicate that the enzymes responsible for generating abnormal Aβ peptides from amyloid precursor protein (APP) are primarily found in cholesterol-rich microdomains of the cell membrane. Interestingly, the extracellular N-terminus of APP contains a site capable of binding cholesterol (Umeda et al. 2012). Numerous studies conducted in vitro and in vivo have demonstrated that the cellular concentration of cholesterol can influence the production and accumulation of Aβ peptides. For example, decreased cellular cholesterol levels can lead to increased cleavage of APP by α-secretase, resulting in reduced formation of toxic Aβ peptides that contribute to amyloid plaque formation (Dietschy and Turley 2001; UJIIE et al. 2003). Unlike less evidence linking plasma

cholesterol-associated AD complications, there has been an established relationship between cholesterol-carrying protein, apolipoprotein E (APOE), and AD pathogenesis. APOE levels in the brain is interrelated with the occurrence of AD as APOE has a binding site for Aβ and, on further investigation, it has been reported when the APOE levels are reduced, the risk of developing AD increases in the mice model (Bales et al. 2009). There exist three isoforms of APOE: APOE2, APOE3 and APOE4, and the inheritance of alleles in an individual is linked with chances of developing AD. Crucially, inheriting the APOE4 allele stands as the most potent known genetic risk factor for late-onset AD development. Conversely, inheriting the APOE2 allele appears to confer protection against AD (Corder et al. 1994). Despite the firmly established association between the APOE4 isoform and AD susceptibility, the precise mechanism underlying why APOE4 increases AD risk remains elusive. Another connecting link between APOE genotype and AD is the observation that APOE3-containing lipoproteins derived from astrocytes demonstrate stronger support for neuron survival than APOE4-containing lipoproteins (Hayashi et al. 2007). However, the most compelling hypothesis likely revolves around the clearance of Aβ deposits, as APOE3 exhibits stronger binding to Aβ peptides than APOE4 (Strittmatter et al. 1993). Supporting this notion, mice expressing human APOE4 tend to accumulate more amyloid in their brains compared to those expressing APOE3 or APOE2 (Bales et al. 2009). Therefore, APOE appears to modulate Aβ level in a manner dependent on the APOE isoform, likely due to differences specific to each isoform in their ability to regulate Aβ degradation.

Cholesterol-associated anomalies have been reported very early in HD (Kacher et al. 2022). A malfunction in the cholesterol biosynthesis pathway at the enzymatic level has been reported. Specifically, mRNA levels for genes involved in the cholesterogenic pathway are significantly diminished in rodent models of Huntington's disease (HD), HD transgenic mice and human post-mortem brain tissue. The dysfunction is driven by a decrease in active sterol regulatory element binding protein (SREBP) levels induced by mutant huntingtin (mHtt). Typically, SREBP migrates from the cytosol to the nucleus when cholesterol levels are low, where it binds to and stimulates transcription of sterol regulatory elements (SRE)-controlled genes. Decreased SREBP translocation in the nucleus was observed in both in vitro and in brain tissue from HD mice, leading to reduced cholesterol synthesis. Intermediates of cholesterol biosynthesis are quintessential in neurite outgrowth and synaptic activity and stability. Neurite loss represents an early manifestation of several neurodegenerative disorders, including HD, which exhibits brain morphological abnormalities and synaptic activity defects (Kacher et al. 2022). Cholesterol transportation by astrocytes exhibits reduced efficiency in HD, characterised by decreased expression of apolipoprotein E (ApoE) and ABCA1 (ABC transporter family). Astrocytes expressing mutant huntingtin (mHtt) produce and release lesser amounts of ApoE, consequently affecting the transportation of cholesterol to neurons (Abildayeva et al. 2006). The levels of 24S-OHC, a by-product of cholesterol degradation in the brain, are reduced in the brains of various HD models and in tissues from patients. Intriguingly, 24S-OHC levels decline in the plasma of patients during early disease

stages and are associated with motor impairment and atrophy of the caudate nucleus (Shankaran et al. 2017). There appears to be a disruption in the overall cholesterol metabolism throughout the body in HD.

Niemann-Pick type C (NPC), a rare disease, is characterised by impaired cholesterol trafficking and accumulation within cells, leading to failure in cholesterol metabolism. In NPC, mutations in the NPC1 or NPC2 genes lead to defective transport of cholesterol from the endosomal/lysosomal compartment to other cellular locations, including the endoplasmic reticulum and plasma membrane (Vanier 2010). NPC1 and NPC2 proteins function in coordination to facilitate the transport of un-esterified cholesterol from late endosomes and/or lysosomes. In cells lacking NPC1 or NPC2, including neurons and glial cells, un-esterified cholesterol and other lipids become trapped within late endosomes and/or lysosomes due to the impairment in cholesterol egress (Vance 2010). Cholesterol dysregulation in NPC has implications for neuronal function and viability. Neurons are particularly sensitive to disruptions in cholesterol metabolism due to their high cholesterol demand for synaptic transmission and myelin production. The sequestration of cholesterol in NPC leads to neuronal dysfunction, synaptic loss and ultimately neurodegeneration, contributing to the neurological manifestations of the disease, including progressive cognitive decline, movement disorders and early death (Vanier 2010).

Studies have revealed several lines of evidence suggesting disrupted cholesterol metabolism in amyotrophic lateral sclerosis (ALS). Firstly, alterations in cholesterol homeostasis have been reported in both animal models and ALS patients. In female ALS patients, there is evidence of increased total 24S-HC plasma levels, whereas male ALS patients do not exhibit this increase. Conversely, male ALS patients show a reduction in total 26-HC, which is not observed in female patients (Wuolikainen et al. 2014). Dysregulated expression of genes involved in cholesterol metabolism has been observed in ALS animal models, including changes in cholesterol biosynthesis pathways and cholesterol transporter genes. LXR (liver X receptors) are nuclear receptors pivotal to efflux of excess cholesterol. Ligands of LXR are side-chain hydroxylcholesterols like 22R-HC, 24S-HC, 25-HC and 26-HC (Kim et al. 2008). There exist two conformations of LXR: α and β; the β-isoform is particularly expressed in the brain and has a key role in regulating both lipogenesis and cholesterol homeostasis in the brain. Moreover, experimental studies have provided mechanistic insights into how disrupted cholesterol metabolism may contribute to ALS pathogenesis. Elevated concentrations of non-esterified cholesterol have been reported in the CSF of ALS patients. This increase can be correlated with a decrease in LXR signalling, which may arise due to reduced levels of oxysterol and cholestenoic acid LXR ligands within the central nervous system (CNS), ultimately leading to motor neuron pathology (Abdel-Khalik et al. 2017).

Overall, accumulating evidence from experimental, clinical and genetic studies supports the notion that defective cholesterol metabolism plays a role in the abovementioned NDD pathogenesis and progression. Further research in this area is aimed at understanding the underlying mechanisms and identifying therapeutic targets within the cholesterol metabolic pathway that may provide novel insights and potential treatment strategies.

6.4 Lipid Dynamics and Mitochondrial Metabolism in NDDs

Mitochondria-linked comorbidities like heightened oxidative stress, deterioration of mitochondrial health and survival, mutated DNA, significantly reduced ATP levels and compromised oxidative phosphorylation have often been linked with the mutated protein accumulation in NDDs (Burté et al. 2015). Notably, most of these neurotoxic proteins have been associated with various impacts on distinct respiratory chain complexes, mitochondrial membrane potential, biogenesis and dynamics. Remarkably, numerous detrimental changes in mitochondrial function, maintenance, dynamics and degradation linked to age-related neurodegeneration are impacted by the composition of mitochondrial lipids and general lipid metabolism. Elevated Superoxide levels produced by mitochondria have been a common feature characterising NDDs and a major factor contributing to lipid peroxidation phenomenon. In addition to their role in energy storage, lipids are involved in crucial functions such as cellular compartmentalisation and signalling. This particular section of the chapter emphasises the link between mitochondrial lipid metabolism and mitochondrial dysfunction in the progression of neurodegenerative decline.

Lipid-associated movement, distribution and metabolism and their regulation in biological systems are collectively termed lipid dynamics. Understanding lipid dynamics is essential for comprehending fundamental biological processes such as membrane formation, cellular signalling, energy metabolism and lipid-related diseases. Due to their striking and remarkable property to aggregate into a bilayer structure, it facilitates them to rotate and move in and out of the cellular components, thereby making them dynamic in nature. Their distribution and metabolism are tightly regulated by various enzymes, transport proteins and signalling pathways.

MAMs (mitochondria-associated membranes) are the sites of contact through which it can communicate with the surrounding organelles and carry out its sustaining functions. The endoplasmic reticulum (ER) is responsible for exporting lipids to mitochondria and other organelles. To facilitate this uptake of lipids, sites of contact are essential (Rowland and Voeltz 2012). The lipid pool of the eukaryotic membrane is primarily composed of glycerophospholipids and its types like phosphatidylcholine (PC) being the most abundant in the membrane, phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylinositol (PI) and phosphatidic acid (PA). The lipid content between the inner mitochondrial membrane (IMM) and outer mitochondrial membrane (OMM) varies; the former maintains a protein-rich environment with lesser lipid content, whereas the latter is enriched with the lipids. The IMM is responsible for generating ATP with the help of integral membrane proteins which powers the ETC cycle and therefore is a site of oxidative phosphorylation.

In contrast, the OMM serves as a barrier between the cytosol and the interior of the mitochondria, and it also contains a variety of proteins involved in processes such as lipid metabolism, protein import and mitochondrial dynamics. However, its lipid composition is notably higher as compared to the IMM (Zinser et al. 1991). The mitochondrial enzyme contributes and is involved in the synthesis of lipids, for

example, IMM-localised cardiolipin biosynthesis is responsible to convert phosphatidylglycerol to cardiolipin (CL). CL is involved in numerous mitochondrial functions like assistance in cytochrome c complex, maintaining membrane permeability, mitochondria-associated fusion and fission, stabilising protein conformation together with PE and many more (Joshi et al. 2012). Ceramide also plays a significant role in determining mitochondrial function, particularly in regulating cell death pathways. Other than the ER, mitochondria is also powered with pathways for the production of ceramide. Within the mitochondria, the concentration of ceramide is notably higher in the outer mitochondrial membrane (OMM) compared to the inner mitochondrial membrane (IMM). This discrepancy in distribution suggests a specific role for ceramide in the OMM, potentially involving its participation in the formation of protein-permeable channels. These channels may facilitate the release of pro-apoptotic proteins from mitochondria, thereby influencing the initiation of programmed cell death pathways (Novgorodov et al. 2011; Siskind and Colombini 2000). Mitochondrial fusion and fission are an important criterion for the survivability of mitochondria. It has been studied extensively in yeast models; the mechanism involves GTPases, Mfn1/2 (yeast Fzo1) and opa1 (yeast Mgm1) of OMM and IMM, respectively. Studies have reported the link between lipid and GTPases; the absence of CL and PE prohibits fusion of mitochondria, whereas the low concentration of the same results in fragmentation of the mitochondria (Frohman 2015; Joshi et al. 2012). These results strongly suggest that lipid homeostasis is important in the regulation of key mitochondrial functions.

Numerous human diseases are linked with alterations in mitochondrial function and structure. Similarly, neurons, due to their heightened reliance on mitochondrial metabolism, are especially vulnerable to alteration in mitochondrial function, leading to energy deficits and the generation of reactive oxygen species (ROS). Mitochondrial fission and fusion play pivotal roles in regulating organelle size and facilitating efficient transport of mitochondria along microtubules, crucial for the elongated dendritic and axonal projections characteristic of neurons. Anomalies in mitochondrial dynamics, such as impaired fission or fusion and aberrant fission activation, are proposed to occur at the time of onset in many neurodegenerative diseases followed by compromised quality of life and an increase in complexity of NDDs.

The exact mechanisms behind the pathogenesis of Alzheimer's disease (AD) remain elusive; however, growing evidences point towards the mitochondria playing a significant role. In AD, there is a notable alteration in the expression of proteins involved in mitochondrial fission and fusion, indicating a potential imbalance in these processes and influence by amyloid beta (Aβ). It has been reported that increased Aβ levels lead to fragmented mitochondria and reduced mitochondrial mass in neurites of cultured neurons. This phenotype is linked with the anomalies in the expression of genes like drp1 (dynamic-related protein 1), Mfn1/2, opa1 and Fis-1 (mitochondrial fission-1). Higher expression of Fis-1 has been reported which correlates with the increased fission activity, whereas the decreased level of drp-1 is linked to altered mitochondrial morphology and distribution in AD patients (Wang et al. 2008, 2009). The autophagy of damaged or impaired mitochondria is pivotal

to mitochondrial homeostasis, the process referred to as mitophagy. The mitophagy phenomenon is weakened in AD patients and this reduced mitophagy is coupled with elevated ROS levels, eventually leading to aggregation and dysfunction of neurons (Fang et al. 2019). Another indication of abnormal mitochondrial function and subsequent energy hypo-metabolism stems from the diminished levels and activity of enzymes crucial for the electron transport chain (ETC) and the Krebs cycle (TCA). Studies on post-mortem brain tissue from Alzheimer's disease (AD) patients have revealed decreased levels and activity of key enzymes such as the α-ketoglutarate dehydrogenase complex, which is pivotal in the ETC cycle, particularly in regions like the temporal cortex, parietal cortex and hippocampus (Mastrogiacoma et al. 1996). Additionally, deficiencies in cytochrome oxidase and pyruvate dehydrogenase enzymes have been observed in AD patients. The interaction between amyloid-β and Aβ-binding alcohol dehydrogenase in the mitochondrial matrix exacerbates mitochondrial and neuronal dysfunction, resulting in increased production of reactive oxygen species (ROS), synaptic dysfunctions and reduced cognitive abilities. Once the mitochondria-associated impairment ensues, a consecutive chain of events initiates such as heightened production of reactive oxygen species (ROS) and oxidative stress, which in turn promotes processing of amyloid precursor protein (APP) to generate Aβ. Consequently, this chain of events leads to the amplification in the process of formation and accumulation of Aβ (Leuner et al. 2012).

Mitochondrial dysfunction plays a significant role in the development of both idiopathic and genetic forms of Parkinson's disease (PD). The direct link between mitochondrial dysfunction and PD was initially identified through post-mortem observations revealing complex I (c1) deficiency in the substantia nigra of PD patients. Following this discovery, similar deficiencies were observed in skeletal muscle and platelets, and a reduction in complex I proteins within the substantia nigra of individuals with PD (Mizuno et al. 1989). The malfunctioning of complex I of the electron transport chain (ETC) leads to an overproduction of reactive oxygen species (ROS), disturbance in the electrochemical potential of the proton gradient and inadequate synthesis of ATP and potentially results in cell demise. The underlying cause of the early onset of PD is mutations in PRKN (encodes parkin) and Pink1 that exhibit similar kind of manifestations. Both PRKN and Pink1 are the members of quality check team where they maintain the quality of mitochondria with respect to mitophagy, fission and fusion and vesicle functions of mitochondria (Ge et al. 2020). Pink1 when recruited to the outer mitochondrial membrane activates parkin which drives the compromised mitochondria to the phagosome-dependent lysosomal degradation. The ATP-producing ETC cycle is the major resource for supplying much required energy to the neurons; therefore, for ETC to work fluently, quality control checkpoints are necessary (Ziviani et al. 2010). Defects in the PRKN and Pink1 impair the complex I, an integral component of ETC, thereby making the mitochondria jeopardised in the early onset of PD. There exists a reciprocal relationship between α-syn-associated PD pathology and mitochondrial health. Mutation in α-syn which gradually progresses in PD is a rare autosomal dominant disease and exerts a devastating effect on the health and mental well-being of the individuals suffering from the same (Kahle et al. 2000).

PD-associated α-syn creates havoc in presynaptic terminals of the brain; it accumulates and inhibits the synthesis and elimination of α-syn. Being soluble in the cytosol, α-syn translocates into the OMM and IMM of mitochondria and hinders mitochondrial homeostasis. As the oxidative stress increases, more α-syn translocates and accumulates in mitochondria impairing the complex 1 of ETC, leading to its complete dysfunction (Vicario et al. 2019).

Several reports have shown mitochondrial dysfunction, characterised by deficiencies in bioenergetics and morphological abnormalities, in the brains of individuals with Huntington's disease (HD) post-mortem and various HD mouse models (Wellington et al. 2002). However, the precise mechanisms by which the pathogenic huntingtin protein (mHtt) disrupts mitochondrial homeostasis remained elusive. Recent findings indicate that mitochondrial fragmentation is not exclusive to HD but likely arises due to expanded polyglutamine (polyQ) repeats. Previous investigations have shown that mitochondrial fragmentation in polyQ diseases leads to build-up of impaired mitochondrial components, heightens reactive oxygen species (ROS) generation, diminishes cellular metabolism and eventually triggers cell demise (Puranam et al. 2006). Elevated oxidative stress has been noted in fibroblasts from individuals afflicted with spinocerebellar ataxia type 2 (SCA2), while animal models of SCA1 have displayed reduced oxidative activity and cellular respiration (Cornelius et al. 2017; Ripolone et al. 2018). Both SCA7 animal models and patient fibroblasts have displayed reduced metabolism and fragmented mitochondrial networks (Ward et al. 2019). Mice with spinocerebellar ataxia type 3/Machado-Joseph disease (SCA3/MJD) have demonstrated depolarised mitochondria and increased fragmentation, which correlates with decreased expression of fusion proteins MFN1/MFN2 and heightened ROS production (Hsu et al. 2017). Since previous studies have associated the expression of pathogenic polyglutamine (polyQ) with decreased mitochondrial respiration and increased ROS production, it is plausible that polyQ-mediated mitochondrial fragmentation is a direct response to cellular stress induced by the accumulation of polyQ (88). Drp1-associated anomalies in polyQ diseases are found to be the underlying cause of mitochondrial fission and fusion. Genes associated with the machinery are altered in larval brains of *Drosophila*, with the increased level of Drp1 and reduced expression of Mfn1/2 and opa1 causing fragmentation (Swinter et al. 2023).

To summarise, mitochondrial dysfunction in neurodegeneration reflects a complex interplay of various factors, including genetic mutations, protein aggregation, impaired mitochondrial quality control mechanisms and environmental stressors. Understanding the mechanisms behind mitochondriopathy in neurodegenerative conditions is imperative for devising efficacious therapeutic approaches aimed at addressing this facet of disease pathology.

6.5 Role of Lipid Metabolism in Protein Aggregation in NDDs

The underlying cause of pathogenicity in neurodegenerative diseases is protein aggregation in different regions of the brain. While much of the research is emphasised on understanding the aggregation of protein, recent studies have suggested the role of lipid metabolism in modulating protein accumulation in neurodegeneration. This intersection between lipid metabolism and protein aggregation in neurodegenerative diseases represents a flourishing area of investigation with profound implications for our understanding of disease pathogenesis and the development of novel therapeutic strategies.

Lipid rafts are specialised microdomains within cellular membranes that are enriched in cholesterol and sphingolipids. They play crucial roles in various cellular processes, including signal transduction, membrane trafficking and protein sorting. In connection with neurodegenerative disorders, emerging evidence suggests the involvement of lipid rafts in pathogenesis and progression. The involvement is linked in context with the aggregation and accumulation of misfolded proteins associated with these disorders. The microdomains serve as the platform for processes like oligomerisation and clustering for these misfolded proteins, including amyloid-beta, alpha-synuclein and tau, contributing to the formation of these toxic proteins.

They may facilitate the internalisation and intercellular spread of misfolded proteins. Once aggregated proteins are released from neurons, they can interact with lipid rafts on the plasma membrane of neighbouring cells, promoting their internalisation and seeding of protein aggregation in recipient cells. This cell-to-cell transfer has been hypothesised as the underlying cause for the progressive and lethal spread of the pathogenesis observed in NDDs.

In the previous sections of the chapter, we have discussed the anomalies in the lipid structure, composition and altered ratio of the crucial lipid classes like sphingolipids that include ceramides, gangliosides and other metabolites and cholesterol with respect to various neurodegenerative disorders as depicted in Fig. 6.2. We also emphasised different cellular processes affected by the alteration of these components in the nervous system. The brain is a lipid-enriched organ, and when the core of an element is altered, all the processes related to it also get affected. Lipid rafts are assumed as central to the cellular signalling and transmission in the brain and the components from which the rafts are composed are severely impacted in NDDs. In recent years, lipid rafts have gained attention as potential regulators for the formation and activities of extracellular vesicles (EVs). EVs are generated by all cell types in the nervous system; they are involved in the endocytosis and play a crucial role in intracellular communication. EVs have been implicated in both physiological and pathological processes associated with inflammation and neurodegenerative conditions which are discussed in the following sections:

The aberrant toxic protein deposits associated with NDDs typically manifest with a spatial distribution that follows a hierarchical pattern, indicating the potential for the pathological proteins to propagate across various regions of the brain (Thal

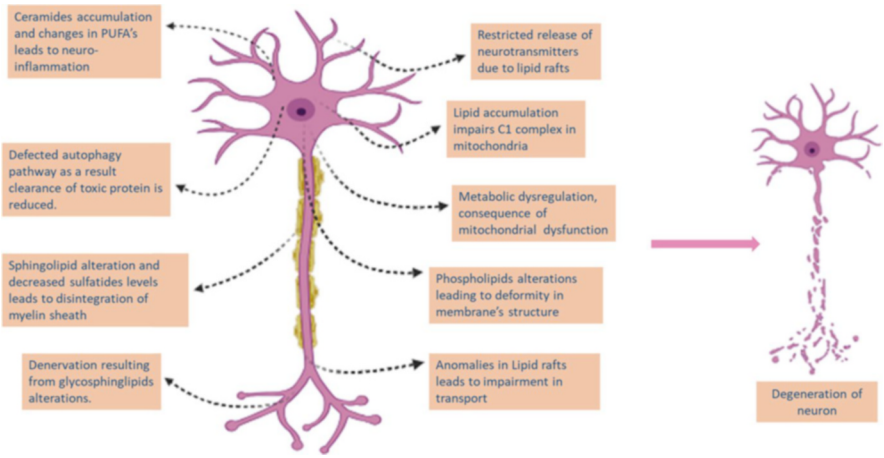

Fig. 6.2 Schematic representation illustrating the impact of altered lipid metabolism in the progression of neurodegenerative disorders

et al. 2000). This suggests that misfolded proteins can spread from one brain region to another through various modes of transportation. Exosomes, tiny extracellular vesicles composed of lipid bilayer, formed from endosomes within multivesicular bodies have recently emerged as pivotal mediators in cellular signalling and the transport of molecules, playing significant roles in both normal cellular functions and disease states, such as neurodegenerative disorders. They are capable of transporting various cargoes, including proteins, RNA and miRNA, and can also encapsulate monomeric forms of Aβ, tau and α-synuclein (Vella et al. 2016).

Peptides associated with Alzheimer's disease (AD) were initially detected within extracellular vesicles (EVs), particularly exosomes, as part of efforts to monitor amyloid precursor protein (APP) cleavage events (Vella et al. 2016). Exosomes consistently harbour full-length (FL-APP), C-terminal fragments of APP (CTF-APP) and various proteases involved in APP processing. The cleavage of APP by β- and γ-secretase enzymes within early endosomes generates amyloid-beta (Aβ), with a portion of Aβ being directed into intraluminal vesicles within multivesicular bodies (MVBs) (Sharples et al. 2008). Consequently, Aβ is exported from cells via exosomes and exosomes facilitate Aβ clearance; they also carry the risk of enhancing Aβ aggregation potential, potentially affecting neighbouring cells. Additional support for this notion comes from a study, where they observed Aβ oligomer-rich exosomes in Alzheimer's brains. Exosomes derived from Alzheimer's disease (AD) patient brains exhibited elevated levels of oligomeric Aβ (oAβ) and co-localisation between oAβ and exosomes within neurons, supporting the notion that exosomes may facilitate the transfer of toxic oAβ from neuron to neuron, thereby suggesting a potential involvement of exosomes in the sorting and oligomerisation of Aβ (Sardar Sinha et al. 2018).

In individuals with Parkinson's disorder (PD) and dementia with Lewy bodies (DLB), there is a notable decrease in cerebrospinal fluid (CSF) exosomes as

compared to the healthy individuals (Stuendl et al. 2016; Vella et al. 2016). DLB-derived exosomes contain amyloid-beta (Aβ) and tau within their cargo. Despite the decrease in total exosomes, DLB-CSF exosomes contain a higher amount of alpha-synuclein (α-syn) per exosome compared to PD-CSF exosomes and promote α-syn aggregation. Additionally, administration of DLB brain-derived exosomes to healthy rodent brain tissue leads to intracellular accumulation of phosphorylated α-syn and tau, indicating their pathogenic potential. The accumulation of human-origin α-syn around the soma further supports the notion that DLB exosomes contain high levels of α-syn. Nonetheless, characterising DLB-derived exosomes provides insight into α-syn pathology and may help distinguish central nervous system-derived exosomal populations in bodily fluids (Ngolab et al. 2017). Several genes associated with Parkinson's disease (PD), such as LRRK2, VPS35 and PARK9, are involved in autophagic and endocytic pathways in consort with the emerging evidences suggesting their role in exosome biogenesis and release (Fraser et al. 2013). LRRK2 is implicated in protein sorting, trafficking and autophagy and it is released in association with exosomes (Fraser et al. 2013). VPS35 plays a role in endosomal trafficking, while PARK9, a P-type transport ATPase found in multivesicular bodies (MVBs), regulates exosome biogenesis (Kong et al. 2014). Studies have shown that elevated PARK9 expression increases the externalisation of alpha-synuclein (α-syn) in exosomes from various cell types, including SH-SY5Y and H4 cells, as well as mouse primary cortical neurons. Interestingly, PARK9 overexpression leads to reduced intracellular α-syn levels in SH-SY5Y cells but increased α-syn externalisation in exosomes. Conversely, PD patient fibroblasts with loss of PARK9 function exhibit a decreased number of intraluminal vesicles in MVBs and reduced release of exosomes into the culture media. The exact implications of PARK9-mediated externalisation are not fully understood. It's hypothesised that increased exosome-associated α-syn export may benefit the exporting cell by reducing intracellular α-syn levels but potentially confer α-syn toxicity to surrounding cells. Notably, it has been proposed that the observed overexpression of PARK9 in surviving neurons of the substantia nigra pars compacta in sporadic PD patients could be linked to increased export of exosome-associated α-syn (Kong et al. 2014; Ramirez et al. 2006).

In polyQ diseases, similar to other neurodegenerative disorders, there is supporting literature suggesting the transmission of disease-causative proteins between cells. Initial studies by Wetzel's group in 2002 demonstrated that synthesised polyQ peptides can enter cultured cells and induce cytotoxic effects when delivered into the nucleus (Yang et al. 2002). Additionally, research by Kopito's group showed that in vitro-prepared aggregates of synthetic polyQ peptides can be internalised by cells and co-aggregate with intracellular polyQ proteins with a normal-length polyQ stretch. These findings indicate that both the polyQ disease proteins and their aggregates have the potential to transmit from cell to cell upon release. Subsequent studies using various experimental models, including cultured cells and animal models of polyQ diseases, have further supported the notion of intercellular transmission of abnormally expanded polyQ proteins and their aggregates (Babcock and Ganetzky 2015). Clinical evidence from Huntington's disease (HD) patients transplanted with

normal foetal striatum allografts also suggests the presence of mutant polyQ protein aggregates derived from patient tissue in the grafted normal tissue within the patient's brain (Cicchetti et al. 2014). Collectively, these reports indicate that intercellular transmission of causative proteins likely contributes to the onset or progression of polyQ diseases.

Despite of the evidence of intercellular transmission, the precise mechanism underlying this process in polyQ diseases remains poorly understood. One proposed mechanism is the secretion and propagation of polyQ proteins via extracellular vesicles (EVs) like exosomes, microvesicles, etc. Studies have shown that abnormally expanded polyQ proteins, along with their mRNAs, can be secreted via EVs. Transplantation of fibroblasts or induced pluripotent stem cells derived from HD patients into mouse brains resulted in cross-species transmission of mutant polyQ proteins, causing behavioural abnormalities in transplanted mice (Jeon et al. 2016). Notably, EVs derived from fibroblasts of HD patients were found to contain mutant polyQ proteins and intraventricular injection of these EVs induced polyQ protein transmission and phenotypic abnormalities in recipient mice, resembling those transplanted with HD fibroblasts.

A key pathological feature of ALS is the presence of TAR DNA-binding protein 43 (TDP 43)-positive inclusions, found in the post-mortem brain stem and spinal cord tissue in over 97% of patients (Mackenzie et al. 2007). Additionally, proteins such as SOD1, fused in sarcoma (FUS), and dipeptide repeat proteins (DPRs) aggregate to form inclusions (McAlary et al. 2019). These misfolded proteins exhibit prion-like behaviour, spreading between cells and inducing further protein misfolding, potentially explaining the contiguous spread of disease in ALS (Basso et al. 2013). Evidences suggest that extracellular vesicles (EVs) contain aberrant protein aggregates in ALS cell and animal models, as well as in ALS patients. These EVs may spread pathological misfolded proteins between cells and exert deleterious effects on recipient cells. Furthermore, EVs have been implicated in the transfer of RNAs, including miRNA, which can alter gene expression in recipient cells, potentially contributing to the progressive spread of neurodegeneration in ALS. Astrocytes with mutant SOD1 overexpression demonstrate increased EV secretion compared to wild-type cells, with these secreted EVs inducing cell death when taken up by motor neurons. Studies also indicate that misfolded SOD1 aggregates spread between motor neuron-like cells via EVs, resulting in cell rupture and death (Grad et al. 2014). Similarly, TDP 43 aggregates can be transferred intercellularly via EVs, leading to intracellular accumulation of TDP 43 and cell death. CSF EVs from ALS patients contain TDP 43 and have been shown to propagate TDP 43 aggregates when introduced to glioblastoma cells (Ding et al. 2015).

Therefore, with all these accumulated shreds of evidence, EVs like exosomes and lipid rafts may be considered as the crossroads in elucidating the mechanism behind the spread of the pathogenic proteins causing NDDs and hold significant revelations in the field of understanding the NDDs.

6.6 Role of Lipids in Autophagy and Its Implication in Neurodegeneration

Lipids play intricate and multifaceted roles in the autophagy process, a dynamic cellular mechanism vital for maintaining cellular homeostasis through the degradation and recycling of cellular components. To ensure autophagy, biogenesis of autophagosome is a crucial step; phospholipids like phosphatidylethanolamine and phosphatidylserine are vital to the formation and expansion of the membranous structure of autophagosome, thereby providing the well-required structural support (Axe et al. 2008). Lipids particularly phosphatidylethanolamine participate in the lipidation of the LC3 (microtubule-associated protein), which is a central player in the autophagy signalling mechanism. Conjugation of phosphatidylethanolamine with LC3 leads to the for formation of LC3 II complex, recruition of LC3 on the membrane of autophagosome is important (Nath et al. 2014). The role of lipid is not restricted till here; reports also suggest its involvement in the intracellular trafficking of autophagic vesicles powered by the networking provided by lipid-rich microdomains called lipid rafts.

These essential macromolecules are also considered as an integral component of lysosomal membranes, pivotal for maintaining lysosomal integrity and functionality, thereby influencing autophagic flux and cellular degradation processes. Moreover, lipids along with the other key factors play a role in specialised forms of autophagy, such as lipophagy, which aims to target lipid droplets for degradation, thereby regulating cellular lipid metabolism and homeostasis. Beyond their structural roles, lipid-derived metabolites, such as phosphoinositides, sphingolipids and cholesterol, act as signalling molecules and are regulators of autophagy-related signalling pathways, modulating various aspects of autophagosome formation, maturation and cargo degradation.

Phospholipids are essential regulators of autophagy, putting together various stages from initiation to fusion with lysosomes. Initiation relies on phosphatidylinositol-3 phosphate (PI3P) enrichment, facilitating membrane elongation and protein recruitment. ATG2 mediates glycerophospholipid transport for phagophore elongation, while the ATG16L1 complex promotes LC3/ATG8 lipidation crucial for autophagosome expansion. Phospholipid turnover, regulated by phosphatases like myotubularins and synaptojanin 1, is vital for autophagosomal maturation and protein release. Additionally, phosphoinositide metabolism modulates lysosomal function, impacting autophagosome-lysosome fusion through channels like TRPML1. Altogether, phospholipids govern membrane dynamics, protein recruitment and fusion events, underscoring their pivotal role in autophagy and cellular homeostasis (Dudley et al. 2019; Fruman et al. 2017; Lystad and Simonsen 2016; Valverde et al. 2019).

Another class of lipids, sphingolipids, plays multifaceted roles in regulating various stages of autophagy. Ceramide (Cer) initiates autophagy by reducing nutrient uptake, activating 5' adenosine monophosphate-activated protein kinase (AMPK), up-regulating Beclin 1 and inhibiting mTORC1. Additionally, Cer can

indirectly induce autophagy by influencing GlcCer levels. Acid sphingomyelinase (ASM) generates Cer from sphingomyelin (SM) in response to stress, promoting autophagy induction. However, dysregulated ASM activity can impair autophagic degradation and contribute to pathological conditions. Cer directly activates Beclin 1 expression and dissociates the Bcl2-Beclin 1 complex, facilitating autophagy induction. Sphingosine-1-phosphate (S1P) levels affect autophagosome formation and lipidation of LC3, impacting autophagy progression. During autophagosome elongation, ceramide-1-phosphate (C1P) and S1P regulate vesicle trafficking and membrane fusion. Furthermore, sphingolipids are involved in target-specific degradation and serve as autophagic substrates (Guenther et al. 2008; Moruno Manchon et al. 2015; Scarlatti et al. 2004; Shen et al. 2014). In conclusion, sphingolipids orchestrate autophagy at multiple levels, influencing autophagosome biogenesis, maturation and cargo degradation, highlighting their significance in cellular homeostasis. Accumulation of protein aggregates in the brain characterises several neurodegenerative disorders. While increased protein aggregation correlates with neuronal toxicity, the significance of understanding clearance mechanisms in neurons became apparent through studies conducted by Yamamoto et al., who revealed that continuous clearance of pathological proteins like huntingtin is crucial for disease progression, suggesting that enhancing aggregate clearance could mitigate neurodegenerative symptoms (Yamamoto et al. 2000). Subsequent research by Hara et al. further highlighted the role of autophagy as a vital mechanism for preventing the build-up of inclusion bodies in neurons (Hara et al. 2006). Autophagic clearance of protein aggregates relies on cargo receptors, such as sequestosome 1 (SQSTM1/p62), NBR1, optineurin (OPTN) and NIX/BNIP3L, which facilitate the sequestration of these aggregates into autophagosomes (Komatsu et al. 2007).

We have elucidated the significance of phospholipids in the formation of autophagosomal structures, underscoring the importance of regulating local levels of various phospholipid species for early autophagosome biogenesis. With the perspective of lipids, we have addressed phospholipids implicated alteration in autophagy in various neurodegenerative disorders.

Perturbation in phosphoinositide metabolism has been implicated in neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and Charcot-Marie-Tooth disease (CMT). Mutation in the phosphoinositide phosphatase is responsible for dephosphorylating phosphoinositide (3,5)-bisphosphate (PI(3,5)P2), which leads to neuronal degeneration in rodent brains and is associated with recessive forms of CMT and ALS in humans (Chow et al. 2007). Similarly, mice with mutations in Vac14, an enzyme involved in PI(3,5)P2 synthesis, also exhibit neuronal loss (Zhang et al. 2007). These defects may affect the autophagic pathway, as evidenced by the accumulation of lipidated LC3 and LAMP2 in neurons and astrocytes of Vac14 mutant mice (Ferguson et al. 2009).

Reducing the activity of PIP4Kγ in primary mouse neurons expressing mutant huntingtin protein in human patient fibroblast results in elevated levels of PI5P, PI3,5P2 and PI3P, which in turn enhance basal autophagy and facilitate the degradation of aggregates and polyQ proteins (Al-Ramahi et al. 2017). Additionally, the up-regulation of huntingtin expression has been shown to promote autophagy and

endo-lysosomal systems in neurons. Moreover, the expansion of polyQ repeats in the pathological form of huntingtin alters its phospholipid-binding affinity, possibly contributing to its localisation to endo-lysosomes and autophagosomal structures in neurons from Huntington's disease patients (Kegel et al. 2009).

Lipidomic analysis of primary fibroblasts from Parkinson's disease (PD) patients with parkin mutations revealed increased levels of gangliosides, phosphatidylinositol (PI) and phosphatidylserine (PS) (Lobasso et al. 2017). This suggests potential autophagic alterations, consistent with findings from parkin mutant animal models. Mutations within the SAC1 domain of Synj1, such as R258Q and R459P, impair phosphatase activity and are associated with early-onset PD (Krebs et al. 2013). *Drosophila* models carrying the R228Q mutation in Synj1, equivalent to the R258Q pathogenic mutation in humans, exhibit age-dependent neurodegeneration of dopaminergic neurons, activity-dependent neurodegeneration of photoreceptors and accumulation of immature autophagosomes (Vanhauwaert et al. 2017). This underscores the crucial role of the SAC1 domain in autophagy and neuronal survival. Similarly, the synaptic protein endophilin-A is essential for neuronal survival, and variations in the endophilin-A1 locus (SH3GL2) are implicated as risk factors for PD (Soukup et al. 2016). Notably, phosphorylation of endophilin-A by the Parkinson protein LRRK2 induces membrane curvature, facilitating ATG3 recruitment. Strikingly, phosphomimetic and phosphodead mutations in endophilin-A lead to the neurodegeneration of dopaminergic neurons and photoreceptors, further emphasising the significance of endophilin-A function in PD pathogenesis (Soukup et al. 2016).

Post-mortem examination of AD patient brains revealed reduced phosphatidylinositol 4,5-bisphosphate (PIP2) levels. This decrease has been attributed to elevated levels of Synj1, an enzyme known to dephosphorylate PIP2 during clathrin-mediated endocytosis (Zhu et al. 2015). Another study demonstrated that dysregulation of PIP2 levels in AD mouse models impacts neurotransmission, spatial learning and memory (He et al. 2019). Recent genome-wide association studies have identified the PICALM/CALM (phosphatidylinositol-binding clathrin assembly protein) loci associated with an increased risk of developing AD (Lambert et al. 2011). PICALM directly interacts with PIP2 on the plasma membrane during clathrin-mediated endocytosis. Genetic evidence supporting PICALM's role as an AD risk factor has been further strengthened by demonstrating that the adaptor complex AP2 and PICALM interact with LC3 to facilitate the degradation of Alzheimer's C-terminal fragment APP via autophagy. Additionally, studies using zebrafish and *Drosophila* tau models have shown that altered CALM levels exacerbate neurotoxicity by suppressing autophagy. Functionally, CALM regulates lipid uptake from the plasma membrane to the phagophore, and down-regulation of CALM disrupts tau degradation by autophagy, leading to the accumulation of tau aggregates (Tian et al. 2013).

Friedreich's ataxia, an autosomal recessive neurodegenerative disorder, stems from diminished expression of frataxin, a mitochondrial protein, resulting in mitochondrial dysfunction. Nevertheless, post-mortem analyses of patient brains have revealed decreased levels of phosphatidylethanolamine (PE), phosphatidylserine

and linoleic acid (Ross et al. 2000). Furthermore, the GAA triplet repeats in the frataxin gene also impact the neighbouring gene PIP5KB, leading to reduced levels of phosphatidylinositol 4,5-bisphosphate (PI4,5P2) (Bayot et al. 2013). Despite the linkage between autophagy abnormalities and Friedreich's ataxia, the precise underlying molecular mechanism remains elusive.

Along with phospholipid alterations, defects in sphingolipid metabolism are also considered to be closely associated with numerous neurodegenerative conditions, not only due to the role of sphingolipids as crucial membrane components but also because few sphingolipids act as signalling molecules in various biological processes. Increased levels of sphingolipids and their derivatives are believed to be neurotoxic, though the precise molecular mechanisms behind this toxicity remain unclear (Ariga et al. 1998). Moreover, alterations in sphingolipid levels, not necessarily due to mutations in enzyme-encoding genes, have been observed in Alzheimer's, Parkinson's and multiple sclerosis. Inherited forms of neurodegenerative lysosomal storage disorders (LSDs), such as Gaucher, Krabbe, Niemann-Pick type 1 and Fabry diseases, result from mutations in genes responsible for enzymes in the sphingolipid pathway (Spassieva et al. 2016). Lysosomes play a crucial role in degrading autophagic cargo, and defects in autophagy are commonly found in LSDs, complicating the differentiation between pure autophagy defects and lysosomal defects affecting autophagy (Lieberman et al. 2012).

Therefore, comprehending the complex relationship between lipids and autophagy in neurodegeneration is crucial for inventing effective therapeutic approaches to regulate autophagy, thereby fostering neuronal well-being to address neurodegenerative disorders. Further exploration in this domain is imperative to clarify the distinct functions of various lipid types and pathways related to lipids in governing autophagy and their relationship with the progression of NDDs.

6.7 Lipidomics and NDDs

Lipidomics is a study of the entire lipidome of an organism. It covers the study of lipid dynamics, structures, interactions and functions. This field is of great importance as lipids play a significant role in various biological processes including cell membrane structure, signalling, energy storage and functioning of neurons (Tracey et al. 2021). Several studies have suggested the prominent role of lipids in diseases, including cancer, metabolic disorders, cardiovascular diseases and neurological diseases (Shamim et al. 2018). Lipidomics has aided in the identification of novel signalling molecules, possible biomarkers and insights into intricate processes and also finding new therapeutics (Astarita et al. 2023).

Lipidomics due to advancements in various techniques has become a promising field for identifying the crucial role of lipids in a biological system including the formation of cellular membranes, acting as a ligand or substrate, as an energy reservoir or serving as precursors for various secondary messengers. For the formation of the central nervous system (CNS), different types of lipids like fatty acyls,

sphingolipids, etc. are needed (Yoon et al. 2022). Thus, any kind of anomaly in the lipid profile or its metabolism can lead to abnormal functioning of the brain contributing to neurological disorders.

Brain lipids are essential for neuronal processes, membrane structure, synaptic transmission and myelination. There are several types of lipids forming more than half of the human brain like cholesterol, glycerophospholipids, fatty acids and sphingolipids. Brain lipid crosstalk between glia and neurons can influence neurotransmission and brain function. The brain lipid metabolism is regulated by the blood-brain barrier (BBB) which selectively allows lipids to enter the brain to maintain a specific concentration (Pifferi et al. 2021). The composition and quantity of each lipid vary according to a specific part of the brain, and thus, if there is any change in the lipid profile of the brain, it is also indicative of disruptive BBB. Studying brain lipids using techniques such as lipidomics provides valuable insights into brain function and dysfunction in health and disease and holds promise for the development of novel diagnostic biomarkers and therapeutic strategies.

Lipidomics is therefore used to study altered lipid metabolism in different biological samples to identify a characteristic feature of a particular disorder. Abnormal lipid content or dysregulation of lipid metabolism can lead to the accumulation of toxic lipid species, oxidative stress, neuroinflammation, neuronal damage and neuronal death (Shamim et al. 2018). Thus, these variations have been associated with various neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), etc. (Yoon et al. 2022). The sample quantities needed for lipidomic analysis are quite minimal, and thus, it is one of the fastest-growing fields. Lipidomics combined with other approaches like genomics and transcriptomics will uncover novel genes and markers.

6.7.1 Techniques Utilised in Lipidomics

Lipid extraction is the most crucial step before performing lipidomics. It differs according to the sample whether the desired tissue is a plant or animal tissue (Yang and Han 2016).

To perform lipidomics some of the techniques employed are:

1. Mass spectrometry (MS)

   MS studies are predominantly used to detect and quantify lipids associated with neurodegenerative studies. In AD, the composition of lipoproteins APOE and APOJ varies from the control brains in having higher cholesterol and phospholipids content as revealed by MS (Hauser et al. 2011). The presence of APOE Ɛ4 is also suggestive of familial AD. In AD, amyloid-β induced oxidation of membrane lipids leads to the accumulation of the by-products, isoprostanes and 4-hydroxy-2,3-nonenal (HNE), and their progressive increase is reported from recent lipidomic studies (Kelley 2022).

LC-MS studies of plasma lipidomics of patients with dementia, multiple system atrophy and progressive supranuclear palsy showed significantly lower concentrations of plasma sphingosine-1-phosphate (SIP) as compared to control brains due to altered lipid metabolism in neurodegeneration. The same study also showed increased levels of two biomarkers plasma monohexylceramide and lactosylceramide in diseased brains (Oizumi et al. 2022). In the case of PD postmortem brains, the cerebrospinal fluid (CSF) shows a higher level of non-CSF lipids including phosphatidylcholine, sphingomyelin and ceramides as observed through the lipidomic profile (Chiurchiù et al. 2022). The lipid alterations are complex and multifaceted in PD including changes in eicosanoids, fatty acids, triglycerides, etc.; thus, understanding these changes could lead to the development of novel therapeutic strategies and alleviate symptoms (Qiu et al. 2023).

Phospholipids like phosphatidylcholine (PC) and phosphatidylserine (PS) are significantly lower in the white frontal cortex of Huntington's disease (HD) brains as mass spectrometric results revealed (Phillips et al. 2022). Recent studies have also shown the reduction of cardiolipins, ganglioside GM1 and glycerophospholipids in HD brains compared to controls, suggestive of lipid alterations in neurodegeneration (Hunter et al. 2021).

Different types of mass spectrometry techniques include:

(a) Liquid Chromatography-Mass Spectrometry (LC-MS): It is a powerful and the most common technique for lipidomic analysis. It involves separating lipid samples using liquid chromatography and then analysing them with mass spectrometry to identify and quantify individual lipid species.
(b) Matrix-Assisted Laser Desorption/Ionisation Mass Spectrometry (MALDI-MS): The advantage of this method is that it allows direct analysis of lipids from the samples without much sample preparation and is a soft ionisation method and thus doesn't affect the sample much.
(c) Gas Chromatography-Mass Spectrometry (GC-MS): It is used for the analysis of volatile and semi-volatile lipids. It involves separating lipid components by gas chromatography followed by mass spectrometric detection (Köfeler et al. 2012).

2. Shotgun Lipidomics: It is also known as a direct infusion-based method in which the lipid extracts are directly injected into a mass spectrometer without any separation. It is usually used to detect new lipid species. Shotgun lipidomics is advantageous as along with lipid profiling it is also used to study the interaction with other lipid species and molecules. It is a technique which offers higher accuracy and sensitivity than mass spectrometry alone (Herzog et al. 2011).
3. Different biomarkers like bis (monoacylglycerol) phosphate (BMP) for lysosomal disorders, GM1-3 for Tay-Sachs disease and ceramides for multiple sclerosis (MS) have been identified by shotgun lipidomic studies (Wei et al. 2023). This technique can be used to quantify several lipid classes efficiently.
4. Nuclear Magnetic Resonance (NMR) Spectroscopy: It is a powerful tool for the characterisation of lipids. It can be used to identify lipid species based on peaks assigned to molecular structures of lipids. Through NMR studies, it was

identified that in the serum of AD brains, there is an increased level of high-density lipoprotein-4 and triglycerides (Berezhnoy et al. 2022).

The lipidomic strategy using NMR spectroscopy successfully differentiated between PD, AD and healthy brains (Pizarro et al. 2019).

5. Chromatography

It is an easy method to separate the individual lipid classes from each other, but to characterise them, it is coupled with mass spectrometry.

(a) Thin Layer Chromatography (TLC): To separate lipid classes based on their polarity. Lipids can be visualised directly on a TLC plate.

(b) High-Performance Liquid Chromatography (HPLC): To separate lipids based on their polarity, size and charge (Cebolla et al. 2022).

Therefore, to comprehensively analyse the lipid structure, function and composition, a branch of science was introduced, i.e. lipidomics. It is dynamic and is influenced by genetics, environmental conditions, diet, lifestyle and most importantly metabolism. Thus, understanding lipidome is essential for knowing the roles of lipids in health and disease and for developing targeted therapies for lipid-related disorders.

6.8 Conclusion

The chapter emphasises the implications of altered lipid levels in the pathogenicity of NDDs. An imbalance in lipid homeostasis has profound and devastating effects on cell survival mechanisms like mitochondrial functions, autophagy signalling, cholesterol synthesis and neuronal well-being. Sphingolipids and phospholipids are multifaceted lipid species which are engaged in several structural cell processes and signalling. These important macromolecules and their metabolites were found to be dysregulated in various aspects of NDDs. The up-regulated ceramide level and their resulting accumulation along with the changes in phospholipids hinder the mitochondrial as well as autophagic machinery and therefore are proven to have lethal consequences observed in a majority of the NDDs. Accumulated evidence has unravelled the role of lipids in accelerating the progression and pathogenesis via facilitating the transport and localisation of the toxic protein in different regions of the brain, associated with neurodegenerative diseases. Along with the lipid dysregulation, genes linked with cholesterol synthesis and its clearance, mitochondrial fission and fusion and autophagy seemed to be deviated from their normal nature, thereby driving the neurodegenerative diseases towards their terminal stages. All this indicates the intricate play between lipids and NDDs and comprehending the same would help in designing a novel approach to tackle the complex networking of these neuronal diseases. One such advanced tool to understand lipid dynamics is lipidomics which comprehensively analyses the lipid structure, function and composition at the cellular level. Lipidomics, via the implementation of different techniques like mass spectrometry, liquid chromatography and NMR, has revealed the

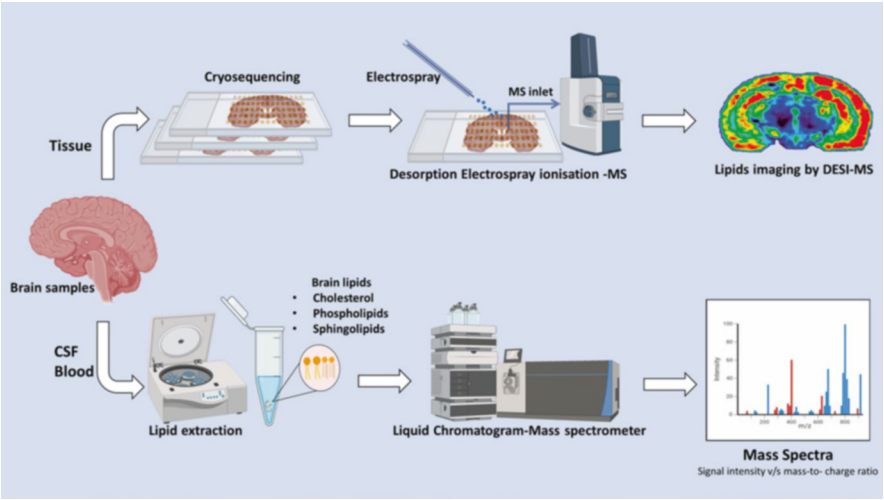

Fig. 6.3 Analytical strategy for the study of brain lipidomics. Mass spectrometry can be utilised to analyse brain tissue and biofluids. Frozen brain tissue can undergo sectioning for lipid imaging via DESI-MS. Another approach involves extracting lipids from fluids and separating and detecting them based on mass/charge ratio using LC-MS. *CSF* cerebrospinal fluid, *DESI-MS* desorption electrospray ionisation-mass spectrometry

discrepancy in the amount of lipids in the brain between the healthy individuals and patients diagnosed with neurodegenerative diseases. Along with this, lipidomics also measures the extent of lipid variations among the patients of NDDs. The intriguing features of lipidomics can be deployed to identify the existing trigger points and targets in NDDs based on which further therapeutic approaches can be designed (Fig. 6.3).

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Chapter 7
Dysregulated Peripheral Metabolism in Neurodegenerative Disorders

Khushboo Sharma and Madhu G. Tapadia

Abstract Neurodegenerative diseases (NDDs), such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS) are relatively common and devastating neurological disorders. Several reported evidences suggest existence of a strong link between metabolic syndrome and neurodegeneration. One common pathophysiological change observed in neurodegenerative diseases is a change in the metabolic function of nervous system and peripheral cells. Process of glycolysis which results in generation of ATP has been reported to be abnormal in the peripheral cells of AD, PD, and MS.

A better understanding of how glycolysis in peripheral cells changes in NDDs is important as it can allow development of biomarkers from easily accessible cells. Additionally, a new therapeutic can be developed for different NDDs that target peripheral glycolysis that could modify the course of the disease.

Keywords Neurodegenerative disease · Peripheral metabolism · Lipid metabolism

7.1 Introduction

Neurodegenerative diseases (NDDs) refer to a category of disease that primarily damages neurons due to the accumulation of abnormal protein aggregates throughout the brain and spinal cord. The most common neurodegenerative conditions are Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). A characteristic pathophysiological hallmark of NDD is the alteration in the metabolic function of the central and peripheral nervous system. These alterations involve changes in mitochondrial metabolic function, lipid metabolism, and glucose metabolism via glycolysis.

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The energy accumulation/allocation provided by nutrients is determined by the balance between the hormones that regulate satiation and hunger signaling, and this is regulated by signaling from peripheral tissue to the central nervous system (CNS), hence allowing adaptation to the response of food intake and energy expenditure (Kennedy 1953). The various peripheral hormones such as leptin, ghrelin, insulin, and others along with nutrients directly coordinate with the hypothalamus to regulate energy homeostasis. This homeostatic regulatory mechanism is mediated by a complex neuronal circuitry within the major center of the brain, the hypothalamus (Fig. 7.1).

The hypothalamus comprises four major regions, the preoptic, anterior, tuberal, and mammillary regions, which project into the peripheral and central nervous systems via neuronal networks. There are multiple interconnected nuclei located in the hypothalamic region, including the arcuate nucleus (ARC), the paraventricular nucleus (PVN), the lateral hypothalamic area (LHA), the ventromedial nucleus (VMN), and the dorsomedial nucleus (DMN). The ARC is essential for the control of energy acquisition in terms of food intake and its allocation (Cornejo et al. 2016). Structurally, the ARC/infundibular nucleus is located in the mediobasal hypothalamic region and extends into median eminence (ME) and forms ARC-ME complex. The ME is a circumventricular organ with high permeability and fenestrated capillaries and lacking blood-brain barrier. Hence, the hormones and nutrients access the ARC circumventing the blood-brain barriers, and this strategic location of ARC makes it the primary peripheral metabolic signaling center. The ARC is composed of two major subsets of neuronal populations. One set expresses anorexigenic neuropeptides and the other co-expressing orexigenic neuropeptides (including neuropeptide Y) and agouti-related peptide. The peripheral metabolic signals such as ghrelin and leptin are in direct contact with these neurons, making them

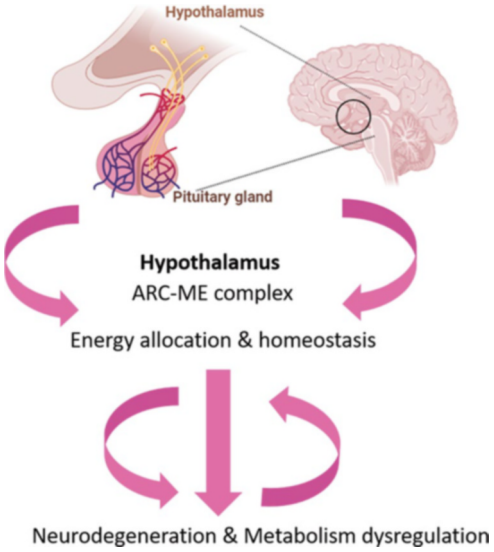

Fig. 7.1 Hypothalamus is master regulator for energy allocation and metabolic homeostasis. ARC-ME complex forms primary peripheral metabolic center for regulation of energy/metabolism homeostasis

first-order neurons, and send signal with axonal network to the second-order neurons. The neuronal projections from ARC are received by VMN which is an important region for glucose homeostasis and satiation center (Gonzàlez et al. 2009). The paraventricular nucleus (PVN) neurons send sympathetic outflow to peripheral metabolic organs such as the liver and adipose tissue (Foster et al. 2010). LHA is the feeding center and comprises neurons expressing two major neuropeptides, the melanin- concentrating hormone (MCH), which is an orexigenic hormone, and orexin, which is also known as hypocretin. The DMN has nerve terminals ending that originate from ARC (Yu and Kim 2012).

It has been proven beyond doubt that insulin is the major regulator of glucose levels. However, in the hypothalamus, insulin, in addition to glucose, also controls lipid metabolism (Scherer et al. 2011). Hypothalamic insulin resistance due to excessive nutrition is far more frequent than that in other insulin-sensitive tissues. There is an essential role of insulin resistance in brain-related diseases as it affects the morphology of the brain directly (Lu et al. 2021). With aging and neurological disease conditions, metabolic homeostasis gets dysregulated that affects the brain directly. Metabolic syndrome which is a group of conditions that includes obesity, hypertriglyceridemia, and hyperglycemia is considered a pre-disease state which affects the cognitive decline with age and other neurological diseases like Parkinson's disease and dementia (Shen et al. 2023). In this chapter, we have discussed various aspects of peripheral metabolism that gets altered in NDD.

7.2 Peripheral Impairments in NDDs

Neurodegenerative diseases are disorders that affect the central and peripheral nervous system, and their progression is highly associated with defects in glucose and energy metabolism. The impairment of peripheral neurons affects cellular homeostasis via mitochondrial dysfunction, ER stress, cytotoxicity, autophagy dysregulation, and apoptosis. Together, these dysfunctions contribute to the progression of NDDs.

Metabolism of glucose, lipogenesis, and ketogenesis occurs in mitochondria, and mitochondrial dysfunction tends to be the cause or effect of metabolic dysfunction. The AMPK/PI3K inactivation leads to insulin resistance and PGC-1α-mediated mitochondrial loss in both peripheral organs and the brain, affecting glucose metabolism and neuronal damage that can be ameliorated by normalizing glucose metabolism and mitochondrial activity, providing new insights into the interrelationship between hyperglycemia and cognitive impairment (Peng et al. 2016). In NDD such as PD, AD, and ALS, metabolism and disease progression are directly correlated. For instance, in HD, altered mitochondrial activity was reported in peripheral tissue (Singh and Agrawal 2022). At the mitochondrial level, there are defects in electron transport chain complex II and III along with mitochondrial enzyme aconitase oxidation and deficient Kreb cycle in aged HD brain.

In Parkinson's disease, accumulation of α-synuclein (α-syn) and formation of filamentous aggregates called Lewy bodies are the primary cause of disease onset. The α-syn is a small cytosolic protein that is expressed highly in the brain and is mainly located in synaptic terminals. It is known that α-syn also has a role in mitochondrial function, specifically as a physiological modulator of ATP synthesis by altering the efficiency of ATP synthase (Ludtmann et al. 2016). The α-syn undergoes a major structural transition from random coil to α-helical structure, and it appears that the binding of α-syn to cardiolipin in the mitochondrial membrane is part of its physiological role as related to mitochondrial metabolism. Cellular environment plays a critical role in the aggregation of α-syn suggesting that dysregulation of lipid levels and lipid pathways may be an important contributing factor in the pathogenesis of PD. It has been observed that the α-syn oligomerization was also enhanced in the presence of polyunsaturated fatty acids (PUFAs) (Alecu and Bennett 2019).

In AD, abnormal lipid accumulation leads to insulin resistance which is a neuronal phenomenon due to decreased responsiveness to insulin at all levels of insulin recepton-IRS-1-P13K-Akt signaling pathway. High-fat diet induced severe body weight gain, hyperglycemia, and hepatic insulin resistance in AD, probably because an inactivated lipogenic pathway by inflammatory factors initiates the substrate flux for glucose production, leading to acute hyperglycemia in AD (Tang et al. 2016). As JNK signaling pathways affect mitochondrial function and mitochondrial bioenergetics, it is reasonable to link mitochondria, ROS, and inflammation with AD. Oxidative stress and inflammation at early stage of AD damage the neuronal membrane potential, mtDNA, TCA cycle, and electron transport chain in mitochondria, thereby reducing ATP generation and exacerbating oxidative damage (Yao et al. 2009).

7.3 Disturbances in Peripheral Lipid Metabolism in NDDs

The prevalence of obesity, metabolic diseases, and neurodegeneration continues to rise in aging population. Lifestyle diseases at early stages predispose individuals to neurodegenerative diseases such as AD and PD which are normally associated with age and obesity (Popa-Wagner et al. 2020).

Leptin, adipocyte-derived hormone, has a profound effect on lipid and carbohydrate metabolism to regulate energy balance. Receptors of leptin are expressed in many brain regions, such as the arcuate nucleus of the hypothalamus, the olfactory bulb, the dorsal raphe nucleus, the hippocampus, the cortex, and the nucleus of the solitary tract (Tartaglia et al. 1995). Leptin regulates lipid metabolism independent of food intake. Central leptin administration inhibits de novo lipogenesis and stimulates lipolysis in adipose tissue and liver via activation of the sympathetic nervous system. The neuroprotective and neurotrophic role of leptin is well established. In AD, phosphorylation of PI3K/AKT/mTOR decreases the GM1 ganglioside (GM1)

and inhibits the assembly of amyloid-β (Yamamoto et al. 2014). In PD, leptin imparts neuroprotection by regulating pERK1/2 expression in dopaminergic neurons (Weng et al. 2007).

Serotonin is majorly expressed in the nervous system in the gastrointestinal tract (GIT), and activation of serotonin receptors (5-HT) controls motility and peristalsis. In GIT, it is regulated by chemicals that increase in concentration following food intake and satiation such as leptin, insulin, glucose, and ghrelin and travels via the bloodstream to the circumventricular subfornical organ, which then contacts the arcuate nucleus of the hypothalamus. There is a decrease in 5-HT circuitry in the brain in AD condition reflected by the downregulation of expression of the 5-HT circuitry key genes and reduction in the metabolism of the neurotransmitter itself (Eremin et al. 2023). In PD, it thereby leads to progressive and nonlinear loss of serotonergic neurons in the brain where degeneration of 5-HT terminals is reported (Politis and Niccolini 2015).

Ghrelin promotes adiposity by the activation of hypothalamic orexigenic neurons, stimulates the expression of fat storage-related proteins, and increases lipogenesis and triglyceride uptake in adipocytes mainly in white adipose tissue (WAT). Hypothalamic nuclei including ARC, PVN, dorsomedial, and ventromedial (VMH) nuclei contain high levels of key enzymes modulating lipid metabolism, such as AMP-activated protein kinase (AMPK), acetyl-CoA carboxylase (ACC), and malonyl-CoA decarboxylase. The central effect of ghrelin on adipocyte metabolism is direct by stimulating lipogenesis in white adipose tissue (WAT) via sympathetic nervous system (SNS) independent of food intake. Hypothalamic fatty acid metabolism mediates the orexigenic effect of ghrelin. It stimulates lipogenesis and decreases fatty acid oxidation in the liver by directly activating its receptor on hepatocytes. In several neurodegenerative diseases including Alzheimer's, Parkinson's, and Huntington's, autophagy is impaired resulting in the presence of misfolded proteins or the accumulation of dysfunctional organelles. Ghrelin activates autophagy in neurons to extend lifespan (Jiao et al. 2017).

Several studies support the direct role of leptin, serotonin, and ghrelin, but few of the many lipid metabolism-regulating candidates have a crucial role in the metabolic aspects of neurodegeneration. They might act at different interfaces in metabolism and neurology where they have a neuroprotective function that delays the progression of neurodegenerative disease. These results suggest that a healthy lifestyle and food habits are essential to procrastinate neurodegenerative disease.

7.4 Altered Peripheral Glycolysis in NDDs

Insulin plays a crucial role in brain function, including learning, memory, neurite growth, and development. It also facilitates glucose metabolism and affects tau protein and Aβ processing in AD. Insulin resistance impairs glucose regulation, resulting in glucose intolerance and disrupting insulin signaling. Insulin resistance has

been confirmed not only in the peripheral tissues of AD patients but also in their brains. Impaired glucose metabolism also affects the glycosylation process. The glycolysis produces four molecules of ATP and two molecules of NADH where glucose is converted to pyruvate via a series of glycolytic steps which include enzymes such as hexokinase (HK), phosphofructokinase (PFK), phosphoglycerate kinase (PGK), and pyruvate kinase (PK). The rate-limiting step enzymes in the glycolytic pathway include the role of enzymes, viz., HK, PFK, and PK (Fig. 7.2). The glucose-6-phosphate may be utilized by other pathways that include pentose phosphate shunt (PPS) and gluconeogenesis. In the liver of HD individuals, there is a reduction in gluconeogenesis along with a decline in the expression level of peroxisome proliferator-activated receptor (PPARγ) and CCAAT/enhancer binding protein α (C/EBPα), hence affecting the metabolism in the during NDD progression.

Glucose metabolism plays an important role in the posttranslational modification of proteins in the hexosamine synthesis pathway to produce O-N-acetylglucosamine (O-GlcNAc), which is known to modify APP and Tau in AD.

Anaerobic glucose metabolism, also termed glycolysis, is defined as metabolic pathways that occur in the absence of oxygen and take place in the cytoplasm of cells. The unavailability of oxygen shifts the metabolic processes toward

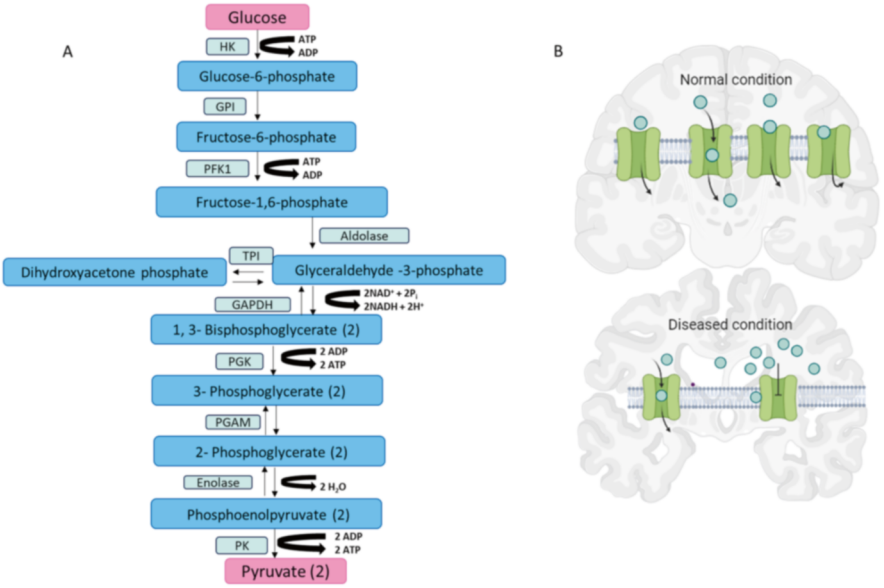

Fig. 7.2 Glycolysis regulation in neurodegeneration. (**a**) Key enzymes HK, PFK1, and PK regulate the process of glycolysis. (**b**) GLUT receptor number decrease and elevation in glucose level affects glycolysis during NDD

fermentation. This further allows the partial breakdown of glucose and other substrates, resulting in the production of only two molecules of ATP per one molecule of glucose.

Glycolysis serves as an alternative means for cells to produce energy when oxygen is limited or unavailable. Figure 7.2 depicts glucose as the primary fuel of the brain. It is known that reactive oxygen species (ROS) production under oxidative stress suppresses glycolysis by inhibiting multiple glycolytic enzymes, viz., pyruvate kinase, phosphofructokinase, and glyceraldehyde-3-phosphate dehydrogenase (Butterfield and Halliwell 2019). For instance, the glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is a ubiquitous enzyme that catalysis the sixth step of glycolysis, i.e., phosphorylation of glyceralde-hyde-3-phosphate (G3P) to 1,3-bisphosphoglycerate using nicotinamide adenine dinucleotide (NAD^+) as a cofactor, and thus serves to break down glucose for energy production. It forms complexes with neurodegenerative disease-related proteins including huntingtin and amyloid beta (El-Kadmiri et al. 2014) and accelerates the disease progression leading to cytotoxicity and neuronal death (Itakura et al. 2015). The ratio of NAD^+/NADH acts as an index for cellular reduction potential, and it is widely dysregulated in AD condition. The branched pathway, the pentose phosphate pathway (PPP) that is directed from the first key step of glycolysis, has a role in the maintenance of substantial NADPH levels and protection against oxidative stress during neurodegeneration. In PD, GD6P, the key enzyme of PPP, regulates chronic inflammation and neurodegeneration (Tu et al. 2019). The PFK1 is another crucial regulator that is known to commit the process of glycolysis and is activated by a low ATP/AMP ratio. The mutation/deficiency due to phosphoglycerate kinase (PGK), which catalyzes the first ATP-generating step, results in Parkinson's disease-related idiopathies (Cai et al. 2019). In HD and ALS, there is enhanced activation of several glycolytic enzymes that further increase glycolysis, in response to WNT/β catenin pathway, hence implying the neuroprotective role of glycolysis in neurodegeneration conditions (Manzo et al. 2019; Powers et al. 2007).

In AD, there is an increase in enzyme expression of the glycolytic pathway with a reduction in the glucose uptake due to the decrease of the glucose transport receptors such as GLUT1 and GLUT3 in aged diseased brain (Fig. 7.2b). There is elevation in mitochondrial abnormalities due to malfunctioning of glycolysis in AD and PD (Fig. 7.2). In the PD model for PINK1 mutation, there is upregulation of glycolysis and glucose uptake, but majorly the mitochondrial dysfunction affects the fate of glucose metabolism. In ALS, the impaired electron transport chain in mitochondria affects energy production in terms of ATP turnover and influences glycolysis and lipid metabolism (Bell et al. 2020).

Advanced glycation end products (AGE) are proteins or lipids with sugar residues attached as a result of exposure to sugars in the glycation process with the participation of RAGE receptors (receptor for advanced glycation end products). There is the generation of advanced glycation end products due to dysfunctional glycolysis that increases the production of methylglyoxal, which is the physiologically toxic by-product of glucose catabolism. This results in increased oxidative stress and has been implicated in neurodegenerative diseases like AD and PD (de Bari et al. 2019). In schizophrenia, glycoxidation increases carbonyl stress and generates oxidative stress via enhanced levels of AGE molecules like pentosidine (Ohnuma et al. 2018).

Conditions that impair brain glucose supply, such as aging, T2DM, or AD, lead to more profound task-associated depletion of local brain glucose correlated with impaired cognitive performance. The insulin acutely stimulates local hippocampal glycolysis. In the periphery, the primary role of insulin is to remove glucose from the blood via GluT4, which moves to the cell surface to permit increased glucose entry into cells when needed. GluT4 is heavily expressed in the hippocampus. Dysregulation of GLUT4 has a key role in disease progression in Alzheimer's disease (McNay and Pearson-Leary 2020). Impairment of glucose supply to neurons after dysregulation of the insulin-sensitive glucose transporter GluT4 may be a unifying mechanism that explains, at least in part, the comorbidity of these two diseases.

Glucose hypometabolism has been seen as a substantial anomaly in the neurodegeneration. Glycolysis is known to have an essential role in the development and neuronal activities of the brain. In neurodegenerative diseases, like AD, PD, ALS, and HD, it has been observed that glycolytic dysfunction has emerged as a common pathway leading to neuronal damage and degeneration. Taken together, it might be seen as one of the key pathways to be targeted for translational research for the development of therapeutics to delay NDD.

7.5 Altered Peripheral Kynurenine Pathway and Its Involvement in NDD Progression

Tryptophan is an essential amino acid that is the precursor to various biogenic amines that are required for biological processes. It circulates in the peripheral system in either bound form (with albumin) or free form. Although tryptophan bound to albumin is the predominant form, it is the free form of tryptophan that exclusively crosses blood-brain barrier via competitive and/or nonspecific L-type amino acid transporter. The kynurenine pathway is the essential pathway for the metabolism of tryptophan in both the central and peripheral systems (Fig. 7.3). The over-activation and dysregulation of the kynurenine pathway leads to immune system activation, neuroinflammation, and accumulation of neurotoxic compounds. The rate-limiting step of this pathway is regulated by tryptophan 2,3-dioxygenase (TDO) and/or indoleamine 2,3-dioxygenase (IDO), which are functionally similar but genetically

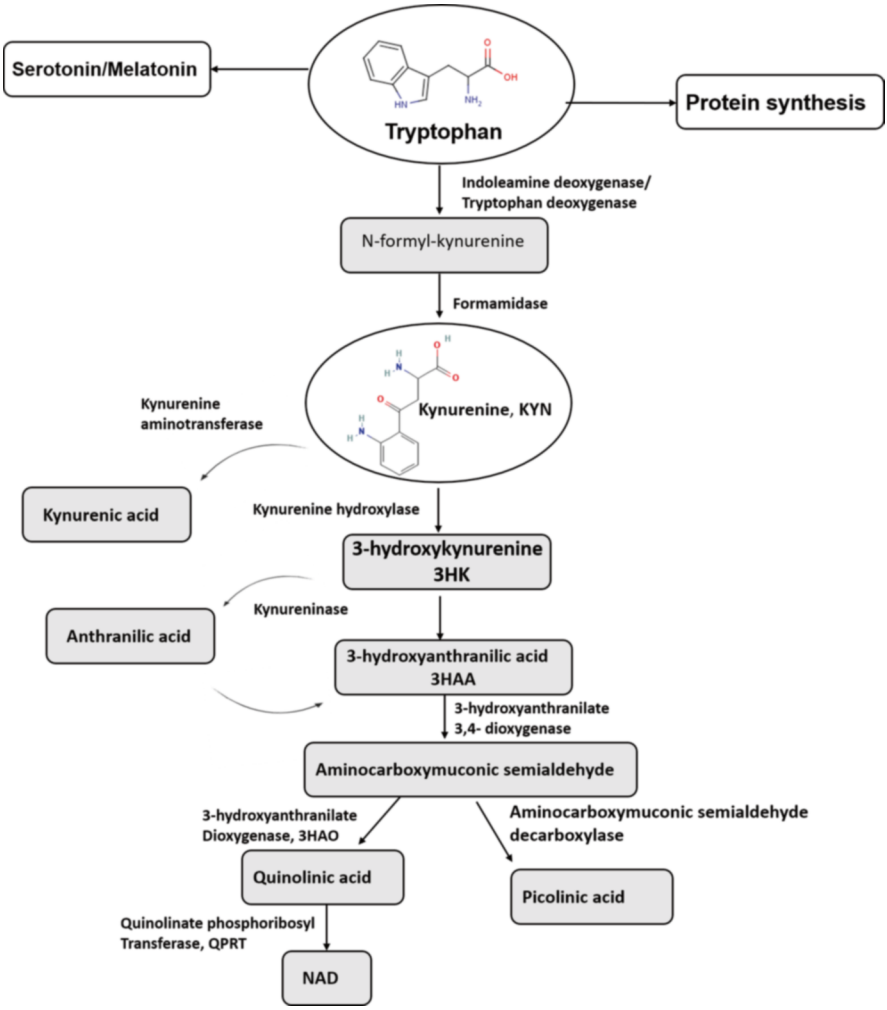

Fig. 7.3 Tryptophan and key components of the kynurenine pathway: Tryptophan conversion to precursor of kynurenine in presence of IDO/TDO is rate- limiting step of the kynurenine pathway, and different intermediates of this pathway have essential role in neuroinflammation and energy homeostasis

distinct. The TDO is substrate- selective homotetramer, expressed mainly in hepatic tissues, while IDO is a monomer found throughout the body and brain including macrophages, dendritic cells, astrocytes, and microglia cells and is less selective by nature (Guillemin et al. 2005a, b, c). The ratio of kynurenine to tryptophan is routinely used as an indicator of IDO activity. In schizophrenia, IDO activation results in higher degradation of tryptophan early in the disease (Zhang et al. 2021). Notably, proinflammatory cytokines enhance the activation of IDO (Zhang et al. 2021). In Alzheimer's disease, a higher level of IDO leads to enhanced level of excitotoxin

and quinolinic acid (QUIN) in the kynurenine pathway (Guillemin et al. 2005a, b, c). Also, in amyotrophic lateral sclerosis (ALS) degeneration of motor neurons is associated with local inflammation where activation of the kynurenine pathway causes toxicity due to QUIN accumulation (Guillemin et al. 2005a, b, c).

Kynurenine (Kyn) is a central molecule of several reactions. The next steps could be (1) the metabolization of Kyn by the Kyn aminotransferases producing kynurenic acid (KA) or (2) the formation of anthranilic acid by kynureninase or (3) the conversion of Kyn into 3-hydroxy-kynurenine (3-OH-Kyn) by Kyn monooxygenases (also named hydroxylases, as they attach a hydroxyl group to the C3 of Kyn).

Several metabolism-related disorders are linked to tryptophan metabolism, which appears to be dysregulated in obese and insulin-resistant (IR) conditions. The level of Kyn in serum is significantly increased in obese adults, probably due to an increased IDO activity (Abedi et al. 2021). The hypoglycemic drug like metformin normalizes the Kyn level in type 2 diabetic individuals by downregulating Kyu pathway (Muzik et al. 2017). The metabolism of fatty acid is also modulated by the IDO-Kyn-AhR (aryl hydrocarbon receptor) pathway, where IFN-γ activates IDO. This leads to the production of Kyn and activation of the AhR, leading to reduced intracellular levels of NAD^+ and increased FA oxidation (Kaiser et al. 2020).

Systemic inflammation in obesity originates primarily from the adipose tissue, in which adipocytes and infiltrated immune cells accumulate and secrete inflammatory factors (Cussotto et al. 2020). A change in gut microbiota plays a role in obesity-induced inflammation. In the gut, TRP is metabolized to various indole derivatives (Roager and Licht 2018; Cussotto et al. 2020), hence affecting the biological processes related to inflammation and metabolization of tryptophan.

7.6 Leptin and Ghrelin at the Regulatory Interface of Peripheral Metabolism in NDDs

Two major hormones have an important role in the regulation of energy balance, viz., leptin and ghrelin (Fig. 7.4). Leptin is a pleiotropic, adipocyte-derived hormone, encoded by the *obese* gene in mammals and is secreted by white adipose tissue. It regulates multiple physiological processes that affect energy homeostasis and informs the brain about energy status by acting as the main peripheral signal for energy balance. The hypothalamus, with the highest expression of leptin receptors, mediates both the appetite-suppressing and energy-expenditure aspects of leptin.

Leptin, an adipocyte-derived hormone, is one of the earliest hormones that is known to provide satiation stimulus by hypothalamic regulation. Leptin crosses BBB and functions in the CNS. It is produced in the periphery as well as in the brain itself. The role in neuromodulation and behavioral performance related to memory

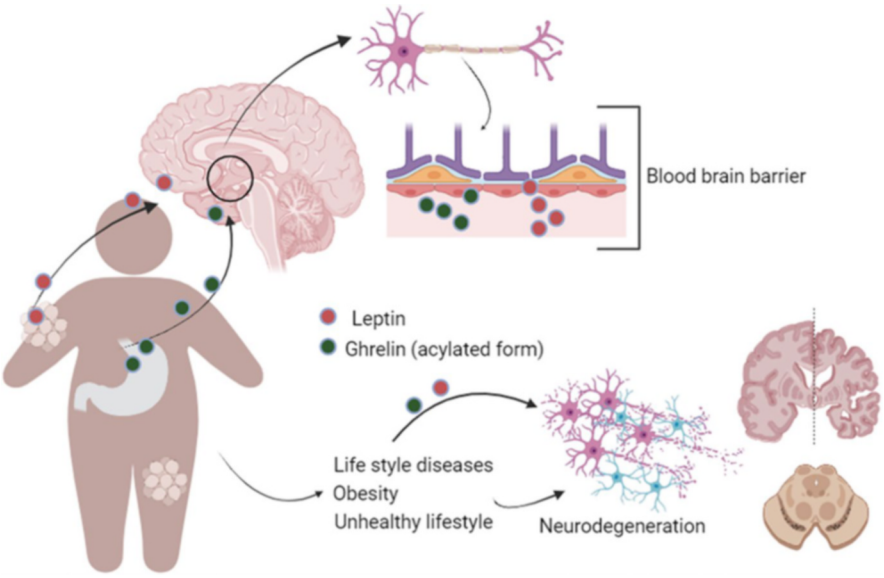

Fig. 7.4 Role of leptin and ghrelin in neurodegeneration. Leptin and ghrelin directly affect the energy metabolism. An unhealthy lifestyle leads to dysregulation of these two major hormones and predisposes individuals toward neurodegenerative disorders

and learning are also affected by leptin due to leptin receptors in the hippocampus region. The functional and structural similarity to the interleukin 6 family of cytokines modulates long-term potentiation in the hippocampus (Oomura et al. 2006). Leptin acts as a vital neuroendocrine mediator of metabolic state; it is known to regulate the energetics associated with innate and adaptive immune responses in NDD (Abella et al. 2017). It is also considered as a link between neuroendocrine and immune systems as it is anorexigenic and proinflammatory by nature (Abella et al. 2017). There is an increase in serum levels of leptin along with inflammation due to modulation in glucocorticoids.

Lifestyle diseases and dietary manipulation with a high-fat diet affect hippocampal functions by inducing glucotoxicity and dysregulating insulin signaling suggesting a role of dietary environment in neurodegeneration (Davis et al. 2014). Leptin resistance, which occurs mainly in the hypothalamus, affects body in two ways. Firstly, it is unable to cross the blood-brain barrier, which means that an insufficient amount of leptin reaches the hypothalamus and secondly results in impaired signaling in the hypothalamic neurons, which is caused by dietary and related factors (Aslam et al. 2021). Leptin affects neurological diseases during metabolic homeostasis. It is known that leptin has a crucial role in the modulation of neurotransmitter and neurotrophic factors as well as known to affect the hypothalamic pituitary adrenal axis. The brain-derived neurotrophic factor expression level is activated in hypothalamic neurons via stimulation of neuronal circuits that activate BDNF synthesis. Leptin temporarily activates ERK1/2 phosphorylation, which impacts CREB

activation, and ultimately affecting cognition and survival of the neurons and astrocytes (Park et al. 2017).

Prolonged metabolic abnormalities lead to leptin resistance and leptin signaling disruption. Leptin induces the neuroprotective and neurotrophic effect on Alzheimer's disease-affected brain. The amyloid β, major component of extracellular plaques in AD, is decreased by leptin treatment. Leptin activates PI3K/Akt/TOR signaling that affects GM1 ganglioside which further inhibits the assembly of amyloid-β (Yamamoto et al. 2014). There is a direct effect of leptin treatment on hippocampus-dependent cognitive behavior, i.e., learning and memory processes where stimulation of NMDA receptors is a crucial event in hippocampal synapses (Kiliaan et al. 2014). PD is characterized by classical motor function deficits due to the loss of dopaminergic neurons in the substantia nigra and the accumulation of proteins into Lewy bodies in the neurons (Duda et al. 2016). In the process of leptin-induced neuroprotection, extracellularly regulated pERK1/2 caused subsequently a MEK-dependent increase in CREB (Weng et al. 2007). Amyotrophic lateral sclerosis (ALS) is another motor neuron disease (MND) characterized by the selective and progressive loss of upper and lower motor neurons of the cerebral cortex, brainstem, and spinal cord. Recently, it has been reported that leptin treatment might be a therapeutic target for ALS disease due to disturbance in metabolic homeostasis in the disease (Ferrer-Donato et al. 2022).

Another hormone that has a crucial role in the regulation of energy homeostasis is ghrelin, an orexigenic hormone, secreted from the stomach, and upon dietary restriction/fasting condition is circulated in the blood providing the necessary hunger signal from the periphery to the central nervous system. Ghrelin is present in acylated and deacylated forms (Yanagi et al. 2018). Additional function of this small peptide is to stimulate the release of growth hormone upon acylation, by binding to growth hormone secretagogue receptor 1a/GHS-R1a (Kojima et al. 1999). Ghrelin receptors are widely distributed in the various regions of the hypothalamus and hippocampus (Mani et al. 2014). Ghrelin stimulates adult hippocampal neurogenesis and hence has positive implications on learning and memory (Li et al. 2013). In AD, there is early damage to the hippocampus region, and the ghrelin administration has positive implications for AD-induced damage (Moon et al. 2011).

Like leptin, acylated ghrelin increases CREB expression leading to activation of ERK1/2 pathway and promoting BDNF expression in the hippocampus (Ferreira-Marques et al. 2021). Ghrelin-induced feeding behavior is controlled by arcuate nucleus neurons that co-express neuropeptide Y and agouti-related protein (NPY/AgRP neurons). Ghrelin enhances AMPK activity in uncoupling protein 2-dependent manner in the hypothalamus. The AMPK activation in dopaminergic neurons is essential for ghrelin-induced neuroprotection in a mouse model of PD (Bayliss et al. 2016). In addition to its role in the regulation of energy intake, ghrelin also plays an important role in the adjustment of immune response by inflammation factors (Kohno et al. 2003; Deng et al. 2015). Notably, ghrelin affects the specialized innate cell inclusive of glial cells, dendritic cells, and macrophages (Moon et al. 2009). Excessive inflammation is reduced by the secretion of inflammatory cytokines like interleukin (IL)-1β, IL6, and tumor necrosis factor-α, TNF1α (Deng et al. 2015),

suggesting the essential role of ghrelin and leptin in the progression of neurodegeneration under unhealthy lifestyle.

7.7 Conclusion

Metabolic alterations in the brain are the primary dysfunctional aspects recognized in the pathophysiology of neurodegenerative diseases. Numerous major candidates have been identified including insulin, glucose, ghrelin, leptin, and glycolysis pathway substrates that directly correlate metabolism and NDD. The hypothalamus regulates metabolic homeostasis and may be considered a crucial target for therapeutic purposes.

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Chapter 8
Protein Metabolism: Critical Factors Implicated in Neurodegenerative Diseases

Jyoti Singh, Bappi Sarkar, Ashim Mukherjee, and Mousumi Mutsuddi

Abstract Protein metabolism involves protein synthesis, posttranslational modifications, and protein folding. Cell has protein quality control systems like ubiquitin-proteasome system and autophagy to degrade misfolded protein. All these processes are precisely regulated to maintain proper proteostasis and homeostasis. Alteration in these processes such as anomalous posttranslational modifications, misfolding, and aberrant protein quality control system results in accumulation and mislocalization of proteins. The aggregated proteins consequently leads to protein toxicity and neuronal death. Formation of aggresome and disrupted proteostasis is the hallmark of neurodegeneration. This chapter highlights the pivotal role of protein homeostasis in neurodegeneration. The crucial role of amyloid-β, α-synuclein, and tau proteins and their processing defects results in aggregate formation in a variety of neurodegenerative diseases and these have been discussed in detail. Additionally, the molecular mechanisms associated with aggregation like posttranslational modifications, such as acetylation, phosphorylation, and ubiquitination have been also described. Defects in the components of ubiquitin machinery and autophagy results in epigenetic and transcriptional dysfunction, abnormal nucleocytoplasmic transport, mitochondrial defects, and increased ROS production along with altered stress granule dynamics and morphology.

Keywords Post translational modifications · Protein misfolding · Protein toxicity · Proteostasis · Neurodegeneration

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8.1 Introduction

The term neurodegenerative disorders (NDDs) encompasses a wide array of clinically and pathologically diverse conditions. It involves slow, progressive, and irreversible impairment of neurons linked with diverse symptoms such as loss of cognition, motor defects, behavioral changes, etc. The prevalence of neurodegenerative diseases is increasing at an alarming rate due to increase in average life expectancy, making it a crucial subject for investigation. Neurodegeneration is a multifactorial disease influenced by genetic, environmental, and endogenous conditions related to aging. One of the key molecular pathology exhibited by most neurodegenerative diseases is the manifestation of protein toxicity. These disorders are also referred to as "protein misfolding diseases" or "proteinopathies" due to the crucial conformational changes in the protein structure (Fig. 8.1). Expansion of unstable repeat causes wide array of neurological disorders. These expansions are caused by slippage during DNA replication or DNA repair. Larger expansion leads to more severe and early onset of symptoms. A pathogenic mechanism observed in majority of the trinucleotide repeat disorders (TRDs) involve toxicity arising from

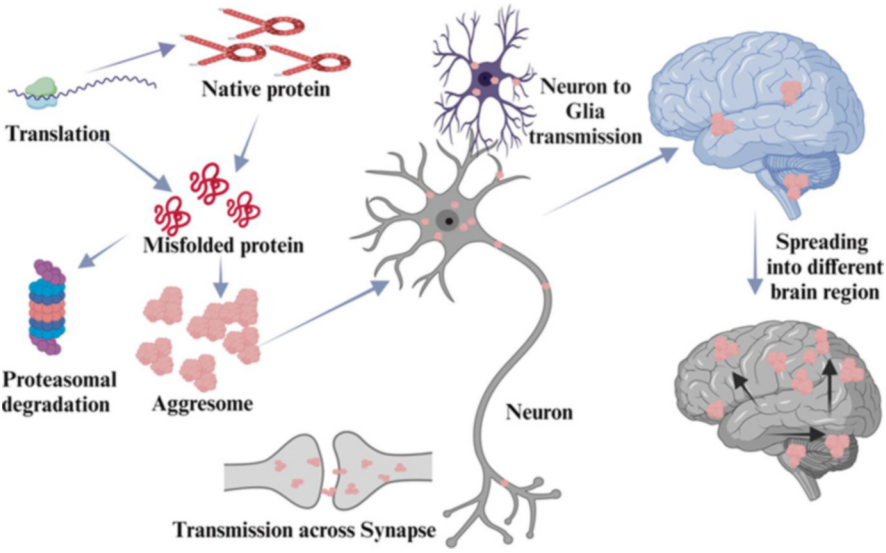

Fig. 8.1 Characteristic features of neurodegenerative disorders are shown. After translation, proteins are folded into their native conformation. Some intrinsic as well as extrinsic factors influence the process and results in misfolding of proteins. Cells have machinery to remove the misfolded proteins or refold them to their native conformation. Due to aging or because of the presence of proteotoxic stress, the quality control system gets exhausted, and the misfolded proteins then begin to form aggregates within the cell. Greater portion of this aggresome show prion-like self-propagation activity during the pathogenesis of NDDs. The pathogenic proteins propagate from a neuron to the other neurons via synapse and from neuron to the glial cells to accelerate neurodegeneration

the messenger RNA or protein produced by the gene containing repeat expansion. Repeat expansion diseases such as Huntington's disease, spinocerebellar ataxia 1, etc are caused by gain of function mechanism (Orr and Zoghbi 2007).

In neurodegenerative proteinopathies, aggregation of misfolded proteins leads to the formation of insoluble structure or inclusion bodies in the central nervous system (CNS). Often, proteins adopts unusual structure resembling amyloids, forming filaments with secondary structures, notably, with abundance in β-pleated sheets. Some of the common aggregates of proteins inside nerve cells consist of tau forming neurofibrillary tangles (NFTs) or Pick bodies, α-synuclein found in Lewy bodies, and TDP-43 present in neuronal cytoplasmic and intranuclear inclusions. These abnormal protein clusters are made up of intrinsic neuronal proteins and other cellular components, which is different from neuronal inclusions in viral infections, where the protein originates from an external source.

Inclusion bodies disrupt normal cellular processes and interfere with organelle function, thus contributing to toxicity and potentially leading to cell damage or death. Gradual malfunction and demise of neurons results from proteotoxic stress leads to disruptions in the ubiquitin-proteasomal and autophagosomal/lysosomal systems, oxidative stress, abnormal calcium signaling, programmed cell death, and neuroinflammation. Protein toxicity encompasses all the pathological changes that ensue from accumulation, mis-localization, and/or multimerization of disease-specific proteins. The protein toxicity may induce cellular abnormalities, including changes in transcription, mitochondrial dysfunction, and a compromised protein/RNA quality control system within the affected neurons. These factors contribute significantly to both, the onset and the advancement of neurodegenerative diseases. While cell death represents the ultimate outcome, preceding this, both animal models and patients often exhibit neurological deficits. Abnormal protein confirmation and neuroanatomical distribution mark the primary histopathological characteristics, and this helps in diagnosis of specific neuropathological conditions. These protein abnormalities may be present before the onset of clinical features (Sparks et al. 1994; Schmitt et al. 2000; Evidente et al. 2011; Frigerio et al. 2011).

Congo red and thioflavin S stains are used to detect protein aggregates like amyloid plaques, neurofibrillary tangles (NFTs) and subpopulation of Lewy bodies, while silver-staining methods are useful for detection of other aggregates (Alafuzoff et al. 2015). Examination of numerous postmortem diseased brain samples, with a wide range of clinical and pathological severities, indicate that several neurodegenerative diseases follow a consistent pattern of advancement, which can be delineated through different stages.

8.1.1 Propagation and Aggregation of Misfolded Proteins

Within the cells, a variety of protein conformations co-exist, including misfolded, unfolded, partially folded, and properly folded forms. In normal cellular conditions, misfolded proteins undergo degradation or get properly refolded with the assistance

of molecular chaperones, which plays vital role in protein folding, transport, and stabilization of protein intermediates. Misfolding of protein results in the exposure of hydrophobic regions which promote aggregation and the amyloid aggregate at higher level and thus demonstrate an intense resistance to degradation. The amyloid state is thermodynamically stable. This thermodynamic stability of amyloid aggregates plays a role in transforming native proteins into amyloid forms (Brundin et al. 2010). Under conditions of proteotoxic stress, cellular aging, or the presence of disease mutations, proteins can escape the cell's quality control system and begin to aggregate into non-native structures which ranges from oligomers and amorphous assemblies to highly ordered amyloid fibrils and plaques called aggresomes or inclusion bodies (Fig. 8.1).

Chaperones monitor the integrity of properly folded protein chains, which in certain cases, have the capability to unfold and subsequently refold misfolded proteins. Studies employing yeast model have revealed that CLIPs (chaperones linked to protein synthesis) are directly connected to the translational apparatus and are responsible for monitoring the quality control of recently synthesized proteins and HSPs (heat shock proteins) in order to protect these proteins from environmental stress. During aging or in misfolded protein-related diseases, cells may undergo "proteostatic collapse". This term refers to the disruption of cellular protein homeostasis and is often linked with the buildup of ubiquitinated inclusion bodies (IBs), commonly observed in numerous neurodegenerative disorders (Hipp et al. 2014).

A significant characteristic of misfolded protein-associated diseases is the ability of pathogenic proteins to propagate to healthy counterparts and induce pathogenic conformations. Following injection of pathogenic proteins into the brain of normal animals, the pathogenic amyloids can propagate to unaffected neuron or glia for initiation of pathophysiology (Fig. 8.1) (Pearce et al. 2015; Brettschneider et al. 2015). Both *in vivo* and *in vitro* research have demonstrated that the misfolding of a single disease-causing protein can prompt the misfolding of other proteins that are prone to aggregation (Brettschneider et al. 2015) and the aggregates of various disease-related proteins can coexist within the same patient (Galpern and Lang 2006). Currently, the mechanisms underlying the spread of misfolded proteins from one neuron to another are being investigated. Recent findings propose that the interneuronal transmission of misfolded proteins involves either activity-dependent secretion via exosomes (Wu et al. 2016) or pathways mediated by molecular chaperones as shown in Fig. 8.2 (Fontaine et al. 2016).

NDDs are classified on the basis of their causal genetic mechanisms which lead to abnormal protein deposits. The protein aggregates involved vary between diseases, for example, amyloid-β (Aβ) and tau aggregates in Alzheimer's disease (AD), misfolded α-synuclein in Parkinson's disease (PD), TAR DNA-binding protein 43 (TDP-43) and superoxide dismutase 1 (SOD1) pathology in amyotrophic lateral sclerosis, and mutated huntingtin (htt) in Huntington's disease. The protein anomalies in these disorders have abnormal conformational properties. Mounting experimental evidence suggests that the abnormal protein conformers may spread from cell to cell along anatomically connected pathways (Dugger and Dickson 2017).

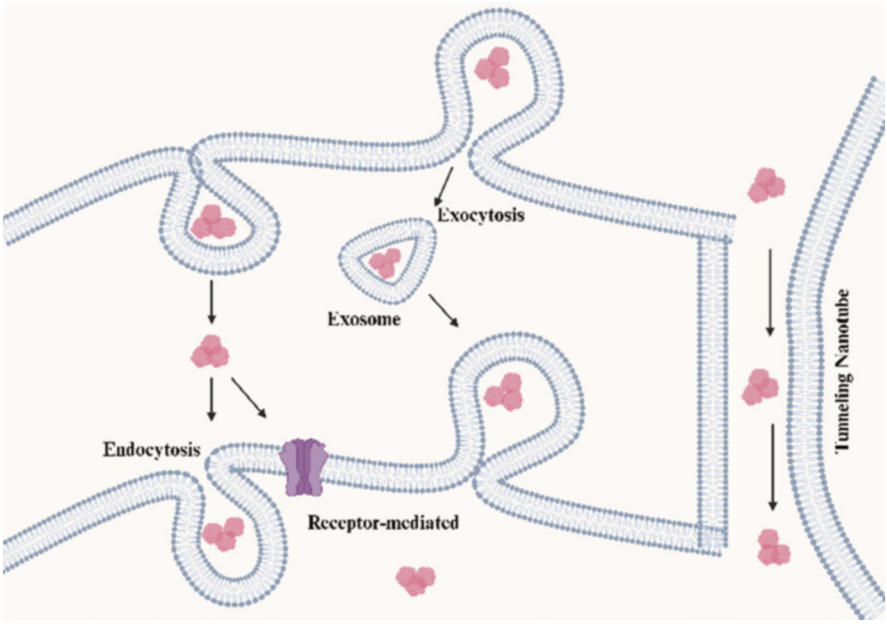

Fig. 8.2 Image showing transmission of aggregated proteins from one cell to other. The aggregated proteins propagate from one cell to other through (i) endocytosis, (ii) receptor-mediated transport, (iii) exocytosis, and (iv) forming a tunneling microtubule between two cells

8.2 Amyloid-β, α-Synuclein, and Tau Protein Metabolism in Neurodegenerative Disorders

8.2.1 Amyloid-β

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, which is characterized by deposition of amyloid plaques and neurofibrillary tangles. The two subtypes, early-onset familial AD (FAD) and late-onset sporadic AD (SAD), are distinguished by their genetic underpinnings. FAD is related to the mutations in presenilin 1 (PS1), presenilin 2 (PS2), and amyloid precursor protein (APP) genes, leading to aberrant aggregation of amyloid-beta (Aβ) peptides (Suh and Checler 2002). Particularly, mutation in APP contributes to Aβ aggregation, whereas PS1 and PS2 mutations enhance proteolytic processing of APP, intensifying FAD severity (Selkoe 2008). In contrast, SAD affects approximately 90% of AD cases, lacking specific gene mutations. The Apo lipoprotein E (ApoE) gene, particularly ApoE4, is a recognized risk factor for SAD (St George-Hyslop 2000). Despite incomplete penetrance, it's likely that environmental factors contribute to sporadic AD, as majority of the cases are devoid of identified genetic factors.

Amyloid precursor protein (APP) is expressed in neurons and undergoes non-amyloidogenic and amyloidogenic cleavages as depicted in Fig. 8.3. While the

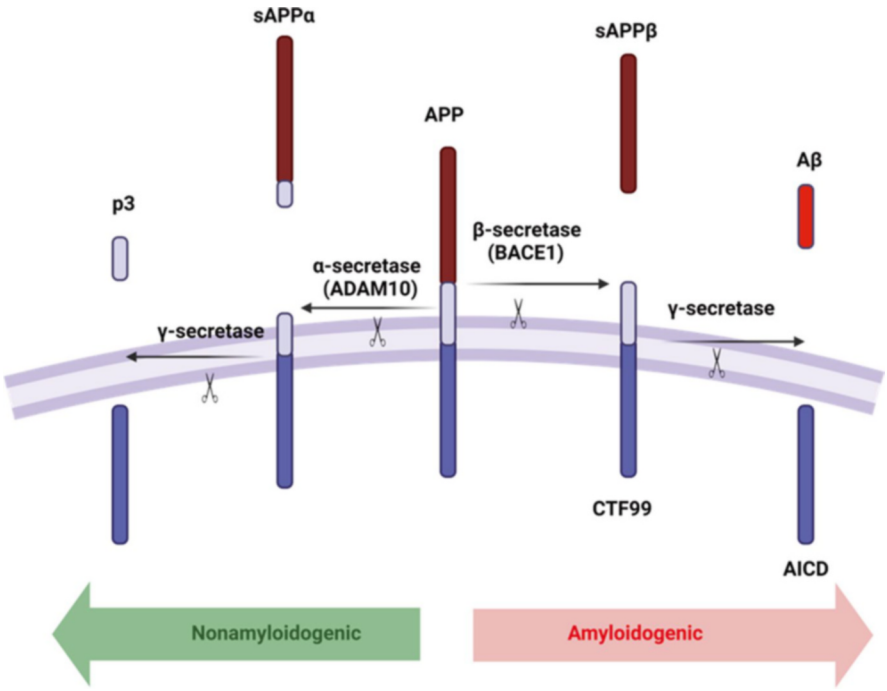

Fig. 8.3 Diagrammatic representation of amyloid precursor protein (APP) processing pathways. The transmembrane protein APP is processed in two ways: α-secretase mediated non-amyloidogenic and β-secretase mediated amyloidogenic pathway. In non-amyloidogenic pathway, α-secretase cleaves the APP in between *β*-amyloid (Aβ) region and releases the soluble APP (sAPP) fragment. The C-terminal fragment 82 (APP CTF-83) is then cleaved by the γ-secretase and releases the APP intracellular domain (AICD) and P3 fragment. In amyloidogenic pathway, first APP is cleaved by *β*-secretase which produces the soluble fragments sAPP-*β* and APP-CTF99. APP-CTF99 is then cleaved by γ- secretase and produces the Aβ_{40}, Aβ_{42}, and AICD

former yields soluble APP and has neuroprotective effects, the later, initiated by β-secretase, generates Aβ peptides which are susceptible to aggregation. Aβ concentration regulation occurs at two levels: α- and β-secretase activities and neuronal genome-associated APP synthesis. Presenilin comprises of γ-secretase, and it crucially regulates Aβ production and contributes to FAD. Certain FAD mutations selectively increase Aβ-42 concentration, exacerbating the disease severity. Presenilin mutations can also impact neuronal function beyond Aβ production, influencing signal transmission, calcium transport, and neurotransmitter release (Zhang et al. 2009). In its native form, Aβ exhibits water solubility, permitting its entry into cerebrospinal fluid and blood. Chaperone-assisted folding leads to physiologically conformed Aβ peptides, while deviations resulted in oligomer formation associated with different pathological consequences. Various enzymes, including angiotensin-converting enzymes and metalloproteinases, mediate the hydrolysis of Aβ, generating multiple intermediate products.

Understanding the intricate interplay of genetic and molecular factors in β-amyloid peptide regulation provides crucial insight into the etiology of AD. The delicate equilibrium between physiological and pathological forms of Aβ highlights potential therapeutic target to mitigate impact of Aβ dysregulation in neurodegenerative diseases.

A myriad of studies have comprehensively examined expression of amyloid precursor protein (APP) glycoprotein and the generation of Aβ peptides in various human tissues, revealing their presence in majority of the organs, for example, the brain, heart, spleen, liver, lung, placenta, testicles, sperm, dorsal roots, ganglia, adrenal glands, blood vessels, cerebrospinal fluid (CSF), blood plasma, fibroblasts, thrombocytes, and leucocytes (Liu et al. 2005). Remarkably, the physiological concentration of Aβ varies in CSF, ranging from 5 ng/ml to 25 ng/ml in healthy subjects and patients with Alzheimer's disease (AD), respectively, with transgenic murine models reflecting a concentration of 20 ng/ml (Gelfanova et al. 2007).

Contrary to the once-held perception in the irreversibility of Aβ accumulation in the brain, the twenty-first century usheredin discoveries of biochemical pathways responsible for amyloid degradation and clearance, prompting a reassessment of our conventional understandings. It's noteworthy that amyloid-degrading enzymes, which include neprilysin (NEP), endothelin-converting enzyme (ECE1), insulysin, and plasmin, have been identified and implicated in Aβ hydrolysis *in vivo*. Deregulation of these enzymes may contribute to Aβ accumulation, leading to the development of neurodegenerative disorders, including AD.

Additionally, glucagon-like peptide (GLP-1) and its receptor plays a role in decreasing endogenous Aβ levels, presenting a potential therapeutic target for AD. Research on mitochondrial pre-sequence peptidase (PreP) provides another layer to the family of amyloid-degrading enzymes, with connections for Aβ regulation within the mitochondrial environment. In the sophisticated process of amyloid metabolism, factors such as age-related changes in APP metabolism, membrane composition alterations, and the role of enzymes like β-site amyloid precursor protein-cleaving enzyme (BACE1) in Aβ formation contribute to the complex Aβ dynamics (Kern et al. 2006).

Even though the accumulation of Aβ has long been related with neurotoxicity, emerging evidences indicate that, at physiologic concentrations, Aβ plays crucial role in neuronal processes and structural and functional plasticity, along with cognitive function (Pearson and Peers 2006; Robakis 2011). These findings highlight the complexity of amyloid metabolism, emphasizing the importance of understanding the delicate balance between Aβ's physiological and pathological roles in neurodegenerative diseases.

8.2.2 α-Synuclein

α-Synuclein (AS) consists of three main domains; a membrane-binding α-helix, a non-amyloidogenic core (NAC), and a variable carboxy-terminal tail that is crucial for chaperone-like activity. The NAC domain induces conformational changes from coil to β-sheet, with residues 66–74 crucial for fibrillation (Giasson et al. 2001). Over half of AS consists of motifs forming amphipathic helices, contributing to lipid affinity (Uversky 2009). The predominant physiological AS forms are helically folded tetramer, or a disordered monomer, with low fibril-aggregation tendency with potential for misfolding and self-aggregation *in vivo*, leading to toxicity (Uversky 2007; Wang et al. 2011). Wild-type AS is monomeric and intrinsically unfolded at low concentration but adopts an α-helical conformation when membrane-bound. Membrane-bound AS serves as a key intermediate in aggregation and fibrillation, providing seeds for accelerated deposition of the less aggregation-prone and disordered free cytosolic form of AS (Breydo et al. 2012). Fibrils formed *in vivo* exhibit amyloid characteristics with antiparallel β-sheet structures. Recent nuclear magnetic resonance studies revealed repeated structural motif in AS fibrils, challenging previously proposed folds (Comellas et al. 2011). The secondary structure of AS is environment-dependent, which is influenced by cytoplasmic or membrane-bound states, with rapid AS exchange between these states facilitating dynamic cellular structures that are regulated by environmental conditions (Bennett 2005).

The predominant theory of Parkinson's disease (PD) categorizes it among neurodegenerative disorders characterized by protein misfolding, which are commonly referred to as "proteinopathies" (Uversky 2009). In certain familial instances of Parkinson's disease, a mutation from alanine to threonine or valine occurs at residue 53 of α-synuclein (Fig. 8.4). It is evident that these mutations enhance the aggregation of α-synuclein into filaments, leading to the generation of Lewy bodies (LB). On the contrary, mutations from alanine to proline at residue 30, glycine to aspartic acid at residue 51, delays its aggregation (Mehra et al. 2021). Proteins associated with neurodegeneration undergo abnormal turnover, elevated concentration, aggregation, and accumulation of insoluble protein deposits due to the inability of chaperones and proteasomes to refold or degrade them (Ebrahimi-Fakhari et al. 2011). Molecular chaperones, associated with the ubiquitin-proteasome system (UPS) and autophagy-lysosome pathway (ALP), play crucial role in maintaining protein homeostasis, modulate neurodegeneration, and exert neuroprotective effect by reducing α-synuclein (AS) neurotoxicity (Gorbatyuk et al. 2008). Dysfunctional chaperone-mediated autophagy (CMA), combined with impaired proteasomal function, contributes to PD pathogenesis (Alvarez-Erviti et al. 2010).

AS concentration alterations may drive AS aggregation and neurotoxicity, with a shift in equilibrium between normal and misfolded conformations. The function of total AS concentration in PD remains unclear and contradictory. The level of phosphorylated AS (pAS) increases in PD, probably promoting neurotoxicity, oligomer formation, and LB pathology, and interferes with important cellular processes. Genetic and pathological observations indicate the association of PD with factors

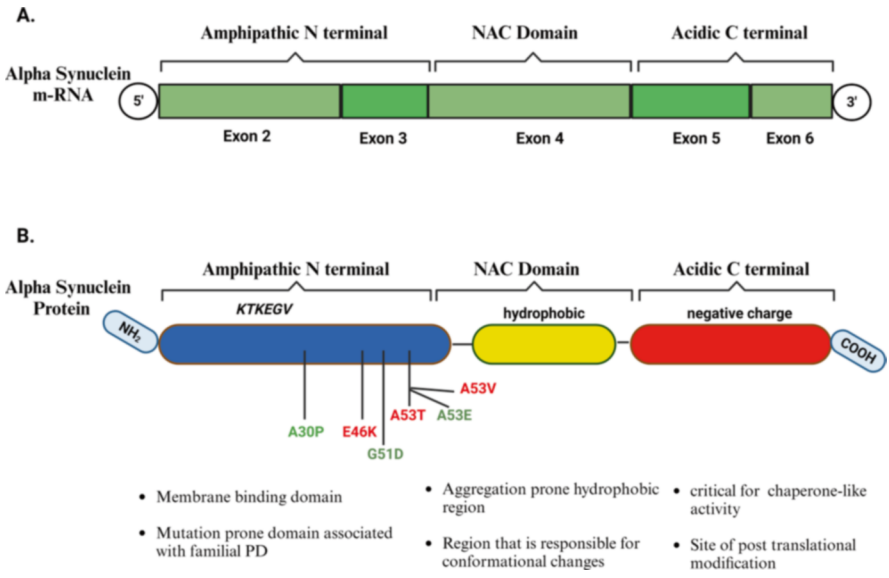

Fig. 8.4 The structure of α-synuclein is shown. (**a**) Schematic representation of α-synuclein mRNA showing different domain consists of different combinations of exons. (**b**) α-Synuclein protein structure and its different domain labeled with known mutations responsible for familial Parkinson's disease. The protein consists of three distinct domains, the amphipathic N-terminal domain (blue) that has a helical folding propensity which is responsible for membrane binding. The non-amyloidogenic core (NAC) domain is hydrophobic in nature and is responsible for promoting aggregation (yellow). The C-terminal acidic tail containing domain (red) have chaperon-like activity and modulates the α-synuclein aggregation

leading to increased production or impaired clearance of misfolded proteins, creating a cycle of protein accumulation, proteolytic stress, toxic oligomer formation, interference with different cellular processes and cell death (Olanow and McNaught 2011). Mitochondrial dysfunctions, abnormal protein aggregation, oxidative stress (OS) and impaired bioenergetics have been identified as major contributors to PD (Pilsl and Winklhofer 2012). Further research is needed to characterize the features of specific neuronal populations that are vulnerable in PD as well as understand the role of inflammation and elucidate other factors contributing to neurodegeneration (Elstner et al. 2011).

8.2.3 Tau Protein

Tau protein consists of four distinct domains; the N-terminal domain (aa 1–150), the proline-rich domain (PRD), the microtubule-binding domain (aa 244–368) (MTBD) and the C-terminal domain (aa 369–441) (Fig. 8.5) (Sexton et al. 2022). The N-terminal domain, also known as projection domain, plays a crucial role in protein

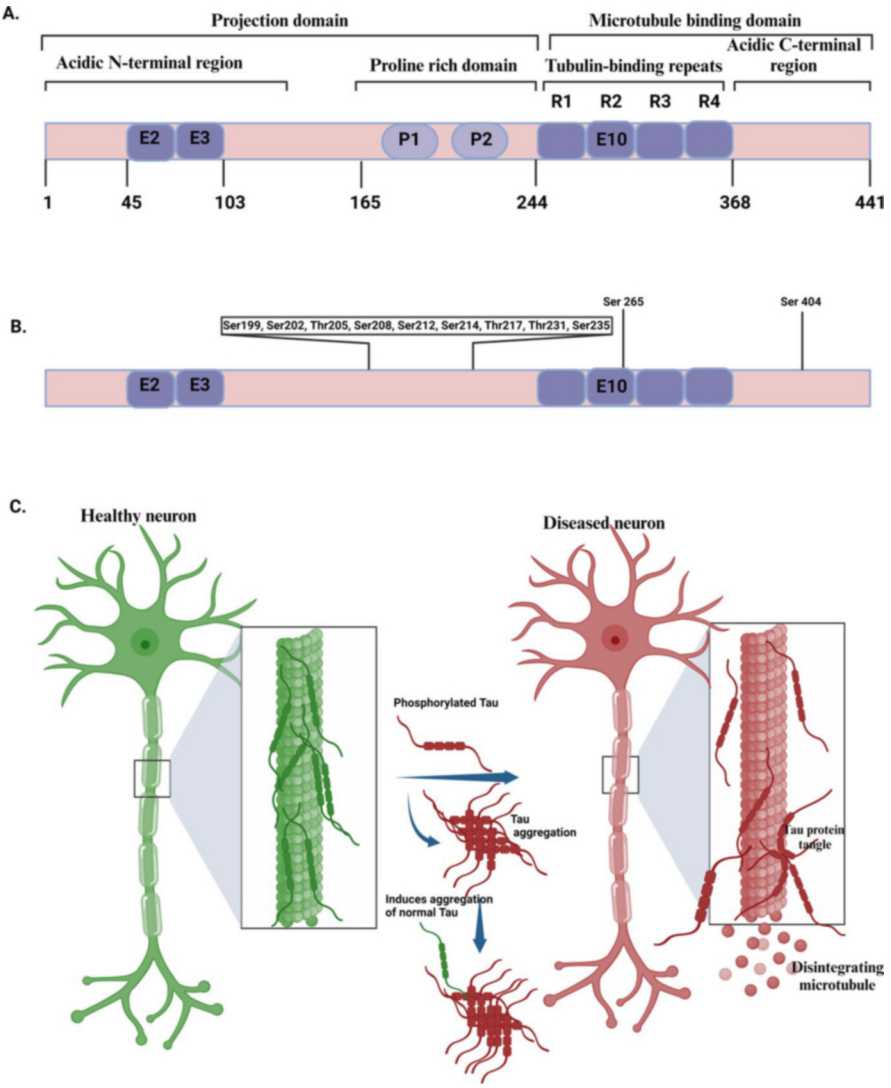

Fig. 8.5 Schematic representation of tau protein structure along with the phosphorylation sites which contribute to neurodegeneration (**a**) The longest human tau isoform of 441 amino acids that contains projection domain and microtubule-binding domain. Projection domain contains 2 N-terminal inserts (E2, E3) and part of proline-rich region. Microtubule-binding domain contains four tubulin binding repeats and C-terminal region. (**b**) Schematic representation of tau protein showing the residues which are prone to phosphorylation. (**c**) Hyperphosphorylated tau forms aggregates known as tau aggregation or tau tangles that attracts the healthy tau and incorporate into the tau aggregation. Phosphorylated tau cannot bind with microtubule and is dislodged

interaction signaling, and thus acts as a functional regulator. Additionally, the N-terminal domain of tau also plays a role in its axonal localization and has been suggested to facilitate interaction with various other neuronal proteins. Especially, the N-terminally truncated tau exhibits an increased association with microtubules (Gauthier-Kemper et al. 2018). The proline-rich domain (PRD) is crucial for interacting with proteins containing SH3 domain and plays a significant role in the folding of tau protein. Additionally, it participates in cell signaling and engages with protein kinases, thereby influencing not only the binding and assembly of microtubule but also the phosphorylation sites on tau. The microtubule-binding domain (MTBD) serves as the mediator for tau's binding to microtubules, and this is responsible for stabilizing microtubule structures (Goedert and Spillantini 2019). The C-terminal domain helps in microtubule binding and also interacts with the N-terminal portion, imparting paperclip conformation to the tau protein (Goedert and Spillantini 2019).

Over 100 mutations in the microtubule-associated protein tau (MAPT) have been linked to neurodegenerative diseases, which are categorized as either missense or splicing mutations (Ruan and Ikezu 2019). Missense mutations primarily affect protein levels, while splicing mutations modulate alternative splicing of tau exon 10. Mutations introducing amino acid substitutions alter tau interaction with microtubules, promoting filament assembly (Nacharaju et al. 1999).

Most missense mutations cluster on or near the MTBR domain of tau, alongside splicing mutations. Mutations impacting exon 10 splicing can be intronic or exonic, resulting in overproduction of 4R tau and filament assembly (Strang et al. 2019). Less commonly, mutations also increase 3R tau expression. Mutations in exons 9–13 associated with 3R tauopathies, such as PiD, include K257T, L266V, G272V, G273R, S305N, L315R, S320F, S320Y, P332S, Q336H, Q336R, K369I, E372G, and G389 (Ghetti et al. 2015). Recently, a deletion from G389 to I392 was described as predominant in 3R tauopathy (Shafei et al. 2020). However, the most characteristic MAPT mutations that impact alternative splicing results in 4R Tau overproduction. Several intronic and exonic mutations that are associated with neurodegenerative diseases are often linked to 4R overproduction.

Other than affecting mRNA splicing of MAPT exon 10, these mutations also disrupt tau protein folding and/or protein-protein interactions, enhancing tau aggregation. Predominantly, mutations that cluster between exon 9 and exon 12, encoding microtubule-binding repeat region (MTBRs) mutations, affect tau interactions with microtubules, promoting filament assembly (Goedert et al. 2018). Markedly, a direct correlation between MAPT mutations and poststranslational tau modifications is yet to be established.

The P301 residue is unique to 4R tau isoforms and is crucial for regulating tau aggregation (Strang et al. 2019). P301L is the most common mutation, inducing aberrant tau hyperphosphorylation and aggregation in transgenic mice (Sotiropoulos et al. 2015). Mutations on P301 (P301L, P301S, P301T) are associated with tau pathology, inducing more oligomer formation compared to that of the wild-type tau (Maeda et al. 2018). A PS19 mouse model with a P301S *tau* mutation spontaneously develops tau pathology (Iba et al. 2013), and tau transgenic mice expressing

P301L or P301S also develops tau-mediated pathology (Jackson et al. 2016). Additionally, combining P301L or P301S tau with S320F generates aggressive tauopathy models without exogenous seeding (Strang et al. 2018). THY-Tau 22 mice (bearing G272V and P301S mutations) show hyperphosphorylation of tau, NFT-like inclusions, and cognitive impairment. Other MAPT mutations, besides P301, support *in vivo* models of tau pathology.

Mutations outside exon 10, such as I260V in exon 9 and K317M, K317N, E342V, and N410H in exons 11–13, alter the 3R/4R ratio. Not all mutations in exons 11 and 12 impact exon 10 splicing, like G335S, G335V, G335A, and V337M; instead, they reduce tau's microtubule assembly. Conversely, Q336H and Q336R mutations increase tau-mediated microtubule assembly (Ando et al. 2020). In spite of not altering the 3R/4R ratio or MT binding ability, the D348G tau mutation is associated with early amyotrophic lateral sclerosis (ALS) onset, where tau accumulation evades proteasomal degradation (Origone et al. 2019). Other mutations (S352L, S356T, P364S, G366R, P397S, R406W, and T427M) were found in FTLD, FTD, or PD patients (Borrego-Écija et al. 2019). Notably, P364S tau has a special propensity for aggregation, exceeding that of P301L tau. C-terminal mutations (P397S, R406W, and T427M) have been associated with late onset and/or longer disease duration, indicating reduced impact of the role of C-terminal for tau-mediated pathology.

Intriguingly, only one N-terminal residue (R5) mutation in exon 1 has been linked to tau-mediated pathology. R5H, R5L, and R5C mutations are associated with AD, PSP, and Parkinson's disease, respectively (Schulte et al. 2015). R5H and R5L mutations reduce tau's microtubule assembly and promote tau fibril formation. Additionally, R5L mutation affects tau polymerization and MT assembly in 0N4R isoforms (Mutreja et al. 2018). Apart from these, genetic mutations are known that contribute to misfolding of proteins, ultimately leading to formation of aggresome. There are multiple posttranslational modifications such as acetylation, phosphorylation, and ubiquitination known to affect protein aggregate formation and cytotoxicity.

8.3 Unveiling the Symphony of Posttranslational Modifications

Posttranslational modifications (PTMs) and defects in protein quality control systems play crucial role in the accumulation of misfolded proteins. Anomalies in PTMs within the cellular environment alter conformation, enzymatic activity, and protein turnover rate and promote generation of toxic aggregates, causing various proteinopathies. PTMs refer to covalent or enzymatic modifications occurring post-protein synthesis. Typically, these modifications take place in the amino acid side chain or at the protein's C-terminal or N-terminal region, depending on the modification type. Classification of PTMs encompasses the addition of functional/

chemical groups (e.g., acetylation, methylation, formylation, phosphorylation, amidation), addition of polypeptide chains (e.g., ubiquitination, SUMOylation, neddylation), addition of complex molecules (e.g., palmitoylation, oxidation, glycation, pegylation, carbamylation), and amino acid modifications (e.g., racemization, citrullination, isoaspartate, proteolytic cleavage) (Xu et al. 2018).

Various studies underscore the involvement of aberrant PTMs in the pathogenesis of proteinopathies, including cancer, heart disease, neurodegenerative diseases (NDDs), diabetes, and metabolic syndromes (Varland et al. 2015). Common NDDs such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and spinocerebellar ataxias (SCAs) are characterized by progressive and slow neuronal death due to the accumulation of misfolded and pathogenic protein aggregates. Conversely, amyotrophic lateral sclerosis (ALS), another prevalent NDD, features rapid disease progression, with median survival time ranging from 20 to 48 months. The resulting neuronal cell death disrupts the proper functioning of the brain's cellular machinery, leading to memory impairment, synaptic dysfunction, learning disabilities, and cognitive defects. In the next part of this chapter, we will discuss about some of the important post translational modifications involved in various proteinopathies.

8.3.1 Phosphorylation Dynamics in Neurodegenerative Disorders

Phosphorylation, a pivotal posttranslational modification (PTM), intricately regulates the metabolism of crucial proteins in neurodegenerative disorders (NDDs). The molecular intricacies of phosphorylation offer profound insight into the pathogenesis of disorders like Alzheimer's disease (AD), Parkinson's disease (PD), and tauopathies.

8.3.1.1 Amyloid-β (Aβ) in Alzheimer's Disease

In Alzheimer's disease (AD), phosphorylation of amyloid- β (Aβ) is an essential molecular process that contributes to the pathogenesis of the disorder. Aβ, derived from the cleavage of amyloid precursor protein (APP), undergoes phosphorylation at specific residues, such as Thr668 within the APP intracellular domain. Key kinases implicated in Aβ phosphorylation include glycogen synthase kinase-3β (GSK-3β) and cyclin-dependent kinase 5 (CDK5) (Town et al. 2002). Aberrant activation of these kinases leads to the accumulation of hyperphosphorylated Aβ, promoting the formation of neurotoxic plaques, a hallmark of AD pathology (Town et al. 2002). Phosphorylated Aβ not only contributes to plaque formation but also exerts detrimental effects on synaptic function and neurotransmission. This disrupts normal neuronal communication, contributing significantly to cognitive decline in

AD. Understanding the intricacies of Aβ phosphorylation is crucial for unraveling molecular mechanism underlying AD and this may offer potential target for therapeutic interventions.

8.3.1.2 α-Synuclein in Parkinson's Disease

In Parkinson's disease (PD), α-synuclein phosphorylation is a crucial event contributing to the pathology of disorder. α-Synuclein is a presynaptic protein, and abnormal phosphorylation at specific residues, notably Ser129, is a hallmark of PD pathology. Multiple kinases, including glycogen synthase kinase-3β (GSK-3β) and casein kinase 2 (CK2), are implicated in this process (Waxman and Giasson 2008). GSK-3β, in particular, plays an essential role in promoting the aggregation of α-synuclein by phosphorylating residues within its aggregation-prone domains (Llorens-Marítin et al. 2014). Phosphorylation of α-synuclein influences its conformational changes, facilitating the formation of toxic oligomers and fibrils, contributing to the formation of Lewy bodies, characteristic pathological inclusions in PD. Additionally, studies have demonstrated that phosphorylated α-synuclein exhibits increased neurotoxicity compared to its non-phosphorylated counterpart (Oueslati 2016).

8.3.1.3 Tau in Tauopathies

Tau phosphorylation is a pivotal molecular event in the pathogenesis of neurodegenerative disorders, particularly tauopathies such as Alzheimer's disease (AD). Tau, a microtubule-associated protein (MAP), plays a crucial role in stabilizing microtubules and promoting their assembly (Fig. 8.5c). In healthy state, tau undergoes dynamic phosphorylation and de-phosphorylation, and this is tightly regulated by various kinases and phosphatases, thus maintaining a delicate equilibrium. However, in the context of tauopathies, this balance is disrupted, leading to abnormal hyperphosphorylation of tau. Numerous kinases contribute to tau phosphorylation, with GSK-3β and CDK5 being the key players. These kinases target specific serine and threonine residues on tau, including Ser199, Ser202, Thr205, Ser208, Ser212, Ser214, Thr217, Thr231, Ser235, and Ser262 (Hanger et al. 2007). Hyperphosphorylation of these residues causes tau to detach from microtubules, leading to microtubule destabilization and disruption of axonal transport, a process that is critical for neuronal function.

GSK-3β, in particular, has been implicated in the aberrant phosphorylation of tau and is activated in conditions of tau pathology. Its role extends beyond tau phosphorylation, influencing the formation of neurofibrillary tangles (NFTs). GSK-3β-mediated tau hyperphosphorylation promotes aggregation of tau into paired helical filaments (PHFs) and straight filaments, which are the primary components of NFTs.

CDK5, another key kinase, also contributes to tau hyper phosphorylation. Activated CDK5 phosphorylates tau at Ser202, Ser235, Ser404, and Thr205 (Hanger et al. 1992). Dysregulation of CDK5 activity has been observed in neurodegenerative conditions, emphasizing its role in the pathogenesis of tauopathies. The consequences of tau hyperphosphorylation are far-reaching. Hyperphosphorylated tau loses its ability to bind to microtubules, leading to their destabilization and subsequent impairment in axonal transport. Additionally, phosphorylated tau adopts a conformation that promotes it's self-assembly into oligomers and larger aggregates. These aggregates can further seed the aggregation of normal tau, creating a self-perpetuating cycle of pathological tau accumulation (Fig. 8.5). Furthermore, phosphorylated tau has been implicated in the spread of disease pathogenesis among the neurons. Studies have demonstrated that extracellular tau, released from neurons, can be internalized by neighboring cells, leading to the templated misfolding and aggregation of intracellular tau (Clavaguera et al. 2009). This phenomenon contributes to the progressive nature of tau pathology in the brain.

8.3.2 Molecular Mechanisms of Acetylation Dynamics in Neurodegenerative Disorders

Acetylation is a reversible posttranslational modification (PTM) involving addition of acetyl groups to lysine residues and plays a crucial role in the molecular mechanisms underlying neurodegenerative disorders (NDDs). Understanding specific targets, enzymes involved, and consequences of acetylation provides insight into the pathogenesis of disorders such as Alzheimer's (AD) and Parkinson's disease (PD). In AD, acetylation of tau protein has garnered significant attention. The enzyme responsible for tau acetylation is p300, which is a histone acetyltransferase (HAT). Acetylation of tau at specific lysine residues influences its conformation, stability, and propensity for aggregation (Min et al. 2010). The acetylation of tau exacerbates its pathology, leading to the formation of NFTs. Histone acetylation, mediated by various HATs and counteracted by histone deacetylases (HDACs), is another critical aspect of acetylation dynamics in AD. Dysregulation in histone acetylation patterns affects the expression of genes associated with synaptic function and neuronal survival, thus contributing to the neurodegenerative process (Gräff et al. 2012). In PD, α-synuclein undergoes acetylation, impacting its aggregation kinetics. The acetylation of α-synuclein occurs at lysine residues, particularly K6, K10, K12, K21, and K23. The acetylation of α-synuclein is mediated by acetyltransferases such as CREB-binding protein (CBP) and p300 (Anderson et al. 2006). Acetylated α-synuclein exhibits increased aggregation propensity, contributing to the formation of Lewy bodies, a characteristic feature of PD pathology.

8.3.3 Molecular Mechanisms of Ubiquitination Dynamics in Neurodegenerative Disorders

8.3.3.1 Alzheimer's Disease

Histologically, AD involves substantial neurodegeneration and synaptic loss, leading to the gradual atrophy of cerebral cortex lobes. Ubiquitinated forms of Tau, amyloid-β, and other proteins contribute significantly to NFTs and extracellular plaque formation.

Amyloid-β, resulting from the cleavage of amyloid precursor protein (APP), has detrimental effect on the neuronal health. Mutations in APP or presenilin protease enzymes are responsible for amyloid- β generation, and this leads to early onset of AD, thus emphasizing the central role of amyloid-beta metabolism in AD pathogenesis. The mechanisms governing hyperphosphorylated Tau generation are less clear, suggesting that amyloid-β stimulates GSK3-B kinase, inducing aberrant Tau phosphorylation (Hernández et al. 2010).

The synthesis, processing, and degradation of these proteins involve intricate molecular mechanisms in which the ubiquitin-proteasome system (UPS) and ubiquitination play pivotal role. HRD1, an E3 ligase associated with endoplasmic reticulum- associated degradation (ERAD), interacts with APP, impacting ER stress and apoptosis. In the Golgi apparatus, ubiquitination of APP, stimulated by ubiquitin-1, hampers its maturation and delays processing, contributing to amyloid-β accumulation (El Ayadi et al. 2012).

UPS also regulates APP internalization and processing thus affecting amyloid-beta production. FBXW7 ubiquitinates the gamma-secretase component, Presenilin 1, paradoxically increasing amyloid-β production. NUB1, a regulator of GSK3- β, diminishes hyperphosphorylated Tau levels and Tau aggregates (Richet et al. 2012). The UPS-mediated degradation of MDM2 oncoprotein influences GSK3 activity and Tau phosphorylation.

UCHL-1, a deubiquitinating enzyme, reverses amyloid-beta- induced diminished brain-derived neurotrophic factor (BDNF) signaling (Poon et al. 2013). GSK3- β is elevated in AD in association with p53 and contributes to Tau hyperphosphorylation. NUB1- and NUB1-regulated Nedd8 influence GSK3-β levels and Tau aggregates. Proven effects of amyloid-β on neurons are influenced by the complex actions of the UPS by indirect methods than just the degradation of the amyloid-β peptide or its precursor. Exposure to excess amyloid-β causes diminished BDNF signaling in AD patient tissue and also in mouse models; however, this reduction can be reversed by the overexpression of the deubiquitinating enzyme UCHL-1 (Poon et al. 2013).

NMDA receptors as well as downstream effectors of ubiquitin-dependent pathways contribute to AD pathogenesis. Ubiquitin-mediated regulation of GluN2B subunit and NMDA receptor turnover by E3 ligases such as Mind Bomb-2 and Fbxo2 highlights the complexity of NMDA receptor involvement (Jurd et al. 2008).

8.3.3.2 Parkinson's Disease

Mutations in α-synuclein have been identified in familial Parkinson's disease (PD), and the proteasome is implicated in its turnover. In PD, proteasome dysfunction in the substantia nigra has been reported, and this leads to formation of protein inclusion and neuron degeneration. Mutant alpha-synuclein directly interacts with the proteasome pathway, thus reducing its proteolytic activity. The E3 ligase Parkin can alleviate this proteasome deficit caused by mutant alpha-synuclein expression.

Nearly 40% of early-onset familial PD cases are associated with mutations in the Parkin gene, resulting in the loss of Parkin function and dysregulation of alpha-synuclein ubiquitination. Accumulation of ubiquitinated alpha-synuclein is observed in both familial and sporadic PD, suggesting Parkin dysfunction playing a potential role in idiopathic PD and Lewy body formation. Parkin acts as an E3 ligase and plays crucial role in ubiquitin-dependent regulation of epidermal growth factor (EGF) signaling through the Akt pathway, thus influencing pro-survival pathways. Dysfunction in Parkin may contribute to global cellular health problems beyond α-synuclein accumulation. Additionally, mutation in the deubiquitinating enzyme UCH-L1 affecting cellular processes regulated by ubiquitin, including mRNA transcription, protein translation, synaptic plasticity, and pro-survival signaling (Das et al. 2006).

These findings underscore intricate involvement of ubiquitination and UPS in Parkinson's disease pathology ultimately affecting various cellular processes that contribute to neurotoxicity in disease context (Cartier et al. 2012). The interaction between ubiquitin-related proteins like CHIP, MDM2, HRD1, and UCH-L1 further emphasizes the crucial role of UPS in the pathological mechanisms shared between Alzheimer's and Parkinson's diseases (Mei and Niu 2010).

8.3.3.3 Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease affecting motor neurons that manifests as a progressive paralysis along with cognitive deficits, ultimately leading to death within a few years of onset. Ubiquitin-rich cytoplasmic inclusions are observed in motor neurons of ALS patients, indicating role of ubiquitination in disease pathology sporadic ALS (SALS) comprises over 90% of cases, with familial ALS (FALS) accounting for the remainder (Andersen and Al-Chalabi 2011). Mutations in Superoxide Dismutase 1 (SOD1) and Transactivation Response DNA-binding protein 43 (TDP-43) genes are well-known in inducing ALS etiology.

SOD1 is crucial for eliminating free radicals; it undergoes ubiquitination which is regulated by UPS. E3 ligases E6-AP and NEDL1, with decreased E6-AP levels preceding neurodegeneration (Mishra et al. 2013). RING-finger-type E3 ligase Dorfin also ubiquitinates mutant SOD1, mitigating motor neuron degeneration in a FALS mouse model.

TDP-43 is a nuclear RNA-binding protein which undergoes ubiquitination that leads to cytoplasmic inclusions in ALS. Parkin-mediating K48 and K63-linked ubiquitination are associated with ALS altering TDP-43 localization, although there is no reduction in TDP-43 levels. In C9ORF72-related ALS, TDP-43 is present in ubiquitin-positive aggregates, along with ubiquitin and p62-positive inclusions containing dipeptide repeat (DPR) (Ash et al. 2013). The role of DPR products remains unclear, suggesting challenges in cellular clearance mechanisms and potential toxic responses. This complex interplay of ubiquitination in SOD1, TDP-43, and C9ORF72-associated ALS underscores its critical role in disease pathogenesis.

8.3.3.4 Huntington's Disease

Huntington's disease (HD), the most common polyglutamine (poly Q) disorder, is characterized by the expansion of CAG repeats in the huntingtin (htt) gene. Expansion of 38 or more glutamine repeats results in severe neurodegeneration. The UPS plays a crucial role in HD pathogenesis by regulating clearance of mutant Huntingtin. HRD1, an E3 ligase, exhibits increased activity with expanded glutamine length and potentially contributes to the degradation of the mutant. TRAF6, another E3 ligase, promotes non-canonical ubiquitination of mutant Huntingtin, fostering aggregation without altering wild-type protein localization (Zucchelli et al. 2011). NUB1, previously associated with Alzheimer's disease, interacts with Cullin-3 to facilitate ubiquitination and clearance of mutant Huntingtin, thus presenting a potential therapeutic target.

8.3.4 Molecular Mechanisms of Sumoylation Dynamics in Neurodegenerative Disorders

Sumoylation has been implicated in HD as well. The striatal protein Rhes acts as a SUMO E3 ligase and selectively binds to mutant Huntingtin (mhtt), promoting its sumoylation and decreasing aggregation. However, sumoylated mutant Huntingtin inhibits transcription, enhances cytotoxicity, and may impair autophagy induction (Mealer et al. 2014). Additionally, the interaction between Huntingtin and the E2 enzyme hE2-25k (Ube2K) promotes aggregation and cytotoxicity with Ube2k potentially cleaving polyubiquitin chains in Huntingtin thus disrupting the degradation signal (de Pril et al. 2007). This intricate ubiquitination and sumoylation processes highlight their vital role in HD pathology, providing potential avenues for therapeutic intervention.

8.4 Involvement of Protein Degradation Pathways in Altered Protein Metabolism in NDDs

Misfolded protein formed in different cellular compartments such as cytoplasm, nucleus, and endoplasmic reticulum are effectively eliminated from the system through a variety of quality control mechanisms such as ubiquitination-mediated proteasome system, chaperone-mediated autophagy (CMA), and macro autophagy. The primary mechanism of degradation involves UPS, in which selective proteins are marked with ubiquitin and unfolded into nascent polypeptide chain which then gets cleaved into short peptides while passing through proteasome complex. The oligomers show resistance to majority of the recognized protein breakdown pathways and may continue to expand, forming either inclusion bodies or extracellular plaques characterized by well-structured fibril-rich β-sheet structure. In contrast to dividing cells, neurons that have ceased to divide are particularly susceptible to the buildup of cytotoxic proteins as they lack the ability to reduce the concentration of harmful substances via cell division (Lee et al. 2011). The cellular structure of neurons makes protein quality control a challenging process. The aggregates reside in dendrites, and axons have to be packaged into autophagic lysosomal bodies, and a retrograde movement to the cell body is created for their degradation (Larsen and Sulzer 2002). The task becomes herculean with aging as the components of CMA, UPS, and autophagy become less efficient with time, since numerous components involved in the process are downregulated at the level of transcription, translation, and posttranslation (Hara et al. 2006).

UPS is an ATP-consuming proteolytic event involved in linking of 76 amino acid ubiquitin to lysine residue of protein to be targeted for degradation. The degradation of misfolded proteins through the UPS begins when chaperones and Ub ligases detect folding irregularities, like exposed hydrophobic residues on the surface and improper disulfide bonds. Ub gets activated by formation of a thioester bond between its Gly76 and cysteine of ubiquitin-activating enzyme E1. The activated ubiquitin is then transferred to E2 ubiquitin-conjugating enzyme via thioester bond. Further, E3 ubiquitin ligase enzyme selectively recognizes and mediates ubiquitination of the substrate by transferring E2-conjugated Ub to lysine residue of the targeted substrate. Lys48 linkage is the most crucial factor for the initiation of degradation signal by proteasome. Ubiquitination produces a sequence of four or more Ub (ubiquitin molecules) at the lysine 48 site; it functions as a secondary signal for the targeted delivery of substrates to the 26S proteasome for degradation. Proteasomes consist of two 19S regulatory particle capping and a 20S core proteolytic unit (Hendil et al. 1998; Tanahashi et al. 2000). The 19S particle attaches and unfolds the poly-ubiquitinated protein substrate, guiding the polypeptide chain to enter into the 20S particle's chamber which is around 13 angstroms in diameter (Hendil et al. 1998; Tanahashi et al. 2000). As the substrates traverse the 20S particle, the β5, β2, and β1 subunits, each possessing chymotrypsin-like, trypsin-like, and caspase-like peptidase activities, cleave the polypeptide into smaller peptides (Fig. 8.6(1)). The pathology of numerous neurodegenerative diseases like

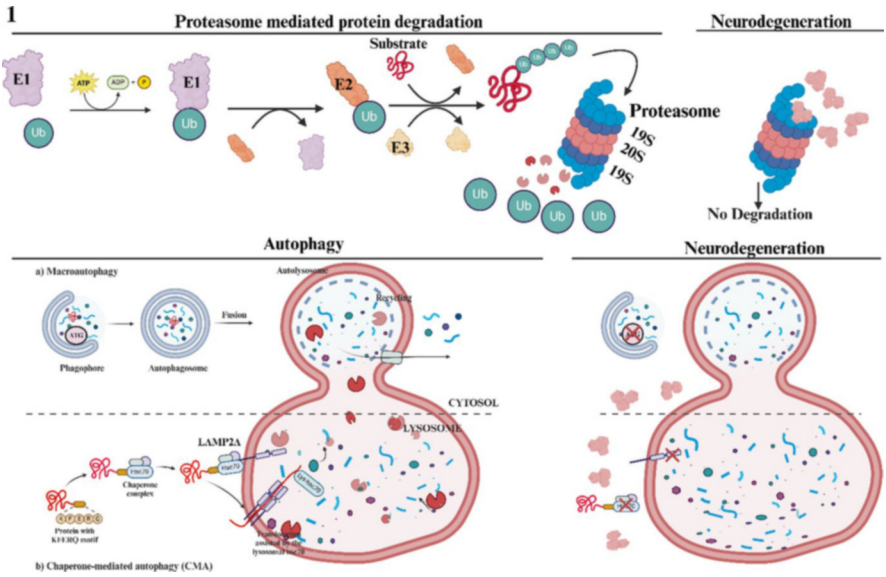

Fig. 8.6 Image showing altered protein degradation pathways in neurodegenerative disorders. (1) Addition of ubiquitin molecule to E1 via thioester bond is a ATP consuming process. E2 replaces the E1 from E1-Ub. E3 ubiquitin ligase helps in replacement of E2 with the misfolded substrate forming the ubiquitinated misfolded protein. This process occurs at least 4 times before misfolded protein is directed to 26S proteasome. The proteasome leads to degradation of misfolded protein. In neurodegenerative condition, the aggregated protein clogs the proteasome entry, exit, and regulatory part. (2a) Misfolded proteins are segregated and digested in autophagosome by lysosomal hydrolases. ATG genes facilitate the formation of autophagosome. Mutation in genes facilitating the initiation and elongation of phagophore disrupts protein degradation. (2b) Misfolded protein carrying KFERQ motif are recognized by Hsc70 complex genes and transported to CMA adaptor LAMP-2A. The misfolded protein gets unfolded and enters the lysosome for degradation. In neurodegenerative background, the mutations in Hsc70 complex proteins and in LAMP-2A impair protein translocation to lysosome causing cytotoxicity

Alzheimer's (AD), Parkinson's (PD), amyotrophic lateral sclerosis (ALS), Huntington's (HD), and prion diseases is linked to and up to some extent exacerbated by the decreased activity of the UPS (Hegde and Upadhya 2011; Dennissen et al. 2012). Several studies indicate that the proteasomal function tends to diminish gradually with age. This decline leads to decreased ability to break down misfolded proteins, thereby playing a vital role in the accumulation of pathological protein aggregates (Keller et al. 2000). Aggregated protein also hinders the UPS component activity, and the β-sheet-rich PrP impedes the opening of 20S proteasome particle, hence altering the proteasomal activity. Aggregated tau obstructs the 19S regulatory unit entrance by binding with recognition site causing traffic jam and inhibiting the degradation process (Dantuma and Lindsten 2010) (Fig. 8.6(1)). Aggregates of beta-sheet-rich prion proteins and Tau found in Alzheimer's disease might hinder the function of 20S and 19S proteasome particles. Similarly, mutations in UPS elements like E3 ligase Parkin, deubiquitinating enzyme ubiquitin carboxy-terminal

hydrolase L1 (UCH-L1), and ATPase valosin-containing protein (VCP) are associated with neurodegenerative conditions (Deriziotis et al. 2011).

Apart from UPS, cells have evolved other machineries to deal with cytotoxicity, and autophagy-lysosome system is one of them. In this process, cytoplasmic aggregates are degraded by lysosomal enzymes. Depending on the mechanism by which cargoes are destined to be recruited to the lysosome, autophagy is categorized into micro-autophagy, CMA, and macro-autophagy.

In macro-autophagy, misfolded proteins are segregated by double membrane structure named autophagosome which is subsequently digested by lysosomal hydrolases. It is predominantly facilitated by a cascade of autophagy-related genes (ATG). In healthy individual, serine-threonine kinase mammalian target of rapamycin (mTOR) senses for autophagy signal. Initiation triggers the "phagophore" formation; a lipid double membrane is produced to encapsulate the target cargo. The phagophore further enters into elongation phase. Phosphatidylethanolamine is covalently bound to cytosolic Microtubule Associated Protein 1 Light Chain3 and GABARAP family (gamma-aminobutyric acid receptor-associated protein) proteins (herein LC3-I), producing an autophagosome-associated LC3-II. Further, a complex of ATG5-ATG12-ATG16 associates with the phagophore membrane and completely encloses the target cargo. The delivery of misfolded protein to autophagosome requires adaptor protein p62/SQSTM-1/sequestosome. The autophagic adaptor, p62, contains a UBA (ubiquitin-associated) domain, which interacts with polyubiquitin chain present on misfolded protein. Additionally, it includes a PB1 domain responsible for self-aggregation, leading to the formation of compact cargo-p62 complexes. Cargo-loaded p62 aggregates move to autophagic vacuole and interact with light chain 3 II present on autophagic double membrane (Filimonenko et al. 2010). Other autophagic adaptors like NBR1, NDP52, optineurin (OPTN), histone deacetylase 6, and NIX26 also mediate the delivery of cargo to autophagosome (Johnson et al. 2012). Mutations in *p62* have been implicated in the pathogenesis of familial as well as sporadic ALS (Fecto et al. 2011). Disruption in autophagy sensing and initiation/nucleation is reported in neurodegenerative disorders, particularly HD (Fig. 8.6(2a)).

CMA is a selective degradation system in which proteins carrying KFERQ sequences are transported to lysosome for degradation. The motif is present in about 30% of cytosolic proteins during the folding process it gets buried inside, and becomes exposed on the surface during misfolding. The sequence is recognized by chaperon Hsc70 along with co-chaperones. Further, the substrates are transported to the CMA adaptor, known as lysosomal membrane-associated protein 2A (LAMP-2A), situated on the lysosomal membrane for unfolding and degradation. The unfolded α-synuclein is a substrate for CMA. Several well-established genes associated with familial PD disrupt CMA (Cuervo et al. 2004). In NDD condition, it has been observed that ubiquitin carboxyl-terminal esterase L1 (UCHL-1) interacts with heat shock protein 70 (HSP70), HSP90, and LAMP2A, thus impeding CMA of α-synuclein (Kabuta et al. 2008). PD associated LRKK2 mutations hinder the CMA translocation complex (Orenstein et al. 2013) (Fig. 8.6(2b)).

8.5 Implications of Dysregulated Protein Homeostasis in NDDs

Protein toxicity is a critical feature of both sporadic and familial neurodegenerative diseases. Aberrant cytoplasmic inclusion formation leads to cellular protein toxicity. Protein toxicity in affected neuron may lead to different cellular anomalies like changes in gene expression, mitochondrial dysfunction, impaired protein quality control system, abnormal RNA quality control system, etc. All these factors are major players for the onset and advancement of neurodegenerative diseases, which ultimately leads to cell death. In the following section, we will discuss about the molecular mechanisms causing protein toxicity in the different cellular compartments.

8.5.1 Nucleus

Nuclear inclusions (NIs) in neurons leading to neuronal dysfunction is one of the key features of multiple neurodegenerative diseases. It is a well-accepted fact that these microscopically visible NIs are self-protective structure or the by-product of pathogenic process. Within the affected neurons, the soluble prefibrillar or oligomeric aggregates are potentially more detrimental when compared to that of the mature fibrillar aggregates which are formed within the nucleus (Bucciantini et al. 2002; Kayed et al. 2003; Woulfe 2007). Nuclear dysfunction such as impaired transcription and altered nucleo-cytoplasmic transport are the major consequence of NIs. As polyQ expands, the protein mis-localize to nucleus and forms aggregates. Ataxin-3 normally resides in the cytoplasm as deubiquitinase protein, upon trinucleotide repeat expansion mutation in the coding region the mutant SCA3 protein, moves to the nucleus. Nuclear accumulation of mutant huntingtin has been also reported (Pouladi et al. 2013).

The identification of various transcription factors like CBP, TATA-binding protein (TBP), nuclear co-repressor (NCoR), and RE1-silencing transcription factor/neuron-restrictive silencer factor (REST/NRSF) within polyQ nuclear inclusions indicates a potential sequestration process through which polyQ proteins could lead to disruption in transcriptional regulation and epigenetic control (Nucifora et al. 2001; McCampbell et al. 2000; Zuccato et al. 2003). Mutant forms of htt and ataxin-3 proteins have the ability to directly interact with histone acetyltransferases like CBP and p300/CBP-associated factor (P/CAF), consequently disrupting the process of histone acetylation within the neurons (McSteffan et al. 2001). Additionally, hypomethylation of DNA with CpG-poor regions in the HD cell culture model was also observed (Ng et al. 2013).

Changes in transcriptional and epigenetic mechanisms have been demonstrated to play a role in diverse range of neuronal phenotypes observed in polyQ diseases, spanning from early neuropathic symptoms to eventual neuronal cell death (Kwon et al. 2017). In mouse models of HD, the administration of histone

deacetyltransferase (HDAC) inhibitors such as sodium butyrate, 4-phenylbutyric acid sodium salt, and suberoylanilide hydroxamic acid was demonstrated to alleviate neurotoxicity (Ferrante et al. 2003; Ying et al. 2006). Apart from the changes in transcriptional and epigenetic processes, issues related to nucleocytoplasmic transport have emerged as a prominent form of nuclear dysfunction observed in neurodegenerative conditions like ALS/FTD, HD, and AD (Boeynaems et al. 2016). These include the sequestration of nuclear pore complex (NPC) molecules by toxic RNA or proteins (Woerner et al. 2016; Grima et al. 2017), as well as the direct obstruction of nuclear pores by toxic pathogenic proteins.

8.5.2 Cytoplasm

A wide variety of proteins associated with neurodegeneration tend to form aggregates in the cytoplasm. The aggregates inevitably place strain on the protein quality control (PQC) system. Increasing the expression of specific components of the UPS has been shown to suppress disease symptoms in neurons across various neurodegenerative disease models (Adachi et al. 2007). For instance, in case of Parkinson's disease, mutant G2019S LRRK2 proteins can undergo ubiquitination mediated by the E3 ligase C-terminus of HSP70-interacting protein (CHIP). Overexpression of CHIP facilitates ubiquitin proteasomal degradation of the mutant LRRK2 proteins (Ko et al. 2009). The accumulation of toxic proteins often induces stress in the endoplasmic reticulum (ER), leading to the upregulation of chaperones, ER-associated degradation (ERAD), apoptotic genes along with global inhibition of protein translation, and formation of stress granules (Pereira 2013). Cytoplasmic accumulation of many cytoskeleton proteins such as neuronal intermediate filament (IF) proteins or the microtubule-associated protein tau (MAPT) has been observed (Cairns et al. 2004). Along with these modifications in the cytoskeletal arrangements, the aggregation of pathogenic proteins can result in disruption of the axonal transport (Kanaan et al. 2013; Brady and Morfni 2017). Several animal models of Huntington's disease have demonstrated abnormalities in both anterograde and retrograde axonal transport (Gunawardena et al. 2003).

8.5.3 Mitochondria

Mitochondria is crucial for ATP production therefore, its dysfunction poses a significant threat to cell survival particularly in the brain. Six types of pathogenic proteins accumulate within the mitochondria: amyloid-beta, amyloid precursor protein (APP), α-synuclein, mutant htt, TDP-43, and poly-GR DPRs (arginine containing dipeptide repeat). The direct interaction of amyloid precursor protein (APP) and amyloid-beta with mitochondrial proteins is adequate to induce oxidative stress, decrease in ATP production, and disruption in mitochondrial membrane potential, leading to

enhancement of the mitochondrial permeability transition pore (mPTP) along with clogging of the opening of mitochondrial translocase TOM40 and TIM23. This significantly contributes to mitochondrial dysfunction in neurodegenerative diseases (Abramov et al. 2017; Spuch et al. 2012). The detrimental interaction between mutant huntingtin and mitochondrial proteins disrupts calcium regulation, increases the sensitivity of mPTP opening, causes depolarization of the mitochondrial membrane potential, and ultimately results in neuronal death (Panov et al. 2002; Choo et al. 2004; Yano et al. 2014). α-Synuclein, the primary aggregating component in Lewy bodies, exhibits a strong affinity for negatively charged lipids including mitochondrial membrane (Rostovtseva et al. 2015). Additionally, TDP-43 contains internal signals that facilitate it's targeting to the mitochondria. The mitochondrial targeting is heightened in patients with ALS or FTD, disrupting oxidative phosphorylation by binding to mitochondria-transcribed ND3 and ND6 mRNA, thereby inhibiting their translation (Wang et al. 2016). Table 8.1 shows comprehensive list of neurodegenerative diseases and their respective cytotoxic effects in distinct cellular compartments.

8.6 Conclusion and Future Perspectives

The complicated landscape of neurodegenerative disease provides a powerful task for both researchers and clinicians. These disorders are characterized by progressive neuronal disorder and the manifestation of various debilitating symptoms, thereby representing a substantial burden on the worldwide healthcare systems. The growing incidence of neurodegenerative diseases are also attributed because of

Table 8.1 Table showing the neurodegenerative disease and associated cytotoxicity

Disease	Phenotype
Nucleus:	
Huntington	Epigenetic and transcriptional dysfunction, nuclear aggregation, nucleocytoplasmic transport dysfunction (Chung et al. 2018)
ALS	Nucleocytoplasmic transport dysfunction (Chung et al. 2018)
Cytoplasm:	
Alzheimer's disease	Synaptic tau interacts with 26S proteasome (Tai et al. 2012)
Parkinson's disease	Perturbation of CMA via blockage of lysosomal transport of substrate (Ko et al. 2009)
ALS	Axonal transport dysfunction (Baldwin et al. 2016)
Mitochondria:	
Parkinson	Supression of mitophagy associated protein, impaired lysosomal clearance of defective mitochondria, abnormal autophagic flux, increased oxidative stress (Bustamante-Barrientos et al. 2023)
Huntington	Mitochondrial fragmentation, reduced mitochondrial complex I activity, ATP depletion, increased oxidative stress (Bustamante-Barrientos et al. 2023)
Alzheimer's disease	Reduced mitochondrial membrane potential, decreased ATP levels (Bustamante-Barrientos et al. 2023)
Stress granules:	
ALS	Altered stress granule dynamics and morphology (Mateju et al. 2017)
Huntington	Increased stress granule formation (Ratovitski et al. 2012)

the demographic shifts in growing aged population which is associated with increase in lifespan and underscores the critical need for the comprehensive investigations into their underlying molecular mechanisms.

At the heart of neurodegeneration lies the phenomenon of protein toxicity, which drives the formation of abnormal aggregates within the central nervous system. These aggregates comprise various misfolded proteins such as tau, alpha-synuclein, and TDP-43 that disrupt essential cellular processes and contribute to the neuronal death. The intricate interplay of environmental, genetic, and age-related factors further complicates our understanding of disease pathogenesis.

The pathological processes involved in neurodegeneration range from proteotoxic stress to neuroinflammation, highlighting the multifaceted nature of these conditions. Disruption in protein homeostasis, compromised cellular clearance mechanism, and misregulated signaling pathways all converge to promote neuronal disorder and eventually cellular death. Importantly, these pathological changes may precede the onset of clinical symptoms, highlighting the importance of early detection and intervention strategies.

This chapter contributes to our understanding of interrelated Aβ, tau, and α-Syn proteinopathies, promoting for multiprotein Aβ/tau/α-Syn-targeted therapeutics. Examples from AD and related disorders accentutate the potential for multi-target therapeutics, offering synergistic benefit. Tailored combination therapies may overcome patient variability, emphasizing personalized treatment strategies for neurodegenerative diseases. The pursuit of optimized regimen, guided by patient-specific factors, represents a promising avenue for improving treatment outcomes in this complex field.

Furthermore, the improvement of dependable biomarkers and diagnostics may be critical for early detection and tracking of disease pathogenesis. Integrating advanced neuroimaging, genetics and molecular biomarkers hold promise for more accurate prognosis and personalized therapeutics. Ultimately, a multidisciplinary and collaborative approach is crucial for tackling neurodegenerative disease detection and therapeutics.

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Chapter 9
Altered RNA Metabolism in Neurodegenerative Disorders

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Abstract RNA metabolism entails steps such as RNA processing, maturation, transport, translation, and decay, which are crucial for the regulation and maintenance of correct transcriptomic and genetic signature across different cell types. RNA-binding proteins (RBPs) interact with RNA to maintain RNA metabolism. Therefore, disruption of this RNA metabolism is linked to dysregulation of cellular processes involved in disease pathogenesis. Neurodegenerative diseases are characterized by irreversible and progressive neuronal cell death. These diseases are caused by factors including microsatellite repeat expansions, RBPs, noncoding RNAs (ncRNAs), etc., which affect RNA metabolism at different levels like transcription, mRNA processing (capping or tailing), maturation, splicing, and even translation. Such altered RNA processing in diseases results in aberrant RNA metabolism leading to formation of RNA foci and even RNA granules that can cause cellular stress and cellular toxicity which has been implicated in worsening neuronal integrity and neurodegeneration. In this book chapter, we have discussed the role of RNA processing and metabolism in neuronal integrity and their deregulation resulting in neurodegenerative diseases.

Keywords RNA metabolism · RNA processing · Neurodegeneration · NDDs · RBPs · Microsatellite

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9.1 Introduction

RNA is an important biomolecule that is crucial for the functioning of cells and tissues. During development, the differentially expressed coding and noncoding RNAs result in unique signatures in different cells and tissues. RNAs are indispensable for performing functions like protein synthesis [ribosomal RNA (rRNA) and transfer RNA, (tRNA)], alternative splicing [small nuclear RNA (snRNA)], gene regulation [ncRNAs like microRNA (miRNA), small interfering (siRNA), etc.], cell signaling [long noncoding RNA, (lncRNA)], and epigenetic regulation (RNA interference, RNAi). RNA processing steps include splicing, tailing, editing, maturation, transport, storage, and turnover, which is collectively referred to as RNA metabolism. RNA-binding proteins (RBPs) are key players in RNA metabolism (Kelaini et al. 2021; Nussbacher et al. 2015). Deregulation of RNA metabolism and the players involved in this process is a key factor in several diseases like cancer, neurodegenerative disorders [amyotrophic lateral sclerosis (ALS)], and spinal muscular atrophy (SMA), Alzheimer's disease (AD), Parkinson's disease (PD), and genetic and metabolic diseases. Therefore, it is crucial to understand the players involved in RNA metabolism and how they can contribute to deregulated cellular processes and diseases.

Recently, altered or defective RNA metabolism is emerging as a common underlying theme of several neurological or neurodegenerative diseases. Altered RNA metabolism may be caused due to erroneous mutations in genes required for transcription, deregulation of regulatory elements, defective RNA synthesis and processing, and RNA-binding proteins (Fig. 9.1). All these components are vital for gene expression regulation and cellular homeostasis of neuronal cell population and thus affecting their survival, synaptic function, and synaptic plasticity. Neurodegenerative diseases characterized by protein aggregation also tend to have defective RNA editing and posttranscriptional modifications. Some RNA-binding proteins like TDP-43 and FUS are also integral to stress response in cells and can result in stress granule formation which has been associated with disease progression (Jain and Vale 2017; Hsieh et al. 2019; Bishof et al. 2018). Furthermore, noncoding RNAs are also involved in epigenetic regulation and regulate other signaling pathways that may contribute to neurodegeneration. In this book chapter, we have shed light on how altered RNA metabolism can affect normal function and have a role in neurodegenerative disorders.

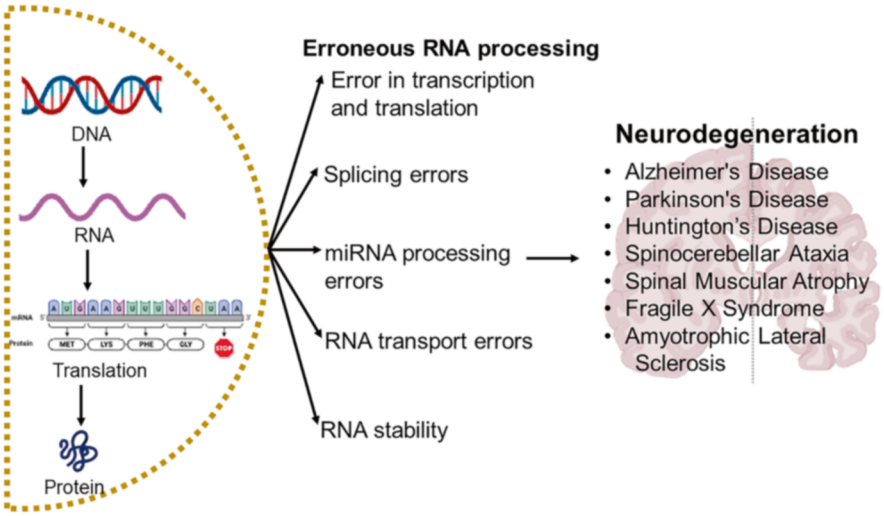

Fig. 9.1 Erroneous RNA processing results in neurodegeneration. The flow of genetic information starts with DNA, which is transcribed into RNA (mRNA) and finally translated into proteins. This process is fundamental to the functioning and development of living organisms. RNA is essential for cellular functions. Erroneous RNA processing like errors in transcription and translation, splicing errors, miRNA processing errors, RNA transport errors, and RNA stability result in neurodegenerative disorders like AD, PD, and ALS

9.2 Microsatellite Repeats Implicated in Neurodegenerative Disorders

Microsatellite repeats (short repetitive elements) are one factor that contribute to deregulated RNA metabolism (Mirkin 2007). There are close to 30 microsatellite-related human diseases (Mirkin 2007) that occur due to expansion in introns or exons, of which nearly 20 are related to the nervous system (La Spada and Taylor 2010). These expansion repeats can accumulate and increase in repeat number over time, over generations, and remains unstable. They also vary across tissue types causing RNA toxicity in several neurodegenerative diseases (La Spada and Taylor 2010). Length of the repeat and nature of the mutant gene are two important factor that determine disease manifestation and severity. Such diseases are also characterized by pathogenic accumulation of RNA foci, which is accumulation of repeat-containing RNA transcripts with other RBPs (Figs. 9.1 and 9.2). These foci render the native gene incapable of function and also can prove to be highly toxic (Fig. 9.2) (Zhang and Ashizawa 2017). Furthermore, it has been noted that there is a critical number of expansion repeats for such disorders, and only once this RNA repeat expansions increase beyond a critical number, they start forming structures called RNA granules due to phase separation and sequence-specific gelation of RNAs (Jain and Vale 2017). Some neurodegenerative diseases caused by microsatellite expansion are discussed below.

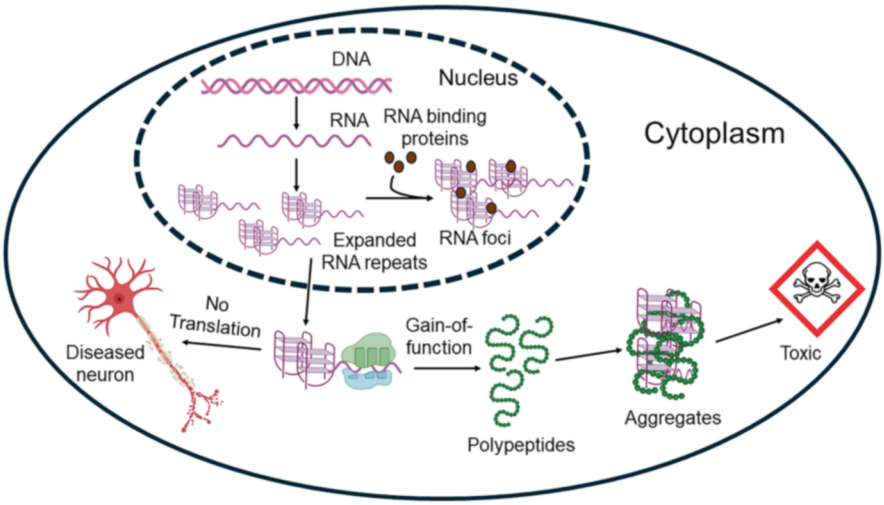

Fig. 9.2 Mechanism of neurodegenerative disease(s) pathogenesis by RNA repeat expansion. The repeat RNA expansion gives rise to abnormal nucleic acid structures. The expanded RNA forms foci, sequestering RNA-binding proteins and causing dysfunction in RNA processing. The creation of RNA repeat expansion hinders regular translation, causing a deficiency in essential proteins, and results in degeneration of neurons. Gain of function in repeat expansion results in the synthesis of harmful polypeptides that further aggregate with RNA structures and further results in cytotoxicity

9.3 Huntington's Disease

Huntington's disease (HD) typically manifests in adults after the age of 30, causing cognitive, movement, and psychiatric issues. It is a neurodegenerative disorder inherited in an autosomal dominant manner (Duyao et al. 1993). In individuals without the condition, the HTT gene normally contains up to 36 CAG repeats (Table 9.1). However, any additional repeats result in the excessive production of a mutant protein, leading to cytotoxic effects (Table 9.1) (MacDonald et al. 1993). Accumulation of mutant HTT protein in human patient brains is a pathological hallmark of HD. This aggregation-prone mutant HTT protein is an outcome of protease action or aberrantly spliced exon1 transcripts (Cooper et al. 1998; Thakur et al. 2009). Studies also show that RBPs can bind to mutant HTT RNA and cause cytotoxic effects by forming RNA foci (Fig. 9.2) (Mykowska et al. 2011; Krauss et al. 2013). Recent research has shown that HD is a result of several pathogenic pathways directly activated due to expansion-dependent RNA toxic gain of function (Marti 2016). Interactome analysis has revealed that the mutant HTT RNA binds to proteins belonging to the spliceosome pathway and results in deregulated splicing (Schilling et al. 2019). Furthermore, human HD brains also show transcriptome wide aberrations in alternative splicing (Schilling et al. 2019; Lin et al. 2016a).

Table 9.1 Microsatellite repeats associated with neurodegenerative diseases

Associated disease	Pathogenic repeat and length	Gene name	Impact of pathogenic repeats
Huntington's disease	>35 CAG repeats	HTT	Expanded tandem repeat RNA transcription and proteins, altered gene expression, splicing and stress
HDL2 Huntington's disease-like 2	>50 CTG/CAG repeats	JPH3	Expanded tandem repeat RNA transcription RNA foci
C9ORF72-associated frontotemporal dementia and amyotrophic lateral sclerosis	>25 GGGGCC repeats	C9ORF72	Expanded tandem repeat RNA transcription and proteins RNA foci
Fragile X syndrome	50–200 CGG repeats in 5′-UTR	FMR1	Translation defects in dendritic spines
Fragile X syndrome	>200 CGG repeats in 5′-UTR	FMR1	Toxic RNA; sequestration of splicing factors
Spinocerebellar ataxia 1	49–88 CAG repeats	ATXN1	Expanded tandem repeat RNA transcription and proteins Length-dependent foci
SCA 2	33–77 CAG repeats	ATXN2	Expanded tandem repeat RNA transcription and proteins Length-dependent foci Protein aggregation; toxic gain of function
SCA 3	55–86 CAG repeats	ATXN3	Expanded tandem repeat RNA transcription and proteins RNA foci
SCA6	21–30 CAG repeats	CACNA1A	Expanded tandem repeat RNA transcription and proteins Length-dependent foci
SCA7	38–120 CAG repeats	ATXN7	Expanded tandem repeat RNA transcription and proteins Length-dependent foci
SCA8	>74 CTG repeats	ATXN8	Expanded tandem repeat RNA transcription and proteins RNA foci
SCA12	66–78 CAG repeats	PPP2R2B	Expanded tandem repeat RNA transcription and proteins
SCA10	500–4500 ATTCT repeats	ATXN10	Expanded tandem repeat RNA transcription and proteins RNA foci
SCA17	47–63 CAG repeats	TBP	Expanded tandem repeat RNA transcription and proteins Length-dependent foci

(continued)

Table 9.1 (continued)

Associated disease	Pathogenic repeat and length	Gene name	Impact of pathogenic repeats
SCA31	>45 TGGAA repeats	TK2/ BEAN	Expanded tandem repeat RNA transcription and proteins RNA foci
SCA36	>650 GGCCTG repeats	Nop56	Expanded tandem repeat RNA transcription and proteins RNA foci
SCA 37	31–75 ATTTC repeats	DAB1	Expanded tandem repeat RNA transcription and proteins

Mutant HTT RNA toxicity has also been associated with increased nucleolar stress, deregulated localization of mutant RNA foci, and defective gene expression pattern (Marti 2016).

9.4 Huntington's Disease-Like 2

Huntington's disease-like 2 (HDL2) is highly fatal and is often mistaken as HD. It is caused due to expansion of >50 CTG/CAG repeats in *junctophilin-3* (*JPH3*) gene (Table 9.1) (Holmes et al. 2001). It usually manifests during midlife with surprisingly fast progression of symptoms associated with movement disorders, psychiatric issues, and cognitive decline. In this disease, there is a rapid decline of both motor and cognitive skills over time (Holmes et al. 2001). The expanded mutant RNA forms large nuclear aggregates and forms toxic foci (Krench et al. 2016).

9.5 C9ORF72-Associated Frontotemporal Dementia and Amyotrophic Lateral Sclerosis

Frontotemporal lobar degeneration (FTLD) is a common form of cortical dementia, often manifesting before the age of 65. It is characterized by rapid and progressive weakness and paralysis. About half of FTLD cases are linked to TDP43 protein inclusions, a hallmark also seen in amyotrophic lateral sclerosis (ALS), suggesting they can be categorized as TDP43 proteinopathies. The most prevalent genetic cause for both ALS and FTLD is a hexanucleotide repeat expansion (HRE) in C9orf72 (Table 9.1) (DeJesus-Hernandez et al. 2011; Renton et al. 2011; Liu et al. 2023; Breevoort et al. 2022; Meijboom et al. 2022). This HRE forms G-quadruplex structures, disrupting nuclear import by sequestering GTPase activator for RAN (RANGAP1), leading to cytoplasmic TDP43 accumulation (Wu and Kuo 2020;

Zhang et al. 2015). The HRE may also be translated into toxic dipeptides, contributing to neurodegeneration. The C9orf72-associated FTD/ALS disease pathogenesis is by three different mechanisms: (1) loss of function of C9ORF72 protein due to reduced production of RNA, (2) gain-of-function mechanism where the sense and antisense repeat expansion can bind and alter other RBPs, and (3) RNA foci of the expansion repeats (Fig. 9.2). In the latter two mechanisms, the RNA structures are known to sequester other RBPs and cause RNA toxicity and even cause nucleolar stress (Yang et al. 2020).

9.6 Spinocerebellar Ataxia

Ataxia is characterized by loss of voluntary muscular coordination and movement causing muscle disorders and defects in speech and vision (eye movement). Spinocerebellar ataxia (SCA) affects mainly the cerebellum and manifests as an autosomal dominant, hereditary, and progressive neurodegenerative disease. There are nearly 40 types of genetically distinct SCAs based on gene affected. The SCA1 (Orr et al. 1993), SCA2 (Imbert et al. 1996; Sanpei et al. 1996), SCA3 (Kawaguchi et al. 1994), SCA6 (Zhuchenko et al. 1997), SCA7 (David et al. 1997), SCA8 (Koob et al. 1999), SCA12 (Holmes et al. 1999), and SCA17 (Nakamura et al. 2001) occur due to CAG repeat expansions (Table 9.1). The genetic basis of SCA 10 is due to expansion of ATTCT (Matsuura et al. 2000), whereas that of SCA 31 (Sato et al. 2009), SCA36 (Kobayashi et al. 2011), SCA37 (Seixas et al. 2017; Loureiro et al. 2019) is due to expansion of TGGAA, GGCCTG, and ATTTT, respectively (Table 9.1). These expansions cause RNA foci-mediated cellular toxicity.

9.7 RNA-Binding Proteins Implicated in Neurodegenerative Disorders

RNA-binding proteins (RBPs) are a crucial component of RNA metabolism as they interact with RNA during processing, maturation, stability, and transport. These interactions lead to various effects on RNA processes such as splicing, transcription efficiency, and stabilization. For instance, RBPs can influence alternative splicing in coding regions, and interactions within the 3′UTR domain can either inhibit or induce mRNA decay, as well as mediate RNA stabilization. The absence of RBP binding to 3′UTR targets can destabilize mRNA molecules. This complex and dynamic process relies on the intricate interplay of RNA-binding proteins (RBPs), which play a pivotal role in fine-tuning of co- and post-transcriptional processing of transcripts (Kelaini et al. 2021). RBPs bind to specific RNA sequences or secondary structures, facilitating various stages of RNA processing in both the nucleus and cytoplasm (Nussbacher et al. 2015). Defective interactions between RBPs and RNA

can result in faulty RNA processing and metabolism and subsequently RNA-RBP aggregates referred to as RNA foci. The foci can trigger aberrant splicing or gene expression in cells and can cause cellular toxicity resulting in disease pathologies.

9.8 Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative condition primarily associated with aging, characterized by the accumulation of amyloid-beta and hyperphosphorylated tau proteins due to cellular stress (Sarkar et al. 2016; Yeates et al. 2019). This leads to speech, memory, and cognition impairments. It is predominantly observed in population older than 65. Tau aggregates tend to form neurofibrillary tangles (NFTs) in brains of AD patients and is associated with disease manifestation and progression (Table 9.2) (Braak and Braak 1991). It is also a RBP that binds to RNA (tRNA, rRNA) and affects several steps of RNA processing like transcription (Montalbano et al. 2021), tailing (Montalbano et al. 2021), splicing (Hsieh et al. 2019; Montalbano et al. 2021; Apicco et al. 2019), and translation (Banerjee et al. 2020). Tau aggregation is also associated with depletion of spliceosome factors like SmB, U1–70K, and U1A resulting in worsened tau-mediated neurodegeneration (Hsieh et al. 2019). Tau-rRNA-ribosomal protein aggregates are formed in vitro and

Table 9.2 RNA-binding proteins associated with neurodegenerative diseases

RNA-binding proteins	Associated disease	Gene alteration
Tau	Alzheimer's disease	Aggregates with RNA and impacts splicing and translation
RBFOX1	Alzheimer's disease	Reduced expression correlated with worse cognition and increased amyloid burden
RBFOX1	Parkinson's disease	Elevated expression
SMN	Spinal muscular atrophy (SMA)	Reduced activity and inactivating mutations affects spliceosome formation
TDP-43	Amyotrophic lateral sclerosis	Mutation leads to protein fragmentation Missense mutations in Gly-rich domain
FUS	Amyotrophic lateral sclerosis	Gain of function
matr3	Familial amyotrophic lateral sclerosis	Thr622Ala (missense mutation)—familial ALS Pro154Ser (missense mutation)—sporadic ALS
Senataxin	Sporadic juvenile-onset amyotrophic lateral sclerosis	Dominant mutation
Senataxin	Ataxia with oculomotor apraxia type 2 (AOA2)	Recessive mutation
Fmr1	Fragile X syndrome	Loss of function
RBFOX1/ A2BP1/FOX1	Autism	Loss of function

in vivo and can directly affect translation (Banerjee et al. 2020). Evidence also show ncRNA colocalization with tau aggregates is implicated in pre-splicing deregulation (Lester et al. 2021). Such tau-RNA-protein aggregates also signal genes involved in Reactive Oxygen Species (ROS)- mediated stress, transcription deregulation, and posttranslational processes (Montalbano et al. 2021). RBPs like LUC7 like 3 pre-mRNA splicing factor (LUC7L3) belonging to the spliceosome have been observed in RNA granules seen in AD (Hsieh et al. 2019; Bishof et al. 2018). RBFOX1, a neuron-specific splicing factor, is also implicated in AD. A recent study shows that RBFOX1 protein localization around amyloid-β plaques and lower RBFOX1 expression is correlated with higher amyloid-β burden and declining cognitions (Raghavan et al. 2020) (Table 9.2). Studies in other model organisms have also proven highly beneficial in identifying modifiers of AD (Cutler et al. 2015; Singh and Irvine 2012; Deshpande et al. 2023; Steffensmeier et al. 2013; Irwin et al. 2020).

9.9 Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disorder affecting about 1% of individuals over 60 years of age. It involves the loss of specific dopaminergic neurons in the brain, leading to motor deficits. The aggregation of α-synuclein in Lewy bodies is a hallmark of PD, and both genetic mutations and environmental factors contribute to its development (Gomez-Benito et al. 2020; Banerjee et al. 2022). Interaction between Parkin and α-synuclein have also been implicated in disease pathogenesis and neuronal loss (Narwal et al. 2024). RBFOX1 is elevated in PD models; they also show increased deregulation of transcriptome, including genes belonging to the synaptic signaling transmission (Lin et al. 2016b). In contrast to wild-type (WT) higher RBFOX1 expression in PD also caused significant differential splicing of genes required for mitochondrial function, cell apoptosis, and cellular redox metabolism (Lin et al. 2016b).

9.10 Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) encompasses a set of neuromuscular disorders resulting from genetic mutations that compromise the survival of motor neurons causing progressive paralysis and degeneration of motor neurons. It is caused by recessive loss-of-function mutation in the human *survival motor neurons 1 (SMN1)* gene (Lefebvre et al. 1995). SMA is characterized by rapid progression and high fatality rate. SMA severity is also directly linked to the levels of full-length SMN protein (Gennarelli et al. 1995). SMN is an oligomeric protein required for the biogenesis and assembly of small nuclear ribonucleoproteins (snRNPs) (Pellizzoni et al. 2002). Furthermore, SMN depletion in mouse models is known to significantly impact spliceosome formation and splicing of U12 snRNP-dependent genes

(Doktor et al. 2017; Gabanella et al. 2007). SMN also associates with SIP1 to form a complex with other spliceosomal snRNP proteins (Fischer et al. 1997). A recent study has also revealed that SMN is a positive genetic modifier of GEMIN5, a protein involved in the core assembly of small nuclear ribonucleoproteins (snRNPs), and loss of function of SMN in SMA patients strongly correlates with GEMIN5 levels (Fortuna et al. 2023). Furthermore, the authors shed light on targeting SMN as a therapeutic strategy for GEMIN5-mediated neurodegeneration (Fortuna et al. 2023).

9.11 Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is mostly sporadic (~90%) and in some cases familial (~10%). It is primarily caused due to ubiquitinated and hyperphosphorylated TAR DNA-binding protein (TDP-43), an RBP, inclusions that are mislocalized in the cytoplasm (Neumann et al. 2006; Mackenzie et al. 2010). Mutations in another RBP, FUS/TLS (fused in sarcoma/translated in liposarcoma, referred to as FUS), is also observed in both sporadic and familial ALS (Rademakers et al. 2010; Corrado et al. 2010; Kwiatkowski Jr. et al. 2009; Vance et al. 2009). FUS is implicated in regulating gene's expression by forming complexes with transcription factors. Furthermore, it interacts with serine/arginine-rich spliceosome proteins and thus impacts RNA splicing (Yang et al. 1998). *Drosophila* model of ALS has also been used to identify highly conserved Hippo pathway as a genetic modifier of FUS-mediated neurodegeneration (Gogia et al. 2020, 2021). Senataxin, another RBP, is also mutated in sporadic juvenile-onset amyotrophic lateral sclerosis (Hirano et al. 2011). It has recently been associated with autophagy pathway genes (Richard et al. 2021). MATR3 is an RNA- and DNA-binding protein that has also been shown to interact with TDP-43 in ALS. Missense mutations of *matr3* is observed in case of both sporadic and familial ALS and is known to affect MATR3 protein structure, length, and interaction with TDP-43 (Johnson et al. 2014).

9.12 Ataxia with Oculomotor Apraxia Type 2 (AOA2)

Ataxia with oculomotor apraxia type 2 (AOA2) is a juvenile form of ataxia caused by recessive mutations in senataxin that is implicated in transcription termination (Moreira et al. 2004; Yuce and West 2013). It is an RNA/DNA helicase that is implicated in DNA damage response and transcriptional regulation by interacting with RNAPII (RNA polymerase II). These mutations are known to cause premature termination in genes required for RNA maturation and termination (Moreira et al. 2004). Recent evidence supports that depletion of senataxin results in genome-wide reduction in levels of RBPs and 3′ end processing factors required for RNA processing (Richard et al. 2021). Additionally, the study also shows that senataxin

knockdown (1) impairs alternative splicing, (2) results in accumulation of double-strand breaks, and (3) significantly impaired autophagy- and lysosome-dependent proteosomal activity (Richard et al. 2021). These aberrations can collectively be the cause of cellular toxicity and neurodegeneration.

9.13 Fate of Noncoding RNAs in Neurodegenerative Diseases

Noncoding RNAs (ncRNAs) refer to untranslated RNAs. They are classified as small ncRNAs comprising fewer than 400 nucleotides and long ncRNAs comprising more than 400 nucleotides. Small ncRNAs encompass various types such as ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), small nucleolar RNAs (snRNAs), microRNAs (miRNAs), short small interference RNAs (siRNAs), and piwi-interacting RNAs. On the other hand, long noncoding RNAs (lncRNAs) include diverse regulatory molecules like long intergenic noncoding RNAs (lincRNAs) and natural antisense transcripts (NATs). Recent research has highlighted the role of ncRNAs in the pathogenesis of neurodegenerative diseases (NDDs). While the primary emphasis in NDD research has traditionally centered on protein-coding genes, the recognition that approximately 97% of the human genetic code consists of noncoding regions has prompted researchers to explore its role in NDDs (Almatroudi 2022; Das et al. 2021). ncRNAs play critical roles in neuronal processes such as transcription of neuronal genes, brain morphogenesis, neuronal cell specification, and formation of memory. Additionally, research indicates that lncRNAs play a role in various pathological aspects of age-related diseases such as neurodegeneration (Zhang et al. 2021a; He et al. 2018).

9.14 ncRNA Mechanisms

ncRNAs play crucial roles in regulating various cellular processes such as DNA replication, RNA transcription, protein translation, cell proliferation, and differentiation (Robinson et al. 2020). Their unique structural characteristics enable them to intricately and precisely modulate gene expression through involvement in epigenetic phenomena, including gene silencing, DNA methylation, histone modification, activation of dormant transposons, RNA editing, and gene methylation (Johnsson et al. 2014).

In the realm of epigenetic regulation, lncRNAs have emerged as significant players, participating in gene transcription by mimicking DNA elements, competitively binding transcription factors, or influencing variable splicing (Wang et al. 2008). Posttranscriptional gene regulation, a complex biological process, involves various steps such as gene processing, modification, and regulation, encompassing RNA splicing, processing, maturation, metabolism, and stability regulation (Corbett

2018). Notably, lncRNAs often play a crucial role in the shearing of mRNA precursors during mRNA processing and metabolism.

Certain noncoding RNAs (ncRNAs) have the ability to impact the progression of diseases and essential cellular processes by binding to specific protein complexes, thereby exerting a crucial influence on gene expression. For instance, spliceosomes, consisting of small nuclear RNAs (snRNA) and other proteins, play a central role in the splicing mechanism, facilitating the removal of introns from precursor mRNAs (Lafontaine 2015). Additionally, ribonucleoprotein (RNP) complexes contribute to the posttranscriptional modification of precursor small nuclear RNAs (pre-snRNA), precursor transfer RNAs (pre-tRNA), and precursor ribosomal RNAs (pre-rRNA). Long noncoding RNAs (lncRNAs) and circular RNAs (circRNAs) play a role in recruiting proteins (Mattick et al. 2023).

Several studies suggest that lncRNAs have pathophysiological roles in the regulation of microRNA (miRNA) expression (Huang 2018). Due to their distinctive length, lncRNA molecules possess miRNA recognition action sites. These sites serve as specific binding sites for miRNAs, impacting in vivo lncRNA stability, facilitating lncRNA degradation, and influencing various cell biological functions (Huang 2018). Additionally, beyond acting as molecules that regulate target gene expression, lncRNAs also function as bait molecules for miRNAs. Through target mimicry, lncRNAs absorb miRNAs, inhibiting their effects on target molecules. Furthermore, lncRNAs may act as molecular bait, indirectly regulating target gene expression by suppressing miRNA effects on their targets. They can also competitively bind mRNA to miRNA, directly influencing target gene expression (Gao et al. 2020).

9.15 ncRNAs and Neurodegenerative Diseases

9.15.1 Alzheimer's Disease

In AD, cellular stress induces an elevation in the expression of BACE1-AS (Beta Secretase-1 antisense) long noncoding RNA (lncRNA) (Faghihi et al. 2008) (Fig. 9.3, Table 9.3). This upregulation subsequently increases beta-secretase and amyloid plaque levels (Table 9.3). The removal of amyloid-beta and cholesterol is facilitated by LRP1 (low-density lipoprotein receptor-related protein 1). However, the antisense lncRNA LRP1-AS negatively regulates LRP1 levels by binding with HMGB2 (high-mobility group protein B2), a chromatin-associated protein (Yamanaka et al. 2015) (Fig. 9.3, Table 9.3). In Alzheimer's patients, there is a significant decrease in LRP1 levels (Holtzman et al. 2012; Deane et al. 2008).

SORL1 (Sortilin-related receptor 1) is another protein whose reduction in AD contributes to amyloid plaque accumulation. Alterations in SORL1 pre-mRNA splicing result in the formation of an antisense lncRNA 51 A, causing a decrease in the protein isoform A. This increase in 51 A correlates with elevated amyloid-beta

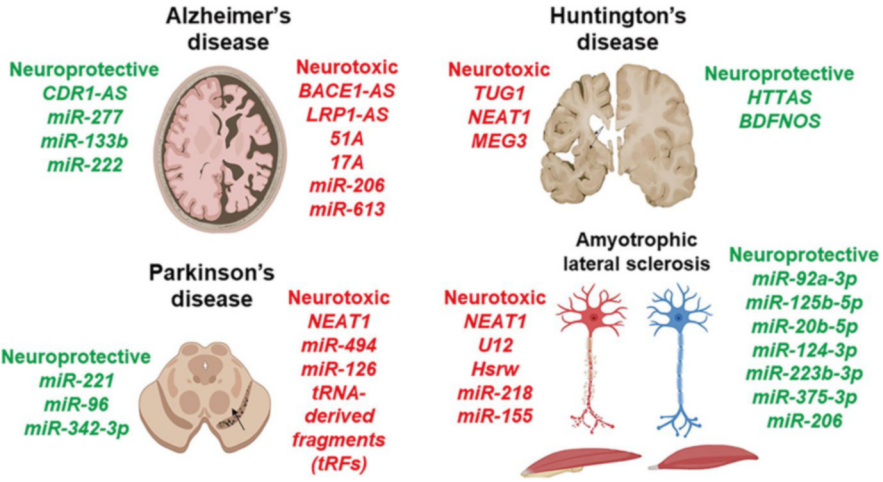

Fig. 9.3 Long noncoding RNA (lncRNA) dysregulation and neurodegenerative diseases. LncRNAs are associated with neurodegenerative diseases like Alzheimer's disease, Huntington's disease, Parkinson's disease, and amyotrophic lateral sclerosis are mentioned

accumulation (Fig. 9.3, Table 9.3) (Ciarlo et al. 2013; Zhang et al. 2021b). Additionally, the GABBR2 gene undergoes abnormal pre-mRNA splicing, leading to the formation of the 17A long noncoding RNA (gamma amino butyric acid type B receptor). 17A is transcribed from the reverse strand of GABBR2 gene (Fig. 9.3, Table 9.3) (Lan et al. 2021). This process results in reduced GABAergic signaling. CDR1-AS (cerebellar degeneration-related antigen 1 antisense) exhibits elevated expression in the normal brain but is suppressed in the hippocampus and cortex of Alzheimer's patients (Fig. 9.3, Table 9.3) (Ma et al. 2020; Lukiw 2013).

MicroRNAs play a role in the growth and programmed cell death of neurons by modulating downstream target genes or signaling pathways associated with the pathological progression of AD. MicroRNAs like miR-277 targets *head involution defective (hid)*, proapoptotic factor, to ameliorate Aβ42-mediated neurodegeneration in *Drosophila* eye model of AD (Deshpande et al. 2023) (Fig. 9.3). miR-206 has been observed to decrease brain-derived neurotrophic factor (BDNF) expression, a protein crucial for neuroprotection and apoptosis prevention, and promote neuron survival (Tian et al. 2014) (Fig. 9.3, Table 9.3). Elevated miR-206 levels in AD transgenic mice suggest a potential contribution to neuronal apoptosis, given the reduced BDNF levels (Moon et al. 2016; Kenny et al. 2019) (Fig. 9.3, Table 9.3). Another miRNA, miR-613, has been associated with decreased BDNF expression in AD, with increased miR-613 levels found in patients with mild cognitive impairment and dementia (Li et al. 2016a) (Fig. 9.3, Table 9.3). miR-133b appears to have a neuroprotective role by targeting epidermal growth factor receptor (EGFR), a player in cell survival and protection against neurotoxicity (Yang et al. 2019). Reduced levels of miR-133b in AD patients correlated with neuronal apoptosis induced by amyloid-beta (Yang et al. 2019) (Fig. 9.3, Table 9.3). Additionally,

Table 9.3 Long noncoding RNAs associated with the neurodegenerative diseases

Noncoding RNA	Associated disease	Upregulated/ downregulated	Biological function
BACE1-AS	AD	Upregulated	Facilitate the binding to BACE1, enhance the mRNA stability, promote the synthesis of BACE1 protein, and further increase the production of Aβ of cells
LRP1-AS	AD	Upregulated	Lrp1-AS suppresses the transcriptional activation of Lrp1 by high-mobility group box 2 (Hmgb2)-mediated Srebp1a
51A	AD	Upregulated	Modify the spliced variant of SORL1 mRNA, leading to the accumulation of Aβ42
17A	AD	Upregulated	Compromise the GABAB signaling pathway by reducing the transcription of GABAB R2
CDR1-AS	AD	Downregulated	Binds miR-7, functioning as a sponge
miR-206	AD	Upregulated	Regulates brain-derived neurotrophic factor
miR-613	AD	Upregulated	The presence of miR-613 was observed to negatively regulate the expression of BDNF
miR-133b	AD	Downregulated	Neuroprotective function
miR-222	AD	Downregulated	Targets CDKN1B to modulate cell cycle progression and apoptosis
TUG1	HD	Upregulated	Unknown
HTTAS	HD	Downregulated	Reduce the levels of endogenous HTT transcripts
NEAT1	HD/PD/ ALS/FTLD	Upregulated	Crucial for maintaining the integrity of the nuclear paraspeckle substructure, promoting cell viability in the presence of oxidative stress
MEG3	HD	Upregulated	Modify the expression of genes in reaction to neuronal activity
BDFNOS	HD	Downregulated	Enhance the transcription of BDNF and have a protective effect on neurons
miR-221	PD	Downregulated	Promotes neuronal survival against oxidative stress
miR-494	PD	Upregulated	Binds to the 3′-UTR of DJ-1 and exacerbates neurodegeneration
miR-126	PD	Upregulated	Promotes neuronal death by downregulating signaling cascades such as insulin/IGF-1/ phosphatidylinositol-3-kinase (PI3K)/AKT and ERK
miR-96	PD	Downregulated	Potential biomarker of PD
miR-342-3p	PD	Downregulated	Circulating miRNA biomarker in AD, PD, MS, and Creutzfeldt-Jakob disease

(continued)

Table 9.3 (continued)

Noncoding RNA	Associated disease	Upregulated/ downregulated	Biological function
GDNF-AS	PD	Not known	GDNF-AS encodes for glial cell line-derived neurotrophic factor (GDNF) and has the capability to enhance GDNF expression by a factor of two
tRNA-derived fragments (tRFs)	PD	Upregulated	Unknown
U12	ALS/FTLD	Upregulated	U12 small nuclear RNA (snRNA) serves a function similar to that of U2 snRNA in the U2-dependent spliceosome, playing a crucial role in the splicing process of U12-dependent introns
Hsrw	ALS/FTLD	Upregulated	Stress-induced satellite III repeat RNA
ncRNACCND1	ALS	Upregulated	In response to DNA damage, ncRNACCND1 interacts with FUS, leading to the suppression of CCND1 gene transcription
Lhx1as	ALS	Not known	Unknown
lncMN-1	ALS	Not known	Unknown
lncMN-2	ALS	Not known	Unknown
miR-92a-3p	ALS	Downregulated	Modify the subcellular location of PTEN by directing the E3 ubiquitin ligase to regulate its localization
miR-125b-5p	ALS	Downregulated	Targets NEFM 3′UTR
miR-124-3p	ALS	Downregulated	Targets NEFH 3′UTR
miR-20b-5p	ALS	Downregulated	Targets NEFH 3′UTR
miR-223b-3p	ALS	Downregulated	Targets NEFH 3′UTR
miR-375-3p	ALS	Downregulated	Targets p53 and ELAVL4, both of which experience increased expression as a result of FUS dysfunction
miR-155	ALS	Upregulated	Regulates expression in microglia
miR-218	ALS	Upregulated	miR-218 can be transported from motor neurons to adjacent astrocytes, effectively reducing the expression of glutamate transporter in astrocytes
miR-206	ALS	Downregulated	Controls the expression of HDAC4 in neuromuscular genes and reinstates the function of the neuromuscular junction (NMJ)
Variant of U1 snRNA (vU1)	SMA	Upregulated	It has an impact on the expression of U1 snRNA
ATXN2-AS	SMA	Not known	The interaction between ATXN1-AS and CAG repeats induces apoptosis through a caspase 3/7-dependent pathway

miR-222, known for its role in regulating neuronal proliferation, is implicated in AD development. Downregulation of miR-222 in AD mice is associated with increased expression of p27Kip1, a protein linked to cell cycle progression and proliferation, contributing to AD pathogenesis (Wang et al. 2015) (Fig. 9.3, Table 9.3).

9.15.2 Huntington's Disease

In patients with Huntington's disease, long noncoding RNAs (lncRNAs) are dysregulated, many of which serve as binding sites for the transcriptional repressor REST (RE1-Silencing Transcription factor). TUG1 (Taurine Up Regulated 1), MEG3, and NEAT1 (Nuclear Paraspeckle Assembly Transcript 1) are upregulated, while HTTAS (Huntingtin antisense) is downregulated, forming epigenetic ribonucleoprotein complexes (Bhatti et al. 2021; Johnson 2012; Ghafouri-Fard et al. 2022) (Fig. 9.3, Table 9.3). Elevated NEAT1 levels in HD contribute to neuroprotective mechanisms, as demonstrated by increased cell viability under oxidative stress in NEAT1-transfected cells (Bhatti et al. 2021). This suggests that NEAT1 upregulation serves a protective role against neuronal damage in neurodegenerative diseases. BDNFOS is an antisense transcript of brain-derived neurotrophic factor (BDNF) that enhances BDNF transcription and translation in Huntington's disease (HD) (Wang et al. 2018; Lipovich et al. 2012) (Fig. 9.3, Table 9.3). Treatment with small interfering RNA (siRNA) targeting BDNFOS increases Htt expression, exhibiting a neuroprotective effect.

9.15.3 Parkinson's Disease

ncRNAs play a role in PD by influencing mitochondrial function, oxidative stress, and apoptosis (Zhang et al. 2022). Mitochondrial dysfunction is a major factor in PD, and ncRNAs are involved in regulating this process. For example, lncRNA NEAT1 and microRNAs influence the stability of PINK1, a mitochondrial kinase associated with PD (Fig. 9.3, Table 9.3) (Boros et al. 2021). Other ncRNAs, like miR-221 and miR-494, impact the function of proteins such as DJ-1 and LRRK2, which are crucial for combating oxidative stress (Table 9.3) (Tryphena et al. 2023; Nies et al. 2021; Oh et al. 2018). Apoptosis, the programmed cell death that contributes to the loss of dopaminergic neurons in PD, is also influenced by ncRNAs. Several microRNAs, including miR-126, miR-96, and miR-342-3p, are implicated in apoptosis regulation by targeting specific genes in PD models (Fig. 9.3, Table 9.3) (Deshpande et al. 2023; Nies et al. 2021; He et al. 2021; Shiau et al. 2023; Kim et al. 2014). Additionally, complex RNA networks involving lncRNAs, microRNAs, and mRNAs contribute to apoptosis in PD. Other mechanisms of PD pathogenesis involve ncRNAs, such as GDNF-AS promoting the expression of glial cell-derived neurotrophic factor (GDNF) to enhance dopaminergic neuron survival (Fig. 9.3,

Table 9.3) (Wu and Kuo 2020; Cortes et al. 2017; Duarte Azevedo et al. 2020). Neuroinflammation, a key feature of PD, is influenced by ncRNAs like lncRNA-p21 and NEAT1. Furthermore, tRNA-derived fragments (tRFs) have been identified in the cerebrospinal fluid, serum, and cortex of PD patients, suggesting their potential use as biomarkers (Tian et al. 2022; Magee et al. 2019). Several lncRNAs have been identified as potential regulators of PD pathogenesis, acting as competing endogenous RNAs (ceRNAs) to modulate gene expression.

9.16 Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis

Dysregulation of small nuclear RNA U12 and ncRNA Hsrw (stress-induced satellite III repeat RNA), associated with neurodegeneration, occurs in TDP43-positive postmortem ALS/FTLD tissues due to the interaction between TDP43 and transcription elongation factor ELL2 (Fig. 9.3, Table 9.3) (Wu and Kuo 2020). Additionally, NEAT1 interacts with TDP43 and FUS/TLS, possibly linking paraspeckle formation to ALS and FTLD. Ribonuclease angiotensin cleavage produces tRNA-derived stress-induced RNA (tiRNAs) that inhibit translation, leading to stress granule formation and motor neuron degeneration (Ivanov et al. 2014). In ALS, antisense transcript ncRNACCND1 represses CCND1 transcription, contributing to FUS-related ALS pathogenesis (Fig. 9.3, Table 9.3) (Wu and Kuo 2020; Wang et al. 2008). Dysregulated ncRNAs, including Lhx1as, lncMN-1, and lncMN2, are found in FUS-P517L ALS mouse models, and circRNAs are dysregulated in FUS-mutated cells and ALS-iPSC-derived motor neurons (Fig. 9.3, Table 9.3) (Wu and Kuo 2020). Whereas, microRNAs play roles in neurofilament aggregation, with miR-92a-3p and miR-125b-5p regulating NEFM and miR-124-3p, miR-92a-3p, miR-20b-5p, and miR-223b-3p targeting NEFH (Table 9.3) (Campos-Melo et al. 2018). Dysregulation of miR-375-3p and NDRG2 occurs in a sporadic ALS mouse model, influencing reactive oxygen species production (Fig. 9.3, Table 9.3) (Rohm et al. 2019). miR-155, upregulated in ALS, regulates microglia expression of survival genes (Fig. 9.3, Table 9.3) (Wu and Kuo 2020). miR-218 transported from motor neurons to astrocytes in ALS downregulates EAAT2, and miR-206 expression slows ALS progression by regulating histone deacetylase 4 and fibroblast growth factor signaling (Fig. 9.3, Table 9.3) (Wu and Kuo 2020; Hoye et al. 2018).

9.17 Spinal Muscular Atrophy

In SMA, U1 small nuclear RNA (U1 snRNA) plays a crucial role in regulating pre-mRNA splicing, and its variant forms (vU1s) show an inverse correlation with U1 expression. In SMA-induced pluripotent stem cell (iPSC)-derived motor neurons,

there is a dysregulation in the ratio of vU1 to U1 compared to healthy controls. Elevated levels of vU1 snRNA are also observed in individuals with SMA, suggesting a potential contribution to the pathogenesis of SMA (Fig. 9.3, Table 9.3) (Vazquez-Arango et al. 2016). SCA2 results from the expansion of CAG repeats in the ataxin-2 (ATXN-2) gene. Interestingly, transcripts of ATXN2-AS containing CAG repeats create RNA foci, triggering caspase 3/7-mediated apoptosis in Purkinje cells of the cerebellum (Fig. 9.3, Table 9.3) (Li et al. 2016b).

9.18 ncRNAs as Biomarkers

ncRNAs have been extensively studied as potential biomarkers for neurodegenerative disorders, particularly alterations in miRNA levels in cerebrospinal fluid (CSF) and peripheral tissues. However, monocentric studies with limited sample sizes and variations in sample handling and analysis have hindered the identification of consensus biomarkers. For example, postmortem delays in sample collection can impact results, emphasizing the need for standardized approaches. Recent findings indicate that measuring miR-206 levels in the olfactory mucosa could be a promising approach for early AD diagnosis. Similarly, RNA and protein species, such as C9ORF72 RNA foci and polyglutamine proteins, show potential as biomarkers in ALS and FTD. Although ncRNAs exhibit stability in body fluids, systematic studies are required to evaluate their potential as neurodegenerative biomarkers. Additionally, targeting ncRNAs present a promising avenue for neurodegenerative disorder treatment. Antisense oligonucleotides (ASOs) against specific transcripts have shown success in experimental models, offering potential therapeutic strategies. Systemic administration of single-stranded oligonucleotides, nanotechnology-based delivery systems like exosomes, and ongoing pharmaceutical efforts indicate a growing interest in ncRNA-based therapeutics. Despite challenges, clinical trials in diseases like ALS and SMA have demonstrated the therapeutic potential of targeting RNA.

9.19 Impact of Defective RNA Processing and Metabolism on Neuronal Integrity

Messenger RNAs (mRNAs) undergo a series of intricate processing steps, encompassing splicing, polyadenylation, editing, transport, translation, and turnover. The intricate mRNA life cycle, from initial transcription to mature mRNA generation, is regulated by a diverse array of RBPs. The human genome harbors over 1200 confirmed RBPs, with ongoing discoveries of new ones. RBPs bind to RNA at RNA binding domains (RBDs) located in coding sequences (intron and exon domains), 5′ untranslated regions (5′UTR), and 3′ untranslated regions (3′UTR) (Kelaini et al.

2021). These proteins have the ability to identify and engage with specific binding motifs known as RNA recognition motifs (RRM) and/or RNA structures, forming ribonucleoprotein (RNP) complexes. A single RBP can engage with different protein complexes, influencing multiple processing steps of its RNA targets. Consequently, disruptions in the interaction between an RBP and its targets can give rise to severe pathological phenotypes. Substantial evidence suggests that irregularities in RNA regulation play a pivotal role in neurodevelopmental dysfunction and neurodegenerative diseases. Nevertheless, the molecular insights include compromised RBP expression, mislocalization and aggregation of RBPs within cells, and the sequestration of RBPs by transcripts or abnormal proteins featuring pathological repeat expansions (Nussbacher et al. 2019). The deregulation of RNA metabolism can have profound effects on neuronal integrity, impacting various aspects of cellular function (Fig. 9.4).

9.20 Alternative Splicing

Eukaryotic genes consist of both exons (coding regions) and introns (noncoding regions). During the maturation of RNA, a crucial process involves removing introns to form mature mRNA, which is then translated into proteins. Pre-mRNA splicing, the removal of introns and joining of exons, is regulated by cis-acting elements and the spliceosome (Vuong et al. 2016). This process generates alternatively spliced mRNAs, contributing to species diversity and tissue-specific functions. This splicing process must be precise because errors can result in unintended consequences such as coding or frameshift mutations. Genetic mutations that alter the sequence of the transcript can introduce new splice sites or enhancer sequences. This can lead to the recognition of new exons, referred to as cryptic exons. Alternatively, these mutations can disrupt splicing sequences crucial for recognizing exons, causing the exclusion of constitutive exons from the transcript. These splicing errors result in the generation of aberrant transcripts, contributing to disease (Fig. 9.4). Similarly, defects in the splicing machinery itself can lead to abnormal splicing of multiple transcripts, further contributing to the disease state (Fig. 9.4).

Mutations in the splicing factors TDP-43 and FUS can cause toxic aggregate formation, disrupting normal splicing and potentially contributing to ALS (Montes et al. 2019). Animal models with mutated TDP-43 or FUS replicate splicing defects seen in ALS (Montes et al. 2019). In AD, the microtubule-associated protein Tau undergoes altered splicing leading to protein aggregates (Montes et al. 2019). Splicing defects play a major role in Huntington's disease, and CAG repeat expansion in SCA type 6 genes induces altered splicing patterns, leading to the accumulation of disease-causing proteins (Aikawa et al. 2017). Strategies like RNA trans-splicing and splice-switching oligonucleotides are explored for therapeutic modulation of splicing defects in neurodegenerative diseases.

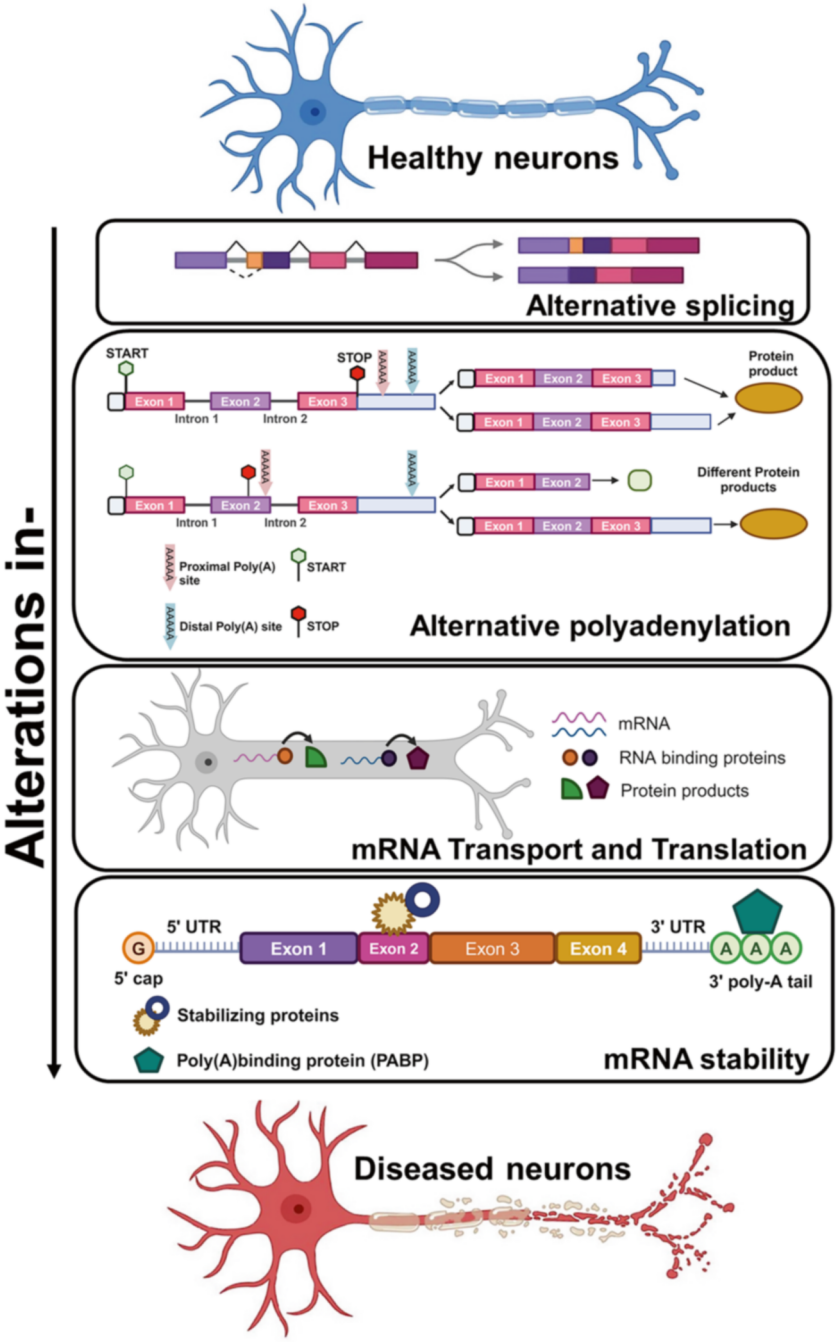

Fig. 9.4 Deregulation of RNA metabolism in neurodegenerative diseases. Alteration in RNA metabolism like alternative splicing, alternative polyadenylation, mRNA transport and translation, and mRNA stability affect the neuronal integrity and causes neurodegenerative diseases like AD, HD, PD, and ALS

9.21 mRNA Alternative Polyadenylation

Alternative polyadenylation (APA) is a process that involves the utilization of multiple polyadenylation sites in primary transcripts, in conjunction with alternative splicing, leading to the generation of diverse mRNA isoforms (Tian and Manley 2017). APA, classified as UTR-APA and CR-APA based on polyadenylation site location, contributes significantly to transcriptomic diversity (Ren et al. 2020). APA sites within the 3′-UTRs of mRNAs result in transcript isoforms sharing the same coding region but possessing varying lengths of 3′-UTR regions (Tian and Manley 2017). This diversity leads to unique interactions between mRNA isoforms and RNA-binding proteins, as well as noncoding RNAs like microRNA and lncRNAs. In contrast, CR-APA directly impacts the coding region, giving rise to proteins with distinct C-termini (Tian and Manley 2017; Di Giammartino et al. 2011). In mammals, around 70% of mRNA-encoding genes undergo APA, and these events can be tissue-specific (Shi 2012; Hoque et al. 2013; Derti et al. 2012). Distinct interactions with RNA-binding proteins and noncoding RNAs, such as microRNA and lncRNAs, arise from APA sites in 3′-UTRs, influencing posttranscriptional gene regulation (Tian and Manley 2017). APA events also impact mRNA stability, translation, nuclear export, cellular localization, and protein diversification (Fig. 9.4). In neurodegenerative diseases like Alzheimer's, Parkinson's, and ALS, APA profiles show disease-specific changes, affecting genes associated with protein turnover and mitochondrial function (Chatterjee et al. 2021). The extended 3′-UTR isoform of α-synuclein mRNA is linked to Parkinson's development, influencing protein accumulation and localization (Rhinn et al. 2012). In Huntington's disease, the huntingtin gene exhibits APA-related variations in mRNA isoforms, affecting their abundance, localization, poly-A tail length, half-lives, and binding sites for miRNAs and RNA-binding proteins (Romo et al. 2017). Additionally, altered APA in diseases like ALS and frontotemporal dementia is associated with reduced gene expression (Melamed et al. 2019). The human tau gene's APA is linked to the expression of specific mRNA isoforms through the binding of miRNAs (Melamed et al. 2019).

9.22 RNA Localization and Transport and Translation

Neurons exhibit distinct morphological features, including axons and dendrites, setting them apart from other cells. Recent findings highlight the transport of mRNAs to axons, where local translation occurs, contributing to axonal maintenance (Dalla Costa et al. 2021; Nagano and Araki 2021). Factors necessary for local translation, like ribosomes, tRNAs, and initiation factors, are localized within axons (Kar et al. 2013). Brain-derived neurotrophic factor (BDNF) and netrin-1 promote axonal protein synthesis, signaling through receptors TrkB and DCC, respectively (Nagano and Araki 2021; Cohen-Cory et al. 2010). Annexin A11 tethers RNA granules to

lysosomes, mitochondria are recruited to axonal branching sites, and late endosomes regulate overall protein synthesis and mitochondrial function in axons through mRNA translation (Nagano and Araki 2021; Liao et al. 2019).

Disruption of local translation in axons has been implicated in various neurodegenerative diseases (Fig. 9.4). In ALS and FTD, mutations in genes like TDP-43, FUS, hnRNPA1, hnRNPA2/B1, and abnormal expansion of the GGGGCC repeat sequence in the C9orf72 gene affect RNA-binding proteins, leading to TDP-43 pathology. These proteins, crucial for RNA metabolism and transport, form stress granules and neuronal RNA granules, impacting the axonal transport of specific mRNAs involved in translation and synaptic function (Nagano and Araki 2021). In SMA, deficiency of the Survival of Motor Neuron (SMN) protein affects axonal transport and local translation of mRNAs crucial for cytoskeletal maintenance and axon elongation (Fallini et al. 2016). SMN interacts with RNA-binding proteins like HuD, hnRNPR, and others to regulate the transport and translation of specific mRNAs in axons (Fallini et al. 2011). AD is characterized by the accumulation of Aβ plaques and tau tangles. Aβ inhibits BDNF signaling and retrograde axonal transport, impacting local translation (Nagano and Araki 2021; Poon et al. 2011). Tau interacts with RBPs like T cell intracellular antigen 1 (TIA1), influencing stress granule formation and translation regulation (Vanderweyde et al. 2016). Fragile X syndrome is caused by FMR1 gene mutations. Fragile X Mental Retardation Protein (FMRP), present in axons, interacts with RNAi molecules, transports specific mRNAs, and modulates their local translation in axons (Nagano and Araki 2021; Bassell and Warren 2008).

9.23 mRNA Stability

To ensure RNA homeostasis, mRNAs produced within the nucleus undergo decay processes directed by cis-acting elements, involving exonucleases and endonucleases (Houseley and Tollervey 2009). Methylation capping at the 5′ untranslated region (UTR) and polyadenylation at the 3′-UTR play protective roles against degradation by nucleases. The stability of mRNAs, a crucial factor in determining gene expression levels, is influenced by their half-lives (Chen et al. 2008). Various mechanisms can either increase or decrease mRNA half-life. Alternatively, spliced mRNAs, by harboring or excluding cis-acting elements or undergoing alternative polyadenylation, have the capacity to regulate mRNA stability (Fig. 9.4) (Porter et al. 2018).

In neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's (PD), nELAVL-mediated changes in mRNA stability are implicated (Scheckel et al. 2016). Recent research highlighted Ataxin2's role in conferring stability to its mRNA target TDP-43, with the poly-Q domain of Ataxin2 playing a crucial role (Ostrowski et al. 2017). Expansion of this domain alters TDP-43 mRNA stability, leading to tau protein aggregation and contributing to the pathogenesis of amyotrophic lateral sclerosis (ALS). Another RNA-binding protein, RBFOX, is involved

in stabilizing mRNAs associated with synaptic transmissions, and its dysregulation is linked to Alzheimer's disease (Alkallas et al. 2017). Proteins traditionally associated with other aspects of RNA metabolism, such as TDP-43, can also influence RNA stability, as observed in its role in stabilizing β-adducin (Add2) mRNA, potentially associated with ALS and frontotemporal lobar degeneration (FTLD) (Costessi et al. 2014). This combination of various RNA-binding proteins ensures the maintenance of mRNA and protein homeostasis within cells through modulation of mRNA stability and translation (Fig. 9.4). Any disruption in this coordinated effort can lead to neurological pathogenicity.

9.24 Transport RNP Granules

The regulation of specific mRNA transfer is crucial, particularly in neurons where mRNAs must navigate intricate dendritic arbors before entering the translation pathway. To prevent premature translation and degradation, mobile and protective units known as transport RNP granules (tRNP granules) are formed (De Conti et al. 2017). These granules, containing silent mRNAs, ribonucleoproteins (RBPs), densely packed ribosomes, and miRNAs, are assembled with the involvement of various RBPs, such as Staufen1, Staufen2, FMRP, CPEB, hnRNPA2, TAF15, SMN, Smaug, Nanos, Pumilio, FUS/TLS, and TDP-43 (De Conti et al. 2017). Once tRNP granules reach their destination, local protein synthesis begins. While the contribution of tRNP granules to neurological diseases is not fully established, mutations or alterations in proteins associated with these granules may potentially disrupt proper neuronal mRNA translation.

9.25 Dendrite and Synapse Attrition

Proper RNA metabolism is crucial for neuronal development, including processes like axon guidance, dendritic branching, and synapse formation. Deregulation can disrupt these processes, leading to impaired connectivity. The structural and functional plasticity of the brain relies heavily on processes such as neuron dendritic branching, synapse formation, and stabilization. Precise development of synapses is essential for accurate neuronal network activity and normal brain function. Deviations in dendrite morphology and defects in neuronal development, including changes in dendrite branching patterns, fragmentation, retraction or loss of dendrite branching, and alterations in spine morphology and number, contribute to various disorders, including ALS, FTD, Alzheimer's disease, Down syndrome, autism spectrum disorders, fragile X syndrome, Rett syndrome, anxiety, depression, schizophrenia, and Parkinson's disease. Neuropsychiatric disorders often exhibit dendritic and synaptic pathology, involving abnormal spine density, morphology, synapse loss, and aberrant synaptic signaling and plasticity. Animal models of

neurodegenerative diseases, including ALS and FTD, display changes in dendritic branches and abnormal spine morphology. RNA-binding proteins, such as FMRP, TDP-43, huntingtin, Staufen-1, Staufen-2, and FUS, play critical roles in maintaining dendrites and spines (Sephton and Yu 2015). Deficiencies in these proteins are implicated in altering dendritic branching and spines, contributing to neurological diseases. For example, in fragile X syndrome, there is an excess of long and thin filopodial-like spines and a reduction in mature spines, likely due to dysregulated protein synthesis at synapses. Studies on Staufen-1 knockout mice reveal deficits in dendritic delivery of β-actin tRNP granules, resulting in reduced dendritic tree and synapse development (Sephton and Yu 2015). Similarly, neurons deficient for Staufen-2 exhibit reduced dendritic spines and increased filopodia due to impaired β-actin mRNA localization (Sephton and Yu 2015). FUS, localized to spines in response to mGluR5 activation, is crucial for spine development, and its mutations in ALS result in fewer mature spines and reduced dendritic branches (Sephton and Yu 2015).

9.26 Conclusion

There are several neurodegenerative diseases that exist affecting the cognition, behavior, movement, etc. These diseases manifest via varied mechanisms affecting different tissues. With the advent in technologies, it is becoming increasingly clear that the gene expression patterns in neurodegenerative disease tissues are highly deregulated when compared to the healthy counterparts. Perturbations occur in several pathways including the signaling pathway genes, cell death pathways, and also proteasome degradation pathway. Such widespread degradation makes it challenging to target just one of the pathways when identifying therapeutic modalities. Defective or altered RNA metabolism is emerging as a new unifying theme across several neurodegenerative diseases. Several of the aforementioned mechanisms involve deregulation of transcription, altered splicing, and even deregulation of gene expression involved in such processes. Therefore, identifying such widespread deregulation might shed light on how they can be used as a therapeutic strategy as well as they can serve as potential biomarkers for tracking progression.

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Chapter 10
Unveiling RNA Dysfunction: A Key Player in Neurodegeneration

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Abstract The complexity of higher organisms is reflected by the tight regulation at the DNA, RNA and protein levels. A well-choreographed RNA metabolism regulates various aspects of the cellular function. In the past few decades, RNA metabolism has gained attention in the context of neurodegenerative diseases, since the underlying cause of a number of disorders is disturbed RNA processing. Alteration in RNA metabolism affects not only the proteins that are encoded by the RNA but also interaction between various proteins and RNAs. The homeostasis maintained by coding and non-coding RNAs along with RNA-binding proteins (RBPs) is crucial for the maintenance of normal cellular physiology. Various non-coding RNAs like microRNA and long non-coding RNAs have been implicated in human disease. In addition, the correct spatio-temporal localization, stability and translation of RNA and RNA-binding proteins are critical for performing highly complex function by the neuronal cells. Here, we describe some of the possible misregulation in RNA processing events by diverse non-coding RNAs that results in neurodegenerative disorders. Both loss-of-function and gain-of-function of the RNA or RBPs are observed in the RNA-mediated pathogenesis. In this chapter, we have highlighted the role of disrupted RNA metabolism primarily in neurodegenerative disorders, like Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis along with other disorders.

Keywords RNA metabolism · RNAopathy · RNA toxicity · ALS/FTD · SCA · RNA-binding proteins · TDP-43 · Microsatellite repeats · miRNA · lncRNA

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10.1 Introduction

Neurons play a central role in the proper functioning of the body and are highly specialized cells which maintain coordination between the brain and other parts of the body (Jefferys and Cooper 2007; Lamptey et al. 2022). In order to perform the complex coordination of the body, a huge number of neurons are required, and these are interconnected with each other. During development, neurons go through various processes like division, migration, differentiation and then synaptogenesis. Most of the neurons originate from the brain, but they then migrate to their appropriate place of action and form complex network (Jefferys and Cooper 2007). The process of neurogenesis is also accompanied by neuronal cell death. Since an excess number of neurons are generated from the progenitor stem cells which migrate, and the ones which do not form correct connections sacrifice themselves for the benefit of the system by apoptosis or programmed cell death. This is generally termed as the "*good neuronal death*" (Chi et al. 2018; Dekkers and Barde 2013; Jefferys and Cooper 2007). As we age, our neurons also get older, and some of these neurons are lost in the aging processes which is a common phenomenon (Chi et al. 2018). However, sometimes due to various environmental, genetic or any intrinsic or extrinsic factors such as physical injury and cellular insult, the neuronal cell death is activated which may go beyond the benefit of the system resulting in excessive loss of neurons. In this condition, the neuronal cell death can occur via necrosis or excitotoxicity, and it also results in the death of the neighbouring cells. This damaging process kills a huge number of active neurons. This is generally termed as the "*bad neuronal death*" (Jefferys and Cooper 2007). This phenomenon is associated with various neurodegenerative diseases (NDDs) like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disorder (HD), dementia, amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), etc.

Neurodegeneration literally means the degeneration of the neurons. In a simpler term, "Neurodegeneration is losing the structure or function of neurons". Neurodegenerative diseases are commonly associated with the progressive loss of neurons with age, creating various cognitive and motor disabilities. Different subsets of neuronal population involved represent the clinical presentation of various neurodegenerative disorders. Among various neurodegenerative diseases, a few which have gained enormous attention are AD, PD, HD and ALS. These are the classical examples of neurodegenerative diseases. The underlying molecular cause of these diseases may be sometimes unique, or overlapping mechanisms may contribute to the pathophysiological symptoms of these diseases. Since several years, problem in proper protein metabolism garnered major attention of scientists and clinicians as the root cause of neurodegenerative diseases; however, since the past few decades, the new emerging branch of RNA-mediated toxicity has come to limelight.

This chapter focuses on how RNA metabolism plays a key role in NDD pathogenesis. RNA molecules can be imagined as the relay race messenger players, without which the ultimate runner, the protein, cannot complete the race. Defects due to

RNA metabolism are found to contribute to the clinical pathology in a wide number of NDDs. These are also termed as RNAopathies, where impaired RNA is the main disease causal molecule. Some of the aspects of RNA metabolism and how these affect the neuronal function and integrity will be discussed in the following sections. This chapter will also deal with a few examples of such diseases and their underlying RNA metabolisms which are involved/altered.

10.2 Non-coding RNAs in Neurodegeneration

Non-coding RNAs (ncRNAs) are those which are not translated into protein, and they include various subtypes like ribosomal RNA (rRNA), transfer RNA (tRNA), small-nuclear RNAs (snRNAs), small-nucleolar RNAs (snoRNAs), microRNAs (miRNAs), small-interfering RNAs (siRNAs), circular RNAs (circRNAs), long non-coding RNAs (lncRNAs), enhancer RNAs (eRNAs), PIWI-interacting RNAs (piRNAs) and translation interfering tRNAs (tiRNAs) (Zhang et al. 2019). After the rRNA and tRNA were discovered in the 1950s, the non-coding region of the genome attracted researchers to explore further, and this lead to the identification of snRNAs in the 1980s, which is needed for the assembly of spliceosome complex, and gradually the other players were added to this growing list. Non-coding RNAs (ncRNAs) modulate various complex functions in the cell like gene expression, modifying chromatin architecture, transcription, RNA splicing and translation (Mattick and Makunin 2006; Yao et al. 2019). ncRNAs are found to be expressed in various mammalian cell types and are found in abundance in the CNS. Hosts of ncRNAs are reported to have roles in neural differentiation and function, and defects in their expression or their interactive network leads to neurodegeneration (Belgard et al. 2011; Wu and Kuo 2020). Some of the important ncRNAs and their role in NDDs are discussed below.

10.3 microRNAs (miRNAs)

miRNAs are the class of small ncRNAs (20–25 nucleotides long) and play an important role in the post-transcriptional regulation of gene expression by repressing gene activation. They regulate more than half of the protein-coding genes. The complexity of gene expression in higher organisms is regulated by the differential gene expression is specific to the stage, cell type or tissue type. miRNAs play a very significant role in this context by repressing the translation of transcripts during various developmental stages. Nervous system is found to be one of the richest source of miRNA, and their role is vital for neuronal differentiation and stage-specific repression of leaky transcripts (Ebert and Sharp 2012; Laneve et al. 2021). Alteration in miRNA biogenesis or their expression can trigger defects in NDD-associated genes thus resulting in neurodegeneration. For example, in fALS and

sALS, that is caused by mutant *TDP-43*, *FUS* and *SOD1,* miRNA biosynthesis is found to be inhibited in these conditions (Emde et al. 2015). It has been also demonstrated that ALS-causing genes like TDP-43 and FUS play key role in miRNA biogenesis. During neuronal differentiation, TDP-43 is an important factor required for regulation of Drosha protein, and thus it's misregulation affects miRNA biogenesis (Di Carlo et al. 2013). In ALS pathogenesis, wild-type TDP-43 or ALS causing mutants, like M337V, can sequester countless miRNAs in the cytoplasmic aggregates (Laneve et al. 2021). TDP-43 itself has been found to regulate the levels of miRNAs like let-7b, miR-663, miR-574-5p and miR-558, out of which let-7b is known to regulate differentiation processes and is also required for neuromuscular development in *Drosophila*. Similarly, FUS is also known to regulate miRNA biogenesis via Drosha. Drosha is an important component of microprocessor complex which is required for miRNA biogenesis. FUS binds to nascent pri-miRNAs and helps in recruitment of Drosha onto the chromatin for proper miRNA biogenesis. In FUS mutants, the level of FUS protein needed for proper regulation of miRNA production becomes depleted and this results in disturbed miRNA biogenesis in disease contexts (Laneve et al. 2021; Morlando et al. 2012). Apart from the neuronal cells, levels of miRNA like miR-22, miR-155, miR-125b and miR-146b have been found to be elevated in the microglial cells of ALS patients (Parisi et al. 2013).

Fragile X-associated tremor/ataxia syndrome (FXTAS) is caused by the CGG repeat expansion in the 5′ UTR and the premutation range (55–200) in the *FMR1* gene. The expanded repeats transcribe and form RNA aggregates in the nucleus which sequesters various RBPs including DGRC8 and its interacting partner Drosha, thus impairing miRNA biogenesis in the neuronal cells (Sellier et al. 2013).

Alzheimer's disease is characterized by β-amyloid plaque accumulation and formation of neurofibrillary tangles (NFT) containing tau protein, and this increases with age and causes symptoms like progressive memory loss, cognitive disability and early death. Alzheimer's disease is generally considered as a protein disorder since the main components in its pathogenesis are mutant β-amyloid and tau. However, with the advent of proteomic and transcriptomic studies, misregulation of various RBPs and splicing factors have been implicated in AD pathology (Hsieh et al. 2019; Johnson et al. 2018). Moreover, tau aggregates have been found to contain various RNA species like tRNA, satellite RNAs, Alu elements, snRNA and snoRNAs (Lester et al. 2021; Rybak-Wolf and Plass 2021).

Parkinson's disease (PD) is the second most common NDD (after AD) and affects predominantly the dopaminergic neurons in the substantia nigra of the brain and causes slow movement of voluntary muscles, behavioural and cognitive deficit, muscle stiffness and eventual instability of gait and posture (Chatterjee et al. 2019). The primary culprit in causing PD is mutant alpha-synuclein. It forms abnormal intracytoplasmic protein aggregates and is a major component of Lewy bodies, which is the hall mark for the disease and are formed in degenerating neurons. α-Synuclein is encoded by *SNCA*, and its increased expression or expression of mutant protein leads to dopaminergic neuron death in PD. miR-7 and miR-53

participate in posttranscriptional modification of *SNCA*, and their altered expression also leads to PD pathogenesis. *PITX3* polymorphism has been also implicated in PD pathogenesis, and miR-133b is known to regulate the passive feedback mechanism of Pitx3. The reduced levels of miR-133b disrupts this balance leading to PD pathology (Li et al. 2023).

Apart from α-synuclein, parkin, DJ-1, ubiquitin C-terminal hydrolase isozyme L1 (UCH-L1) and nuclear receptor-related factor 1 are also involved in PD and PD-like pathogenesis (Snyder and Wolozin 2004). The emerging evidences of ncRNAs as biomarkers in the AD and PD pathology are providing new links for their role in these disorders. Reports have suggested that miRNAs like miR-20 family (miR-20a, miR-17-5p and miR-106b), miR-106a, miR-520c miR-101 and miR-16 downregulate APP protein by binding to its 3′UTR region. miR-128 and miR-1908 are shown to play role in Aβ clearance, and their misregulation in AD results in accumulation of Aβ peptides (Rybak-Wolf and Plass 2021).

Various miRNAs are now known to act as biomarkers for AD and PD pathology. For example, miR-112, miR-161, let-7d-3p, miR-5010-3p, miR-26a-5p, miR-1285-5p and miR-151a-3p were found to be upregulated and miR-103a-3p, miR-107, miR-532-5p, miR-26b-5p and let-7f-5p were found to be downregulated in transcriptomic analysis of blood samples from AD patients (Leidinger et al. 2013). It has been well established that miR-107 downregulates BACE1 (Nelson and Wang 2010), and decreased mir-107 levels cause increase in *BACE1* mRNA levels which is a known risk factor in sporadic AD (Leidinger et al. 2013). miR-144-5p, miR-200a-3p and miR-542-3p were found to be upregulated, and miR-626 was found to be reduced in cerebrospinal fluid of PD patients. Besides, circulating miRNAs such as miR-29a, miR-29c, miR-30c-5p, miR-132-3p, miR-146a-5p and miR-373 can act as the biomarkers for PD pathogenesis (Nies et al. 2021). Change in the levels of many of these miRNAs in NDDs can be detected prior to the onset of disease or can evaluate the severity of disease, thus serving as promising biomarkers which can be also targeted for the therapeutic purpose.

10.4 Long Non-coding RNAs (lncRNAs)

lncRNAs are the class of ncRNAs with length greater than 200 nucleotides. They interact with DNA, RNA, protein and miRNAs and thus regulate gene expression by chromatin modifications, regulating stability and translation of cytoplasmic mRNAs, assembly of membrane less organelles and nuclear bodies (Statello et al. 2021). lnRNA also regulates neural cell fate determination and neuronal-glial fate switching and are thus broadly expressed during neuronal development (Li et al. 2019). Dysregulation of lncRNA is found in various human disorders including NDDs like AD, PD, ALS and HD. *BACE-1 AS* is an antisense transcript which regulates *BACE-1* expression. During stress response, *BACE-1 AS* elevates the levels of *BACE-1*, which has been found to be upregulated in post-mortem brain samples from AD patients. Knocking down *BACE-1 AS* using siRNA in HEK-SW cell lines

with mutant APP leads to the reduction in the levels of Aβ1–40 and Aβ1–42. These findings were further confirmed in mice model where *BACE-1* mRNA and protein levels in mice brain were found to be reduced after treatment with siRNA (Faghihi et al. 2008).

In addition, nuclear paraspeckle assembly transcript 1 (NEAT1) is found to be elevated in the brain of AD, PD, HD and ALS patients. NEAT-1 acts as a sponge for miR-124, miR-107 and miR-27a-3p and thus leads to the increase in levels of Aβ peptides as well as elevated tau phosphorylation, and this ultimately leads to disease pathogenesis. NEAT-1 also interacts and stabilizes PINK, thereby hampering PINK1-induced autophagy, and promotes mitochondrial permeability transition pore (MPTP)-induced autophagy. Studies have reported the activation and upregulation of the tumour protein (*TP53*) gene in HD patients, and NEAT1 upregulation is induced via p53 activation, since NEAT1 has a binding site for p53 (Li and Wang 2023; Liu et al. 2017). NEAT1 has been reported to be elevated in neurons of the anterior horn of the spinal cord as well as in the cortex of ALS patients and at the molecular level is known to physically interact with TDP-43 in both FTLD and ALS patients (Zhou et al. 2021).

Heat-shock RNA ω (*hsrω*) lncRNA in *Drosophila* binds and sequesters various RBPs, related to ALS and polyQ expansion disorders, which are crucial for transcription and translation of mRNAs. Sat III lncRNA in humans (functional analogue of hsrω) is also linked to FTLD (Singh 2022). Hsrω is a modifier of Spinocerebellar ataxia type 1 (SCA1), which is associated with polyglutamine (polyQ) expansion in ataxin-1 protein (Fernandez-Funez et al. 2000). Suppression of hsrω-n lncRNAs using RNAi led to suppression of neurodegeneration in poly-Q expansion disorders in *Drosophila* models (127Q, ataxin-1 Q82 (SCA1), MJDTR-Q78 (SCA3) or Httex1p Q93 (Huntington's disease)) (Mallik and Lakhotia 2009). dTDP-43 (TBPH) interacts with *hsrω* locus and activates its transcription. dFUS partners with *hsrω* and modulates the nucleo-cytoplasmic distribution of FUS (Laneve et al. 2021). hsrω-n lncRNAs (constituting hsrω-RB, hsrω-RG and hsrω-RF transcripts) form nuclear omega speckles which sequester various hnRNPs (hnRNPA1, hnRNP A, hnRNP D, hnRNP K and hnRNP M) and RBPs like TDP-43, FUS, ZNF236 and Hsp90 (Singh 2022). These studies suggest a crucial role of hsrω-n lncRNAs in NDDs like ALS, SCA1 and HD.

10.5 Transfer RNA (tRNA)

Other ncRNAs like tRNAs also play important role in neurodegeneration. For example, in Charcot-Marie-Tooth (CMT) disease, peripheral neuropathy and mutations in aminoacyl-tRNA synthetases (enzyme which attach amino acids to tRNA molecule) have been identified. Mutation (R140H) in *CLP1* (cleavage and polyadenylation factor I subunit 1), which helps in splicing of tRNA, causes brain atrophy and microcephaly. Loss-of-function mutations in *ANG* (angiogenin), which cleaves

tRNA during stress to inhibit translation, have been identified in ALS patients (Liu et al. 2017).

10.6 Exploring the Significance of Microsatellite Repeat Sequences in Neurological Disorders

Only a very small fraction of the human genome, ~2%, code for proteins, and the rest contains what have been earlier referred to as the "Junk DNA" (Palazzo and Gregory 2014). The term Junk DNA was historically used by Susumu Ohno, in 1972. Gradually it became a notion that all the non-coding sequences are junk DNA; however, we have ample evidence that this is not the case. The so-called non-functional junk DNA caught the attention of scientists, and challenging claims have been made about the significance of the so-called "non-significant" portion of the human genome (Havstad and Palazzo 2022). Around 10% of our genome consists of repetitive sequences, out of which about 3% comprises of microsatellite repeats (Sawaya et al. 2013), and this is double to that of the protein coding genes.

Microsatellites comprise of tandem arrays of short repeat units, usually <10 bp (Ramel 1997; Richard and Pâques 2000). They are found in abundance in the genome of higher eukaryotes and can be found in both coding and non-coding regions of genes. They are found in high density near the promoter region and thus play a regulatory role in gene expression. Microsatellites are often polymorphic, and variation in their length occurs during DNA replication (Sawaya et al. 2013). This dynamic property can also result in dynamic mutations which cause diseases. Many repeat expansions have been linked with the various neurological disorders. Thus, microsatellites gained popularity after the repeat expansion disorders came into attention in the 1990s. Till then microsatellites were also considered as "junk DNA" because their biological roles were unknown.

A major breakthrough in the context of diseases associated with microsatellites came in 1991 when fragile X syndrome (FXS) (Fu et al. 1991; Verkerk et al. 1991) and spinal bulbar muscular dystrophy (SBMA) or Kennedy's disease (Spada et al. 1991) were found to be linked with microsatellite repeat expansions. Another example of the neurological disease caused by microsatellite repeat expansion is myotonic dystrophy in which CTG repeat is found to be transcribed and located in the 3′ UTR region of the *DMPK* gene (Brook et al. 1992; Liu et al. 2017). Later on in 1993, Huntington's Disease Collaborative Research Group reported a $(CAG)_n$ repeat expansion in patients affected with Huntington's disease (MacDonald et al. 1993).

Till date, more than 50 neurodevelopment, neuromuscular and neurodegenerative disorders have been linked to microsatellite repeat expansions (some important ones are mentioned in Table 10.1). There are different mechanisms through which these repeat sequences can expand and cause onset of disease. These repeat expansions can be present in either coding or non-coding region of the gene, depending

Table 10.1 Neurodegenerative diseases caused by microsatellite repeat sequences

Disorder	Gene involved	Normal function of gene	Repeat expansion in disease/healthy condition	Location	Possible altered RNA metabolism known	RBPs involved/ sequestered	References
FXS	*FMR1*	Translation regulation, mRNA transport, nuclear export of m6-A-containing mRNAs	$CGG_{(>200)/(6–44)}$	5′UTR	Gene silencing and loss of gene product		Fu et al. (1991), Malecki et al. (2020)
FXTAS	*FMR1*	Translation regulation, mRNA transport, nuclear export of m6-A-containing mRNAs	$CGG_{(55–200)/(6–44)}$	5′UTR	RNA toxicity, protein toxicity (FMRpolyG) by RAN translation	hnRNP A2/B1, MBNL1, lamin A/C, Pur α, CUGBP1, Sam68, Rm62	Hagerman and Hagerman (2004), Kong et al. (2017)
DM1	*DMPK*	Ser/Thr protein kinase plays role in cell-cell communication	$CTG_{(50–\geq1000)/(5–37)}$	3′UTR	Toxic RNA production, aberrant alternative splicing	MBLN and CUGBP	Das et al. (2019), Miller et al. (2000)
DM2	*CNBP/ ZNF9*	Regulates cell proliferation	$CCTG_{(75–11,000)/(\sim26)}$	Intron	RNA gain of function and loss of protein	MBLN and CUGBP	Day et al. (2003), Meola (2020)
ALS/FTD	*C9orf72*	Regulates autophagy, vesicular trafficking	$G_4C_{2(22–3500)/(2–23)}$	Intron	Bidirectional transcription of repeat containing allele, RAN translation, RNA foci formation, haploinsufficiency	SC35, hnRNP K, hnRNP A1, ALYREF and hnRNP H, TDP-43	Barker et al. (2017)
SCA8	*ATXN8OS/ ATXN8*	No functional protein encoded	$CTG_{(54–250)/(15–50)}$	3′UTR	Toxic gain-of-function of RNA		Das et al. (2019), Tripathi et al. (2016)
SCA4	*ZFHX3*	Maintains calcium homeostasis	$GGC_{(42–74)/(14–26)}$	Exon	Toxic gain-of-function of RNA, transcriptional dysregulation		Wallenius et al. (2023)

SCA1	*ATXN1*	Regulates transcription and RNA processing	$CAG_{(39–81)/}$ (6–39:interrupted by 1–3 CAT tracts)	Exon	PolyQ disorders: various cellular pathways affected due to expanded PolyQ	Zühlke et al. (2002)
SCA2	*ATXN2*	Polyadenylation and translation regulation	$CAG_{(32–63)/(15–31)}$	Exon		Pulst et al. (1996)
SCA3 (Machado-Joseph disease)	*ATXN3*	Deubiquitinating enzyme, ubiquitin-dependent protein quality control	$CAG_{(60–81)/(12–43)}$	Exon		Paulson (2012)
SCA6	*CACNA1A*	α1A subunit of the Cav2.1 calcium channel, regulates muscle contraction	$CAG_{(20–33)/(\leq 18)}$	Exon		Shizuka et al. (1998)
SCA7	*ATXN7*	Component of the SPT-ADA-GCN5 acetyltransferase complex (SAGA), regulates transcription	$CAG_{(37–306)/(4–35)}$	Exon		Paulson et al. (2017)
SCA17	*TBP*	Transcription factor	$CAG_{(>47)/(25–42)}$	Exon		Yang et al. (2016)
HD	*Htt*	Regulates axonal transport, apoptosis, nuclear export	$CAG_{(36–121)/(6–35)}$	Exon		Martí (2016)
Spinal and bulbar muscular atrophy (SBMA)/ Kennedy's disease	*AR*	Androgen receptor	$CAG_{(38–70)/(<34)}$	Exon		Alves et al. (2018)

on which it can alter either the protein or RNA structure and function. When the repeat is located in the non-coding region, it does not affect the protein structure directly, but the transcribed RNA impedes the mRNA function (Brouwer et al. 2009). The repeat expansions can cause loss- and gain-of-function in the cell leading to disease pathogenesis. The gain-of-function can be at either at the RNA or protein level. When the repeats are not translated but transcribed, RNA serves as the molecular culprit.

Several neurological disorders are caused via sequestration of RNA-binding proteins by the expanded repeat transcripts. One of the prominent examples is that of myotonic dystrophy (*dystrophia myotonica*, DM) in which the RNA metabolism is altered because of the expansion of $(CTG)_n$ repeat in the 3′UTR region of the *DMPK* gene. The first description of DM was given by Hans Steinert in 1909, with the earliest cases reported in 1886 (Adie 1923). The molecular basis of DM was identified to be triplet repeat expansion by Brook et al., and it became the third disease to be identified that was caused by repeat expansion (after Kennedy's disease and fragile X syndrome) (Brook et al. 1992). The $(CTG)_n$ expansion transcribes into repeat containing mRNA which forms nuclear RNA foci. These foci contain toxic RNA whose secondary structure is altered, and they sequester away various critical RNA-binding proteins away from their target mRNAs and thus alters cellular metabolism (Brouwer et al. 2009; Liu et al. 2017). The pathogenic DMPK transcripts form RNA foci which sequesters away RBPs like muscle-blind-like proteins (MBLNs) and CUG RNA-binding protein family (CUGBP), which helps in polyadenylation of target RNAs as well as in alternative splicing (Das et al. 2019; Miller et al. 2000).

Another parallel example is that of fragile X-associated tremor/ataxia syndrome (FXTAS), in which the expansion of trinucleotide $(CGG)_{55–200}$ in the 5′UTR region of *FMR1* gene causes the underlying clinical symptoms in patients (Hagerman and Hagerman 2004). The level of abnormal repeat containing mRNAs is found to be elevated, and these mRNAs infer a toxic gain-of-function effect, similar to molecular pathogenesis of DM. The expanded CGG repeat forms secondary structures and titres away vital RBPs and therefore depletes these proteins from the cellular pool which in turn affects normal physiology of the cell (Mutsuddi et al. 2004). This also results in the increased mRNA copy number and number of CGG repeats and also alters the secondary/tertiary structure of the mRNA (Hagerman and Hagerman 2004). Along with other RBPs, MBLNs are also present in the intranuclear inclusions of the brain of FXTAS patients (Tassone et al. 2004).

One of the prevalent genetic causes of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) is a hexanucleotide repeat expansion (G_4C_2) in the non-coding region of *C9orf72* gene. The repeat expansion lies in the intron1 between the exon 1a and 1b and ranges from hundred to thousands in the ALS/FTD patients as compared to 2–30 repeats in healthy individuals (DeJesus-Hernandez et al. 2011; Yang et al. 2020). This hexanucleotide repeat is transcribed into sense or antisense RNA, and the mutant RNA then forms abnormal nuclear RNA foci (Gendron et al. 2013). Reports have shown that proteins like SRF2, hnRNPs, ALYREF, ASF/SF2, Pur-α, Zfp106, RanGap1, ADARB2 and nucleolin are present in RNA foci in the ALS/FTD patients (Cooper-Knock et al. 2014; Zhu et al. 2020). These transcripts

have been also shown to undergo repeat associated non-AUG (RAN) translation which results in the production of dipeptide repeat (DPR) proteins, which are prone to aggregation. There are five DPRs known to be translated from these bidirectional transcripts depending on the direction of transcription and reading frame: poly(GA), poly(GR), poly(GA), poly(PR) and poly(PA). Aggregates of these DPRs recruit p62, which selectively mediates autophagy (Zhu et al. 2020), thus interfering with its normal function. Another consequence of the expanded repeat sequences is the reduction in C9OF72 protein levels, i.e. haploinsufficiency of C9ORF72. The main function of C9ORF72 protein has not been well studied. Few reports have suggested that it plays a role in vesicle trafficking, lysosome homeostasis, mTORC1 signalling and autophagy-lysosome pathway (Pang and Hu 2021; Smeyers et al. 2021). The haploinsufficiency of the protein can be a consequence of various mechanisms including epigenetic modifications, hypermethylation of the *C9orf72* promoter or methylation of *C9orf72* repeat expansions, and this may ultimately underlie the disease pathogenesis (Yang et al. 2020).

Other repeat expansions have been also studied such as ALS/FTD-linked polyglutamine repeat expansions in *Ataxin-2 (ATXN2)* gene (Elden et al. 2010) and *NIAP1* polyalanine repeat expansions causing ALS (Blauw et al. 2012). CAG repeat expansions in *ATXN2* gene is linked to sporadic and familial cases of ALS as well as spinocerebellar ataxia type2 (SCA2) (Van Damme et al. 2011). Various spinocerebellar ataxias (SCAs) are known to be caused because of repeat expansions. Most of the SCAs are caused by trinucleotide repeat expansion, specifically CAG (SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA12 and SCA17) (Conlon and Manley 2017) and GGC in case of SCA4 (Wallenius et al. 2023). SCA2 responsible gene *ATXN2* has a CAG polyQ expansion in its 5′ coding region which has around 31 repeats in healthy individuals (Elden et al. 2010); however its number varies from 36 to 52 in the SCA2 (Pulst et al. 1996) and 27–33 in ALS disease condition (Van Damme et al. 2011). SCA4 is a poly-glycine disorder caused by repeat expansion in *ZFHX3* gene (Wallenius et al. 2023). SCA8 is caused by CUG repeat expansion in a non-coding RNA (Mutsuddi and Rebay 2005), and this was the second disorder identified after DM to be caused by the CTG expansion in a non-coding region (Koob et al. 1999). The transcribed RNA gains a toxic function and has altered secondary structure which sequesters away RNA-binding proteins and thus leads to the disease pathogenesis. In a genetic modifier screen for SCA8 pathogenic phenotype, mutations in *muscleblind*, *split ends* and *Staufen* were found to enhance SCA8-mediated phenotype, and in vivo RNA-binding assay revealed that Staufen, which is important for mRNA transport in neuronal dendrites, along with roles in memory formation, is recruited by the pathogenic SCA8 transcripts. In the same study, *Spoonbill* was also identified as a suppressor of the disease phenotype (Mutsuddi et al. 2004). Further observations revealed that the RNA-binding KH domain of the Spoonbill protein binds to the SCA8 transcripts and is responsible for the disease suppression by depleting toxic SCA8 transcripts (Tripathi et al. 2016).

Various RBPs are now known to interact and sequestered at the repeat expansions in non-coding RNA (Table 10.1), thus resulting in the depletion of these vital RBPs from their normal physiological pool and leads to impaired physiological

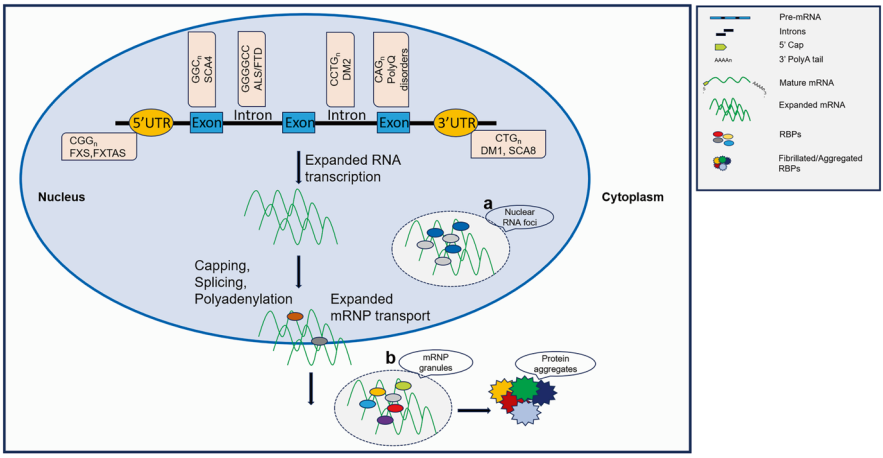

Fig. 10.1 Microsatellite repeat expansion. In case of the repeat expansion disorders, the expanded RNA may face various events depending on the region where the repeat sequences are located in the genome. If the coding region is transcribed and translated, the protein product is affected. (**a**) If the non-coding region is transcribed into expanded RNA, it may reside in the nucleus to form nuclear RNA foci and sequester multiple RBPs into these foci disturbing their own functions, or (**b**) it may be transported to the cytoplasm, and there it may reside into different granules like transport granules, mRNP granules, stress granules, P-bodies, etc. and sequester various RBPs inside them again disturbing their own functions, or it may result into the formation of aggregates of RBPs, like TDP-43, FUS and tau, causing the proteinopathy

functions. In a recent review by Baud et al., these RBPs have been referred to as "partners in crime" (Baud et al. 2022). These proteins in turn can also then call upon other partner proteins which may or may not be the direct interactors of expanded RNA. The gain-of-function of the expanded RNA and also the RAN translated transcript lead to disturbed physiological activities in the cell and thus contribute to the disease pathogenesis in repeat expansion disorders. *Drosophila* models of the repeat expansion disorders have been utilized extensively to understand the molecular mechanisms of disease pathogenesis (Das et al. 2019). A generalized schematic of repeat expansion disorders is shown in Fig. 10.1.

10.7 Deregulated RNA Processing Events: A Key Driver in Neurodegeneration

The message in the cell from DNA to proteins runs via RNA, and thus RNA molecules are very crucial for gene expression. The nascent RNA molecules after transcription also needs to undergo different modifications to become functional RNA. As soon the RNA is transcribed, first addition is 5′ cap of 7-methylguanosine cap. As transcription ends, the pre-RNAs are subjected to polyadenylation, i.e. addition of a poly-A tail at the 3′ end. Finally most of the eukaryotic mRNA undergoes

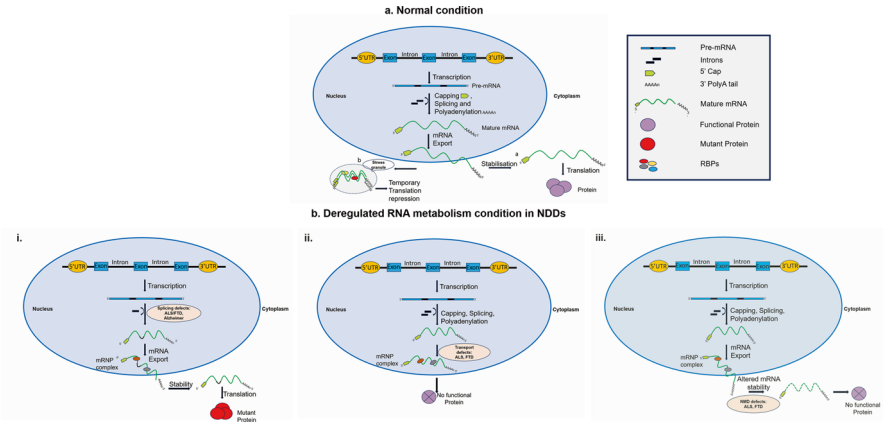

Fig. 10.2 Altered RNA metabolism in neurodegenerative disorders. (**a**) In a healthy neuron, RNA metabolism is regulated at different stages: pre-mRNA is synthesized after transcription from the DNA strand. As soon as the transcription starts, various proteins start the processing of this pre-mature transcript to produce mature mRNA. mRNA processing includes capping, splicing and polyadenylation. Various isoforms of a protein are synthesized from the same transcript by alternative splicing. The mature mRNA is bound by various RBPs to form mRNP complex, and this complex is then transported from nucleus to the cytoplasm. After completing the mRNA export, these RBPs are released from mRNA. If everything goes well, these transcripts are stabilized and further proceeded for translation into functional protein. If a cell faces any stress, such as oxidative insult, it can repress the translation of the rest of the proteins temporarily by accumulating various mRNAs and protein in the stress granules and focus on the recovery from the stress, after which it generally restarts the translation. (**b**) In the diseased conditions, the processing of mRNA, its nucleo-cytoplasmic transport or its stability is disturbed ultimately disturbing the protein homeostasis. (i) Defects in splicing, for example, inclusion of cryptic exon or skipping of exons results in mutated protein. (ii) Defects in mRNA transport may result in retention of mRNA in the nucleus, and thus no protein is formed. (iii) Defects in balance between switching towards NMD and translation result in disturbed protein balance. If a pre-mature codon is read by the NMD machinery, it degrades the transcript. Any defect in this machinery which ultimately translates the mutated transcript may result in production of wrong protein product

a process called as splicing, which removes the introns and joins the coding sequences (exons) together (Cooper and Adams 2023). These RNA processing events regulate various aspects of RNA like translation, stability, splicing and localization (Fig. 10.2). RNA molecules do not function alone; they require a team of proteins to work along with them and maintain a proper traffic of pathways in the cell. Any alteration in the RNA processing, via RNA-binding proteins or the RNA itself, can alter the fate of the upcoming events. We have discussed the case of the neurological diseases where the pool of RBPs gets sequestered by mutated transcripts and their actual role at other transcripts gets completely disturbed. Other mechanisms like mislocalization of RBPs, alterations in microRNA biogenesis as well as fate of non-coding RNAs (discussed in later sections) are also affected by altered RNA processing (Liu et al. 2017). Earlier, mutations in the coding regions were given importance in disease contexts, but now mutations and the repeat

expansions in the non-coding regions have gained lot of importance. Some of the possible mechanisms that cause neurodegeneration are the consequences of altered RNA metabolism and are discussed below (Fig. 10.2).

10.7.1 Splicing

Eukaryotic gene expression requires precise splicing of pre-mRNA to remove the intronic region and ligate the exons to form mature mRNA. One single gene can produce variety of mature mRNAs depending upon the regions spliced out from the pre-mRNA by alternative splicing (Li et al. 2021). RNA processing, especially alternative splicing, is a vital process in various neuronal functions like neurogenesis, axon formation and synapse maturation, and thus any error in this major processing makes the neurons vulnerable to degeneration and ultimately loss. Splicing is a tightly regulated process and involves the assembly of spliceosome complex which recognizes and binds to cis-acting components of exon-intron junctions and precisely executes the removal of introns and ligation of exons. Alternative splicing requires specialized cis-acting regulatory sequence elements (enhancers or silencers) which interacts with trans-acting splicing factors and regulate the tissue/cell specific production of isoforms of a gene. Earlier these trans-acting elements were divided into main family of proteins, serine-arginine (SR) proteins and heterogeneous nuclear ribonucleoproteins (HNRNPs), but many RBPs other than these families were also found to regulate alternative splicing like RBFOX1, RBFOX2, FUS and TDP-43 (Ule and Blencowe 2019). For the proper development of neural system and neuron function, the splicing event is very crucial. It is now well studied that splicing factors like KH domain-containing, RNA-binding, signal transduction-associated (KHDRBS) proteins, NOVA2 and muscleblind-like 2 (MBNL2), regulate synaptic plasticity and RNA-binding protein Fox-1 homologue 1 (RBFOX1) and neuronal ELAV-like (nELAVL) regulate neuronal excitability (Vuong et al. 2016). Any aberration in the splicing machinery can lead to neurological defects as seen in many neurodegenerative diseases (Fig. 10.1b(i)). One prominent example of such a case is ALS/FTD-linked *TARDBP* gene encoding TAR DNA-binding protein (TDP-43). TDP-43 regulates splicing of various hnRNPs (Li et al. 2021); it also regulates expression of non-coding RNAs like microRNAs and long non-coding RNAs (lncRNA) (Barker et al. 2017). Mutations in the *TARDBP* gene which may lead to the mislocalization of TDP-43 from nucleus to cytoplasm and may cause loss-of-function of TDP-43 protein or over expression of TDP-43 protein that might lead to aggregate formation and depletion of functional protein, and this ultimately leads to the disruption of splicing machinery. One of the crucial tasks of TDP-43 is to repress the inclusion of non-conserved cryptic exons during splicing. Cryptic sites are the stretches of nucleotides surrounded by sequences similar to actual splice sites, and these are not spliced into mature RNA (Barker et al. 2017; Ma et al. 2022). Depletion of TDP-43 functional protein can cause inclusion of these cryptic exons into mature RNAs and thus leads to introduction of pre-mature stop codon

and formation of truncated protein or mRNA decay by nonsense-mediated decay pathway. *Fused in sarcoma* (*FUS)* gene also shares similarity with *TARDBP* in its activity and is aggregated in familial cases of ALS. FUS interacts with hnRNP A1 and C1/C2, thus playing a role in RNA splicing. Mutation in *FUS* results in the mislocalization of FUS from nucleus to cytoplasm and formation of aggregates, thus leading to disease pathology (Kolb et al. 2010). Another ALS-linked gene *peripherin* encodes a neuronal intermediate filament protein and also forms intraneuronal protein aggregates. Peripherin has three splice variants in mouse: Per58 and Per56, which are normal neuronal isoforms in wild-type mice, and Per6, which is expressed in *SOD1* mutant transgenic mice. Per61 is expressed because of the in-frame retention of intron 4 leading to a 32 amino acid insertion within a domain of peripherin crucial for intermediate filament assembly. *SOD1* mutant therefore causes defects in peripherin mRNA and produces Per61 which is toxic to primary motor neurons and induce peripherin and neurofilament aggregation (Gallo et al. 2005).

Alzheimer's disease and frontotemporal dementia (FTD, particularly FTDP-17) are also subjected to splicing defects. Several pathways and mechanisms are involved in the pathogenesis of AD, most commonly known are Aβ and Tau proteinopathy. Pathological tau aggregates are found to be common in neurons and glia in diverse tauopathies including AD, FTD, progressive supranuclear palsy, Pick disease, corticobasal degeneration, chronic traumatic encephalopathy and argyrophilic grain disease (Strang et al. 2019). Depending on the location of genetic mutations in *MAPT* (microtubule associated protein tau) gene, which encodes tau, the binding of tau to microtubules is altered, and thus the aggregation and splicing outcomes are also altered or disrupted. There are six isoforms of tau found to be expressed in human brain via alternative splicing of exon 2, 3 and 10. Alternative splicing at exon 10 results in two types of tau transcripts: exon 10 inclusion results in 4R, and exon 10 exclusion results in 3R isoform of tau. In adult human brain, both the transcripts are found to be expressed at equal levels; however only 3R is expressed during development. A proper ratio of 3Rand 4R tau is crucial for normal brain function (Nikom and Zheng 2023). 4R is reported to be more toxic and promotes microtubule assembly compared to that of 3R. Mutations resulting in the disruption of stem loop structure between 3′ end of exon10 and 5′ end of intron 10 result in the enhanced *MAPT* exon 10 splicing and its increased inclusion into the mature RNA and thus increased production of 4R isoform leading to tauopathy in patients (Li et al. 2021). Similarly, another important protein involved in the AD pathogenesis is Aβ, a proteolytic product of amyloid precursor protein encoded by the APP gene. Aβ has two major isoforms, Aβ40 and Aβ42, depending on the site at which γ-secretase cleaves APP. Aβ42 is found to more prone to aggregation. Mutations disturbing the cleavage site of APP for β- and γ-secretase disturb the ratio of Aβ40 and Aβ42. Mutations in the splice sites in *PSEN1* and *PSEN2*, which are the components of γ-secretase complex, also result in the disturbed ratio of Aβ40/42 and regulate the pathogenesis in AD (Arber et al. 2020; Braggin et al. 2019)

10.7.2 Nucleo-cytoplasmic Transport

As soon as transcription starts, the RNA is never left alone. Various RBPs bind and start the processing of pre-RNA to mature RNA. The capped, spliced and polyadenylated RNA needs to be taken out of the nucleus for translation in the cytoplasm. Again, the RNA is not exported alone but in the form of mRNPs (ribonucleoproteins), which facilitate its export from the nucleus (Fig. 10.1a). This mRNP complex is transported from the nucleus to cytoplasm via nucleopore complexes (NPCs). Smaller molecules (<20–40 kDa, diameter <5 nm) can move through the NPCs by passive diffusion, but larger molecules (≈25–50 MDa) require a carrier-mediated translocation (facilitated diffusion) (Yang et al. 2004). Members of β-karyopherin superfamily act as carriers for most of the nuclear trafficking pathways, but the translocation of mRNP complexes utilizes the Mex67: Mtr2 heterodimer (Stewart 2007). This heterodimer binds to mRNP complex prior to the transport, and as it reaches to the cytoplasmic side, it is removed from the mRNP complex. This removal is facilitated by a DEAD-box RNA helicase Dbp5 which utilizes ATPase activity to unwind the RNP complexes. This ATPase activity of Dbp5 is activated by another proteins Gle1 and InsP6 (IP6) (Cole and Scarcelli 2006; Kolb et al. 2010). Mutations in *GLE1* gene, which encodes GLE1 protein, are found to be the cause of a severe motor neuron disease called lethal congenital contracture syndrome (LCCS), which is an autosomal recessive disorder characterized by lack of anterior horn motoneurons, severe atrophy of the ventral spinal cord and hypoplasty, nearly absent skeletal muscles, pulmonary hypoplasia, pterygia and multiple joint contractures, hydrops, micrognathia and akinesia. These symptoms ultimately result in prenatal or immediate postnatal death (Nousiainen et al. 2008).

A proper nucleo-cytoplasmic transport is very essential for the cell to function properly, and any imbalance may result in loss of functional protein or disturbed protein homeostasis (Fig. 10.1b(ii)). Recent studies have also linked formation of protein aggregates, the hallmark of neurodegenerative diseases, with damage in NPC structure thus disturbing mRNA and protein transport. ~97% of ALS and ~50% of FTD cases present cytoplasmic mislocalization of predominantly nuclear protein TDP-43 and aggregates containing its hyperphosphorylated and ubiquitinated C-terminal fragments (CTF). The TDP-43 aggregates were found to be positive for the proteins involved in nucleo-cytoplasmic transport and mislocalization of various nucleoporins and transcription factors. Mutant and aggregated TDP-43 protein also cause morphological defects in NPCs resulting in defects in nuclear protein import and mRNA export (Chou et al. 2018). Proteins with PolyQ expansion like huntingtin (htt) are found to accumulate in the nucleus and disrupt the NPC resulting in aberrant nucleo-cytoplasmic transport (Grima et al. 2017).

10.7.3 Nonsense-Mediated Decay

The fidelity of mRNA is enhanced by the surveillance pathways so that if any mRNA is not spliced out or mis-spliced, or if there is introduction of any pre-mature stop codon, it can be stopped from being translated. The quality control mechanisms in the cell inhibit cells to produce truncated proteins. Nonsense-mediated mRNA decay (NMD) is a surveillance mechanism to recognize and degrade any premature translation termination codon containing RNA and nonsense mutations containing mRNA and thus aiding in regulation of mRNA stability (Howe and Patani 2023). NMD regulates normal biological events like modulating neuronal function (Bruno et al. 2011), axonal growth and guidance (Howe and Patani 2023) and gene expression (Usuki et al. 2019) by targeting normal error free transcripts formation. Some of the prominent neurological disorders like ALS and FTD, autism spectrum disorders, intellectual disability, attention deficit hyperactivity disorder (ADHD) and schizophrenia involve NMD as one of the causes of disease pathogenesis (Howe and Patani 2023). Mutations and copy number variations in the genes encoding proteins involved in NMD have been linked to neuro-developmental disorders (Lee et al. 2021). NMD core machinery is composed of three major proteins in eukaryotes: up-frameshift proteins 1, 2 and 3 (UPF1, UPF2 and UPF3). Complementary factors that aid these core proteins involve suppressor of morphological defects on genitalia (SMG): SMG1, SMG5, SMG6 and SMG7 (Zuniga et al. 2023). *Upf2* copy number variants result in the intellectual disability disorders and autism spectrum disorders, and conditional removal of UPF2 from the forebrain of mice has been shown to cause communication and memory loss and also elevated neuroinflammation (Howe and Patani 2023). Loss-of-function mutation in *UPF3B* has been shown to cause X-linked intellectual disability (XLID), childhood onset of schizophrenia and ADHD. *UPF3A*, a paralogue of *UPF3B*, is shown to compensate the function of *UPF3B*, but in the *UPF3B* mutant patient cells, it cannot fully compensate the function of *UPF3B* (Jolly et al. 2013).

In this chapter, above sections have already shed light on how erratic RNA and protein levels get in the context of NDDs. ALS has many underlying causative genes such as *C9orf72*, *TDP-43* and *FUS*. Pathogenesis in case of *C9orf72* is caused by hexanucleotide repeat expansion (G_4C_2) (DeJesus-Hernandez et al. 2011), and these transcripts undergo non-canonical form of translation called RAN translation producing DPRs (Zhu et al. 2020). This interferes with the global localization of multiple proteins, and greater extent of cytoplasmic mislocalization of proteins is found to occur in the pathogenesis caused by *C9orf72* repeat expansions. One such factor is eRF1, which plays an important role in balancing the translation termination and NMD. eRF1 is a translation termination factor. It recognizes the stop codon and promotes cleavage of nascent peptide from the ribosome. If it recognizes any premature stop codon or mis-spliced mRNA, it triggers NMD and degrades the mRNA by recruiting UPF1 (Ortega et al. 2020). In the cells expressing expanded pathogenic repeats, eRF1 was found to be enriched in the cytoplasmic side of the nuclear membrane within discrete puncta, and an increase in UPF1 levels was also

found in these cells. eRF1 makes a shift from protein translation to NMD-dependent mRNA degradation of *C9orf72* transcript conferring a protective role for the cell (Howe and Patani 2023; Ortega et al. 2020).

Mutations in *TARDBP* is another cause of ALS (Li et al. 2021). TDP-43 is an important RBP which plays role in RNA maturation (especially in splicing), stabilization, transport and its translation (Versluys et al. 2022); thus its nucleocytoplasmic shuttling is very important for proper RNA processing. TDP-43 aggregates are the hallmark of >95% of ALS cases (Howe and Patani 2023), where hyperphosphorylated and ubiquitinated C-terminal fragments of TDP43 are found to form insoluble cytoplasmic inclusions (Eck et al. 2021). TDP-43 levels are tightly regulated in the cell by a negative feedback loop where it regulates its own transcripts by inducing the splicing of alternative introns in its mRNA and thus initiates the degradation of its cytoplasmic transcript by NMD (Koyama et al. 2016; Weskamp and Barmada 2018). A correct ratio between the nuclear and cytoplasmic TDP-43 protein is critical for a healthy cell which ultimately depends upon the balance between the protein synthesis and NMD. In case of age-related TDP-43 pathogenicity or the ALS-causing mutations, this balance is disturbed by cytoplasmic accumulation of protein possibly because of splicing or NMD defects (Howe and Patani 2023). Similarly, mutations in *FUS*, another RBP, have been linked to familial ALS cases. FUS is predominantly nuclear protein, and it also has a significant role in splicing and translation of mRNA (Birsa et al. 2020). TDP-43 and FUS share structural and functional features. Similar to TDP-43, FUS also gets depleted from the nucleus and gets accumulated into the cytoplasm in case of ALS/FTD (Birsa et al. 2020). FUS inclusions are also found to be positive for NMD factors, and cells expressing *FUS* mutant proteins were found to have elevated levels of UPF1, p-UPF1, UPF3B and XRN1, and UPF3A was found to be downregulated. In these cells, UPF1 is found to interact less with its own transcript and *UPF3B* mRNA, but more with mutant FUS, thus suggesting an impairment of NMD pathway in these cells (Howe and Patani 2023).

Unlike these pathophysiologies, where NMD has been found to be elevated, tauopathy has been linked to decreased levels of NMD as unravelled in the transgenic *Drosophila* model. In human post-mortem brain of Alzheimer's disease and transgenic mice model of tau, pathogenic forms of tau are found to disrupt proper nucleo-cytoplasmic transport of RNA and protein. Using *Drosophila* model of tauopathy, a lack of RNA quality control has been shown to be the cause of aberrant RNA transport and accumulation at the nuclear envelope invagination and neurodegeneration in these flies. The faulty RNAs which were subjected to NMD degradation accumulate in the nuclear invaginations and escape the mRNA surveillance and are thus translated into faulty proteins. The NMD machinery is found to be saturated in this condition due to increased RNA transport. Increasing the levels of NMD machinery, by increasing UPF1, rescues the tauopathy-induced aberrant RNA accumulation (Zuniga et al. 2023). Thus, any disturbance in the NMD machinery or the imbalance between switching to NMD or translation may disturb the protein equilibrium (Fig. 10.1b(iii))

10.7.4 RNA Editing

The diversity of the RNA and protein is maintained not only by the alternative splicing of RNAs but also via RNA editing mechanism, which includes modification of nucleotides in the sequence of RNA. RNA editing includes many enzymatic mechanisms, and type of editing events may differ in different organisms (Simpson and Emeson 1996). The most common type of RNA editing is the adenosine deamination (adenosine, A to inosine, I editing), and it is catalysed by the adenosine deaminases acting on RNA (ADAR) family of RBPs. The edited base inosine pairs with cytosine and generally read as guanosine thus changing the codon. This event thus diversifies the neuronal transcripts and protein expression and is very essential for proper brain function in mammals (Lundin et al. 2020). A–I editing is most abundant in the CNS, and any defect in this editing is associated with diseases (Nishikura 2016; Tariq and Jantsch 2012). RNA editing plays a key role in cognitive development of brain by modulation of neurotransmission and synaptic firing (Mattick and Mehler 2008). Many genes involved in NDDs undergo editing (Eran et al. 2013; Mattick and Mehler 2008). Alterations in RNA editing were found in the patients of autism spectrum disorder (ASD) (Eran et al. 2013). In *Drosophila*, ADAR mutants are found to have behavioural defects and are conditional lethal (Palladino et al. 2000). Several studies have reported changes in editing patterns in mRNA of serotonin 2C receptor, 5HT2CR, in the patients with schizophrenia, major depression and bipolar mood disorders as well in rodent disease models (Gardiner and Du 2006). Altered RNA editing events are found in various neuropathological diseases like AD and PD (Ma et al. 2021; Pozdyshev et al. 2021). Thus, it is clear that RNA editing plays a critical role in the neuronal functions, and alteration in these events contribute to the neurodegenerative diseases.

10.8 Deregulated RNA Metabolism and Neuronal Health

Aging is a natural process in which many cells undergo different changes in their structure and functions. Many cells with increased age change their shape and lose the ability to divide and multiply. During aging, brain gradually shrinks mostly in frontal and temporal lobes, and the capacity to hold memory, learning and the cognitive ability decreases. These changes occur naturally but get aggravated because of environmental and genetic factors leading to neurodegenerative diseases. During aging (as well as in NDDs), neurons face a variety of stress like oxidative stress, DNA damage, altered apoptosis and protein aggregate formation (hallmark of various neurodegenerative disorders). These changes ultimately lead to disturbed neuronal integrity and ultimately death (Mattson and Magnus 2006). Developing neurons require proper spatio-temporal regulation of protein for their proper development, and various RBPs play a key role. Disturbed RNA metabolism in NDDs, via RNA or RBPs, can regulate the distribution of the required proteins especially

in neuronal cells thus affecting their function. Less severe mutation in genes required for RNA metabolism is not tolerated by neuronal cells (Thelen and Kye 2020). Various genes like TDP-43 and FMRP are associated with RNA metabolism are also required for the proper neuronal function. One such family of protein is Musashi family of RBPs. These are known to be the master regulators of neuronal development as they control neural proliferation, neural stem cell maintenance, neuronal circuit formation, morphogenesis, neuron migration, axonal guidance, synapse formation and maintenance (Landínez-Macías and Urwyler 2021). They play a significant role in supressing translation of mRNA encoding cell cycle inhibitory proteins, thus keeping the stem cells in an undifferentiated state (Taggart et al. 2016). Musashi-1 (Msi-1) plays a role in tau RNA maturation in tauopathy degenerating neurons, and Msi-1was found to be upregulated in the brain regions of AD and Pick's disease (Lovell and Markesbery 2005). The role of TDP-43 and other RBPs required for RNA metabolism have been already discussed in brief in the previous sections. Any perturbations in their levels affect RNA metabolism in neurons and impede normal functioning of neurons.

Neuronal cells are asymmetrical in shape and structurally polarized and perform very complicated functions. To accomplish this, genes expressed in neurons are tightly regulated at both transcriptional and translational levels. mRNA, after transcription are spliced, undergo quality check and are transported from cell body to cytoplasm and further translocated via axonal transport system, to the region where it is required in the axon (Fig. 10.3a). These cells need to rapidly sense the stimuli in their distal parts and respond promptly and thus require to translate the mRNA locally at the requisite site. mRNAs are translocated along the neurons as mRNPs, and they often have localization sequence (also called as zip code) in their 3′ UTR. RBPs read this code and regulate localization of mRNAs. For example, zip code-binding protein, ZBP1, binds to β-actin transcripts at its 3′UTR and represses it's translation initiation in the nucleus and promotes its translocation to the actin-rich distal ends of the neuron (Hüttelmaier et al. 2005). The developing axons are reported to have an active RNA silencing machinery which represses translation of mRNA and also various miRNAs in their growth cones which regulate the local translation (Hengst et al. 2006). miR183 binds to 3′UTR of *mTOR* RNA and represses its translation in the axons (Kye et al. 2014; Thelen and Kye 2020). As mentioned above, RBPs play a crucial role here, since their interactive function decide the spatio-temporal localization, stability and translation of various mRNAs. Spino-muscular atrophy (SMA) is a lower motor neuron disease caused by reduction in an RBP named SMN (Survival Motor Neuron). Humans have two genes for SMN protein, *SMN1* and *SMN2*. They encode identical proteins, but *SMN1* encoded protein is full length, and *SMN2*-encoded transcripts lack exon 7 (Monani et al. 1999), and this encodes an unstable protein which is degraded by the proteasome pathway. In SMA patients, loss of SMN1 protein due to mutation or deletion in *SMN1* gene cannot be compensated by SMN2 protein. SMN is a crucial component of RNA metabolism like snRNPs biogenesis, transcription, splicing, histone mRNA processing and DNA repair (Singh et al. 2017) and also required during assembly, stability and transport of axonal mRNPs (Fallini et al. 2012). SMN is reported to

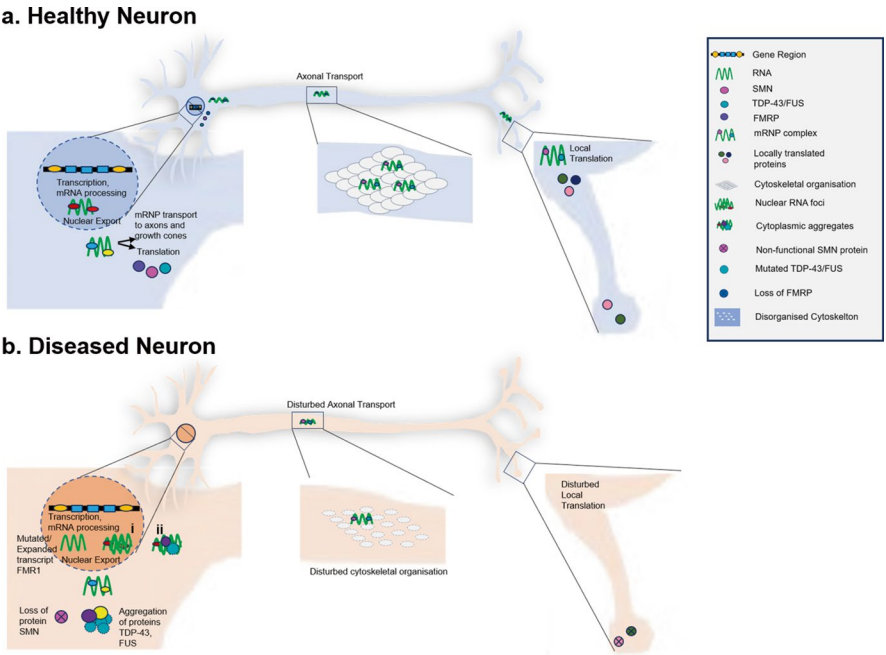

Fig. 10.3 RNA deregulation and neuronal health. Neurons undergo a tight regulation in context of the RNA and protein metabolism. (**a**) In a healthy neuron, RNA is transcribed and processed, and it is either translated in the cell body or transported in the form of mRNP complex via axonal transport to the site of requirement, where it is locally translated when required such as during responding to various stimuli. Properly organized cytoskeletal structure helps translocate the mRNP complex through axons to the dendrites and growth cones. (**b**) In a diseased neuron, mutated/expanded transcript may result in the formation of mutated proteins like TDP-43, FUS, SMN or loss of protein like FMRP. (i) The expanded transcripts often form nuclear RNA foci recruiting the vital RBPs to them and hampering their normal function, (ii) or the mutated proteins may form cytosolic aggregates with other vital RBPs. The loss of function of these vital RBPs like TDP-43, FUS, SMN and FMRP affects various neuronal aspects like axonal transport and local translocation. The disorganized cytoskeletal structure also causes the disturbed axonal transport which ultimately results in the absence of local translocation. The proteins required at the dendrites and growth cones are not available for sensing of the stimuli, and thus these neurons cannot respond to the stimuli properly. These aspects affect the overall neuronal integrity and thus result in NDDs

bind to mRNAs directly or indirectly via RBPs like hnRNP-R/Q, KSRP (KH-type splicing regulatory protein) and FMRP (fragile X mental retardation protein) (Rossoll et al. 2002) and Hud (ELAV4) (Fallini et al. 2011). SMN also helps to translocate the β-actin mRNA via binding to hnRNP R across the axon and growth cones of motor neurons (Rossoll et al. 2003). Depletion of SMN protein in SMA results in total disturbance of many aspects of RNA metabolism and that itself explains the severity associated with the disorder. Other RBPs like TDP-43, FMRP and FUS also play a significant role in axonal transport and local translation (Thelen and Kye 2020) (Fig. 10.3b).

Another very important factor needed for maintaining the unconventional structure and proper neurogenesis is the correct cytoskeletal organization, which plays a key role in axonal transport of RNAs and proteins in neurons and is generally found to be impaired in NDDs. Axonal regeneration and neural plasticity also strongly depends on the cytoskeletal rearrangements, and after any stress, injury or cellular stress, these cytoskeletal structures reorganize themselves rapidly to regenerate the axons. In case of NDDs, the disturbed cytoskeletal organization fails to regenerate these axons, and thus with age, the neurons lose their integrity and results in their loss and nervous system defects (Triantopoulou and Vidaki 2022). Neurodevelopment and neurodegenerative disease caused by disturbed axonal transport machinery are mentioned in Table 10.1. NDDs like ALS, PD, AD and CMT have a common feature where aggregation of neuronal cytoplasmic intermediate filament proteins have been observed. It is also reported that the levels of intermediate filaments encoding mRNA are also altered in the case of ALS, and some miRNAs like miR-9 and miR-105 are found to be dysregulated in spinal cord of ALS patients. These miRNAs are reported to regulate the stability of mRNAs of neuronal intermediate filaments (Hawley et al. 2019; Theunissen et al. 2021). Thus, the RNA transport machinery is crucial for proper neuronal function.

Defects in nuclear pore complex have also been reported in NDDs, and they are often precarious for neuronal cells leading to their death. The accumulation of Tau (neurofibrillary tangles) and β-amyloid plaques in neurons in AD patients are the hallmarks of the disease pathology, and these NFTs are found to be associated with dysfunctional nuclear lamina and irregular nuclear pore complexes, thus disturbing the mRNA trafficking across the nucleus and cytoplasm as well translation of the vital transcripts. This ultimately leads to the disturbed neuronal integrity and death (Spead et al. 2022).

10.9 Conclusions

The complexity of human genome has always attracted researchers to unravel the molecular mechanisms underlying neurodegeneration and cell death. In the past few decades, significant shift of interest of researchers have been made towards RNA biology. It is important to identify therapeutic targets and for this one needs to uncover the early processes that contribute to the disease mechanism. Disrupted RNA metabolism in various NDDs have revealed the prominent role of various RNA and RBPs in disease pathogenesis. From the discovery of double helical structure of DNA in 1953 to deciphering the genetic code for amino acids in 1961 to ultimately identifying introns in the DNA in 1977, we have come a long way, and now the focus is on non-coding RNA and RNA-binding proteins. Earlier it was considered that the message in the genome is encrypted in the form of coding genes, and these are transcribed into RNA and then to proteins, which perform majority of

the cellular functions. The non-coding regions of the human genome were thought to be junk or just the gap filling sequences, with no function. The publication of the Human Genome Project in 2004 revealed how little was known since only ~2.0% of the human genome is protein coding (having ~21,000 protein-coding genes), and these are dwarfed by functional conserved non-coding elements (CNEs). Rest of the genome is non-coding, but interestingly majority of the genome is transcribed into RNA.

Many species of RNA came into focus when their dysregulation led to disease onset. For example, miRNAs are now proving to be the key regulator of gene expression, where a single miRNA can regulate the expression of multiple genes. Targeting miRNA for therapeutics can prove to be a promising choice for many of these multifactorial disorders. miRNAs and lncRNAs are also known to regulate neuroinflammation in the case of NDDs. lncH19 is found to be upregulated in latent period of epilepsy and contribute to glial cell activation via JAK/STAT pathway during epilepsy (Han et al. 2018). LncRNA-GAS5 negatively regulates miR-223-3p and increased expression of GAS5 which can inhibit the miR-223-3p-mediated anti-inflammatory role (Xu et al. 2020). All these examples clearly support the role of RNA metabolism in disease pathogenesis, thus understanding the crosstalk created by RBPs in the cell, and their role in regulating different aspects of RNA metabolism has provided us a handle in understanding the molecular mechanism of disease pathogenesis. These factors play combinatorial role and disturbance in one can break/distort the whole chain, leading to catastrophic situations in neuronal cells. Various miRNAs, circular RNAs and lncRNA are expected to be promising biomarkers in the AD, PD, HD and ALS. CRISPR/Cas9 technique has become a potential tool and can be used to target specific mutated/toxic DNA/RNA. Recently, antisense oligonucleotides (ASO) are being used to bind targeted RNA and modulate their expression. In SMA, ASO against *SMN2* has been successfully administered to correct splicing issues in *SMN2* gene so that it includes the missing exon7 and thus is effective in overcoming the loss of SMN1 protein. Nusinersen, the first ASO-mediated treatment for SMA, is the first Food and Drug Administration (FDA)-approved treatment for SMA (Thelen and Kye 2020). With the advent of cutting-edge techniques like ASO and gene therapy, new opportunities have opened up for researchers to delve into and utilize the knowledge gained about the intricacies of altered RNA mechanisms and their contribution to NDDs. This will not only help in solving many unanswered questions but also pave the pathway for generating better therapeutic approach towards these devastationg diseases.

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Chapter 11
Emerging Relationship Between the Gut Microbiota and Neurodegenerative Disorders

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Abstract A growing body of evidence indicates that the multitude of organisms residing in our gut can profoundly affect our health. These organisms are loosely termed as gut microbiota and have been known to affect the function as well as the behavioral aspects of human health. Recent research shows that the microorganisms in our gut play a crucial role in determining our health and susceptibility to disease. Newly identified intricacies of connection between nervous system and gut microbiota are specially intriguing, since nervous system intersects and in a manner regulates almost every other function of the body. Interestingly, gut microbiota has been found to be affected in cases of nervous system disorders, including neurodegeneration, such as but not limited to Alzheimer's disease, Parkinson's disease, Huntington's disease, and multiple sclerosis.

The number of people worldwide with neurodegenerative disorders grows yearly, but effective treatments with few side effects remain limited. There is a new avenue of translational research, which evaluates the gut-brain-microbiome axis for management and therapeutic ideas for neurodegenerative disorders. It is therefore important to understand the newer intervention techniques using microbiota, which can be employed for holistic cure of neurodegenerative disorders. This chapter encompasses a comprehensive review of the relationship between gut microbiota in the context of specific neurodegenerative disorders.

Keywords Neurodegeneration · Gut-brain axis · Microbiota · Central nervous system · Neuroinflammation · Neurotransmitters

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11.1 Introduction

Neurodegeneration has been one of the major causes of death and poor quality of life worldwide and has been reported to result in around nine million deaths every year (Feigin et al. 2020). Neurodegenerative diseases are primarily characterized by the loss of specific types of neurons further affecting other neurons throughout the body (Banerjee et al. 2022). Since the central nervous system (CNS) is protected by the blood-brain barrier (BBB), any defects in the brain and related structures resulting in corresponding functional defects are difficult to target and treat, eventually leading to neurodegeneration. This further progresses with defects in functions like cognition, gut health, movement, and learning during the pathophysiology of the diseases (Lamptey et al. 2022). Off the various neurodegenerative disorders (NDDs), the most prevalent condition is Alzheimer's disease (AD) followed by Parkinson's disease (PD). In terms of people getting affected, AD has been reported to have affected around 51.62 million globally (Li et al. 2022). PD has been found to affect around 6.1 million globally as of 2016 (Dorsey et al. 2018). Huntington's disease (HD) has been found to be prevalent with a ratio of 0.47:1.21 per 100,000 incidence and prevalence of 7.25–9.33 per 100,000 annually (Shaw et al. 2022). Multiple sclerosis (MS) is another condition majorly reported to impact 2.8 million people worldwide (Walton et al. 2020). As name suggests, neurodegeneration in context to AD, PD, and HD is characterized by degenerating neurons and thereby majorly affecting nervous, muscular, and eventually cognitive functions in patients. Because the symptoms are multifactorial for neurodegeneration, no 100% cure or therapeutic intervention is available for neurodegenerative disorders.

With newer available research, it has been identified that food habits affecting the gut health affect the onset and progression of chronic disorders including those of neurodegeneration. And, therefore, it is important to extract the understanding of native gut resident microorganisms in order to identify potential therapeutic interventions and lifestyle management.

There are more than 100 trillion microbes in human gut alone consisting of around 150 times more genes than human genome. Microbiota is understood as an assemblage of microorganisms that form an ecological community in a specific area. Microbes are also present in the skin, vagina, and mouth other than gut and have been characterized in the human microbiome project in 2009. Various reports have highlighted the importance of gut microbiota pointing their role in epithelial development, innate immunity, and metabolic regulation. Disturbance of this ecosystem is known to coincide with occurrence of diseases (Altveş et al. 2020). Numerous studies have already established a relationship between gut flora and a range of disorders including musculoskeletal diseases, neurodegenerative diseases, inflammatory bowel disease, and metabolic diseases. In humans, during antenatal development, the colonization of the gut microbiome co-occurs with the progression (maturation) of the nervous system. The disparity in the gut microbiome during the stages of fetal development can impact neuronal development (Klann et al. 2022). This has led to the hypotheses that neurological disorders are not limited to

the brain and the central nervous system (CNS), and the idea of a microbiome-gut-brain axis has been developed. Particular changes in the abundance of the gut microbiome have been linked with the progression of neurodegenerative disorders. Changes or reduction in the diversity of the gut microbiome are affiliated with inflammation, which is one of the features in the progression of NDDs (Klann et al. 2022). If this microbiome balance gets disrupted, it is called gut dysbiosis which leads to increased gut permeability and systemic inflammation (Klann et al. 2022). Another instance to cite this intricate relationship of the gut microbiome with NDDs is protein misfolding. There might be an indirect link of the microbial metabolites affecting the aggregation and folding of the proteins which are crucial in accelerating the disease progression (Klann et al. 2022). In recent years, the research interest in the relationship between the gut microbiota and NDDs has escalated manifold. This chapter provides a comprehensive review of the bidirectional relationship between the progression of NDDs and gut microflora, emphasizing its influence on NDDs like AD, PD, HD, and MS.

11.2 Microbiome Gut-Brain Axis

The gut microbiota-brain axis is believed to be a two-way communication, allowing the microbes in the gut to communicate with the brain and vice versa. Changes at either side of this axis can cause changes on the other side; thus, changes in the gut-microbial health and/or composition can significantly contribute to the progression and onset of neurodegenerative disorders (Menozzi et al. 2021). Similarly, since changes on one side of the axis can affect the other, the gut-brain axis (GBA) can also be implicated in treating NDDs, which is an emerging field of research. Research from different groups indicates that novel long-term solution against the NDDs can utilize the GBA to devise treatment. To achieve treatment strategies involving the GBA, the exact mechanisms underlying the GBA and NDDs need to be elucidated The involvement of the GBA has been implicated and subsequently proven in NDDs, though the exact mechanisms of how it affects the brain are not yet known. There are neurons present that are integrated within the epithelial cells of the gut, and the network of these neurons constitutes the enteric nervous system (ENS) (Klann et al. 2022). It is believed that neurodegenerative diseases are manifested in the ENS due to degraded gut microbiome health and/or composition and then make their way to the CNS via the ENS and affect the brain. Owing to this relationship, the gut microbiome opens avenues in the field of therapeutics, probiotics, and prebiotics. Such strong links between gut health and NDDs propound the development of various advanced strategies like fecal microbiota transplantation (FMT) and personalized therapeutic interventions targeting gut microbiota to manage the NDD and prevent its onset (Klann et al. 2022).

According to the GBA hypothesis, the neurodegeneration that occurs in NDDs is not just localized to the regions of the CNS that are deteriorating, but, this damage or the disease pathology begins from the ENS that innervates the gut. The ENS, also

called as the second brain, comprises network of neurons, and glial cells, that innervate the GI tract and regulate its functions. The GBA reflects a bidirectional constant communication between the CNS and the gastrointestinal tract. The intestinal microbiota plays a major role in these interactions and different time points from the gut lumen to the CNS. The mechanisms of this communication include neural, immune, endocrine, and metabolic signaling. It is believed that this GBA is directly related to the barrier integrity of the gut and the BBB. The BBB is the monolayer of endothelial cells lining the blood vessels linked through tight junctions, and it maintains a controlled microenvironment that ensures proper neuronal activity (Palmer 2011). Along with endothelial cells, there are other contributors that help the formation of the BBB. These include the foot processes of astrocytes which surround the endothelial cells, pericytes that span the region between the endothelial cells and the astrocytes, macrophages, and a basement membrane (Palmer 2011). This creates a transport barrier that can mediate solute and ion transport between the blood and the brain (Palmer 2011). The BBB separates the immune system and the brain which ensures proper composition of the interstitial fluid of the CNS for normal functioning. Hence, the disruption of the BBB and neuroinflammation are common features among NDDs (Palmer 2011; Zenaro et al. 2017) .

Microbiota also influence peripheral immune activation and cytokine profile, in turn affecting systemic and CNS inflammation and neurodevelopment. In addition, gut microbiota also affects CNS function by the synthesizing neurotransmitters and neuromodulators like serotonin, dopamine, and short-chain fatty acids (SCFAs). SCFAs are known to mediate the integrity of the gut barrier by regulating tight junction expression in the intestinal epithelial cells. They also modulate the functioning of enterochromaffin cells, which produce hormones and neurotransmitters (Yadav et al. 2023). There is a growing body of evidence suggesting disruption and alteration of the microbiome in AD, and therapeutic interventions may be a viable scope for mitigating or preventing AD. As the microbes have a coating of lipopolysaccharide (LPS), the plasma concentration of LPS is a measure of intestinal barrier stability, which, if breached, leads to endotoxemia. This results in an inflammatory response, triggering cytokine release, systemically affecting the CNS via BBB, leading to neurodegeneration and neuroinflammation (Murray et al. 2022). A healthy gut microbiome promotes the integrity of the BBB by maintaining the intestinal barrier integrity which prevents microbial or chemical translocation through the gut epithelial cells and into the bloodstream (Klann et al. 2022). Alterations in the gut microbiota can cause dysfunction of the gut barrier, leading to altered immune response, initiation of pro-inflammatory pathways, or even direct damage to the intestinal epithelial cells (Klann et al. 2022). The BBB is also a part of the neurovascular unit (NVU) that is composed of pericytes, vascular smooth muscle cells from vessel walls, neurons, and glia. The NVU maintains BBB permeability, cerebral blood flow, and brain interstitial fluid chemical composition that is important for neuronal circuit functioning. The BBB is stabilized by the proper functioning of immune cells throughout the body. According to recent reports, the circulation of pro-inflammatory cytokines in the body affects the BBB. One of the major players in controlling this circulation and maintaining stability of the BBB is the gut

epithelial barrier. A defective gut barrier leads to a weakened mucosa layer and a persistent inflammatory response resulting in neuroinflammation spreading via the ENS (Zenaro et al. 2017).

11.3 Pathophysiology of NDDs

11.3.1 Alzheimer's Disease

AD is a multifactorial condition majorly characterized by progressive episodic memory impairment in early stages, death of synapses coupled to death of neuronal cells, and degeneration of the brain manifested by cognitive domains like memory, visuospatial ability, and executive dysfunction. AD has been found to affect around 0.8% to 1.1% of the global population in different geographical locations worldwide with the numbers rising steeply with age up to 17% in the age group 90 and above (Gustavsson et al. 2023). Considering the large number of people affected with the disease annually and the lack of clear understanding of the pathogenesis and diagnosis of the disease, AD has been known to be the most prevalent neurodegenerative disease. AD is defined as a slowly progressing neurodegenerative disease involving neurofibrillary tangles and neuritic plaques as a result of amyloid-beta (Aβ) accumulation. The most affected regions of the brain are the medial temporal lobe and neocortical structures. Aβ is a protein involved in various synaptic and neural functions and is found to be one of the leading causes of senile plaques. This protein plays a role in axonal guidance, synaptic function, and plasticity regulation (d'Errico and Meyer-Luehmann 2020). β and γ secretases are responsible for the synthesis of peptides from amyloid precursor protein (APP) of varied lengths, 43, 45, 46, 48, 49, and 51, and these eventually form Aβ40 and Aβ42. These accumulate on the neural structures and cause neurotoxicity by forming denser plaques in the hippocampus, amygdala, and cerebral cortex, leading to stimulation of astrocytes and microglia causing damage to axons and dendrites while causing cognitive impairments (Breijyeh and Karaman 2020. The tau protein is a phosphoprotein encoded *microtubule associate protein tau* (*MAPT*) gene. It is enriched in mature neurons' axons and regulates microtubule stability. Phosphorylation is fundamental for tau protein where the affinity of tau for tubulin decreases, leading to its accumulation in the cytosol of somatodendritic compartments (d'Errico and Meyer-Luehmann 2020). Neurofibrillary tangles (NFTs) are abnormal filaments of hyperphosphorylated tau protein that twist and form paired helical filaments and accumulate in axons, dendrites, and cytoskeletal microtubules. These lead to loss of dendritic spines, presynaptic terminals, and axonal dystrophy (Breijyeh and Karaman 2020). The NFTs also disturb the microtubule network and alter the axioplasmic flow compromising the functions of the neurons. It spreads from the entorhinal cortex through the limbic and reaches the hippocampus and neocortex (d'Errico and Meyer-Luehmann 2020).

One of the major pathways by which AD pathology occurs is via neuroinflammation. It is well-known that the CNS is an immune-privileged organ, with no lymphatic system, and is shielded from the peripheral circulation by the BBB. The BBB can respond to soluble factors and plasma proteins and communicate with peripheral immune system cells. This supports the view of the contribution of neuroinflammation in AD pathology and BBB disruption (Zenaro et al. 2017). Between the blood and cerebrospinal fluid, there are two sites: arachnoid epithelium and choroid plexus epithelium (Abbott et al. 2006). The barrier is maintained by tight junctions and adherent junctions to reduce the permeability of the barrier (Abbott et al. 2006). They comprise the brain microvessel endothelial cells (BMECs) that support three essential functions: establishing a paracellular diffusion barrier to small hydrophilic molecules and ions on the apical side, forming a passive/active receptor channel on the luminal surface for macromolecules, and serving as an interface for communication between CNS and periphery w.r.t. immune cells especially (Daneman and Prat 2015). Sufficient reports suggest the role of the NVU dysfunction in promoting dementia and AD. Studies have suggested the downregulation of proteins occludins, zona occludins, and claudin-5, which are crucial for tight junction functioning, along with inducing matrix metalloproteases like MMP-2 and MMP-9 expression, on induction of Aβ42 (Halliday et al. 2016). Aβ42 has also been found to downregulate cadherin expression, which is crucial for adherent junction functioning. The brain vasculature of AD patients has also been reported to have collapsed endothelium along with altered expression of proteins like glucose transporter-1. The basement membrane has also been found to be disrupted with altered expression of proteins like laminins, leading to migration of leukocytes into the brain during inflammation. AD patients have been reported to have significant loss of pericytes in the cortex and hippocampal regions, which are important for memory and cognition.

11.3.2 Parkinson's Disease (PD)

About 1% of the world's entire population is affected by PD. Its motor symptoms include tremor, rigidity, and bradykinesia, while the non-motor symptoms may include cognitive impairment, gastrointestinal issues, and olfactory dysfunction (Kouli et al. 2018). It is an age-related disorder, that is, the prevalence of the disease increases with age. Most affected are individuals above the age of 60, while individuals before 40 are rarely affected (Uwishema et al. 2022). PD is pathologically characterized by the loss of dopaminergic (DA) neurons in the *substantia nigra pars compacta* (SNpc) region of the brain, although the neurodegeneration is not limited to only this region (Kouli et al. 2018). On the basis of its origin, PD is classified into two types: sporadic where the exact causative agent or factor is unknown and familial or genetic. Sporadic PD includes various environmental factors including pesticides (rotenone) and heavy metals (lead, aluminum, iron, and zinc). The common feature of PD, whether sporadic or familial, is the inhibition or dysfunction of the

mitochondrial electron transport chain (ETC) (Kouli et al. 2018). One of the major effects of mitochondrial dysfunction is the accumulation of reactive oxygen species (ROS) due to electron leakage from the ETC. Accumulation of ROS can lead to destructive events in the cell, which are mainly due to lipid peroxidation, DNA damage, inflammation, and protein modification, which in turn lead to cellular dysfunction and, at many instances, even cell death (Hemmati-Dinarvand et al. 2019). The hallmark of PD is the presence of aggregates containing oligomerized α-synuclein. It is a presynaptic nerve terminal protein, and mutations in the protein lead to its aberrant function and oligomerization. It is suggested that α-synuclein may act in a prion-like mechanism during PD pathogenesis, i.e., misfolded α-synuclein proteins may initiate misfolding of nearby α-synuclein protein, thereby turning healthy forms of α-synuclein into pathogenic ones (Perez-Pardo et al. 2017). Accumulation of ROS causes the oligomerization of α-synuclein (A30P and A53T mutations) via oxidative damage, and this oligomeric form loses its ability to interact with lipid membranes (Emamzadeh 2016).

In PD, the disruption of the BBB and neuroinflammation are common features even among other NDDs. Certain pesticides and herbicides, that are known to cause PD, can cross the BBB, enter the brain, and cause neurodegeneration via various mechanisms. These compounds include rotenone and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Rotenone is a lipophilic isoflavonoid, and, due to its lipophilicity, it can directly cross the BBB and move into the brain easily when exposed. Rotenone is known to cause PD by inhibiting the mitochondrial complex I, blocking electron transport (Ibarra-Gutiérrez et al. 2023). MPTP, also a lipophilic compound, readily crosses the BBB, but it does not directly cause neurodegeneration. After crossing the BBB and entering the brain, MPTP is metabolized intracerebrally to MPP+, which causes neurodegeneration by inhibiting the mitochondrial complex I (Lin et al. 2010). But to reach the BBB and subsequently cross it, these compounds need to gain access to the circulating blood (Menozzi et al. 2021). There are two ways by which such compounds can access the bloodstream; first, if the compound is inhaled as gas or aerosol and then via gaseous exchange in the lungs moves into the bloodstream. Second, compounds like these could be ingested through the mouth cavity, and during assimilation in the gut, they make their way into the bloodstream via the gut and subsequently to the brain (Huang et al. 2020; Ibarra-Gutiérrez et al. 2023). The latter mechanism is via the GBA; it is thus hypothesized that gut health plays a role in neurodegenerative disorders such as PD (Klann et al. 2022).

During the initial stages of PD, aggregated and phosphorylated α-synuclein reportedly was found in the neurons of the ENS. These findings suggest that α-synuclein accumulation might begin in the ENS where a toxin or pathogen might cause hyperinflammatory responses due to gut microbiome alteration, start neurodegeneration in the ENS, and then traverse in a specific pattern to the SNpc and other regions of the CNS (Perez-Pardo et al. 2017). This hypothesis is backed up by the fact that one of the most prevalent non-motor symptoms of PD is the dysfunction of the GI tract, which includes nausea, constipation, drooling, delayed gastric emptying, and prolonged intestinal transit time. These symptoms are a consequence

of damage to the enteric neurons due to the accumulation of misfolded α-synuclein within them. One major observation among PD patients is that they exhibit an increased intestinal permeability, known as a leaky gut, which is correlated with the presence of intestinal α-synuclein accumulation (Perez-Pardo et al. 2017). This increased permeability might cause the translocation of bacteria and their inflammatory products, leading to inflammation and oxidative stress in the GI tract, which in turn promotes α-synuclein accumulation in the ENS (Perez-Pardo et al. 2017). Zonulin, a cytosolic tight junction-associated protein, is used as a marker for reduced integrity of the intestinal barrier. An increase in fecal zonulin levels indicates decreased intestinal barrier integrity. A significantly increased level of fecal zonulin is found in PD patients compared to age-matched controls (Menozzi et al. 2021). According to the GBA theory, α-synuclein appears in the gut before it makes its way into the CNS. It is believed that the potential pathway for α-synuclein transport into the CNS is through the vagus nerve, in a retrograde manner between the ENS and the brain (Menozzi et al. 2021). This hypothesis has been confirmed by Menozzi et al., where sublethal doses of rotenone when injected into rat stomach chronically induced an increase in the α-synuclein levels in the ENS and spread subsequently to the SNpc. After chronic exposure to rotenone in this manner, these rats also developed PD-like motor symptoms with selective DA neuronal degeneration (Menozzi et al. 2021).

11.3.3 Huntington's Disease (HD)

HD, a progressive neurodegenerative disorder, is caused by a trinucleotide expansion (CAG) in the huntingtin gene on the short arm of chromosome four. Despite being a hereditary condition, several environmental factors, such as stress, physical activity, and diet, can influence the onset and severity of symptoms (Gubert et al. 2020). Progressive motor, cognitive, and behavioral deterioration are hallmarks of HD, where every patient may have a different and unique pattern of symptom development (Ghosh and Tabrizi 2015). Alex et al., in their review, estimated the global prevalence of HD to be 2.7 per 100,000 people. An increase in prevalence was observed in the studies conducted between 2011 and 2022 (Medina et al. 2022). HD is characterized by several symptoms; however, progressive weight loss and metabolic dysfunction are two of the most common non-neurological symptoms (Lakra et al. 2019). In contrast, a small proportion of HD patients are pathologically overweight, despite having CAG repeat lengths similar to those of normal-weight and pathologically underweight patients (Aziz et al. 2008; Sanberg et al. 1989). HD severely affects the basal ganglia; however, the effects of HD progress to both gray and white matter, generalizing to a range of cortical and subcortical structures (Tabrizi et al. 2022). Despite extensive research, the etiology, progression, and optimal treatment of HD remain largely unknown. It is one of the rare autosomal dominant genetic disorders that is characterized by neurodegeneration and primarily

affects the CNS. The underlying mechanism that causes HD is the mutation in the *HD*, located on the short arm of chromosome 4. *HD* codes for the protein called HTT. The role of this protein is not well established, but it is insinuated that it participates in nuclear transport, transcriptional regulation, and axonal transport and regulates apoptotic signaling (Schulte and Littleton 2011). The genetic cause and progression of this disorder are associated with the expansion of CAG repeats. The majority of the mutation arises from intermediate alleles (IAs) containing CAG repeats. The normal range of expansion lies between 6 and 37 (and repeats beyond this range, e.g., 40 repeats, are considered pathological. This marks the early onset of the disease (Möncke-Buchner et al. 2002). The size of the repeats increases significantly even before the onset of the disease, and the length of CAG repeats is affiliated with the severity of the disease (Kennedy et al. 2003). The expanded CAG repeats translate the mutated Huntington, which is in a misfolded state and subsequently leads to the formation of insoluble aggregates (Cisbani and Cicchetti 2012).

A few recent studies have highlighted the probable involvement of microbial dysbiosis and gut microbiome in the pathogenesis of this disease. A different gut profile has negatively affected the motor, cognitive, and behavioral responses. The two major outlooks of HD are neuroinflammation and imbalance in neurotransmitters like serotonin, GABA, and dopamine (Yano et al. 2015). In a study conducted by Yano et al. (2015), the role of gut microbiota in regulating the levels of serum and colon serotonin (5-hydrodytryptamine or 5-HT) was demonstrated. They also showed that variations in the gut microbe population can amend the 5-HT-related disease symptoms. Some studies were also conducted on the activation of microglia cells which are the immune cells of the brain. These immune cells get activated in response to the inflammatory signals that are sent by the gut, leading to peripheral inflammation. Such signals may breach the integrity of the BBB causing the release of inflammatory molecules in the brain. HD also includes psychiatric features like anxiety, depression, and irritability. This is also related to neuroinflammation which is mediated by gut dysbiosis (Yano et al. 2015).

11.3.4 Multiple Sclerosis (MS)

Multiple sclerosis (MS) is a long-term condition characterized by inflammation in the body. This condition affects the nervous system and leads to various neurological impairments, physical and mental limitations, and damage to the central nervous system (CNS). The telltale signs of this condition include the proliferation and activation of glial cells, also known as gliosis, and the destruction of the myelin sheaths surrounding nerve fibers, also known as demyelination. It has been reported that the presence of macrophages and T-lymphocytic infiltration in inflamed areas, along with the death of oligodendrocytes, is responsible for the breakdown of the myelin sheath in the CNS, thus causing further impairments. Therefore, this results in the formation of lesions that display a combination of inflammatory cells' damaged axons and astrogliosis in both white and gray matter. The onset of MS is tightly

connected to the occurrence of oxidative stress, and the pathophysiology of the disease involves complex redox reactions that disrupt the balance between oxidants and antioxidants. These redox disturbances contribute to the advancement of the disease. The infiltration of the CNS by immune cells triggers inflammation, leading to cytokine production in both white and gray matter tissues. Moreover, the development of MS is closely linked to mitochondrial dysfunction, worsening the existing redox imbalance. Additionally, a noteworthy aspect of MS pathology is the buildup of iron in the brain, which has been linked to increased oxidative stress and neurodegeneration (Ghasemi et al. 2017). This is compounded by the dysregulation of axonal bioenergetics, resulting in impaired production and utilization of energy that significantly contribute to the progression of the disease. These intricate redox processes and their associated mechanisms also have a significant impact on the cognitive function and memory of individuals with MS (Adamczyk-Sowa et al. 2017). T helper (T_H) cells play a crucial role in initiating both adaptive and innate immune responses by interacting with antigen-presenting cells (APC). However, signal transduction in neurons is still disrupted due to neuronal dysfunction, causing an array of clinical symptoms such as autonomic and sensory dysfunction, visual disturbances, ataxia, fatigue, cognitive impairments, and emotional disturbances (Ghasemi et al. 2017). Extensive research has shown that environmental factors significantly contribute to the development of MS. There are a multitude of factors that may contribute to the development of the disease which include being exposed to infectious agents, lacking important vitamins, smoking tobacco, and having a genetic predisposition (Ghasemi et al. 2017).

Recently, a significant connection between the gut and brain in the development of MS. Reports on an experimental mouse model of MS describe experimental autoimmune encephalomyelitis (EAE), which have shown increased intestinal permeability, gastrointestinal issues, and altered gut microbiota compared to age-matched controls. Furthermore, experiments conducted on EAE mice have demonstrated that gut microbiota plays a crucial role in regulating the response of both effector and regulatory T cells, driving the progression of the disease. These findings have shed light on the significant contribution of the gut microbiome in the development and progression of MS (Parodi and Kerlero de Rosbo 2021). The connection between the gut and the brain in MS and EAE is complicated, but two major consequences have been identified. First, inflammation in the gut that leads to increased gut epithelial barrier permeability (known as dysbiosis), alters the communication between the gut and the CNS, resulting in inflammation in the CNS along with the disease pathogenesis, via cholinergic afferent fibres. Second, as the disease progresses, neuroinflammation affects the transmission of cholinergic signals out of the CNS, contributing to gut inflammation. Recent research using germ-free (GF) mice or treatment of mice with antibiotics has shed light on the role of microbiota in modulating the immune response of the CNS to be anti-inflammatory. This suggests that gut dysbiosis plays a significant role in the pathogenesis of MS.

Research on the microbiota of MS patients has advanced our understanding of its potential to regulate EAE (Parodi and Kerlero de Rosbo 2021). Several factors influence the onset and progression of MS which include genetic predisposition,

environmental immunity (such as exposure to viruses), changes in BBB functioning, and the ability to form myelinoclastic plaques in the CNS. The maintenance of proper CNS function relies on a balanced interplay between biochemical and immunological processes (Ortiz et al. 2014). However, certain elements such as zinc, copper, iron, and gadolinium (Gd^{+}) can disrupt the BBB's integrity and potentially lead to neurological complications. Recent use of 3T dynamic contrast enhancers has revealed that BBB disruption is an early indicator of optic neuritis progression to MS (Balasa et al. 2021). While the disruption of the BBB is typically short-lived, there is a possibility of relapse in the same or different areas over weeks. The progression of lesions is not consistent and can involve a variety of factors such as axonal migration, demyelination caused by the immune system, and leaky BBB (Höftberger and Lassmann 2017).

11.4 Microbial Signatures in NDDs

There have been studies that have reported that a certain profile of gut microbiome or a microbial signature is involved in the GBA of NDDs. Since there is an implication of barrier integrity (the gut barrier as well as the BBB), recent research delves into the involvement of various microbial species in this complex axis, shedding light on the role of SCFA and LPS-producing bacteria. Studies suggest that alterations in the abundance and composition of these bacteria can contribute to gut dysbiosis, a condition characterized by an imbalance in the gut microbial community. SCFA-producing bacteria, such as those belonging to the *Firmicutes* and *Bacteroidetes* phyla, are implicated in modulating host metabolism and immune responses (L et al. 2023; Murray et al. 2022). Conversely, an overabundance of LPS-producing bacteria, such as *Proteobacteria*, has been linked to increased gut permeability and systemic inflammation. The translocation of microbial products, such as SCFAs and LPS, from the gut into systemic circulation may exacerbate neuroinflammation and influence the progression of NDDs. The gut microbiome signature is characterized by the alpha diversity, the study of species abundance and richness; beta diversity, the similarity or dissimilarity between pairs of species; and the phylogenetic analysis of the species of microbes present in the gut. The species that are involved in the GBA of NDDs are the SCFA- and LPS-producing bacteria, which directly influence the gut barrier and BBB integrity due to their relative abundance within the gut (L et al. 2023; Murray et al. 2022). Primarily, studies have revealed three phyla to be involved, in the maintenance of the gut barrier and the BBB, though species affected are not just limited to these phyla: *Firmicutes*, *Bacteroidetes*, and *Proteobacteria* (Table 11.1).

Firmicutes: Consist of families and genera of bacteria that can ferment indigestible carbohydrates, in return producing health-promoting metabolites like SCFAs (L et al. 2023; Murray et al. 2022).

Bacteroidetes: This phylum includes anaerobic Gram-negative bacteria characterized by an outer LPS layer (L et al. 2023; Murray et al. 2022).

Table 11.1 Microbial signatures in each NDD

Condition	Genera/species more abundant	Genera/species less abundant
AD (L et al. 2023; Murray et al. 2022)	*Escherichia coli* *Proteobacteria* *Bilophila* *Eubacterium eligens* *Clostridium* *Lactobacillus* *Blautia* *Dorea* *Ruminococcus* *Peptostreptococcaceae* *Clostridiaceae* *Phascolarctobacterium* *Eggerthella lenta* *Pseudomonas aeruginosa* *Verrucomicrobia* *Tenericutes* *Helicobacteraceae* *Desulfovibrionaceae* *Helicobacter*	*Sutterella* *Eubacterium rectale* *Lachnoclostridium* *Butyrivibrio* *Turicibacter* *Dialister* *Paraprevotella* *Coriobacteriia* *Adlercreutzia* *Bacteroides fragile* *Faecalibacterium prausnitzii* *Eubacterium hallii* *Odoribacter* *Prevotella*
PD (Li et al. 2023; Sun et al. 2018; Uyar and Yildiran 2019; Zhu et al. 2022)	*Escherichia* *Shigella* *Klebsiella* *Enterobacter* spp. *Proteobacteria* *Acinetobacter* *Christensenella* *Veillonella* *Prevotella* *Anaerotruncus* *Alistipes* *Desulfovibrio*	*Bifidobacterium* *Firmicutes*
HD (Patil et al. 2021)	*Bacteroidetes*	*Firmicutes*
MS (Altieri et al. 2023; Parodi and Kerlero de Rosbo 2021)	*Akkermansia* *Bifidobacteria* *Ruminococcus* *Blautia*	*Bacteroides* *Parabacteroides* *Prevotella* *Lactobacillus* *Parabacteroides distasonis*

Proteobacteria: This phylum consists of the *Enterobacteriaceae* family, which includes the pro-inflammatory *Escherichia/Shigella* and *Klebsiella* genera. This phylum also has Gram-negative bacteria causing endotoxemia (L et al. 2023; Murray et al. 2022).

11.4.1 Microbial Signatures in the GBA of AD

The microbiome in general has been understood to be very important for its hosts in general. The three phyla described earlier are altered in patients with AD, while two other phyla, *Actinobacteria* and *Verrucomicrobia*, are altered in relatively fewer patients. In terms of diversity, studies in normal aging have demonstrated that gut microbiome increases alpha diversity, but the composition grows unique among individuals, with a decrease in core taxa and enrichment of rare taxa (L et al. 2023; Murray et al. 2022).

As mentioned earlier, SCFAs are crucial for maintaining the gut-intestinal barrier by providing nutrition for epithelial cells, regulating immune cell functions, and protecting against endotoxemia. One particular SCFA, butyrate, is important for the abovementioned functions. Interestingly, it has been found to interfere with Aβ accumulation. Studies measuring Aβ by PET and in CSF have found decreased levels of *Eubacterium rectale* in AD patients. Furthermore, studies in patients with mild cognitive impairments (MCI) have shown enrichment of *Eubacterium eligens*. The members of the phylum *Firmicutes* also produce many useful metabolites like *Lactobacillus* producing GABA and *Clostridium sporogenes* producing indole propionic acid. Studies in AD patients have shown decreased levels of *Clostridium* but enhanced *Lactobacillus* w.r.t. controls. Other genera, including *Bacillus* (producing nor-adrenaline and dopamine), *Streptococcus* (producing serotonin), and *Enterococcus* (producing serotonin), are enhanced in AD patients. Some genera affecting health like the *Blautia* and *Dorea* are also enhanced in AD patients. Studies in mouse models of AD have shown these genera to secrete membrane vesicles containing fragmented bacterial DNA in the bloodstream, contributing to endotoxemia. Apart from these genera, *Lachnoclostridium*, *Ruminiclostridium Peptostreptococcaceae*, *Clostridiaceae*, and *Butyrivibrio* are decreased, while *Ruminococcus* and *Subdoligranulum* are increased. The *Bacillus* class is enhanced, and the genera *Turicibacter*, *cc115*, and *Dialister* are decreased. *Lactobacillus* and genus *Phascolarctobacterium* are found to be enhanced (L et al. 2023; Murray et al. 2022).

The genus *Bacteroides* has a vital role in maintaining the ecosystem of the gut, maintaining the gut epithelial barrier and immune system, and preventing colonization by pathogens. Bacteria like *Bacteroides* translocate resulting in chronic exposure to LPS resulting in plaque formation and endotoxemia. The abundance of *Bacteroides* was found to be positively associated with CSF biomarkers like p-tau and p-tau/Aβ42. Moreover, individuals in the *Bacteroides* group were characterized by greater white matter hyperintensities and cortical and hippocampal atrophy. Some studies report *Bacteroides* to be decreased in patients with AD, mild cognitive impairments, and dementia, while some appeared to be enhanced along with *Bacteroides fragilis*. *Odoribacter* spp., *Parabacteroides*, *Alistipes*, and *Paraprevotella* were found to be decreased, whereas *Prevotella* is increased in AD patients (L et al. 2023; Murray et al. 2022).

E. coli and *Klebsiella* spp. can form *curli* gene-based biofilms for their survival, and it has been reported that these bacteria-derived amyloids may act as prions in the host, cross-seeding neuronal Aβ in AD patients. The *Proteobacteria* have been found to increase in a dose-dependent manner, increasing from healthy patients with MCI to AD patients. *Escherichia coli* has also been detected with LPS and Aβ in the brains of AD patients in autopsy. More abundance of *Escherichia/Shigella* has been reported to be associated with greater peripheral inflammation and amyloidosis, even dementia. Other genera like *Sutterella* are decreased in AD, but enhanced levels of *Bilophila* have been found in AD (L et al. 2023; Murray et al. 2022).

Bacteria belonging to *Actinobacteria* phylum are generally associated with positive health effects, and genera like *Bifidobacterium* have been extensively used in probiotic compounds as well, helping maintain intestinal barrier function, anti-inflammatory effects, and decreased LPS levels. However, there are mixed reports on *Actinobacteria* abundance in AD patients. *Adlercreutzia* have decreased, whereas *Eggerthella lenta* is increased in AD (L et al. 2023; Murray et al. 2022).

There are various reports highlighting the effects these genera have on the inflammatory pathways. Bacteria like *Bacillus fragilis*, *Bacteroides fragilis*, *E. rectale*, *Eubacterium hallii*, *Bifidobacterium*, and *Faecalibacterium prausnitzii* stimulating anti-inflammatory response have been reported to be lower in elderly MCI patients. Other studies suggest a decrease in levels of IL-10 and bacteria like *E. rectale*, *Eubacterium hallii*, *Faecalibacterium prausnitzii*, and *Bacteroides fragile* triggering anti-inflammatory response in the blood of AD patients and mice models of AD. Other studies have observed increased *Bacteroidetes*, *Verrucomicrobia*, *Tenericutes*, and *Proteobacteria* along with an increase in cerebral Aβ amyloid load in aged mutant mice (L et al. 2023; Murray et al. 2022). There have been reported alterations in the microbiome composition and circulating inflammatory mediators, in antibiotic-treated mutant mice along with reduced Aβ depositions but increased Aβ levels and reduced reactive gliosis surrounding Aβ plaques and significantly altered microbial morphology (Minter et al. 2016). A remarkable increase in abundance of *Helicobacteraceae* and *Desulfovibrionaceae* family and *Odoribacter* and *Helicobacter* genera was found to be increased, and *Prevotella* was found to be lowered in mutant mice (Vogt et al. 2017). Studies from yet another mouse mutation suggested altered fecal microbiota composition with age, reduced trypsin amount in fecal proteins, and the presence of human APP in the gut and brain (Kowalski and Mulak 2019). Studies in *ApoE*$^{-/-}$ mice showed active invasion of *Porphyromonas gingivalis* and infection-induced complement activation in the brain (Dominy et al. 2019). AD rat model with intra-hippocampal injection of A*β* showed learning and memory deficits with oxidative stress (Chen et al. 2017). Transgenic fly models made using the Gal4-UAS technique have shown that *Enterobacteriaceae* infection exacerbates the progression of AD by promoting immune hemocyte recruitment to the brain, whereas genetic depletion of immune effector cells attenuates neuroinflammation and alleviates neurodegeneration in certain model systems (Doifode et al. 2021).

11.4.2 Microbial Signatures in the GBA of PD

In the case of PD, it is suggested that disruption of the gut microbiota, especially the bacteria that produce SCFAs, is a causative factor. Some of these SCFA-producing bacteria include *Lachnospiraceae*, *Ruminococcus*, *Faecalibacterium*, *Eubacterium*, *Bacteroides*, and *Prevotella*, and a decrease in their numbers has also been observed in PD patients compared to human controls (Li et al. 2023). Another observation made in the gut microbiota is that along with the decrease in bacteria that produce SCFAs, there is an increase in the population of bacteria that are pathobionts or induce GI distress or related diseases. In the fecal samples of PD patients, there is an increase in the levels of *Escherichia*, *Shigella*, *Klebsiella*, *Enterobacter* spp., *Proteobacteria*, *Acinetobacter*, *Christensenella*, *Veillonella*, *Prevotella*, *Anaerotruncus*, *Alistipes*, and *Desulfovibrio* compared to human controls (Li et al. 2023).

Additionally, a higher abundance of *Akkermansia* has been observed in the gut of PD patients, specifically *A. muciniphila. A. muciniphila* is a mucin-degrading bacterium found in the mucus layer of the digestive tract and is a positive modulator of mucus thickness and gut barrier integrity. It synthesizes SCFAs from the degraded mucin, thereby promoting mucus thickness. *A. muciniphila* can also modulate the immune response and inhibit inflammation, consecutively making it a potential probiotic. However, studies have shown that *Akkermansia* enrichment caused a significant trend effect for disease duration, and relatively higher *Akkermansia* have been found in older PD patients (Li et al. 2023). Overall, the loss of bacteria that produce SCFAs and an increase in potentially pathogenic bacteria together cause gut dysbiosis that leads to the impairment of the intestinal as well as the BBB integrity via the stimulation of systemic and neural inflammation that begins at the ENS and makes its way to the CNS and cause PD and/or PD-like symptoms (Li et al. 2023).

11.4.3 Microbial Signatures Involved in the GBA of HD

The microbiome, which is obtained during birth and develops throughout childhood and adolescence, is believed to significantly influence on overall development, in particular the development of nervous system. Dysregulation of the gut microbiome can have an impact on neurodevelopment via the microbiome-gut-brain axis. The gastrointestinal (GI) tract produces the mutant huntingtin (mHTT) protein leading to GI dysfunction, such as impaired gut movement diarrhea and difficulty absorbing food. This malabsorption is closely linked to weight loss, a characteristic symptom of HD observed in both HD patients and various transgenic mouse models of HD. Several studies have shown a link between gut dysbiosis and neurological disorders, specifically HD (Du et al. 2020; Kong et al. 2020). A study revealed a significant variation in the gut microbiome composition. The study highlights alterations in the gut microbiomes of WT versus HD organisms using two metrics:

Bray-Curtis index and unweighted UniFrac index. A notable difference in bacterial abundance between WT and HD conditions was shown by the shift in the Bray-Curtis index. However unweighted UniFrac index remained relatively unaltered which explained the evolutionary relationship among the bacterial species are comparable between the two groups. This indicates that although the bacteria in the WT and HD gut microbiomes show phylogenetic similarity, they differ in abundance (Giloteaux et al. 2016).

There are certain microbial species that influence the disease progression or are associated with the severity of the symptoms in people with HD. According to a recent study, the gut microbiome of mice with HD was characterized by an increase in *Bacteroidetes* and a corresponding decrease in *Firmicutes*. Also an increase in *Ruminococcaceae* and a decrease in *Prevotellaceae* were reported (Sharma et al. 2023). The study noted that gut dysbiosis coincided with challenges in body weight gain despite higher food consumption and the presence of motor deficits at 12 weeks of age in the HD mice. The study also identified higher fecal water content in HD mice at 12 weeks of age, indicating alterations in the gut microenvironment (Kong et al. 2020). Another study found positive associations between the abundance of *Intestinimonas* spp. and plasma interleukin 4 (IL-4) levels. Considering that plasma IL-4 levels were lower in patients with HD, these findings indicate that the gut microbiota and inflammatory response may play a role in HD pathogenesis. Moreover, interestingly, the study also found that there is an inverse relationship between *Bilophila* and the pro-inflammatory IL-6 levels. This indicates that *Bilophila* might have a role in reducing inflammation in HD patients (Du et al. 2020). A study has observed enriched *Actinobacteria* at the phylum level; Deltaproteobacteria and *Actinobacteria* at the class level; *Desulfovibrionales* at the order level; *Oxalobacteraceae*, *Lactobacillaceae*, and *Desulfovibrionaceae* at the family level; and *Intestinimonas, Lactobacillus, Oscillibacter*, *Gemmiger*, and *Dialister* at the genus level. *Clostridium XVIII* at genus level was found to be down-regulated (Du et al. 2020).

11.4.4 Microbial Signatures Involved in the GBA of MS

Similar to AD, PD, and HD, the GBA of MS involves three main phyla of microbial signatures: *Firmicutes*, *Bacteroidetes*, and *Proteobacteria*. Together, these phyla make up the bulk of the gut microbe population, accounting for over 97%. Even with different measurement techniques, the variety of microorganisms in the human gut surpasses their functional diversity. This suggests that multiple microbial combinations can generate similar functional outcomes. Specifically, findings showed higher levels of *Treponema* in women and elevated levels of *Eubacterium/Blautia* in men, adding another layer to the complexity of gut microbiota composition (Altieri et al. 2023).

The presence of *Bifidobacterium* in patients' CSF and plasma has been associated with lower levels of IL-17A. The pathophysiology of MS is impacted by the

production of pro-inflammatory Th1 and Th17 cells, which produce IFN-γ and IL-17. Interestingly, there have been reports of coexisting cases of Guillain-Barre syndrome and MS since both are autoimmune demyelinating diseases (Morton et al. 2023). Analysis of the gut microbiota of 34 sets of monozygotic twins at risk for MS revealed an increased presence of *Akkermansia* in the twins. Additionally, transplanting microbiota from MS patients into healthy mice has been shown to induce autoimmune responses, highlighting the potential influence of gut microbiota on MS development. Furthermore, studies have indicated that a combination of *Bifidobacterium* and *Lactobacillus*, specifically *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Lacticaseibacillus paracasei*, and *Limosilactobacillus reuteri*, can have positive effects. Interestingly, *Acinetobacter* species have been linked to MS in healthy human guts. When exposed to *Acinetobacter calcoaceticus* or microbiota from healthy individuals the lymphocytes showed an increased capacity to transform into Th1-type cells, while the number of $CD25^+$ $FoxP3^+$ T_{reg} cells are decreased. However, the effects of *Parabacteroides distasonis* extract were found to stimulate T cells (Zhao et al. 2023).

11.5 Gut Microbiome as a Potential Modifier and Microbiome-Based Therapies in NDDs

Over the past decade, the GBA has been extensively characterized to develop clinical therapies for NDDs. Furthermore, research has shown that the gut microbiota is linked to several neurodevelopmental processes, including neurogenesis, myelination, microglial maturation, and the formation of the BBB (Sharon et al. 2016). Therefore, therapies using prebiotics, probiotics, and synbiotics for the regulation of NDDs are being extensively studied. Given the observed and hypothesized effects of the gut microbiome on NDDs, microbiota transplantation, enrichment, and supplementation are potential means for long-term treatments of NDDs. These supplementation and/or transplantation may include administration of probiotics, prebiotics, postbiotics, and synbiotics. Probiotics are living microorganisms that are proven to confer health benefits to the individual. A specific class of such probiotics that deliver mental health benefits to the individual is called psychobiotics (Zhu et al. 2022). Prebiotics include the fibers and nondigestible substances that facilitate growth of beneficial microbes within the gut. Postbiotics are the bioactive compounds secreted by live bacteria or released by lysed bacteria, conferring health benefits to the host. Lastly, synbiotics are a combination of prebiotics and probiotics, where the prebiotics specifically support the probiotic strain(s) (Zhu et al. 2022). Studies have reported that the gut microbiome can be potentially used as a modifier for various NDDs. These studies have tested such gut microbiome-based or targeted therapies in various in vitro and in vivo studies (Fang et al. 2020). This section describes the gut as a modifier in NDDs and how the gut microbiome can be modified as a treatment for NDDs.

11.5.1 Modification of the Gut Microbiome and Microbiome-Based Therapies in AD

Based on various reports, there has been significant interest in the role played by the microbiome of the gut in the pathophysiology of AD. Oral microbe *Porphyromonas gingivalis*, one of the main causative agents for human periodontitis, is also associated with an increased risk of AD and higher cerebral Aβ load (Doifode et al. 2021; Dominy et al. 2019). A mouse model also demonstrated that repeated intraperitoneal injections of LPS could enhance hippocampal Aβ-42 accumulation and learning/memory deficits (Athari Nik Azm et al. 2017). In another study human brain cells exhibited an increased NF-κB expression and pro-inflammatory cytokine levels when exposed to *Bacteroides fragilis*-derived LPS (Lukiw 2016). Reports also suggest that microglial morphology, maturation, and function are modulated by SCFAs and other microbial products from gut microbiota (Doifode et al. 2021). To better understand the impact of microbial alteration on disease progression, a study reported approaches on germ-free (GF) and specific pathogen-free (SPF) mice models. GF mice showed increased spontaneous activity and anti-anxiety behavior, along with higher expression of synaptophysin and postsynaptic density-95 proteins (Heijtz et al. 2011).

Animal model studies have shown probiotic supplementation to ameliorate neuropathology and cognitive performance, reduce Aβ accumulation, and increase ACh levels in the cerebral cortex and hippocampus. A report highlighted studies performed spanning 12 weeks of treatment and probiotic formulation with lactic acid bacteria and *Bifidobacterium*. Four out of five studies showed improved cognitive performances after probiotic treatments. A study has demonstrated supplementation of *L. acidophilus*, *L. casei*, *B. bifidum*, and *L. fermentum* led to reduced inflammatory and metabolic markers, such as hs-CRP and insulin resistance in AD patients (Murray et al. 2022; Akbari et al. 2016). It has been found that supplementation of *Lactiplantibacillus plantarum C29*-fermented soybean in patients with MCI was associated with improved cognition and memory. Agahi et al. (2018), on the other hand, showed no improvement in response to probiotic supplementation with *Limosilactobacillus fermentum*, *Lactiplantibacillus plantarum*, *B. lactis* or *L. acidophilus*, *B. bifidum*, and *B. longum* (Murray et al. 2022). There is variability depending on the formulation, dose, treatment paradigm, and AD model used (Chandra et al. 2023).

A study exposed Aβ-injected rats with probiotics including *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, and *Bifidobacterium longum* that resulted in rats performing better in the Morris water maze test (Rezaei Asl et al. 2019). There have been beneficial effects of SLAB51 (*Streptococcus thermophilus*, *Bifidobacteria longum*, *Bifidobacteria breve*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, *Lactobacillus brevis*). These effects include novel object recognition test improvement, reduced brain damage, decreased plaques, increased SCFAs, decreased plasma cytokine levels, and increased Sirtuin-1 levels (Chandra et al.

2023). A recent study showed formulation of *Bifidobacterium longum*, *Lactobacillus acidophilus*, vitamin A, vitamin D, omega 3 fatty acids in cod liver oil, and vitamins B1, B3, B6, B9, and B12, combined with exercise reduced Aβ and increased cognitive performance in *APP/PS1* mice (Chandra et al. 2023).

A study by Corpuz et al. (2018) used mutant mice models exposed to *Lacticaseibacillus casei* subsp. *case 327* and *Lacticaseibacillus paracasei K71* and found decreased cognitive decline, escape latency, increased time spent in the target hole, increased step through latency, serum serotonin levels, serotonin in brain extract, decreased mRNA of MAOA and MAOB in the hippocampus, and MAOA in the cortex after supplementation with *Lactobacillus*. Higher BDNF, CREB, and pCREB were found in the hippocampus. Fecal microbial transplant (FMT) is another therapeutic technique involving the use of microbiota in fecal samples from healthy control to patients (L et al. 2023).

Rats with Aβ42 hippocampal injection when exposed to *Morinda officinalis* for 8 weeks and were found to show increased learning and memory ability. The levels of physiological markers were also found to be positively affected. A study on APP mutant mice-exposed prebiotics containing fructooligosachhcrides (FOS) found enhanced cognition, decreased deposition of Aβ in the cortex, decreased JNK activation, and increased synaptic plasticity (Doifode et al. 2021).

11.5.2 Modification of the Gut Microbiome and Microbiome-Based Therapies in PD

For management of PD, the most commonly used probiotic strains in clinical practice are *Bifidobacterium*, *Lactobacillus*, and *Streptococcus*. A combination of *L. acidophilus* and *B. infantis* has been shown to improve the symptoms of bloating and abdominal pain (Zhu et al. 2022). Another probiotic mixture with four strains *B. bifidum*, *Limosilactobacillus reuteri*, *L. acidophilus*, and *Limosilactobacillus fermentum* has been shown to decrease movement disorders upon administration (Zhu et al. 2022). In MPTP-induced PD mice, *Lactiplantibacillus plantarum* was identified as an effective psychobiotic and reduces α-synuclein aggravation, regulating oxidative damage, inflammation, and gut microbiota dysfunction. Another widely used bacteria, *Lactiplantibacillus plantarum*, in mouse models of PD has been shown to suppress glial cell hyperactivation, MPTP-induced oxidative damage, and neuroinflammation, promote intestinal motility and mucin production, modulate gut microbiota, and alleviate motor deficits and neurotoxicity (Zhu et al. 2022). *PS128* has also been demonstrated to increase serotonin and dopamine levels in the striatum and improve anxiety-like behavior in germ-free mice. *Ligilactobacillus salivarius AP32* has been shown to enhance the antioxidant activity of the host antioxidant enzymes through direct and/or indirect means in a rat PD model (Zhu et al. 2022). A probiotic mixture of *B. animalis* subsp. *lactis* and *L. acidophilus* has been shown to increase the levels of butyrate, an SCFA that maintains gut and brain

barrier integrity, and rescues nigral DA neurons from MPTP- and rotenone-induced neurotoxicity. The effects of butyrate producing *C. butyricum* have been observed in mouse PD models, and it has been reported that protective effects are via stimulation of colonic glucagon-like peptide-1 secretion, but the exact mechanism for this observation is not yet known (Zhu et al. 2022). Among prebiotics, dietary fiber has been used in various studies, but no study has evaluated their effects on PD alone. Prebiotics have been shown to mitigate GI dysfunction and provide a promising strategy for the treatments. The combination of prebiotics with probiotics, or synbiotics, provides better efficiency in restoring gut dysbiosis than probiotics or prebiotics alone. Synbiotics such as polymannuronic acid with *Lacticaseibacillus rhamnosus GG* has been reported as a novel synbiotic that conferred neuroprotection against PD and could be an ideal oral treatment for PD (Zhu et al. 2022).

The use of FMT has also proven to be a potential therapeutic approach for treating PD. By introducing a healthy gut microbiome from a donor into a PD patient, FMT is found to alleviate both motor and non-motor symptoms of PD by fortifying gut barrier integrity, pathogen suppression, and immunomodulation. Multiple studies have reported that in human patients, there have been improvements in motor functions, sleep state, anxiety and depression, and gut function post-FMT(Zhu et al. 2022). Moreover, in mice models of PD, FMT has been shown to increase the striatal levels of both dopamine and serotonin (Sun et al. 2018). An effect of diet on the onset of NDDs has also been reported by multiple epidemiological studies. Diets with high vegetable, fruit, and omega-3 fatty acid components have been shown to have a neuroprotective influence on PD (Uyar and Yildiran 2019). Mediterranean diet, which is high in fiber and polyphenols, and its consumption has been related to a lower risk of PD onset (Zhu et al. 2022). In contrast to this, consumption of high caloric macro- and micronutrients is correlated to worsen PD-like symptoms (Zhu et al. 2022). The effect of diet on neurodegeneration and the brain is not due to the inflammatory responses, instead the effect the diet composition has on the gut microbiota. The composition of the diet could be the most significant determining factor of the structure and metabolic function of the gut microbiome. If the host diet is more favorable for the growth and metabolism of the gut microbiota, the more efficiently the microbes in the gut will utilize the components of the diet to produce beneficial metabolites such as SCFAs for NDDs (Zhu et al. 2022).

Calorie restriction and fasting have also shown neuroprotective effects against PD. The subsequent microbiota changes due to calorie-restricted diets and fasting selectively enrich the growth of *Lactobacillus*-predominant microbial communities in the gut and also suppresses the expression of microbial genes that are part of the LPS biosynthesis pathway, reducing the overall LPS levels in the gut and systemic inflammation (Zhu et al. 2022).

11.5.3 Modification of the Gut Microbiome and Microbiome-Based Therapies in HD

NDDs alter various parts of the brain, spinal cord, and nerves, leading to a gradual decline in cognitive, motor, and/or sensory function. Many different functions, including memory, executive functioning, communication, awareness, organization, and visuospatial abilities, are impacted by HD, leading to gradual deterioration of these functions over time (Wasser et al. 2020). Evidence suggests that the pathology of HD can partly be attributed to GI dysfunction (van der Burg et al. 2011). The gut microbiome has been shown to play a role in the pathogenesis of HD in animal studies (Al et al. 2022; van der Burg et al. 2011). Moreover, a recent study suggested an altered gut microbiome in HD gene expansion carriers (Wasser et al. 2020). Therefore, exploring therapeutic interventions centered on microbial signatures is crucial, considering the microbiome's implication in the pathogenesis of HD.

Interestingly, SCFAs, majorly produced by the gut microbiome, have shown neuroprotective effects by increasing nerve growth factors and reducing inflammation in the brain (Hou et al. 2021). Modifications in diet can also lead to SFCA-induced neuroprotection, for example, acquiring high-fiber diet or ketogenic diet stimulates the production of SFCAs like butyrate, thereby affecting HD pathogenesis (Sharma et al. 2023). Prebiotics have also been shown to have psychophysiological effects in several studies conducted on mice. A study using a rat model and prebiotic galactooligosaccharides (B-GOS), FOS, or placebo revealed changes in key receptors for memory and synaptic plasticity (Savignac et al. 2013). Similarly, in another study on the emotional appraisal and the psychophysiological effects of the prebiotic treatment, when B-GOS was consumed by healthy human subjects, their cortisol awakening response—a sign of emotional disorders like stress and depression—improved noticeably (Peterson 2020). This suggests that prebiotics may modulate neural networks associated with emotional attention. Consistent with the above findings, a recent study showed that *Lacticaseibacillus rhamnosus* HA-114, a non-commercial probiotic, imparted neuroprotective effect in *C. elegans* models of HD. This indicates the potential of probiotics for the treatment of age-dependent NDDs (Labarre et al. 2022). Apart from prebiotics and clinical therapies, many alternative traditional medical approaches have been studied regarding their neuroprotective effect. Certain components of herbal medicines, such as berberine, baicalein, and ginsenosides, are shown to have antioxidant, anti-inflammatory, and neuroprotective properties. These components promote the growth of beneficial bacteria while simultaneously inhibiting the growth of pathogenic bacteria (Guan et al. 2024). Given the complexity of the pathophysiology of NDDs, dietary interventions, targeted probiotic or prebiotic administrations, and traditional medicine alternatives may be used as therapeutic approaches for managing the NDDs.

11.5.4 Modification of the Gut Microbiome and Microbiome-Based Therapies in MS

In the realm of MS research, two prominent microbial signature models stand out: experimental autoimmune encephalomyelitis (EAE) and transgenic mice models. Through the utilization of the EAE model, researchers have made significant strides in unraveling the immunological processes at play in MS. However, it is crucial to acknowledge the fundamental differences between EAE and classical MS and the intricate nature of the disease itself. Animal studies have also indicated that antibiotics may hold the potential for alleviating MS-like symptoms observed in EAE. A transformation in the gut microbiome, catalyzed by broad-spectrum antibiotics, reduces the severity of EAE through its relationship with T_{reg} cells. This notable effect is exclusive to oral antibiotics, underscoring the crucial role of gut microbiota regulation (Sharifa et al. 2023). Studies have proven that administering antibiotics before EAE development or in its initial stages can act as a safeguard. However, their use during clinical EAE runs the risk of exacerbating symptoms.

As a treatment for MS, probiotics have been identified as potential options (Sharifa et al. 2023). In EAE models, specific probiotics, notably *Lactobacillus* strains, have showcased promising results in alleviating disease symptoms. Research has indicated that increasing levels of SCFAs through high-fiber diets or direct supplementation may effectively mitigate the severity and inflammation associated with EAE. A study involving EAE mice reported the presence of *Prevotella cisticola* effectively inhibits the initiation of EAE after being induced by PLP91–110. It has also been reported that FMT from twins to transgenic mice with a specific T-cell receptor targeting myelin autoantigens resulted in the gut microbiota of MS-affected twins being more likely to trigger CNS-specific autoimmunity as compared to the microbiota of healthy twins (Sharifa et al. 2023). Moreover, when utilizing tumor tissues from MS patients in animal models, FMT has been shown to exacerbate EAE (Watane et al. 2022).

GF mice have shown decreased disease activity and lower morbidity when exposed to EAE. Probiotic therapy has emerged as a potential treatment strategy, as demonstrated by delayed onset and altered clinical and histological features of EAE in mouse models following FMT (Zhao et al. 2023). Numerous pathways work to control inflammation, such as microbiota-mediated sialic acid metabolism and mucus breakdown, as well as the regulation of SCFA, prostate-specific antigen, and estrogen levels. These pathways are crucial in regulating inflammation through the gut microbiome. Imbalances in the gut microbiome can contribute to the development of MS due to gut dysbiosis, promoting immune responses that favors the proliferation of pro-inflammatory Th1 and Th17 cells while impeding the action of anti-inflammatory T_{reg} cells (Zhao et al. 2023).

Alternative approaches have also shown promise in relieving MS-specific symptoms. For example, phosphorus can improve optic neuritis; Cuprum Metallicum and nux vomica have both shown effectiveness in addressing spasms; and *Secale* is known to ease sensory symptoms (Whitmarsh 2003). Studies report significant

shifts in the microbial composition in the gut microbiome of MS patients were observed, with a decrease in *Actinobacteria* and *Faecalibacterium prausnitzii* and an increase in *Prevotella stercorea*. Interestingly, these changes were particularly distinct in individuals with MS, with *Gemella* on the rise and *Ruminococcus* levels showing a decrease. Furthermore, it has been noted that the *Bacteroidetes* members are declining, while the *Firmicutes* and *Actinobacteria* are enhanced. These findings suggest significant alterations in the gut microbiome of MS patients, warranting further investigation (Vacaras et al. 2023).

It has been reported that interferon beta can modify the interaction between microorganisms and epithelial cells (Vacaras et al. 2023). FMT has been found beneficial for the recovery of a beneficial bacterium, *Echinococcus*, in the guts of MS patients (Mirza et al. 2020). This treatment has been found to decrease levels of a butyrate producing bacteria *Clostridium* in the guts of MS patients. Butyrate is crucial for the development of T_{reg} cells and the anti-inflammatory cytokine IL-10 (Miyake et al. 2015; Vacaras et al. 2023). Additionally, MS patients who received FMT have significantly higher *Lachnospiraceae*, *Ruminococcus*, and *Eubacterium oxidoreductase* members in their gut microbiomes post FMT (Mirza et al. 2020).

It has been reported that members of the *Lachnospiraceae* family play a crucial role in reducing mucosal permeability by increasing the synthesis of tight junction proteins and releasing SCFAs (Rinninella et al. 2019). Recent research has found a strong connection between MS and changes in the members of *Streptococcus*, *Firmicutes*, and *Prevotella*. Additionally, the abundance of these bacteria was also enhanced in individuals with enhanced Th17 cells. The roles of *Acinetobacter calcoaceticus* and *Akkermansia muciniphila* on MS in mono-colonized mice and human peripheral blood mononuclear cells have been recently reported (Dunalska et al. 2023). Another important factor in MS pathology is the levels of SCFAs (Dziedzic and Saluk 2022). Interestingly, SCFAs not only affect myelination and T_{reg} proliferation in the gut but also does so without involving microglia in the CNS (Mossad and Erny 2020). This highlights the potential therapeutic potential of SCFAs in treating MS.

Studies have also found differences in the prevalence of certain bacterial taxa, such as *Pseudomonas*, *Mycoplasma*, *Haemophilus*, *Blautia*, *Dorea*, *Faecalibacterium*, *Methanobrevibacter*, *Akkermansia*, and *Desulfovibrionaceae*, in MS patients compared to non-MS controls. In a recent study, a discernible difference in the microbiome compositions of MS patients and healthy individuals have been reported. Specifically, bacteria from the *Bacteroidetes* phylum, as well as *Clostridia XIVa* and *IV*, showed notable variations. Additionally, the members of *Prevotella*, *Sutterella*, and *Akkermansia* were found to be higher in the gut microbiomes of the patients receiving disease-modifying medications compared to those who were not (Dunalska et al. 2023). Conversely, the members of *Sarcina* were lower in the medicated group. Interestingly, treatment with citrate derived from glutamine for MS also resulted in modifications of bacterial species, such as those belonging to *Bacteroidaceae*, *Faecalibacterium*, *Ruminococcus*, *Lactobacillaceae*, *Clostridium*, and other *Clostridiales*, within the microbiome (Dunalska et al. 2023).

It has been reported that when individuals with MS were given vitamin D supplements, increased levels of the *Akkermansia*, *Faecalibacterium*, and *Coprococcus* spp. were observed in their gut microbiota. By simply taking probiotics orally, dysbiosis-related levels of the members of *Akkermansia* and *Blautia* decreased, while *Lactobacillus* colonization in the gastrointestinal tract enhanced. Use of probiotics as a treatment for MS patients also led to a reduction in methane metabolism, inflammatory monocyte count, and dendritic cells. Thus, incorporating probiotics into the diet may be beneficial in lowering the risk of MS (Dunalska et al. 2023).

11.6 Conclusion

The gut and brain work in a collaborative manner where trillions of bacteria strike the axis through the secretion of various metabolites like SCFAs. Dysregulation of the gut microbiome or dysbiosis prompts the activation of the immune system and chronic inflammation leading to the progression of NDDs in general, but we have discussed AD, PD, HD, and MS here. Besides the secretion of short-chain fatty acids, the gut microbiome influences the aggregation of α-syn, HTT, Tau, and Aβ proteins among others, which are major biomarkers of proteinopathies in these NDDs.

Research from various reputable groups across the globe have established that microbes in the human body and especially in gut play a vital role in shaping and regulating the metabolism and immunity of the host. There are specific members from the phyla including *Bifidobacterium*, *Lactobacillus*, *Actinobacteria*, *Acinetobacter*, *Prevotella*, and *Ruminococcus*, as summarized in Fig. 11.1, among others that metabolize and produce SCFAs, in addition to metabolites like neurotransmitters. Every NDD described in previous sections has representative examples from these phyla with varied colonized population of members' population in clinical samples as well as animal model studies. In most cases, lower population of "good" or beneficial bacteria and relatively higher population of less beneficial or harmful bacteria have been identified associated with inflammatory response. However, there could be a few exceptions, which warrants further research to identify the mechanistic underpinnings. The microbiota patterns if observed closely will answer the stages of impact of a particular disease. There have been various lessons of managements learned through decades of research which have been implicated to manage the symptoms and improve quality of life for the patients affected with NDDs. A few of these interventions have been mentioned in previous sections for four NDDs. However, it is difficult to pinpoint one or two specific species or genera or phyla to be beneficial for a specific NDD described here. Since, the pathogenesis of the NDDs is also varied mostly from patient to patient. As mentioned, a combination of different species as probiotic and prebiotic or for FMT method appears promising from the perspective of management as well as therapeutic interventions.

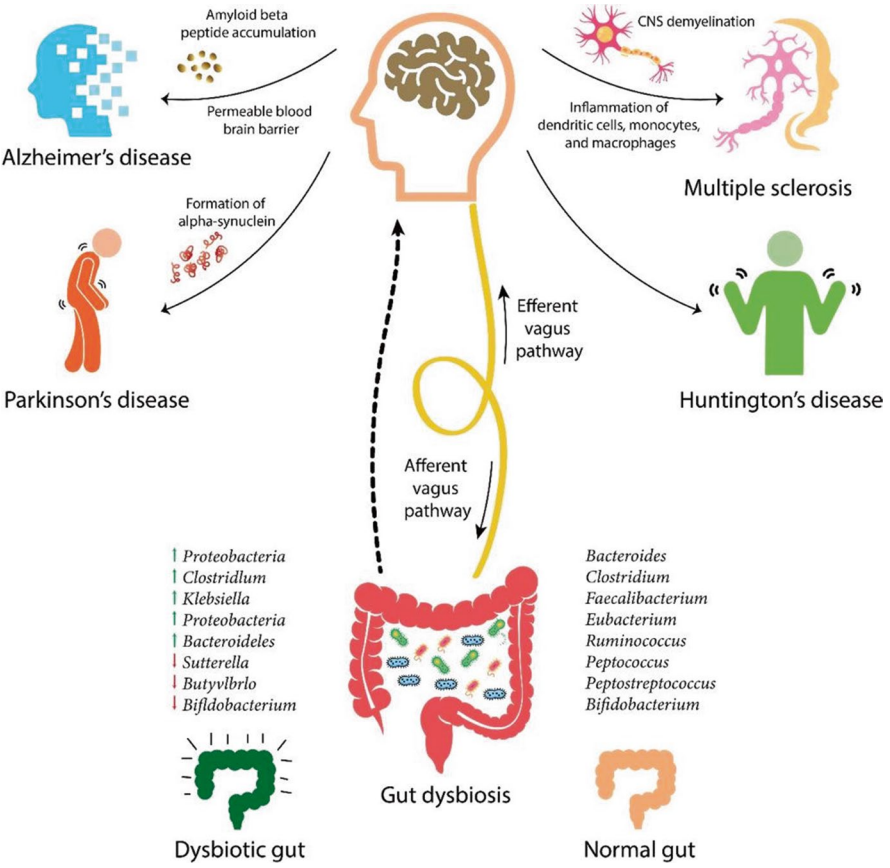

Fig. 11.1 Graphical depiction showing some of the common bacteria affected and found to be altered during the disease progression for all the four diseases. This figure summarizing the effects of Huntington's disease, Alzheimer's disease, Parkinson's disease, and multiple sclerosis on the gut microbial population, eventually leading to gut dysbiosis. The gut-brain axis is constituted by the CNS, gut, and the vagus nerve pathway connecting them. It is through this pathway that NDDs progress and cause pathogenesis of the disease. (Figure created using CANVA using the citations used in the paper)

Studies conducted on animal models have provided a comprehensive understanding of the pathways that connect the GBA and neurodegeneration. However, majority of these are yet to be explored in human studies. There is still a lot left unexplored, and even basic mechanistic understanding for much of observations is lacking from perspectives of prevention as well as cure. NDDs among other diseases progress in patients depending on a variety of factors including gender; hence the pathogenesis is also different from person to person. There is still wide scope of research in this field of disease pathogenesis study, paving way to increased chances of improving quality of life and even cure for NDDs.

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Chapter 12
Signaling Pathways in Neurodegeneration

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Abstract Neurodegeneration is the progressive loss of specific subsets of neurons present in the central nervous system leading to cognitive disability, including dementia. Neurodegenerative diseases are usually characterized by the accumulation of misfolded proteins in the neuronal cells and malfunction of proteasomal, lysosomal, autophagosomal, or mitochondrial systems that ultimately lead to neurodegeneration. Emerging evidence suggests that dysregulation of cell signaling pathways plays a pivotal role in the pathogenesis of various neurodegenerative diseases. Here, we describe cell signaling pathways that have been well studied to play a major role in different neurodegenerative diseases. Alterations in these pathways in neuronal disorders have been reported to manifest at protein quality control level, impaired mitochondrial dynamics, dysregulated autophagy and lysosomal pathways, abnormal accumulation of stress granules, neuroinflammation, perturbed immune response, and synaptic toxicity. Understanding the role of various cell signaling pathways and their crosstalk and signal integration in the pathogenesis of neurodegenerative diseases at the molecular level is critical for the development of effective treatments for neurodegenerative disorders.

Keywords Signaling pathways · Neurodegeneration · Proteinopathy · Parkinson's disease · Alzheimer's disease · Huntington disease · Tauopathies

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12.1 Introduction

The human brain is the most fascinating, complex, and equally essential part of the human body. It is the initiator of body movement, controller of behavior, interpreter of the senses, and the seat of intelligence. The brain including the rest of the nervous system is made up of different types of cells, but the primary functional unit is called a "neuron." A neuron functions to receive sensory input from the external environment, send motor commands to the muscles, and transform and relay the electric signals at every single step in between.

Progressive loss of neurons, disruption of its structure and function leading to a dysfunctional synapse, aberration of the neural circuit, and deposition of abnormal variants of the proteins in the brain are termed "neurodegeneration." Neurodegenerative diseases (NDDs) are a heterogeneous group of complex and serious neurological disorders that are characterized by abnormal accumulation of the misfolded peptides or proteins in the central nervous system and peripheral nervous system. The accumulation of such insoluble deposits occurs over time and mainly affects the aged neurons. Apart from pathological protein aggregation, NDDs are also associated with dysfunction of synapse and neuronal networks, perturbed proteostasis, cytoskeletal abnormalities, disruption of energy metabolism, defects of RNA and DNA, inflammation, and neuronal cell death (Wilson et al. 2023). These hallmarks linked with NDDs have been traced in different neurological diseases including Parkinson's disease (PD), Alzheimer's disease (AD), frontotemporal dementia (FTD), primary tauopathies, amyotrophic lateral sclerosis (ALS), synucleinopathies (e.g., Lewy body dementia [LBD] and multisystem atrophy [MSA]), prion disease (PrD), Huntington disease (HD), and related polyglutamine (poly Q) diseases including spinocerebellar ataxia (SCA), multiple sclerosis (MS), traumatic brain injury (TBI), spinal cord injury (SCI), and chronic traumatic encephalopathy (CTE) (Wilson et al. 2023).

Across the globe, neurodegenerative diseases are the ultimate cause of physical and cognitive disability affecting nearly 15% of the worldwide population (Feigin et al. 2020). Over the past 30 years, the absolute patient count for neurodegenerative disorders has significantly increased, and the weight of chronic neurodegenerative diseases is expected to double over the next two decades. The expansion of these diseases worldwide at an alarming rate calls for pushing the current knowledge boundaries of neurology and next-generation neurology-based research in a multilevel effort to deal with increasing burdens related to the mushrooming of neurodegenerative diseases. The research regarding neurodegenerative diseases should be aimed at (1) improving our understanding of neurological disease's etiology, (2) outlining novel strategies for the prevention of the disease, its modification, and curation, and (3) generating new biomarkers for early diagnosis of the disease, monitoring its progression and response to treatments.

12.2 Pathological Mechanisms Underlying NDDs

12.2.1 Proteinopathic Neurodegenerative Disorders

Proteinopathies are a class of NDDs characterized by aggregation of abnormal peptides or proteins. Some of the NDDs identified under the class of proteinopathies are AD, PD, ALS, FTD, LBD, MSA, SCA, etc. Multiple factors contribute to the pathogenic mechanisms responsible for the aggregation of proteins leading to neurological perturbations. Identification of disease-causing mutations in the inherited forms of NDDs, resulting in increased encoded protein accumulation, supports a toxic gain-of-function mechanism as one of the leading causes of proteinopathies. Mutations in genes encoding for Tau (AD and tauopathies), amyloid precursor protein (APP) (AD), α-synuclein (PD and synucleinopathies), SOD1 (ALS/FTD), PrPC (PrD), FUS (ALS/FTD), TAR DNA-binding protein 43 (TDP-43) (ALS/FTD), and huntingtin (Htt) (HD) have been linked with abnormal increased accumulation of the encoded protein in different NDDs. Additionally, mutations have also been identified in genes *Presenilin 1* and *2* (*PSEN 1* and *PSEN 2*) that do not enhance the aggregation of the encoded protein; instead, these mutations boost the accumulation of main NDD proteins. Protein aggregation and sequestration in one region of the cell lead to its deficit in another region, thus leading to loss of its endogenous function. This simultaneous toxic gain and loss-of-function effects target processes that drive neurodegeneration (Wilson et al. 2023).

In PrDs, the mechanism underlying abnormal protein aggregation includes the misfolding of the prion protein and the prompt propagation of its aggregation. The rapid loss of neurons and disruption of the neural network leading to protein aggregation and its spread to different regions of the brain is the characteristic feature that drives neurodegenerative processes in this condition. This pathological mechanism as a driver of NDDs led to the identification of different strains of prion-like seeds in NDDs that are coupled with toxicity, aggregation, and propagation propensity. As a result, prion-like processes have been elucidated to be major players in driving the neurodegenerative processes in different proteinopathies (Wilson et al. 2023).

12.2.2 Non-Proteinopathic Neurodegenerative Disorders

The source of the etiology of major NDDs is attributed to abnormal aggregation of misfolded proteins. However, some of the NDDs associated with primary traumatic, ischemic, and/or inflammatory components do not have a clear link with protein aggregation. Some of the NDDs where primary insult is not related to protein accumulation are SCI, TBI, stroke, CTE, and MS. These diseases on the contrary show protein aggregation as one of the secondary effects leading to a chronic aggravating

phase. Some of the diseases listed with protein aggregation as a presumed secondary effect are SCI with Tau aggregation, MS with Tau and neurofilament accumulation, and TBI with Tau and TDP-43 aggregation (Wilson et al. 2023).

Some of the genetically inherited NDDs also do not exhibit the feature of protein aggregation such as recessive parkinsonism, spinal muscular atrophy (SMA), and some cases of genetic PD (e.g., *LRRK2*).

Proper neural network functioning requires precise synaptic functioning and controlled modulation of stabilization and elimination of synapses. The regulation of synaptic function is controlled by neurotransmitter, calcium levels, cytoskeletal alterations, presynaptic vesicle movements, and postsynaptic signaling. Proper functioning of the synapse also requires suitable mitochondrial dynamics and energy to regulate the homeostasis of the calcium and maintenance of ionic balance, proteostasis, RNA and lipid metabolism, and autophagy. Insults to these processes disturbing the synaptic function and, subsequently, disruption of the neural network have been linked to many NDDs. For example, loss of synaptic functioning and perturbation of calcium homeostasis leading to concomitant depletion of energy have been reported to play a major role in stroke. ALS has been reported to be caused by hyperexcitability of the neurons and glutamate-mediated excitotoxicity. A similar mode of neurodegeneration has also been described in AD, HD, MS, SCI, and TBI. Alternatively, mutations in the genes encoding proteins that are implicated in synaptic functioning may also underlie pathophysiologic NDDs. For example, mutations in *SYNJ1, SNCA, DNAJC13*, and *DNAJC6* in PD and *C9orf72* in ALS/FTD have been reported.

Further, evidence of aberrant proteostasis has also been presented in various NDDs. The ubiquitin-proteasome system (UPS) and autophagy lysosomal pathway (ALP) are the major cellular mechanisms that regulate proteostasis. Dysregulation of both these mechanisms associated with cell death is a major contributor to the neuronal death leading to NDDs. Mutations in *UBQLN2* and *VCP*, the components of UPS, have been linked to ALS/FTD. Additionally, the *Parkin* gene, implicated in PD, encodes a ubiquitin-protein ligase, and *UCHL1* encodes ubiquitin carboxy-terminal hydrolase associated with a form of rare progressive NDD, which strongly suggests the role of UPS in NDDs. Additionally, mutations in *atg* genes associated with the regulation of autophagy have also been shown to be linked with NDDs.

Cytoskeletal abnormalities are yet another source of mechanisms responsible for neurodegeneration. Disruption of the neuronal cytoskeleton leads to deprivation of cargo and information transmission, including in the mitochondria leading to an energy deficit. Also, the movement of essential core components from the cell body to the synaptic endings gets compromised ultimately leading to neuronal death. Charcot-Marie-Tooth disease (CMT) linked with mutations in the neuronal intermediate light filament (*NEFL*) gene and tauopathies associated with mutations in *MAPT*, encoding microtubule-binding protein Tau, are some of the compelling evidence of the implications of the cytoskeletal abnormalities in NDDs. Further, mutations in kinesin and dynactin genes have also been associated with CMT and other

NDDs. Notably, hyperphosphorylation of intermediate filaments leading to the formation of neurofibrillary aggregates has been observed in various NDDs. Recently, the concentration of neurofibrillary aggregates in the biofluids has transpired to be a promising clinical biomarker for neurodegeneration in various NDDs, including dementias, ALS, MS, TBI, and stroke (Wilson et al. 2023).

Defects in DNA and RNA have also greatly contributed to the pathogenesis of NDDs. Mitochondrial oxidative phosphorylation produces ROS which is presumed to be the primary genotoxin in the CNS. Persistent changes in the CNS may result in chromosomal rearrangement, mutagenesis, the collapse of DNA replication fork, arrest of RNA transcription, etc., that can culminate in loss of cell function and eventually cell death. To overcome such insults, DNA repair mechanisms have evolved to ensure the integrity of the DNA and restore normal functionality of the genome. Similar mechanisms exist to regulate RNA metabolism and maintain RNA homeostasis. Defects in these mechanisms or biogenesis of RNA that include RNA transcription, translation, splicing, processing of noncoding RNAs, etc., may result in the formation of stress granules that involve ribonucleoproteins (RNPs). Mutations in genes encoding for proteins that are involved in the DNA repair pathways that resolve DNA double-strand breaks and replicative stress (e.g., ataxia telangiectasia [AT]) may result in brain atrophy later in life, coupled with endogenous damage of DNA that might lead to progressive loss of neurons. Ataxia with oculomotor apraxia type 2 (AOA2) is associated with mutations in *senataxin*, a gene encoding an RNA-DNA helicase. DSB response kinase mutated in AT (i.e., ATM) can be activated by α-synuclein aggregates, whereas fibrillization by α-synuclein can be accelerated by elevated levels of poly(ADP)ribose which is a product of hyperactivity of poly(ADP-ribose) polymerase 1 (PARP1). RNA binding protein, TDP-43 upon being mislocalized, results in alteration of RNA splicing, RNA transport, and RNA stability. Mutations in FUS might cause mislocalization of nuclear proteins to the cytoplasm that may result in perturbation of RNA metabolism. RNA metabolism defects are related to *C9orf72-linked* FTD/ALS (Wilson et al. 2023).

Further, neuronal inflammation, i.e., reactive microglia and astrocytes, works in conjunction with other NDD hallmarks to exacerbate the disease progression. Neuroinflammation drives synaptic dysfunction, perturbation of energy homeostasis, aggregation of proteins, and neuronal death. Death of the neurons is also largely attributed to intrinsic and extrinsic necrosis and apoptosis. Apart from these, other mechanisms including ferroptosis, necroptosis, autophagic cell death, phagoptosis, and pyroptosis have also been documented (Wilson et al. 2023).

It is widely accepted that NDDs have a multifactorial nature and their hallmarks are significantly interconnected (Table 12.1). Recent breakthroughs in neurological research have paved the way to the identification and understanding of yet another novel mechanism emerging as a potential root cause of NDDs. Signal transduction pathways are being identified to be significantly implicated in the origin of neurodegeneration, and their association with the hallmarks of NDDs is opening avenues for exploring the role of these cell signaling pathways in neurological disorders consequently offering advancement of novel therapeutic targets and strategies.

Table 12.1 Classification of neurodegenerative diseases and their pathogenic mechanisms

Neurodegenerative diseases		Pathogenic mechanisms
Proteinopathies	Alzheimer's disease, Parkinson's disease, frontotemporal dementia, amyotrophic lateral sclerosis, multisystem atrophy, Lewy body dementia, spinocerebellar ataxia	Mutations in genes encoding for Tau, *APP*, *α-synuclein*, *SOD1*, *PrPC*, *FUS*, *TDP-43*, *Htt*, *LRRK2*, and *PRKN* Protein dimer aggregation from repeat-associated non-ATG (RAN) translation Formation of intermediate assemblies of oligomers Aggregation of misfolded prion protein and their prompt propagation
Non-proteinopathies	spinal cord injury, traumatic brain injury, stroke, chronic traumatic encephalopathy, multiple sclerosis, recessive parkinsonism, spinal muscular atrophy, Charcot-Marie-tooth disease, ataxia telangiectasia	Neural network disruption Synaptic dysfunction and toxicity Disruptions in calcium levels Cytoskeletal alterations Perturbation in presynaptic vesicle movement and postsynaptic signaling Perturbation in mitochondrial dynamics Defective proteostasis and lipid metabolism Mutations in the genes such as *SYNJ1*, *SNCA*, *DNAJC13*, *DNAJC6*, *C9orf72*, *UBQLN2*, *VCP*, and *UCHL1* Neuronal cell death Defects in RNA and DNA Mislocalization of RNA binding proteins

12.3 Cell Signaling Pathways

Cells have evolved mechanisms to respond to the changes in the immediate external environment. They can receive and process the signals originating outside their borders. The cells are capable of receiving multiple signals parallelly, and this information is often integrated to bring about a unified action. Several signaling pathways have a chemical nature such as in prokaryotic unicellular organisms that harbor sensors to detect the signal from the source of nutrients and respond to it by moving towards the food source. In multicellular organisms, chemical signals are present in various forms such as hormones, growth factors, neurotransmitters, etc. These chemicals may exert their effect in a localized manner, or they may cover a long distance before reaching their destination. For example, neurotransmitters are short-range chemical signals that travel to the minute spaces present between two neurons or muscle cells. On the other hand, follicle-stimulating hormone travels from the

mammalian brain to the ovary via blood circulation to induce the release of the egg. Based on the distance covered, the signals have been characterized as autocrine (acting on the same cell that produces the factor), endocrine (long-range communication), juxtacrine (contact-dependent signaling), paracrine (short range/localized), and signaling at synaptic junctions (Fig. 12.1). The cells are also capable of sending out signals to other nearby or distant cells. Apart from the chemical signals, there are mechanical stimulations that can trigger the cells to respond (mechanotransduction). For example, sensory cells present in the skin respond to touch, whereas similar cells present in the ear respond to sound wave movement. Further, cells also respond to electrical stimulations (electrotransduction).

The cells receive these various forms of signals via the protein molecules called receptors present on the surface or inside of the cell. Upon binding with the signaling molecules or the ligands, the receptor changes its conformation. A cascade of biochemical reactions is initiated following the binding of the ligand to the receptor. The signal transduction cascade functions to amplify the relayed information and culminates in a physiological response. Some of the major signaling pathways that are evolutionarily conserved are Notch signaling, Wnt signaling, Hedgehog signaling, receptor tyrosine kinases pathway, transforming growth factor-β pathway, decapentaplegic signaling, mitogen-activated protein kinase signaling, Janus kinase/signal transducer, and activator of transcription and signaling pathways including

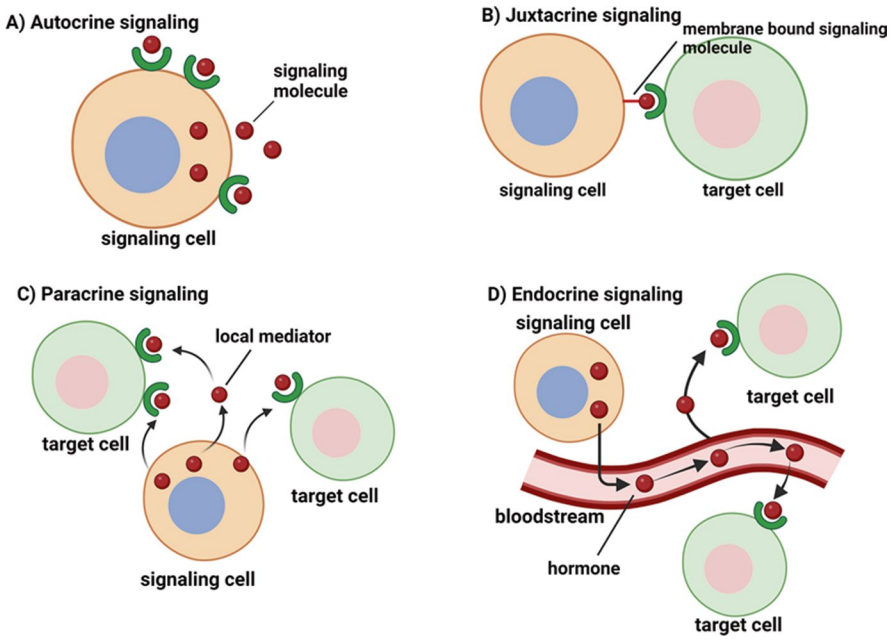

Fig. 12.1 Modes of cell signaling pathways. (**a**) Autocrine signaling. (**b**) Juxtacrine signaling. (**c**) Paracrine signaling. (**d**) Endocrine signaling

nuclear receptors.

Secondary messengers, part of signal transduction cascades, are synthesized following the activation of the receptors upon binding with the ligands. These secondary messengers operate to start and coordinate the intracellular signaling pathways. Some of the common secondary messengers involved in different cell signaling pathways are cyclic AMP (cAMP), diacylglycerol (DAG), and inositol 1,4,5-triphosphate (IP3).

Further, the activity of many enzymes involved in the signal transduction cascades is regulated by phosphorylation. The addition of the phosphate group from the ATP molecule to an enzyme by the protein kinases may activate or inhibit the enzymatic activity. On the other hand, phosphatases may remove the phosphate group from the enzymes thereby leading to the reversal of the effect on the enzymatic activity. The common sites for phosphorylation within a protein are serine, threonine, and tyrosine residues. A single protein kinase may add the phosphate group in a protein at multiple points, and also a single protein could harbor sites acting as substrates for multiple protein kinases and phosphatases. Also, a single secondary messenger, kinase, and phosphatase may simultaneously regulate several signaling pathways. It is due to this exceptional level of pleiotropism and redundancy that multiple points of intersections exist in the signaling system and an exceptional level of integration and crosstalks occurs among these pathways resulting in various physiological alterations.

12.4 Cell Signaling Pathways in Neurodegeneration

Studies to unravel the molecular mechanisms underlying different NDDs have identified various factors that contribute to the pathogenesis of NDDs. However, the vastness and complexities of the nervous system and the rapid increase in the patient counts affected by the disease compel us to fully understand the mechanisms behind the demise of the neurons. This will lead to the generation of novel therapeutic approaches to address the ever-growing challenges associated with NDDs. Recently gathered pieces of evidence highlight a novel mechanism involving the role of cell signaling pathways in NDDs. Perturbations in the signal transduction cascades, resulting from molecular alterations in particular proteins or genes, have been identified to be associated with many NDDs. These signaling pathways are intricately connected and show a complex level of crosstalk (Fig. 12.2). Perturbations in one of the proteins belonging to this network may disrupt an entire pathway cascade or cross-communication with other signaling pathways. Most well-studied signaling pathways implicated in NDDs will be discussed in this chapter.

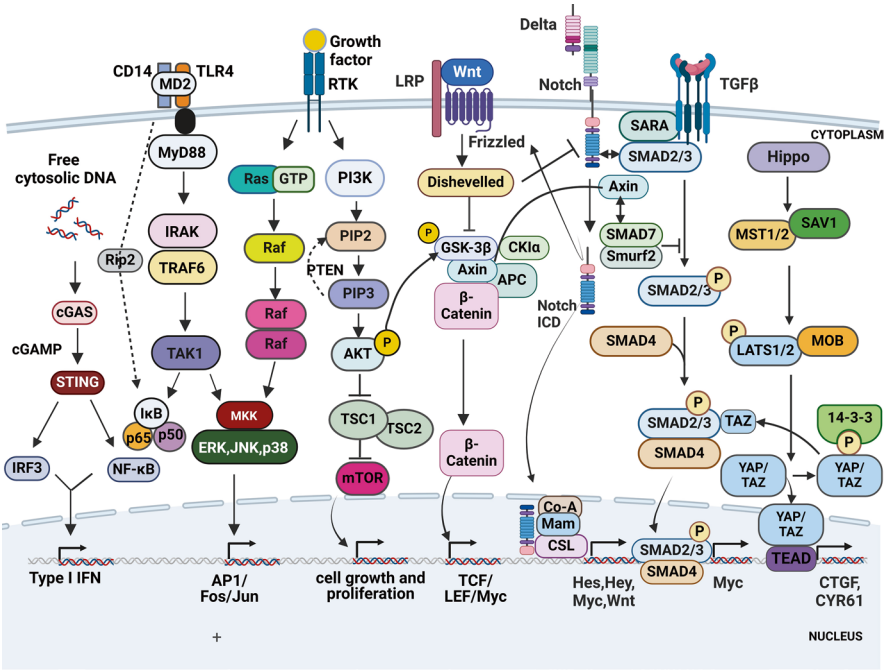

Fig. 12.2 Schematic showing extensive crosstalk among major cell signaling pathways involved in neurodevelopment and neurodegenerative diseases

12.4.1 Sirtuins

The discovery of sirtuins (SIRTs) can be traced back to 40 years ago with the identification of Sir2 for the first time in the budding yeast *Saccharomyces cerevisiae.* This was originally called mating-type regulator 1 protein. Later on, the function of Sir2 was studied, and it was determined to play significant roles in repression of the transcription at ribosomal DNA loci, at silent mating type loci, and in telomeres. In the 1990s, a remarkable investigation on Sir2 revealed that they can prolong the lifespan of yeast by abrogating genomic instability. Upon loss, Sir2 can shorten the lifespan of the yeast, whereas the presence of an extra copy of Sir2 can extend the lifespan by 40%. Sir2 was found to exhibit NAD+ -dependent activity of HDAC. This suggested the role of NAD deacetylation of histones in genome silencing and yeast aging.

Sirtuins play a significant role in multiple cellular processes, including transcription, response to various stress stimuli from low calorific conditions of feeding to inflammation, apoptosis, aging, etc. (Chandramowlishwaran et al. 2020).

The transcription of the nuclear genes encoding for mitochondrial components is regulated by the peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) and the NAD+ -dependent deacetylase SIRT1, thereby contributing to the

mitochondrial biogenesis. The PGC/SIRT pathway might be associated with a complex neural network controlled by micronutrients. Changes in basal NAD+ levels may be detected and responded to by SIRT1. The metabolic decline can be prevented by resveratrol, an activator of SIRT, which can induce the biogenesis of mitochondria (Majeed et al. 2021). Intracellular levels of NAD+ play a crucial role in the viability of the neurons by modulating oxidative phosphorylation under conditions of oxidative stress and dysfunction of the mitochondria. The levels of PGC-1α, nuclear respiratory factor (NRF) 1, and NRF2 were found to be drastically reduced in the hippocampal neurons of AD and in subcutaneous adipose mesenchymal M17 cells from APP mice model (Wareski et al. 2009). Other studies suggest that overexpression of PGC-1α may lead to cytotoxic conditions and subsequent loss of the dopaminergic neurons thereby causing neurodegeneration.

12.4.2 Nrf2

Nuclear factor erythroid 2-related factor 2 (Nrf2) functions to regulate various aspects of physiological cell function including maintenance of homeostasis and proliferation. The signal transduction cascade controls redox balance and antioxidant-related activities, induction of proteasomal degradation, metabolic reprogramming, and transcriptional activation of metabolic, antioxidant, detoxification, and proliferative genes.

One of the pivotal causes of neurodegeneration is oxidative stress. The implication of oxidative damage in the early stages of AD and PD paved the way for studying the role of Nrf2 in NDDs. Identification of Nrf2 with its antioxidant properties opened avenues for studying its role as a possible therapeutic candidate in NDDs. An interesting evidence was presented where a different subcellular expression of Nrf2 was observed in the brains of the patients affected with AD and PD. Nrf2 was found to be majorly cytoplasmic in the hippocampal neurons of AD-affected patients, whereas this localization was found to be altered in the dopaminergic cells of the patients affected with PD. Here, Nrf2 was observed to be localized in the nucleus. This study suggested that under elevated conditions of oxidative stress, Nrf2 translated to the nucleus to trigger the transcription of genes implicated in antioxidant response. The presence of Nrf2 in the cytoplasm in AD patients highlighted the failure of the neurons to acclimatize to conditions with oxidative stress. In PD patients, Nrf2 staining was not apparent in the dead dopaminergic neurons, but the alive neurons maintained normal functions with Nrf2 in the nucleus.

In the double transgenic mice model of APP/PS1 that overexpress presenilin 1 (PS1) and APP gene mutations, a defective expression of Nrf2 and its downstream targets was observed in the hippocampal and cortical regions of the brain parallel to the increase in aggregation of Aβ plaques. Aβ aggregates were found to be significantly reduced, and an improvement of the learning deficit was observed upon upregulation of Nrf2. Loss of Nrf2 exerted similar effects on Aβ aggregation, learning, and memory in other murine models of AD (Ren et al. 2020).

Besides the implication in oxidative stress, Nrf2 is also involved in NDDs owing to its linkage to inflammation and autophagy. Nrf2 has been found to interact with the autophagy receptor p62 which is a multifunctional protein present throughout the cell and mediates the proteasomal degradation of ubiquitinylated proteins (Ren et al. 2020). The association of Nrf2 with p62 shows a positive feedback loop as the oxidative stress response is initiated in case of defective autophagy. Perturbation in this association may underlie the pathogenesis of neurodegenerative disorders.

12.4.3 cGAS/STING-TBK1-IRF

The detection of invading pathogenic DNA is mediated by stimulator of interferon genes (STING) which acts as an innate immune system receptor and notifies the immune system to elicit a response against the infectious agent. cGas association with the immune adaptor protein STING is indispensable to elicit an interferon-based immune response to defend the host.

DNA ligand binds to the dimeric cGAS protein which leads to the activation of the latter. Activated cGAS generates a cyclic dinucleotide 2′,3′-cGAMP that binds to the STING receptor localized in the endoplasmic reticulum. This leads to the dimerization of STING receptors and their translocation to the perinuclear structures such as the Golgi apparatus. STING is subsequently bound and phosphorylated by TANK binding kinase 1 (TBK1). Following this, phosphorylated STING binds to the interferon regulatory factor 3's (IRF3) positively charged surfaces and phosphorylates and activates it with the help of TBK1 (Guo et al. 2019). IRF3 is a master regulator of type I interferons. Activated IRF3 moves to the nucleus and induces transcription of the genes encoding for interferons and cytokines. This may also lead to the activation of NF-κB. Type I interferons upon secretion bind to the type I IFN receptors (IFNAR) present on the target cells stimulating the expression of various interferon-stimulated genes (ISGs) which collectively counteract the viral replication. The role of STING is associated with oxidative stress like the inflammatory activation of the nervous tissue implicated in neurodegeneration.

The role of STING-TBK1-IRF signaling axis has recently been identified in NDDs. It leads to the production of type I interferons and cytokines in different neurological diseases. STING pathway may play a significant role in cellular mechanisms underlying the pathogenesis of several NDDs associated with oxidative stress response. Recent studies suggest a link between the STING pathway and microglia implicated in neurodegeneration in AD (Chen et al. 2022). In viral herpes simplex encephalitis (HSE), activation of the microglia occurs via the STING pathway which launches antiviral defense pathways owing to the production of interferons. Hence, mice lacking STING may become highly susceptible to HSV (Reinert et al. 2016). In chronic NDDs, prolonged activation of the STING pathway may lead to the induction of type I interferons that shape the microglia and accelerate the progression of the disease.

In ataxia-telangiectasia (A-T), a neurodegenerative disorder, the deficit in the DNA damage response elicited by ataxia-telangiectasia mutated (ATM) protein may lead to the induction of the cGAS-STING pathway. In Huntington's disease, an elevation of the cGAS-STING pathway has been reported in the postmortem striata of the patients (Jauhari et al. 2020). Also, in PD and ischemic stroke, an upregulation of the STING pathway has been described.

12.4.4 TLRs

Toll-like receptors (TLRs) are the transmembrane pattern recognition receptors (PRRs) that activate biochemical signals in response to various pathogen-associated molecular patterns (PAMPs). Hashimoto and colleagues in 1988 first described the role of Toll signaling in the innate immunity in *Drosophila*. Following the description of the host defense against fungal infection in *Drosophila*, the first orthologue of TLR was identified in humans that recognized lipopolysaccharide (LPS) a key component of the cell wall of gram-negative bacteria. Eventually, a family of proteins with structural similarities to *Drosophila* Toll was identified, and it was collectively referred to as TLRs. Each TLR complex can recognize PAMPs from various microorganisms based on their arrangement on the cell either in homo- or heterodimer form (Kawai and Akira 2006).

TLRs constitute the converging point for innate as well as adaptive immunity and form a focal point of immunological response in the nervous system. In the nervous system, TLRs find their expression in the neurons and the resident macrophages (Kawasaki and Kawai 2014). In the CNS of mice and humans, TLRs are expressed in a similar pattern in the neurons and microglia. However, their expression differs in the astrocytes and the oligodendrocytes (Goethals et al. 2010). In the PNS also the expression of TLRs is similar in the neurons and microglial cells. However, their expression is different in the Schwann cells that generate myelin as the oligodendrocytes. In *Drosophila*, TLRs are involved in neural system development. Studies by Zhang and the group have suggested that TLRs can also be activated without being triggered by microbial infection (Zhang and Schluesener 2006). Further, in vitro studies have suggested that TLRs, specifically TLR2 and TLR4, express on the adult neural stem/progenitor cells (NPCs), and they regulate self-renewal and cell-fate decisions associated with NPCs. Here, the studies highlight the involvement of TLRs in neurogenesis. Studies by Bsibsi et al. have reported that the expression of TLRs is upregulated in the brain during the development of lesions in MS patients. It has been observed that vesicle-localized TLRs in microglia are more common in early lesions, whereas membrane-associated expression in the astrocytes is linked with older lesions (Bsibsi et al. 2002). Transcription of the genes encoding for TLR gets altered with aging (Bsibsi et al. 2002). Studies on murine models of PD, AD, ALS, Pick's disease, and olivopontocerebellar atrophy suggested an implication of TLR signaling as evident from the upregulated expression of TLRs (Bsibsi et al. 2002).

In AD, the innate immune response is triggered leading to the activation of the glial cells which marks a key event, and the inflammatory response is mainly concentrated around the deposition sites of Aβ plaques. Pro-inflammatory cytokines, components of the complement system, and proteases are majorly delivered to the site of plaques via activated astrocytes and microglial cells. In the murine models of AD and the patients, TLR's expression is upregulated. Further, activated glial cells in AD express high levels of TLR2 and TLR4 around Aβ plaques.

A remarkable upregulation in the TLR4 transcription upon overexpression of amyloid precursor protein (APP) was described in the APP transgenic mouse model (Walter et al. 2007). In APP mice, administration of the inflammatory component lipopolysaccharide-LPS that binds with the TLR4 for 12 weeks resulted in the activation of a large number of microglial cells and astrocytes in the hippocampal and neocortex regions of the brain and aggravated the accumulation of amyloid-β (Aβ) in the neurons surrounding the activated microglia. Studies have reported that TLR4 upregulation in the neurons makes them susceptible to Aβ accumulation in AD.

12.4.5 Cell Cycle Pathways

Meticulously timed series of cellular events leading to the duplication of the genetic material forms the cell cycle. The cell cycle is broadly divided into interphase, mitosis or M phase, and cytokinesis. The advancement of the cell through the various stages of the cell cycle is stringently regulated by cell cycle checkpoints. Cyclins, cyclin-dependent kinases (CDKs), and a group of regulatory proteins facilitate the execution of the cell cycle. The neurons do not undergo mitosis. However, they can be driven into the cell division process upon misregulation of the cell cycle pathways. Such an event has been described in the degenerated neurons. Abnormal replication of the DNA may drive the neurons to mitosis; however, failure to divide may cause neurodegenerative diseases.

An elevated expression of the cell cycle components including cyclins, CDKs, and related genes has been reported in the brains of patients afflicted with various NDDs, including AD, PD, ALS, and HD. In patients with AD, CDK4, CDK5, cyclin B, and proliferating cell nuclear antigen (PCNA) have been reported to be increased (Joseph et al. 2020). S/G2/M phase markers were found to be elevated in the hippocampal regions in the brains of the patients and murine models of AD. Reentry in the cell cycle has been reported in the AD experimental models due to accumulated Aβ plaques. This reentry induces the activation of certain genes in these models. Protection from cell death induced by amyloid accumulation was the result of reentry into the cell cycle (Ippati et al. 2021). Cell cycle components are responsible for the hyperphosphorylation of Tau which culminates in the misregulation of the cell cycle pathway. Targeting of the cell cycle components such as modulation of the CDK5's abnormal activity rescued AD symptoms in the mice model.

An abnormal expression of retinoblastoma protein (Rb), PCNA, CDK2, and CDK5 has been reported in PD. Elevated levels of cyclin D1 in HD led to increased

expression of the HTT gene in the YAC-18 HD experimental model. This leads to the reentry of the neurons in the cell cycle causing reactive neuroblastomas (Manickam et al. 2020). In PD models, a misregulation of the cell cycle pathways has been shown by the neurons. An increase in CDK5 activity and expression has been reported in the PD dopaminergic neurons upon treatment with a mitochondrial toxin, MPTP. Upon pharmacological inhibition of CDK5, a reduction in the MPTP-induced dopaminergic cell loss was observed. Also, overexpression of α-synuclein resulted in enhanced expression of cyclin B (Lee et al. 2003).

12.4.6 p53

The "guardian of the genome" tumor suppressor p53 protein is encoded by the gene *TP53*. The main objective of p53 is to fortify the DNA integrity of the cell. It also plays a significant role in development, cell differentiation, and aging. p53 is a transcription factor that regulates the biological outcomes of cells depending on the stress signal input. Replication stress, oncogene activation, DNA damage, etc., are some of the stress signals that induce the activation of p53. p53 engages in the processes such as DNA repair, cell cycle arrest, apoptosis, senescence, etc. The cellular stress input signals resulting from DNA damage, telomere erosion, oxidative stress, hypoxia, and replication/translation stress trigger the sensor kinase proteins such as Chk1, Chk2, ATM, ATR, DNA-PK, and p14ARF. These sensor proteins induce the phosphorylation of p53, leading to its oligomerization, stabilization, and binding with p53 response element (p53RE). MDM2 facilitates the stabilization of p53 which is also a target of p53. This forms a negative feedback loop. Further, the transcriptional activity of p53's target genes is modulated by binding partners of p53. The multistep regulation of p53 allows it to translate the cellular stress signal to an appropriate biological outcome (Borrero and El-Deiry 2021).

In NDDs the expression of p53 remains unaltered; however, its localization is changed. p53 and its phosphorylated form remain in the nucleus in the control brains, whereas in the AD and PD brains, their localization is changed to the cytoplasm. The perturbation of p53 localization from the nucleus to cytoplasm in the neurons of NDDs may be due to the presence of p53 aggregates and destabilization of microtubule assembly in the perinuclear region of the cell. The p53 accumulation in the cytoplasm has been linked with both Tau and amyloid pathologies. Studies have suggested an interaction of p53 with Tau and presenilin 1. The expression of the genes APP, Tau, and presenilin 1 can modulate the function of p53 in experimental models of AD. Further, the loss of function of APP and presenilin 1 has been found to reduce p53 levels. The transcription of the *Presenilin 1* gene is governed by p53 in AD, whereas in PD it has been known to reduce the transcription of genes coding for Parkin and α-synuclein showing a reciprocal feedback loop (Checler and Alves da Costa 2014). In patients with HD, the levels of p53 were found to be high in the brain. Further, its expression positively correlated with the severity of clinical manifestations. In the experimental mice model of HD, $Hdh^{Q140/Q140}$, overexpression

of the gene's mutant form causes HD. Elimination of p53 in these models rescues the degeneration of the neurons and behavioral abnormalities (Ryan et al. 2006). In the PD experimental mouse model DAT-p53KO, knocking p53 out had a protective role in MPTP-mediated neurodegeneration, thus ameliorating the coordination of motor abilities (Qi et al. 2016).

12.4.7 Hippo

The key signaling pathway that controls organ size and development is the Salvador-Warts-Hippo (SWH) pathway or simply Hippo signaling. The name Hippo signaling comes from the protein kinase Hippo which is a key component of the signaling pathway. The *hpo* gene encodes for Hippo, mutations which have been reported to cause tissue tumor overgrowth. Hippo signaling has been known to be involved in cell differentiation, tissue regeneration, and mechanotransduction.

The Hippo pathway triggers the activation of mammalian sterile 20-like kinases 1 and 2 (MST1/2). This, in turn, leads to the phosphorylation and activation of two adaptor proteins, SAV1 and MOB1A/B. Following the activation of the adaptor's second core kinase of the cascade, LATS1/2 gets activated upon a change in their conformation. This change in the conformation leads to the interaction of MST1/2 with LATS, thus giving way to the phosphorylation of LATS1 and LATS2 at Thr 1079 and Thr 1041, respectively. Subsequently, Yes-associated protein (YAP) and TAZ get phosphorylated by LATS. Phosphorylation of these proteins leads to either the sequestration or degradation of YAP/TAZ in the cytoplasm and failure to translocate in the nucleus, thus rendering the YAP-dependent pro-proliferative genes inactive. When the Hippo signaling is off, unphosphorylated YAP/TAZ gets inside the nucleus and drives the transcription of genes involved in cell proliferation and survival (Zhang 2015). Although the significance of Hippo has been well known in tumorigenesis, recent studies suggest its implications in neurodegeneration.

In the distinct regions of the brains of the patients affected with AD, Hippo pathway genes were found to be downregulated. The transcription of YAP was downregulated early in the experimental AD models. A perturbed intracellular localization of YAP was observed in the brains of the patients affected with AD as well as having mild cognitive impairment (MCI) (Tanaka et al. 2020). Aβ plaques have been known to sequester YAP, thus rendering them to accumulate in the cytoplasm and fail to translocate to the nucleus. Further in the experimental models of AD, YAP was observed to be localized in the cytoplasm before the onset of the symptoms. Overexpression of YAP in this background resulted in increased nuclear YAP, thus reducing the Aβ plaques and improving the behavioral aspects (Tanaka et al. 2020).

An altered localization of YAP was also observed in the brains of the patients affected with HD. YAP was mainly found to localize in the cytoplasm in the cortical neurons of HD patients. Further, total YAP and unphosphorylated YAP were found in high levels in the striatum and cortex of HD mice model $Hdh^{Q111/Q111}$ (Mueller et al. 2018). In the neurons of the AD and HD patients, YAP's cytoplasmic

localization is linked with TEA domain (TEAD)-YAP-dependent necrosis (TRIAD) shown in different models of NDDs. TRIAD is described as the enlargement of endoplasmic reticulum owing to the presence of YAP in the cytoplasm. Overexpression of YAP can rescue this enlargement of the endoplasmic reticulum (Tanaka et al. 2020). Further, MST1 and LATS1/2, the components of Hippo signaling pathway, have been implicated in various NDDs.

In the experimental models of ALS and ALS patients, abnormally high levels of phospho-MST1 were observed in the spinal cord's motor neurons (Kovall et al. 2017). The reduction in the number of dopaminergic neurons in PD has been linked with MST1. A proapoptotic receptor belonging to the netrin family, the uncoordinated-5 homolog B receptor (UNC5B) is acted upon by the activated MST1. This leads to a reduction in the loss of dopaminergic neurons and impairment of motor abilities in the substantia nigra. Also, patients with HD showed an overexpression of MST1 in their brains (Tanaka et al. 2020).

12.4.8 TGF-β

TGF-βs or transforming growth factor receptor β comprises a superfamily of proteins, including TGF-βs, bone morphogenetic proteins (BMPs), and activins. These show a similarity in their structure and function. In mammals, three distinct isoforms of TGF-β have been reported: TGF-β1, TGF-β2 and TGF-β3. TGF-β signaling is initiated from the serine/threonine receptor complex which is a heterotrimeric transmembrane complex consisting of TGF-β type II and TGF-β type I (activin-like kinase or ALK5) receptors that bind to the ligand. Additionally, the availability of ligands is modulated by beta-glycan, TGF-β type III receptors, present on almost all the cell types, and endoglin expressed preferentially on the endothelial cell surface. SMAD 2, SMAD 3, and SMAD 4, the cytoplasmic and nuclear signal transducer proteins, mediate TGF-β signaling from the receptor complex to the nucleus. Activation of ALK5 leads to the phosphorylation of SMAD 2 and SMAD 3 proteins. This requires the aid of Smad anchor for receptor activation (SARA). Receptor-activated SMAD 2 and SMAD 3 form various heterodimers along with SMAD 4 that translocate to the nucleus to activate or suppress the transcription of TGF-β downstream target genes. TGF-β signaling plays a pleiotropic role in the regulation of multiple cellular processes.

TGF-β receptors have a poor expression in the nervous system albeit it is reported to play a role in the inflammation and repair in post-brain injury. The main source of TGF-β is astrocytes, whereas only a few selected neurons express TGF-β receptors. Studies conducted by Tesseur and the group on mice model of AD suggested that the loss of TGF-β signaling resulted in age-dependent neurodegeneration and induced the accumulation of Aβ plaques, neurofibrillary tangles (NFT) formation, and loss of dendrites. Reducing TGF-β signaling in the cultured cells resulted in neurodegeneration and elevated levels of secreted Aβ and β-secretase cleaved APP (Tesseur et al. 2006). In AD, the phosphorylation of Smad is affected leading to its

anomalous localization in the nucleus which is responsible for hyperphosphorylation of Tau. Several studies suggest an implication of TGF-β signaling in processes related to aging, diminished adaptability, and durability of tissues and organs (Tominaga and Suzuki 2019).

Other conflicting reports suggest that TGF-β signaling-related molecules are increased in the CNS of AD individuals. Here, an increased TGF-β signaling has been associated with the deposition of amyloid perturbing the brain vasculature and leading to cerebral amyloid angiopathy (CAA) observed in AD brains. Several studies contradict the role of TGF-β in neurodegenerative diseases. According to some reports, TGF-β plays a beneficial role in the onset of PD, AD, and other diseases, while other studies state the opposite. Several reports suggest a context-dependent role of TGF-β in regulating neuronal processes. In AD patients, TGF-β molecules were found to be reduced in the plasma, whereas they were observed to be increased in the cerebrospinal fluid (CSF) (Von Bernhardi et al. 2015). Controversial reports about TGF-β signaling have also been available in patients affected with Huntington's disease. TGF-β plasma levels were found to be increased in patients with Huntington's disease (Chang et al. 2015) in some of the investigations. According to other studies, blood levels of TGF-β were found to be decreased.

TβRIIΔk-Fib, a transgenic mouse model of systemic sclerosis expressing TGF-β type II receptor (TβRII) truncated form, showed an altered activity of the signaling pathway in the cortical and hippocampal neurons. A higher count of astrocytes and a reduced number of neurons were reported in these studies. Upon breeding of TβRIIΔk-Fib mice with the AD mice model, the accumulation of Aβ plaques was enhanced owing to the increased APP level, thus substantiating the paramount role of TGF-β signaling in AD. Aβ-induced impairment of cognition was improved, and the formation of Aβ plaques was diminished upon administration of TGF-β (Chen et al. 2015). Contradicting investigations suggested an elevated amyloid deposition upon overexpressing TGF-β. Studies conducted in the mice model of PD lacking TGF-β showed a significant reduction in the number of dopaminergic neurons. Such mice exhibited degeneration of the nigrostriatal system and age-related motor deficits, thus indicating a significant role of TGF-β signaling in the survival of dopaminergic neurons (Tesseur et al. 2017).

12.4.9 PI3K/AKT/mTOR

PI3K/AKT/mTOR signaling pathway is involved in regulating several cellular processes including cell survival, growth, and proliferation in eukaryotes. The pathway is responsive to the availability of nutrients, growth factors, and hormones. PI3Ks induce the phosphorylation of phosphatidylinositol 4,5 bisphosphate (PIP_2) to phosphatidylinositol 3,4,5-triphosphate (PIP_3). This in turn leads to the phosphorylation of a serine/threonine kinase Akt causing an effect on cell cycle, growth, and survival. mTOR is a serine/threonine protein kinase that is present downstream of PI3K and Akt.

Apart from roles in cell survival, motility, metabolism, cell growth, and proliferation, the PI3K/AKT/mTOR signaling pathway has been extensively studied in cancers. Its components have also been found to be altered in NDDs. In AD and PD, an upregulation of the PI3/Akt/mTOR pathway has been reported. An altered distribution of Akt and phospho-Akt was described in the AD temporal cortical neurons compared to the control neurons. An abnormal perinuclear position was described with no changes in the total Akt levels. In contrast to this, several cases of AD showed a downregulation of PI3K/AKT pathway (Curtis and Bandyopadhyay 2021). The activity of Akt pathways was investigated to be reduced in PD brains (Luo et al. 2019), and its upregulation in mice model of PD was observed to play a protective role.

In various NDDs, implications of AKT targets, mTOR, and glycogen synthase kinase-3 beta (GSK3β) have been described in various processes, including aggregation of amyloid plaques, phosphorylation of Tau, and autophagy. mTOR is activated, and GSK3β is repressed through phosphorylation by activated phospho-Akt. mTOR increases concurrently in the early stages of AD brains and AD models accompanied with a reduction in the expression of autophagy markers, thus suggesting that abnormalities in autophagy are linked with PI3K/AKT/mTOR signaling. For the phosphorylation and activation of Tau in AD brains, GSK3β is paramount. Increased Akt decreased the Tau phosphorylation. However, phosphorylated Tau was elevated in the diseased brain, thus denoting the involvement of PI3K/AKT/mTOR signaling in Tau-associated pathologies (Tramutola et al. 2015).

12.4.10 MAPK

Mitogen-activated protein kinase (MAPK) forms a superfamily that is comprised of the signaling pathways that are activated by receptor tyrosine kinases (RTKs). These pathways include c-Jun N-terminal kinase (JNK), MAPK/extracellular signal-regulated kinase 1 and 2 (ERK1/2), big MAP kinase-1 (BMK-1), and protein 38 (p38) signaling families. Upon activation of the MAPKs, the transcription factors localized in the cytoplasm or the nucleus get phosphorylated and activated. This results in the transcription and activation of genes that lead to a biological response.

MAPK plays a key role in the regulation of cognitive processes; hence it contributes immensely to the functioning of the nervous system. Directly or indirectly, MAPK facilitates the genesis of neurons and the glial cells. Also, it is involved in the proper synaptic transmission (Asih et al. 2020). JNK, ERK, and p38 are involved in the survival of striatal dopaminergic neurons and consequently govern the dopaminergic signaling. The levels of phosphorylated MAPK and ERK have been observed to be elevated in the brains of AD and PD patients compared to the control cases. An upregulation of different components of the MAPK pathway has been reported in several experimental models of AD and PD. Phosphorylated p38 has been found to be upregulated in the early stages of AD. In AD, JNK was investigated to be increased in the brain and cerebrospinal fluid (CSF), and in PD it was

found to be involved in the dopaminergic cell loss. Some of the members of the MAPK signaling co-expressed with hyperphosphorylated Tau protein aggregates, neurofibrillary tangles (NFTs), and senile plaques. The cognitive impairment associated with aggregation of Aβ plaques in experimental models of AD was significantly improved upon pharmacological or transgenic ablation of JNK, p38, and pERK (Du et al. 2019).

The deposition of Aβ plaques in AD models was significantly reduced upon downregulation of p38 linked with reduced β-secretase activity. Expression of APP has been associated with MAPK activity. Further, JNK inhibition has led to a reduction in the plaques in the cortical and hippocampal regions of the brain, decreased activity of secretase, and expression of phosphorylated APP leading to amelioration of cognitive abilities. In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced model of PD, suppression of JNK2 was found to have a protective role. Also, pharmacological suppression of JNK3 ameliorated MPTP-induced loss of dopaminergic cells. α-Synuclein in the glial cells induced the expression of JNK, p38, and ERK (Rai et al. 2019). This triggered the inflammatory response of microglia. An elevated level of JNK and phosphorylated p38 was described in the striatum of the brain of HD experimental models. Further, mutations in the huntingtin gene (HTT) led to an upregulation and activation of the MAPK cascade.

12.4.11 Notch

Notch signaling, first identified in *Drosophila*, is a highly pleiotropic evolutionarily conserved signaling system. It is involved in multiple cellular processes including, cell proliferation, cell death, cell fate determination, stem cell maintenance, etc. These processes are also implicated in proper regulation and cross-communication of the nervous system. Four Notch isoforms are found in mammals (Notch1–4), while *Drosophila* possesses a single Notch receptor, although all bear similar structural homology.

Notch is initially synthesized as a 300-kDa precursor protein. During maturation in trans-Golgi network, it is first cleaved by furin-like convertases (S1 cleavage) and results in a 180-kDa N-terminal extracellular domain (NECD) and a 120-kDa C-terminal transmembrane intracellular domain (NTM). This heterodimeric Notch receptor translocates to the cell membrane where it interacts with ligands of the DSL family (*Drosophila* Delta and Serrate (Jagged in mammals) and *C. elegans* LAG-2), and this interaction leads to second proteolytic cleavage (S2) by ADAM family of metalloproteases which is followed by an intramembranous cleavage (S3) by γ-secretase complex (presenilin, nicastrin, PEN-2, and APH-1). Notch intracellular domain (NICD) is then released from the membrane and gets translocated to the nucleus with the aid of importin α3. Within the nucleus, NICD interacts with the CSL family of transcription factors and regulates the transcription of downstream target genes such as basic helix-loop-helix (bHLH) families of transcription factor, *Enhancer of Split* [*E(spl)*] in *Drosophila*, and HES and Hey in mammals. These

bHLH transcription factors, in turn, repress *achaete-scute complex* (As-C) proneural genes (reviewed in Sachan et al. 2023). Several studies have suggested that Notch plays a paramount role in neurogenesis, neuronal maturation, and synaptic plasticity (Basak et al. 2012).

The final cleavage of the Notch receptor is mediated by the enzyme γ-secretase having presenilin as a catalytic component. Missense mutations in the presenilin gene have been reported in the pathogenesis of AD. Further, these mutations may result in the generation of neurotoxic $A\beta_{42}$ instead of normal protein $A\beta_{40}$ leading to the formation of amyloid plaques. Notch plays a pivotal role in learning and memory, neural development, and maintenance of neural stem cells. Owing to the regulatory role of Notch in neuronal plasticity, its loss results in defective long-term memory. Additionally, loss of Notch-Jagged-1 signaling results in defective spatial memory. Generating null mutation in the presenilin1 gene in mice leads to embryonic lethality accompanied with loss of neurons, critical hemorrhages in the central nervous system, and deformed skeletal structure formation. FK506-binding proteins (FKBPs) regulate protein folding and trafficking and have been identified as modulator of presenilin. Loss of FKBPs shows strong genetic interactions with Notch and further results in loss of Notch signaling targets, presenilin protein, and impaired γ-secretase activity. microRNA-124 (miR-124) expressed in the CNS regulates Notch ligand Delta. Mutations in miR-124 result in climbing defects in the flies along with reduced lifespan. The loss of Delta restores the learning defects and ameliorates the lifespan of AD flies, thus suggesting a neuroprotective role of miR-124 in AD fly models by targeting Delta ligand (Kong et al. 2015). Notch signaling is also required for the stabilization of the microtubule assembly. Mutations in Notch lead to disruption of microtubules leading to neuronal loss (Bonini et al. 2013). Further, the accumulation of Notch aggregates in plaque-like form in the brain parenchyma of AD patients led to defects in the filtration of CSF. Also, Notch signaling was found to be significantly reduced in sporadic cases of AD.

In autosomal-dominant familial and idiopathic PD, leucine-rich-repeat-kinase2 (LRRK2) has been reported as a causative agent. Further GWAS have suggested LRRK2 and SNCA/α-synuclein as risk loci for sporadic PD. Two LRRK2-binding proteins NEURL4 and HERC2 have been shown to associate physically and genetically with Notch ligand Delta-like 1 (Dll1)/Delta (Dl). PD-associated mutation in LRRK2 led to increased negative regulation of Notch by Delta via cis inhibition. This resulted in acceleration of neural stem cell differentiation, thus affecting the survival and functioning of dopaminergic neurons (Imai et al. 2015). The progressive neurodegenerative disease, spinocerebellar ataxia type 1 (SCA1) and spinocerebellar ataxia type 2 (SCA2), is characterized by expansion of the trinucleotide CAG repeat in the coding region of the *ataxin-1 (ATXN1)* and *ataxin-2 (ATXN2)* genes, respectively. Ataxin-1 is a component of Notch signaling and ataxin-2 binds with ataxin-2-binding protein 1 (A2BP1 or Rbfox1) which is a context-dependent positive regulator of Notch signaling during neurogenesis (Shukla et al. 2017). Further studies report the involvement of Su(H)/RBP-J in the pathogenesis of SCA17 (Costa et al. 2006). Hat-trick (Htk) is a component of the Su(H) activation complex that binds with Notch and leads to activation of the target genes (Singh

et al. 2019). Sreedharan and the group have reported that loss of Htk in *Drosophila* models of ALS suppresses TDP-43-mediated age-dependent neurodegeneration (Sreedharan et al. 2015). Notch target genes have been found to be increased in TDP-43-associated neurodegeneration (Zhan et al. 2015). All these studies highlight the crucial role of Notch signaling in various neurodegenerative diseases.

12.4.12 Wnt

The Wingless/Wnt pathway is primarily involved in regulating various cellular processes including cell proliferation, cell patterning, stem cell maintenance, cell differentiation, gene stability, cell migration, apoptosis, etc. These processes play a paramount role in the different developmental processes, e.g., organ development, determination of cell polarity, axis formation, gastrulation, etc. Three signaling cascades of Wnt signaling have been studied: the canonical Wnt/β-catenin pathway which is most extensively studied, the noncanonical PCP pathway, and the Wnt/calcium pathway. Perturbations in Wnt pathways are implicated in cancer, autoimmune diseases, and neurodegenerative diseases.

In a canonical pathway, Wnt ligands bind to the Frizzled (Fzd) family receptor which is a seven-pass transmembrane receptor and lipoprotein receptor-related proteins5/6 (LRP5/LR6). This leads to the recruitment of Dishevelled (Dvl) protein that in turn results in the inactivation of β-catenin destruction complex. This destruction complex is composed of axin, tumor suppressor adenomatous polyposis coli (APC), casein kinase 1 (CK1), and glycogen synthase kinase-3β (GSK-3β). The inactivation of this complex followed by the binding of Wnt ligand to the Frizzled receptor leads to the prevention of β-catenin phosphorylation and its proteasomal degradation. Consequently, β-catenin accumulates in the cytoplasm first and then moves to the nucleus where it leads to the transcription of more than 50 Wnt target genes such as *cyclin D1*, *c-myc*, *Axin 2*, metalloproteinases, PPARγ, CD44, etc., upon binding with lymphoid enhancer-binding factor 1/T-cell specific transcription factor (Lef/Tcf). These genes activated in the cascade are involved in cell survival, proliferation, neurogenesis, and inflammation (Hooper et al. 2008).

The Wnt signaling pathway plays a pivotal role during the development of the brain. It regulates neurogenesis and the development and activity of the synapse. As per various reports, the components of Wnt signaling have been observed to be altered in age-related disorders and associated with the formation of aggregates in NDDs, including AD (Folke et al. 2019). In the cortical neurons of the diseased brains, an upregulation of the Wnt receptor's extracellular ligand Dickkopf-1 (DKK1) has been reported. DKK1 negatively regulates the Wnt signaling, thus activating GSK-3β, the phosphorylating enzyme of Tau. In AD brains, expression of DKK1 was increased in the degenerating neurons. Further, this expression co-localized with NFTs and dystrophic neurites. Further, in the temporal cortex of AD patients, LRP6 expression was observed to be downregulated. This was consistent with decreased expression and inefficient translocation of β-catenin in the nucleus (Liu et al. 2014).

In several experimental models of amyloid plaque deposition and Tau pathology, an elevated expression of DKK1 was reported along with downregulated β-catenin levels. Several studies advocated the increase in amyloid deposition upon perturbation of Wnt signaling components (Rosi et al. 2010). Also, misregulation of the genes regulated by Wnt signaling has been described in the brains of PD patients (Rosi et al. 2010; Zhang et al. 2016). The perturbation of the Wnt pathway in cell regeneration and synapse formation has also been linked with dopaminergic cell loss.

Some controversial reports suggest the opposite role of the noncanonical Wnt signaling in AD where the signaling cascade prevents alterations occurring in the mitochondrial fission and fusion (Arrázola et al. 2015), an important event indispensable for the energy metabolism in neurons. The alterations of the mitochondrial structure and functions have been reported in NDDs. These alterations may include disruption of the enzymatic activities, elevated oxidative stress, and increased levels of Aβ. These studies open novel avenues of mitochondrial functioning and related cell signaling pathways in the nervous system, thus offering them as a potential therapeutic target in NDDs.

12.4.13 Myc

Myc was discovered during early studies of tumors in fulminant chickens caused by the oncogenic retrovirus resulting in the identification of v-myc oncogene which is responsible for causing myelocytomatosis (leukemia and sarcoma). v-myc was co-opted from the host genome containing c-myc or a proto-oncogenic version. Consistent alteration of myc in Burkitt lymphoma by balanced chromosomal translocation labeled it as an oncogene. Myc belongs to the family that contains MYCC (C-Myc), MYCL (L-Myc), and MYCN (N-Myc). Myc is an early response gene present downstream to various ligand-receptor complexes. Myc lies at the crossroads of multiple cell growth-promoting signaling pathways. The organization and structure of Myc family members are strikingly similar. c-myc has been found to be implicated in various developmental events including the growth of the cell. c-myc undergoes dimerization with MAX and upon binding with E-BOX (sequence 5'-CANNTG-3′) results in the transcription of genes involved in proliferation and apoptosis. The activity of c-myc is stringently connected with other signaling pathways including Ras/Raf/ERK, Ras/phosphoinositide 3-kinase (PI3K)/AKT/GSK3, and Wnt signaling (Hsieh and Dang 2016).

c-myc is related to the reentry of the neurons in the cell cycle upon onset and progression of AD and other NDDs (Marinkovic and Marinkovic 2021). Studies revealed a dysregulation of c-myc in the brains of AD and HD patients. In the brains of AD patients, a reduction in the level of n-myc was observed. Whereas the expression of c-myc was found to be affected in HD patients, no alterations in the myc protein levels have been reported in PD patients. In the hippocampal regions of the AD brains, no changes in the expression of Myc were observed. However, an abnormality in its phosphorylation status was reported. Phosphorylated c-myc was

observed in the neurons of AD, Pick's disease, and other NDDs. These neurons were found to be positive for NFT and senile plaques. c-myc's transcript levels were elevated in the brains of AD patients and murine Tg-ArcSwe AD model that overexpressed human APP characterized by perivascular and neuropil-confined plaques (Blom et al. 2011). c-myc-mediated loss of neurons from the hippocampal region and impairment of memory was observed in CaMKII-Myc transgenic mice with conditioned expression of c-myc in the neurons (Lee et al. 2009). Neuregulin 2, codified by a cell stress response gene *NDRG2* which is regulated by n-myc, was found to be elevated in the hippocampal region of AD brains. Primarily, neuregulin 2 is expressed in the astrocytes (Ichikawa et al. 2015). Knockout of *NDRG2* in the murine models of AD resulted in the downregulation of the proteasomal activity and led to worsening of AD-like phenotypes. Further, an increase in the expression of *Nrg2* resulted in elevated APP, leading to the formation of Aβ plaques (Tao et al. 2020).

12.4.14 Rho

The Rho family of GTPases regulates cytoskeletal dynamics right from embryonic development continuing throughout the entire lifetime. The Rho GTPases are implicated in various signaling pathways where they function as molecular switches, switching from the inactive GDP-bound state to the active GTP-bound state. The Rho GTPases are encoded by 20 genes. The switching from active to the non-active state is facilitated by the regulatory proteins. The GTP-bound state is mediated via guanine nucleotide exchange factors (GEFs), whereas hydrolysis of the GTP is brought about by GTPase-activating proteins (GAPs). Guanine nucleotide dissociation inhibitors (GDIs) associate with some Rho-GTPases and confine them to the cytoplasm, thus preventing their interaction with the downstream effectors. The effect of GEFs, GAPs, and GDIs on Rho-GTPases varies from cell to cell resulting in an intensive complex of regulatory mechanisms. Rac1, Cdc42, and RhoA are some of the best characterized Rho-GTPases. These GTPases regulate cytoskeletal dynamics including the formation of stress fibers and focal adhesion by RhoA, formation of lamellipodia and membrane ruffling by Rac1, and filopodial formation and actin microspikes by CDC42. Ras homolog gene family member A (RhoA) GTPases and associated downstream effector molecules modulate several signaling pathways and downstream functions. The expression of RhoA is abundant in the nervous system, and abnormal RhoA signaling has been reported in NDDs. An elevation of RhoA and Rho-associated protein kinase (ROCK) was observed in the substantia nigra of mice treated with MPTP. Inhibition of ROCK has been known to play a protective role in the MPTP-induced loss of dopaminergic neurons. This could be probably because of the abrogation of MPTP-induced microglial inflammatory response (Borrajo et al. 2014).

In the neurons generated from human stem cells carrying the *park 2* gene mutation, an elevation of Rho A signaling pathway was observed. The absence of *park 2* in these neurons resulted in a reduction of the formation of neurites and modified its migration owing to the upregulation of the RhoA cascade. A rescue in these

abnormalities was observed upon treating the neurons with Rhosin, an inhibitor of Rho A (Bogetofte et al. 2019). In the cultured neurons, treatment of the hippocampal region and dopaminergic neurons with the neurotoxic pesticide rotenone increased the Rho A signaling pathway leading to a reduction in the neurite outgrowth. This was rescued by using a ROCK inhibitor Y27632 (Sanchez et al. 2008). Rotenone was found to increase the activity of RhoA in primary mesencephalic culture from mice. Suppressing RhoA by C3 transferase or simvastatin rescued the dopaminergic loss caused by rotenone (Mattii et al. 2019). In these studies, RhoA has been presented as a therapeutic target to prevent neuritic and axonal degeneration, an early feature of PD (Gcwensa et al. 2021).

The dopaminergic neurons MN9D, derived from the fusion of embryonic ventral mesencephalic and neuroblastoma cells, showed suppression of α-synuclein due to reduction in the serum response factor (SRF), a ubiquitous nuclear transcription factor, upon inhibition of RhoA (Zhou et al. 2011). Inhibition of RhoA in PC12 pheochromocytoma-derived cells and dopaminergic neurons by microRNA miR-133b reduced the axonal degeneration caused by MPTP-induced elevation of α-synuclein. The microRNA miR-133b plays an important role in the maturation and function of dopaminergic neurons of the midbrain within a negative feedback loop. Inhibition of ROCK by a ROCK inhibitor Fasudil decreased the accumulation of α-synuclein in a transgenic murine model of PD harboring A53T mutation expressing human α-synuclein. This improved the motor and cognitive abilities (Tatenhorst et al. 2016). Also, overexpression of A53T mutation in SH-SY5Y neuroblastoma-derived cells induced aggregation of α-synuclein which was cleared by Fasudil by triggering the activation of the JNK/Bcl-2/Beclin 1/Vps34 pathway leading to induction of autophagy (Liu et al. 2016). Rho also facilitates α-synuclein-induced reactive oxygen species (ROS) generation mediated by integrin CD11b in the microglia. Here, Rho involves nicotinamide adenine dinucleotide phosphate [NADPH] oxidase (NOX). Rescue in the abnormal mitochondrial fission and apoptosis induced by dynamin-related protein 1 (Drp1) was observed upon treatment with Y27632 in MPTP-treated PC12 cells and an MPTP murine model (Zhang et al. 2019). In recent studies, it has been demonstrated that abrogation of ROCK resulted in increased recruitment of Parkin to the damaged mitochondria, thus enhancing the removal of defective mitochondria from the cells (Moskal et al. 2020; Zhang et al. 2019). In rats, dopaminergic lesions induced by using 6-hydroxydopamine resulted in L-DOPA-induced dyskinesias (LID). This situation also led to increased levels of RhoA/ROCK expression. Treatment with Fasudil reduced L-DOPA-induced dyskinesia. RhoA can be targeted to develop new therapeutic strategies for more advanced stages of the disease (Lopez-Lopez et al. 2020).

12.5 Concluding Remarks

Disabilities associated with the decline in motor and cognitive abilities due to the loss of neurons in NDDs pose a social, financial, and enormous psychological burden on individuals and families affected by these debilitating conditions. Research conducted to study the pathogenesis of these diseases has led to the unraveling of various mechanisms that cause the degeneration of the neurons and their subsequent death leading to impairment of the physical and cognitive abilities. However, the complex processes leading to the NDDs are far from being fully elucidated. NDDs are mainly characterized by the death of the neurons. Identification of intracellular mechanisms that cause neuronal death may help to slow down or obstruct the event. Recently, several signaling transduction pathways have been identified to function in the nervous system which has assisted in unraveling the mechanism resulting in neurodegeneration (Table 12.2). The intra- and intercellular signaling pathways were identified as eminent players of pathogenesis. Alterations in the components of these pathways including the effectors and the target gene activation have been reported in the progression of NDDs as well as in the initiation of these abnormalities. The presence of extensive and vast levels of crosstalks among these signaling pathways poses a major challenge to identifying the molecular causes underlying the pathogenicity of NDDs. Recent studies in this field have certainly expanded our knowledge about the various cell signaling pathways implicated in neurodegeneration. Identification of these pathways and the points of intersection in this vast hypernetwork of crosstalk may open avenues to study in detail the role of these cascades in the pathogenesis of NDDs and will help advance the therapeutic approaches to treat neurodegeneration.

Emerging technologies such as single-cell genomics and advanced imaging techniques hold the potential to provide deeper insights into the molecular mechanisms driving neurodegeneration. Future research with the help of recently invented sophisticated technologies to explore the involvement of signaling pathways and molecular mechanism of their function in different disease conditions will advance the search for therapies of neurodegenerative diseases targeting cell signaling pathways.

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Table 12.2 Major signaling pathways, their function, and implications in neurodegenerative diseases

Signaling pathway	Function	Pathogenic mechanisms and manifestation in neurodegenerative diseases
Sirtuin	Mitochondrial biogenesis (respond to changes in NAD+ levels)	Downregulation of sirtuin results in AD
NRF2 signaling	Redox balance and antioxidant-related activities, metabolic reprogramming	Altered localization of Nrf2 observed in PD in response to oxidative stress. Perturbed expression observed in the hippocampal and cortical regions of the brain along with the aggregation of Aβ plaques
c-GAS/ STING signaling	Role in innate immunity	Associated with oxidative stress response in neurodegenerative diseases including AD, HSE, AT, HTT, and PD
TLR signaling	Role in innate and adaptive immunity, neural system development	Expression in microglial cells. Perturbed expression of TLR correlates with lesions in MS patients, formation of Aβ aggregates, and neurofibrillary tangles in AD patients
Cell cycle pathways	Regulation of cell cycle via triggering the activation of CDKs, cyclins, and other components	Hyperphosphorylation of Tau, reentry of neurons in the cell cycle in AD, abnormal expression of Rb, PCNA, CDK2 and CDK5 in PD
p53	Tumor suppressor	Altered localization in tau and amyloid pathologies. Higher p53 observed in HD
Hippo signaling	Cell proliferation and survival	Mild cognitive impairment in AD models, also implicated in HD and ALS
TGF-β signaling	Role in cell cycle regulation, functions as bone morphogenetic protein and activin	Involved in age-dependent neurodegeneration, deposition of amyloid in AD, and degeneration of dopaminergic neurons in PD
PI3-AKT/ mTOR signaling	Role in cell survival, growth, and proliferation	Aggregation of amyloid plaques, phosphorylation of Tau, autophagy in PD
MAPK signaling	Implicated in cell proliferation, survival, and growth	Perturbed expression of MAPK has been observed in CSF, dopaminergic cell loss in PD, hyperphosphorylated Tau, NFTs, senile plaques in AD
Notch signaling	Cell fate determination, cell proliferation, cell death, stem cell maintenance	Loss of neurons, hemorrhages, and deformation in skeletal formation. Implicated in sporadic cases of AD, autosomal dominant familial and idiopathic PD, SCA1, SCA2, and ALS
Wnt signaling	Cell proliferation, cell patterning, stem cell maintenance, cell migration	Aggregate formation in AD. Involved in neurogenesis
Myc pathway	Cell proliferation	Induces reentry of neurons in the cell cycle in neurodegenerative diseases. Perturbed expression observed in AD, Picks disease, loss of neurons, and impairment of memory
Rho pathway	Cytoskeletal dynamics and molecular switches	An increase in the Rho A signaling pathway leads to a reduction in the neurite outgrowth

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Chapter 13
An Overview of Imaging Techniques for Diagnosis of Debilitating Neurodegenerative Diseases

Kamlesh Kumar, Tannu Rachna Dahiya, Janvi Aggarwal, and Narender K. Dhania

Abstract Neurodegenerative diseases (NDDs) are the leading cause of physical and cognitive disabilities across the globe and affecting approximately 50 million people worldwide. Till date, despite significant understanding about the mechanisms involved in the disease, none of the treatment regimens have been proved to prevent or suppress it.

Neuroimaging has revolutionized the understanding of brain function and its abnormality and has become an essential tool for researchers and clinicians to study neurodegenerative disorders. By visualizing brain structures with the available advanced sophisticated neuroimaging techniques, one can understand how different regions of the brain are involved in various cognitive and behavioral processes. Neuroimaging techniques are crucial in studying the state of NDDs, and designing of drugs according to the need of individual patient might be one of the biggest breakthroughs in the field of the disease.

A comprehensive overview of the neuroimaging techniques along with their importance and impact in the key NDDs has been enlisted in the present chapter.

Keywords Neuroimaging · Radiology · Diagnostics · Radiofrequency · Hemodynamic

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13.1 Introduction

The acquisition of data holds a pivotal role in disease diagnostics, facilitating healthcare providers in collecting, analyzing, and interpreting pertinent information for precise diagnosis and optimal patient management. Among other imaging methodologies, neuroimaging emerges as a distinctive tool, offering medical professionals and researchers unparalleled access to explore and comprehend the intricate mechanisms underlying neurodegenerative diseases. It enables the investigation of inner workings of the brain, revealing variations in blood flow across its different regions and aiding in pinpointing specific location of various diseases. Neuroimaging was first introduced in the field of medicine during late nineteenth century with the growing interest in human circulation balance. The inventions that followed, including X-ray, cerebral angiography, magnetoencephalography, positron emission tomography/single-photon emission tomography (PET/SPECT) scans and xenon computed tomography (CT) scanning, etc., increased the utilization manifolds with functions like identification, tracking, monitoring progress of vital biomarkers, and even in treatment of neurological disorders.

Owing to the prevalent occurrence and disabling consequences of neurodegenerative diseases (NDDs) like Alzheimer's (AD), Huntington's disease (HD), Parkinson's (PD), and others, it has become a sizeable burden for individuals, their families, and healthcare systems worldwide. Diagnosing NDDs today is easily achieved through readily available neuroimaging tools; earlier the diagnosis relied on medical history, clinical assessment, and neurological examinations. This previous approach entailed numerous shortcomings such as the subjective nature of clinical observations, hampering accuracy of the diagnosis. NDDs' clinical symptoms such as motor symptoms in PD or memory loss in AD are often devoid of any specificity. Additionally there are chances of overlapping conditions that could lead to delayed or misdiagnosis. During the initial stages of NDDs where there are only subtle or nonspecific symptoms, an early detection method is a crucial challenge. PET and MRI are some of the neuroimaging techniques that have tackled the challenge of early detection through visualization of the brain to trace any subtle pathological changes and facilitate the identification of NDDs at its initial stages when treatments could be more effective.

Neuroimaging tools are also used to identify neurodegenerative areas by analyzing specific markers for therapeutic trials. These tools can screen individuals that are at the higher risk for targeting their pathological sites, and therapeutic agents can be administered for primary and secondary therapeutic trials. Without neuroimaging tools, assessment of disease progression as well as monitoring individual's response to the treatment in NDDs was problematic. Tracking the structural changes in the brain and its functionality could not be achieved by using clinical evaluations alone. MRI and other neuroimaging techniques facilitate for valuable insights into progression of disease through detection of moderation in the brain volume, atrophy, and aggregation of pathological markers. This helps clinicians to gauge severity of disease, adjust treatment approach, and evaluate effectiveness of intervention.

Neurodegenerative disorders are most commonly screened using CT and MRI where mild to moderate structural changes like mild abnormalities in PD are detected using CT. On the other hand, MRI plays a crucial role in diagnosing numerous degenerative illnesses related to the central nervous system. In comparison to CT, MRI is superior in visualizing several cerebral abnormalities such as periventricular white matter pertaining to dementia. The lack of neuroimaging biomarkers leads to heavy reliance on clinical diagnosis of NDDs that lacked sensitivity and specificity. Neuroimaging biomarkers, such as β-amyloid imaging in AD or dopamine transporter imaging in PD, provide objective measures of underlying pathological changes, enhancing diagnostic accuracy and prognostic assessment (Oh et al. 2021). Additionally, technologies such as positron emission tomography (PET) and single-photon emission tomography (SPECT) contribute significantly in diagnosis by detecting potential pathophysiological brain changes and demonstrating early stages of cognitive impairment. Both PET and SPECT enable the analysis of topographic brain function and the identification of cognitive domain impairments. PET imaging detects β-amyloid deposition in AD, while MRI reveals characteristic brain atrophy patterns in different NDDs. This improved understanding has facilitated the development of targeted therapies and interventions tailored to underlying pathological mechanisms of each disorder. One recent scientific advancement in neuroimaging involves the development of ultrahigh-field MRI technology. At lower field strength like 1.5T or 3T, ultrahigh-field MRI scanner or operating at 7 Tesla provides superior spatial resolution and sensitivity, as compared to MRI system (Kraff et al. 2015). Moreover, these technologies promote the investigation of brain function and connectivity with accuracy. In addition to this, AI algorithms can analyze neuroimaging data to identify patterns and biomarkers associated with neurological disorders, such as in AD and PD. By leveraging machine learning and deep learning techniques, AI models can learn from large data sets of neuroimaging scans to detect subtle abnormalities and predict disease progression with high accuracy. In clinical settings, AI-powered decision support systems are being developed to assist radiologists and neurologists in interpreting neuroimaging findings and making accurate diagnoses.

These systems provide automated image analysis, treatment recommendations, and quantitative measurements that are personalized based on clinical history and individual day-to-day monitoring. Visual images of certain disease related changes in the brain especially for NDDs pathology are accessible through these collective tools. In case of cognitive disorders, molecular imaging acquisition facilitates a unique diagnostic perspective with objective measures of brain function, structure, and pathology. Certainly, neuroimaging tools have transformed the management and diagnosis of NDDs by addressing many limitations faced earlier. The mild to moderate changes and abnormalities in the brain of individuals suffering from neurodegenerative diseases can now be explored using these methods. The primary significance of neuroimaging tools in NDDs is to identify optimal markers for therapeutic targets by checking and treating patients with selective drugs. In this chapter, we have discussed various imaging techniques utilized to monitor neurodegenerative diseases, including MRI, CT, PET, SPECT, electroencephalography (EEG),

magnetoencephalography (MEG), magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), HD-transcranial electrical stimulation (HD-tES), and high-resolution magnetic resonance imaging (HRMRI).

13.2 Computed Tomography (CT)

CT is a radio technique of imaging, but it serves different purposes and provides distinct types of information about the body's structure and function. The first viable commercial CT scanner was discovered by Godfrey Hounsfield in 1967, and the first brain scanning of a patient was done at Atkinson Morley Hospital in Wimbledon, England, in 1971 (Lameka et al. 2016). It offers unique advantages and is employed in different clinical and research contexts. The principle of CT involves the use of X-rays to create detailed cross-sectional images of the body. The technique is based on principles of X-ray absorption and mathematical algorithms for image reconstruction. A CT scanner uses an X-ray tube to emit a focused beam of radiation through a patient lying on a movable table. The X-rays pass through the body and are absorbed differently by various tissues, with bones absorbing more than muscles (Fig. 13.1). The X-ray tube is positioned opposite the detector array for optimal alignment. More dense tissues like bones appear white during scanning in CT, and less dense tissues, such as muscles and organs, absorb more X-rays during scanning and appear darker (Fig. 13.1). During scanning, the detector array and X-ray tube rotate around the patient several times. The detector records the amount of intensity of X-ray that passes through the body during scanning and plotting data. Advanced mathematical algorithms, such as filtered back projection or reconstruction, are used to convert the collected data into detailed, two-dimensional images called slices. The reconstructed images consist of pixels, which are individual picture elements. Each pixel corresponds to a specific area in the scanned cross section. The stack of slices creates three-dimensional voxel (volume pixel) representation of the imaged anatomy. The final CT images can be displayed on a computer monitor, providing a detailed view of internal structures with high contrast and spatial resolution. Radiologists interpret these images to diagnose and assess various medical conditions. In some cases, contrast agents, often containing iodine, may be injected into the bloodstream to enhance the visibility of blood vessels and certain tissues for additional information about vascular structures and abnormalities. CT is widely used in medical imaging due to its ability to visualize a wide range of anatomical structures in various parts of the body. It is particularly valuable for detecting and diagnosing conditions such as infections and vascular abnormalities in NDDs. The rapid acquisition of high-resolution images makes CT a versatile tool in both diagnostic and interventional radiology (Shan et al. 2014).

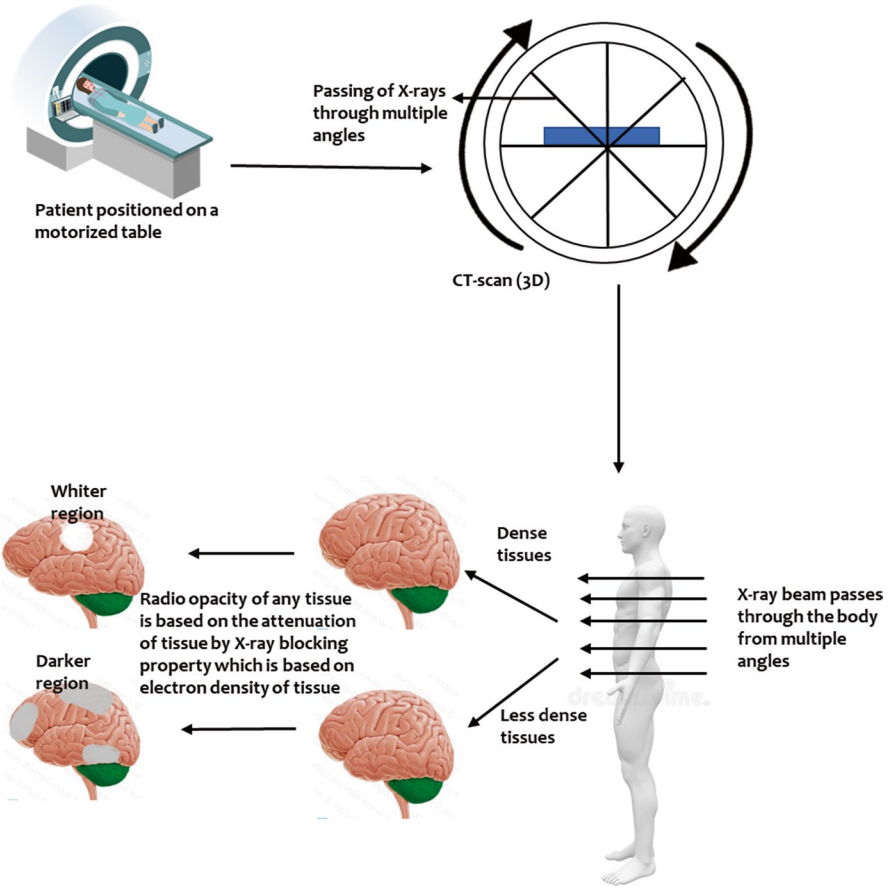

Fig. 13.1 Schematic of CT depicting the use of X-rays to create detailed cross-sectional images of the body, showing X-ray absorption and thereby obtaining the scanned images of the brain based on the attenuation property of X-rays

13.2.1 CT Application

- CT is often the imaging modality of choice in cases of head trauma and suspected traumatic brain injury (TBI). It can quickly identify fractures, hemorrhages, contusions, and other traumatic lesions. This helps in assessing the severity of the injury and guiding appropriate medical intervention. Computed tomography angiography (CTA) is a specialized form of CT that visualizes the blood vessels. It is used to identify conditions such as ischemic strokes (due to blood clots) or hemorrhagic strokes (caused by bleeding). It is also used for detection of vascular abnormalities like aneurysms or arteriovenous malformations (AVMs) (Wong et al. 2002; Parsey and Mann 2003).

- CT is used in the identification of structural changes in the brain associated with infections, abscesses, or inflammatory conditions. It helps visualize changes in brain tissue density, ventricular enlargement, and presence of abnormal fluid collections.
- CT is an effective tool in imaging bones of the skull and cranial base. It helps in identifying fractures or congenital abnormalities that may contribute to certain neurological conditions (Jacobs et al. 2012).

13.2.2 Limitation of CT

CT scans are invaluable in medical imaging for their ability to produce detailed cross-sectional images of internal body structures. But there are limitations: the first limitation is the concern regarding exposure, since CT scans use ionizing radiation, which poses as a minute risk of tumor, especially with frequent high-dose scans. Even though dose reduction techniques have only advanced the cumulative radiation exposure, still it poses a threat especially for young individuals. Second, CT scans cannot offer a high contrast for soft tissues as compared to dense structures and bones and thus are unable to distinguish particular abnormalities. Small lesions and low contrast differences cannot be detected in CT; hence thorough assessment requires supplementary imaging and tests. Additionally, the contrast agents used in CT scans may lead to allergic reactions or other negative effects, especially in case of patients with hypersensitivity and kidney issues. The image quality can be compromised because of patient motion or malfunctioning equipment leading to misinterpretation of reports. CT scans are expensive which is another added financial concern. Furthermore, the lack of metabolic or functional data in CT scans necessitates other modalities for a comprehensive evaluation. Despite the above limitations, CT scans are crucial tools in diagnostics, and current technological advancements further attempt to mitigate these limitations.

13.3 Positron Emission Tomography (PET)

PET is a radio technique which provides information regarding physiological processes at the cellular and molecular levels of the body. In this technique a radioactive tracer (radioactive material that gets introduced into the body) emits positrons which help measure and visualize metabolic activity. The radioactive compound encounters positron emission once it binds with a biologically active molecule (Fig. 13.2). Before encountering an electron, a positron travels a small distance within the tissue. This causes disintegration resulting in emitting two gamma-ray photons that travel in polar directions (Fig. 13.2). The time and location of each gamma-ray event are detected by the specialized detector. The PET system detects coincident events and simultaneously traveling gamma-ray photons in polar

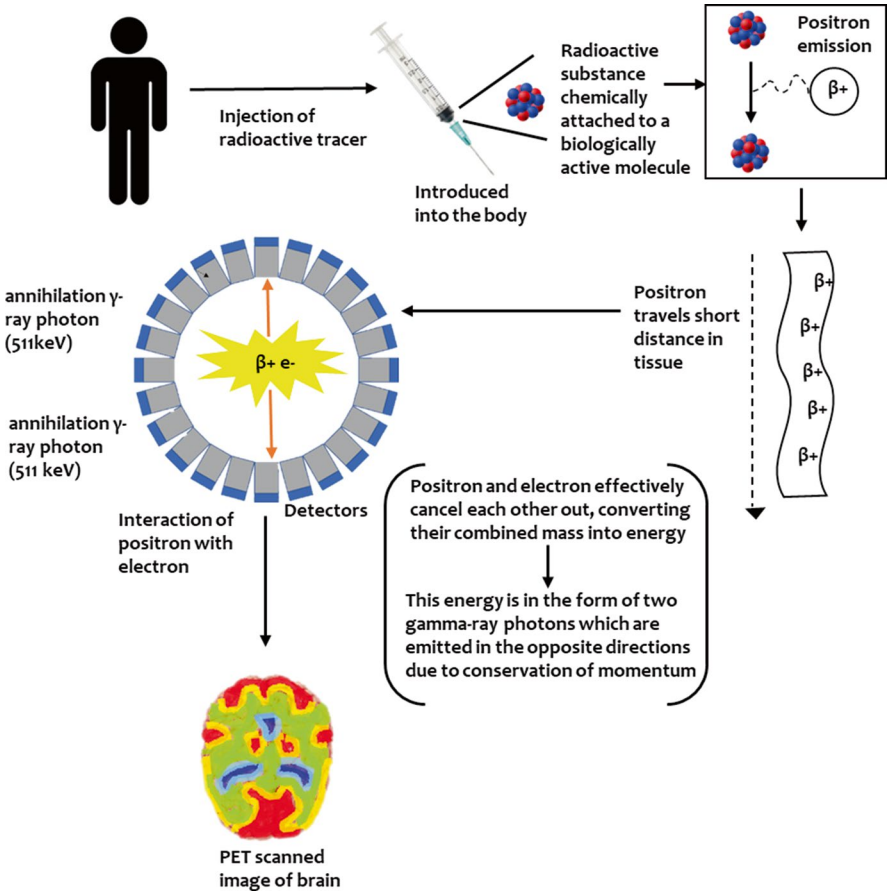

Fig. 13.2 Diagrammatic representation of PET showing the use of a radioactive tracer, which emits positrons and subsequently resulting in annihilation of γ-ray photon upon the interaction of positron and electron which upon detection finally generate a scanned image of the brain

directions (Fig. 13.2). The annihilation occurrence is found using data through an established line of response. The collected data of coincidental events are processed using mathematical algorithms, and the images are then reconstructed to depict the concentration and distribution of radiotracers within the body. Rather than the anatomical structure, these images represent functional and metabolic activity. The PET signal intensities of different areas of reconstructed images correlate with the concentration of the radiotracer (King et al. 2002). Higher metabolic activity or physiological processes within the tissue are represented via increased intensity of the radiotracer uptake. Magnetic resonance imaging (MRI) or computed tomography (CT) is frequently added to the PET images. This correlation facilitates a holistic understanding of both structural and functional aspects. PET applications help assess neurological conditions and evaluates myocardial perfusion which is

especially useful in a clinical range of cancer staging. In academic research, PET imaging of brain functions is inspected to monitor molecular processes and to regulate the impact of therapeutic interventions. The choice of radioactive is determined by the half-life, which examines longer-lived substances in the body. Radiotracers with short half-lives might require on-site cyclotron facilities for production with limited availability, whereas longer half-life radiotracers may be distrusted to multiple sites (Pecorale et al. 2024). Overall, PET provides valuable information on the physiological and metabolic processes within the body, making it a powerful tool in clinical diagnostics and medical research. The combination of functional and anatomical information contributes to a more comprehensive understanding of various diseases and conditions.

13.3.1 Application of PET

- PET measures the uptake of radiolabeled glucose analogs, such as fluoro-deoxyglucose (FDG), to assess cerebral glucose metabolism. Changes in glucose metabolism can indicate altered neural activity. PET scans can help identify regions of hypo- or hypermetabolism, offering valuable information for conditions like Alzheimer's disease or epilepsy (Herholz and Heiss 2004).
- PET is useful to study specific neurotransmitter systems in the brain. Tracers targeting receptors for neurotransmitters like dopamine, serotonin, and others provide insights into the functioning of these systems. This is particularly relevant in psychiatric disorders where neurotransmitter imbalances are implicated (Kraff et al. 2015).
- PET can assess brain function and detects changes associated with Alzheimer's disease. FDG-PET can reveal patterns of glucose metabolism alteration, thereby helping in the early diagnosis and differentiation of various types of dementia.
- PET investigates psychiatry in the neurobiology of various psychiatric conditions. For example, it can assess dopamine receptor binding in schizophrenia, serotonin transporter levels in depression, or regional cerebral blood flow changes in mood disorders.
- Using tracers like $H_2{}^{15}O$ (15O isotope of oxygen), PET can assess cerebral blood flow and perfusion, providing information about vascular function and identifying areas of compromised blood supply. Tracers targeting specific molecular markers associated with neuroinflammation or infection can be used to visualize inflammatory processes or infectious lesions in the brain (Hooker and Carson 2019).
- PET is a valuable tool for monitoring response to therapeutic interventions. Changes in metabolic activity or receptor binding seen in follow-up PET scans can indicate treatment efficacy or need for adjustments in the management plan.
- PET is extensively used in research to investigate novel biomarkers, understand disease mechanisms, and assess potential therapeutic targets. It also plays a role in clinical trials for evaluating the effects of new treatments. Combining PET

with other imaging modalities such as CT or MRI provides a comprehensive understanding of both structural and functional aspects of brain disorders.

13.3.2 Limitations of PET

PET is a valuable neuroimaging technique utilized in diagnosing and assessing various brain pathologies. However, it presents inherent limitations necessitating careful consideration during result interpretation and clinical decision-making. Specifically, PET exhibits lower spatial resolution compared to MRI, impeding precise localization of cerebral lesions or anomalies (Pichler et al. 2008). Furthermore, its temporal resolution is inferior to EEG, restricting its capacity to capture rapid alterations in brain activity. PET scans necessitate radioactive tracer administration, posing infrastructural challenges in tracer production and handling, thereby limiting accessibility in certain healthcare settings. Ionizing radiation exposure is inherent in PET due to tracer usage, warranting caution, particularly in vulnerable patient cohorts. The high cost associated with PET scans, inclusive of tracer production, renders them less accessible for routine screenings or in resource-constrained regions. The efficacy of PET hinges upon the availability of specific tracers targeting pertinent physiological or biochemical processes, potentially restricting its utility in certain pathologies lacking established tracers. Dynamic alterations in metabolism, blood flow, or receptor binding in brain disorders may not be fully captured by PET, offering only a snapshot of the condition during imaging. Integrating PET images with anatomical data from CT or MRI enhances diagnostic accuracy; however, challenges in co-registration may affect precise lesion localization.

13.4 Single-Photon Emission Computed Tomography (SPECT)

SPECT is an imaging technique based on nuclear medicine tracer and tomographic reconstruction methods. SPECT works on how blood flows through different tissues to organs. Similarities in PET and SPECT are that both imaging techniques functionally analyze the information about patients. The principle of SPECT works on single-photon radioactive substance in the body that emits energy by analyzing the event in detectors by rotating the detectors around the body. A computer is used to create a three-dimensional image (tomogram) of the radioactivity detected. The tracer will emit gamma rays that can be detected by the scanner. The computer collects the information emitted by the gamma rays and translates them into 2D cross sections. These cross sections can be added back together to form a 3D image. The radioisotopes generally used in SPECT to label tracers are iodine-123(^{123}I),

technetium-99 m (^{99m}TC), xenon-133 (^{133}Xe), thallium-201(^{201}Tl), and fluorine-18 (^{18}F) (Crișan et al. 2022). The distribution of radioactive-labeled pharmaceuticals is allocated in the different organs and tissue types in patients depending on the biodistribution properties of the radiopharmaceutical (Crișan et al. 2022). In SPECT, emitting γ-ray photons are labeled with radionuclides (nucleus of the atom is unstable), where an imaging device is a lead collimator associated with scintillation camera. This system permits photons to guide through a large-area scintillator (commonly NaI (Tl) crystal) that converts energy of γ-ray photons to lower-energy photons which are in turn converted to electric signals by photomultiplier tubes (PMTs). These signals of PMTs form a cluster that is regulated by electronic circuitry to reflect the information about the position at which a photon interacts with the crystal. The radiopharmaceutical taken up shows different views around the patient and exhibits 3D image picture into 2D and reconstruction image from multiple projections.

13.4.1 Application and Limitation

SPECT is a nuclear medicine technique which offers the analysis of perfusion abnormalities, including the brain and detecting the radiotracer distribution in the body. Diagnosing of NDDs by SPECT exhibits lower spatial resolution as compared to MRI or CT (Belhocine et al. 2008). It provides lack of information about anatomical and functional information and contributes low detecting rate of change in physiological activity. Moreover, the application of SPECT is limiting to availability of radiotracer as this technique relies on the well-established tracers. Involvement of radiotracers radiation has become a concern to the patients as the exposure of radio doses typically deemed safe. Moreover, SPECT provides the challenging information about the perfusion abnormalities and distinct information about the brain lesions or benign/malignant conditions. Applications of SPECT technique are a is valuable tool for scanning perfusion abnormalities, and evaluating brain function in certain neurological and psychiatric disorders (Adak et al. 2012; Czernin et al. 2017).

13.5 Functional Magnetic Resonance Imaging (fMRI)

fMRI is most widely used neuroimaging technique discovered by Seiji Ogawa in 1990 and is a noninvasive method to examine the brain's neuronal activity and connections (Hooker and Carson 2019). The key role of fMRI is to exclude brain lesions, identify the pattern of atrophy, and evaluate vascular burden. fMRI helps plot brain activity by detecting variations in the blood flow and oxygenation of the blood (Stahl et al. 1986). This technique is based on the fact that cerebral blood flow and neuronal activation are dependent on each other. The blood flow in a particular

area of the brain rises when it is being used. fMRI is particularly valuable for investigation of the cognitive processes, such as perception, memory, and decision-making. fMRI works on the principles of nuclear magnetic resonance (NMR) to measure changes in blood flow and oxygenation levels in the brain (Homer 1975). He fMRI technique utilizes both the magnetic field and radio waves. In fMRI, the MRI scanner produces a strong magnetic field. It is well documented that 70–80% of weight of the body consists of water, the presence of H^+ protons is randomly distributed in the body, and when the external magnetic field is applied to the body, all H^+ protons are aligned along with the axis of the applied magnetic vector (Schenck 1996). This magnetic field aligns the protons (hydrogen nuclei) of the water molecules in the body, particularly in the brain (Fig. 13.3). Radiofrequency (RF) pulses are applied to particular parts of the body with the alignment of H^+ excited protons in a new direction. These pulses temporarily disrupt the alignment of protons, letting them move out of their equilibrium state. After the RF pulse is turned off, the protons gradually align in the axis of the magnetic vector, a process known as relaxation. There are two types of relaxation processes involved during the course used for the realigning of protons with the external magnetic field (Fig. 13.3). The protons lose phase coherence due to interactions with each other. A relaxed proton emits signals and returns to its equilibrium state which is detected by an MRI scanner. These emitted signals provide information about the tissue properties and its characteristics. fMRI is based on the blood oxygen level-dependent (BOLD) contrast. Any remodeling in neural activity alters blood flow and oxygenation that leads to change in magnetic properties of the surrounding tissue that also affects signals in scanning MRI. By providing gradient magnetic field, the MRI can scan the detailed images of the brain. Variations in BOLD signals can detect and identify regions of the brain associated with specific activities or neural processes. When a specific part of the brain becomes more active, the blood flow in that region increases. Indirectly, the BOLD signal is used to measure changes in the neural activity of the brain by sensing alterations in blood flow and oxygenation levels (Mielke and Heiss 1998). Neural activity triggers an increased demand for oxygen and nutrients to support the metabolic needs of active neurons, resulting in heightened oxygen consumption during firing and signaling processes (Phelps et al. 1982). This increased activity elicits subsequent changes in blood flow, known as the hemodynamic response, wherein the brain's vascular system delivers more oxygenated blood to the active region (Yablonskiy et al. 2013). The BOLD signal utilized in fMRI relies on distinct magnetic properties of oxygenated and deoxygenated hemoglobin, with deoxyhemoglobin exhibiting paramagnetic properties that affect local magnetic resonance signal (Yablonskiy et al. 2013). Functional activation maps generated from the BOLD signal highlight brain areas undergoing activity changes during specific experimental conditions, aiding in the identification of regions involved in cognitive processes (Mielke and Heiss 1998). The temporal resolution of the BOLD signal is slower compared to direct measures of neural activity such as EEG or MEG, typically peaking a few seconds after the onset of neural activity and lasting for several seconds. Resting-state fMRI utilizes the BOLD signal to examine spontaneous fluctuations in brain activity, revealing

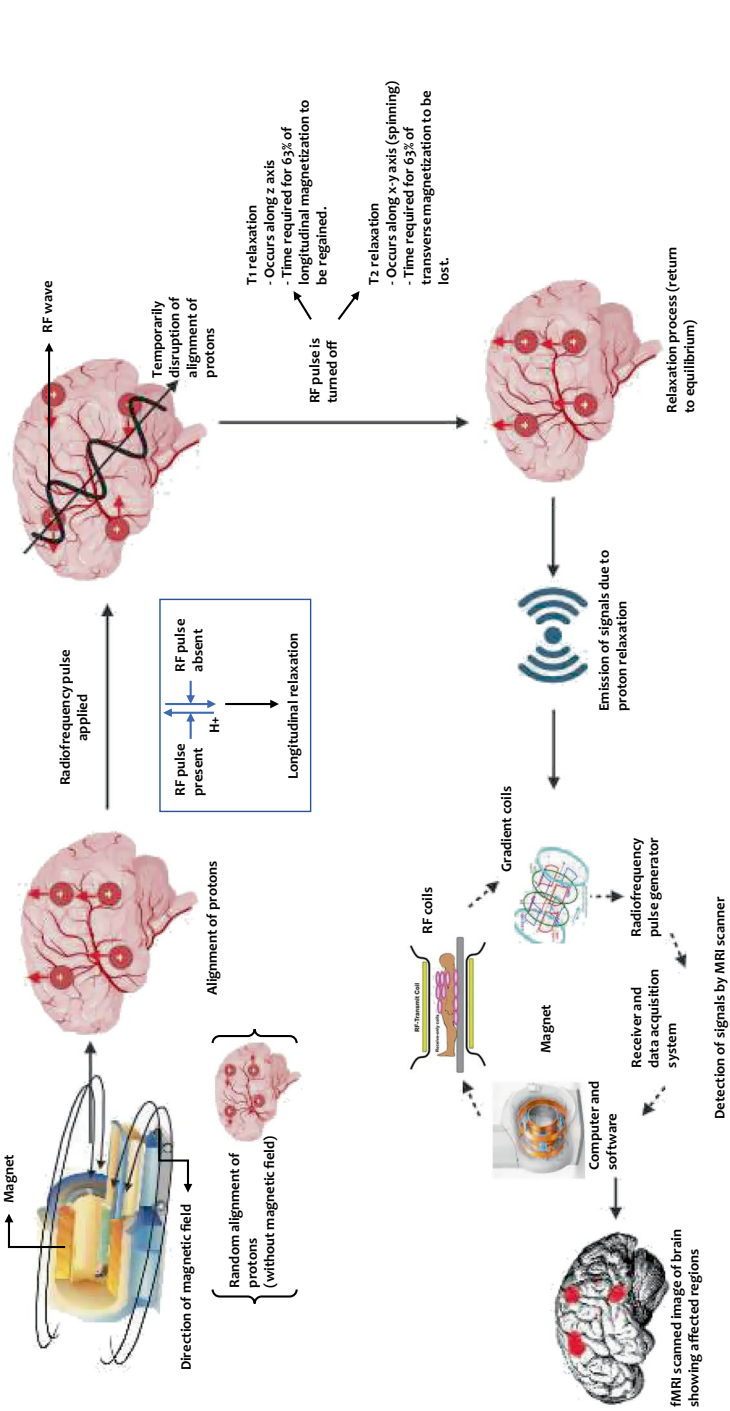

Fig. 13.3 Representation of fMRI principle of nuclear magnetic resonance to measure changes in blood flow and oxygenation levels in the brain. Here, it is shown how magnetic field and radio waves are utilized in the fMRI technique and detection of signals by MRI scanner

patterns of connectivity and functional networks without a specific task (Mielke and Heiss 1998). It is essential to interpret BOLD fMRI results cautiously, recognizing that the signal reflects a correlation between neural activity, changes in blood flow, and oxygenation, rather than a direct measure of neural firing. Researchers and clinicians must consider the intricate relationship between neural activity and the hemodynamic response when interpreting BOLD fMRI data.

13.5.1 Applications of fMRI

fMRI is one of the widely used radio techniques both in the area of clinic and research. In clinical applications, it can be used to identify abnormalities in brain function related to conditions such as Alzheimer's disease, schizophrenia, and other neurological disorders. It captures real-time changes in brain activity and is therefore a valuable tool for both research and clinical applications. The following are the key fMRI applications to understand brain disorders:

- fMRI is not typically used as a stand-alone diagnostic tool; it provides valuable insights into brain function and connectivity. MRI is used to map brain function by identifying regions that are activated during specific cognitive tasks. This mapping helps researchers and clinicians to analyze localization of cognitive functions, such as language, memory, and motor control. In the assessment of cognitive disorders, fMRI can be employed to study patterns of brain activation related to cognitive processes. It helps in identifying abnormalities or alterations in brain function associated with conditions like Alzheimer's disease, dementia, or attention disorders (Dickerson and Sperling 2009).
- fMRI can be utilized in the localization of epileptic foci in individuals with epilepsy. By analyzing brain activity during seizures or interictal periods, fMRI can help identify specific regions responsible for seizure initiation, aiding in surgical planning. In neurosurgery, fMRI plays a role in presurgical planning. By mapping functional areas of the brain, surgeons can avoid damaging critical regions involved in motor control, language, and sensory functions during procedures such as epilepsy surgery. Resting-state fMRI is used to investigate functional connectivity between different brain regions. Alterations in connectivity patterns can be indicative of various brain disorders, including schizophrenia, autism spectrum disorders, and mood disorders (Parsey and Mann 2003).
- fMRI is helpful to study psychiatric disorders, providing insights into the neural basis of conditions such as depression, anxiety, and schizophrenia. fMRI also detects traumatic brain injury by identifying its functional changes in the brain and its connectivity associated with disorders and also helps in classifying the individual with multiple sclerosis.
- fMRI is used in clinical trials and research to assess the effects of pharmacological interventions on brain function. It provides objective measures of treatment efficacy and can contribute to the development of novel therapeutic approaches.

While fMRI is a powerful tool, its clinical applications may vary, and results should be interpreted in conjunction with other diagnostic methods. Integration with structural imaging, clinical assessments, and other neuroimaging modalities enhances the diagnostic value of fMRI in context of brain disorders.

13.5.2 Limitations of fMRI

fMRI measures changes in perfusion and oxygenation which measures the alteration in neural activity, but fMRI does not directly measure electrical activity in neurons. In comparison with other techniques like EEG, fMRI has low temporal resolution (Tocchio et al. 2015). This indicates that fMRI is a less suitable tool for detecting any changes in neural activity. fMRI provides lack information about the exact locations of small subcortical structures or individual neurons but also analyzes good spatial resolution. Interpretation of the blood oxygen level-dependent (BOLD) signal measured by fMRI can also be challenging due to variability influenced by factors such as baseline cerebral blood flow, vascular anatomy, and physiological variables. Furthermore, fMRI is sensitive to motion artifacts, and even slight head movements can introduce errors in the data, posing challenges, particularly in populations prone to movement, such as children or individuals with movement disorders. Certain brain regions, especially those near air-filled structures like sinuses, are susceptible to susceptibility artifacts and signal dropout in fMRI images, limiting the accurate assessment of activity in those regions. Lastly, the BOLD signal reflects changes in blood flow and oxygenation, but these changes can occur for reasons other than neural activity. Despite these limitations, fMRI remains a valuable tool in neuroscience and clinical research, providing insights into brain function and connectivity.

13.6 Electroencephalography (EEG)

Electroencephalography (EEG) is a noninvasive neuroimaging technique that measures and records electrical activity of the brain. This method involves placing electrodes on the scalp to detect and amplify electrical signals produced by the neural activity in the brain. EEG is widely used in clinical and research settings to study brain function, diagnose neurological conditions, and monitor brain activity during various tasks. The basic principles of electroencephalography involve recording of voltage difference among different points using a pair of electrodes that compares one active electrode site with another or the differential amplification. Neurons in the brain communicate through electrical impulses. EEG records summation of these electrical activities from thousands to millions of neurons. Small metal

electrodes are attached to the scalp at various locations, typically following a standardized placement system such as the international 10–20 system (Fig. 13.4). The electrodes are connected to an amplifier that amplifies and records electrical signals.

EEG measures brainwave activity, which is categorized into different frequency bands:

1. Delta (0.5–4 Hz) is associated with deep sleep and some neurological disorders.
2. Theta (4–8 Hz) is present during drowsiness and in certain meditative states.
3. Alpha (8–13 Hz) is dominant during relaxed wakefulness and closed eyes.
4. Beta (13–30 Hz) is associated with active thinking, problem-solving, and concentration.
5. Gamma (30 Hz and above) is involved in higher cognitive functions and perception (Van Deursen et al. 2008).

EEG recordings are displayed as a series of waveforms, known as an EEG trace (Fig. 13.4). The state of brain activity can be understood by analyzing the change in amplitude and frequency of the wave applied during the process. EEG can be time locked to specific stimuli or events, such as presentation of a visual stimulus or the onset of a motor movement. These event-related potentials (ERPs) reveal specific brain response associated with sensory, cognitive, or motor processes. EEG recordings may be affected by artifacts, such as eye movements, muscle activity, or environmental interference. Signal processing techniques are employed to remove or minimize these artifacts.

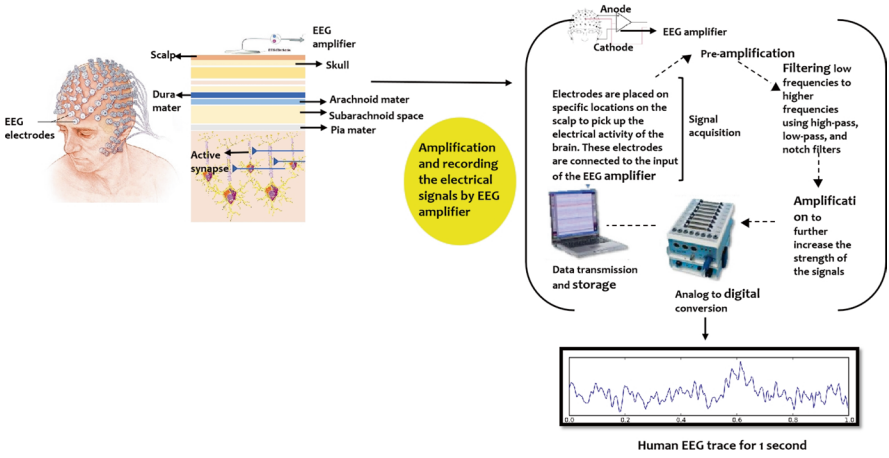

Fig. 13.4 Picture description providing framework of EEG technique. It depicts placement of electrodes on the scalp in order to detect voltage differences between different points on the scalp. These voltage differences reflecting the electrical activity generated by the bran's neurons are then amplified and recorded for analysis

13.6.1 Application of EEG

- EEG is a fundamental tool in the diagnosis of epilepsy. It helps identify abnormal electrical discharges, known as epileptiform activity or spikes, which are characteristic of seizure disorders. Long-term EEG monitoring (video EEG) is often used to capture and characterize seizures and aids in the diagnosis and classification of epilepsy. Electroencephalography helps in localizing the source of seizure activity within the brain. This information is crucial for planning surgical interventions, such as epilepsy surgery, where the removal of the seizure focus can be a potential treatment.
- It is extremely helpful in the diagnosis of sleep disorders such as insomnia, sleep apnea, and parasomnias. Sleep studies (polysomnography) combine EEG with other physiological measurements to assess sleep architecture and identify abnormalities (Phelps et al. 1982).
- It is a valuable tool in assessing patients with altered consciousness, delirium, or encephalopathies. It can reveal patterns associated with metabolic disturbances, toxic exposures, or structural brain abnormalities.
- It is used in measuring certain movement disorders, including tremors and myoclonus. Abnormal EEG patterns may provide insights into the fundamental neurological mechanisms contributing to these movement abnormalities (Kelloff et al. 2005).
- EEG is not as specific as other imaging modalities, EEG can contribute to assessment of neurodegenerative disorders such as Alzheimer's disease. Changes in EEG patterns, such as slowing of background rhythms, may be observed in these conditions.
- It detects cerebral blood flow with the finding of abnormalities associated with cerebrovascular disorders, such as ischemic strokes or hemorrhages. It aids in understanding the impact of vascular events on brain function. EEG is utilized in the evaluation of neuropsychiatric conditions, including attention-deficit/hyperactivity disorder (ADHD), schizophrenia, and mood disorders. It can provide insights into neural correlates associated with these conditions.
- EEG is explored as a tool for assessing and monitoring individuals with traumatic brain injuries, including concussions. It can help detect abnormal brainwave patterns associated with injury (Jacobs et al. 2012).
- During anesthesia, it is used to monitor brain activity to ensure that the depth of anesthesia is appropriate and there are no signs of awareness during surgery. EEG is often used in conjunction with other neuroimaging techniques, such as CT or MRI, to provide a comprehensive understanding of brain structure and function.

13.6.2 Limitations of EEG

EEG is primarily focused on recording electrical activity from surface regions of the brain, rendering it less effective in assessing abnormalities in deeper brain structures, particularly subcortical regions. Furthermore, the interpretation of EEG

results is challenged by the significant variability observed in normal EEG pattern among individuals. Factors such as age-related changes and variations in baseline brain activity must be considered to accurately interpret EEG findings. Additionally, interpreting EEG recordings in pediatric patients presents unique challenges due to age-related differences in normal brain activity, necessitating expertise to distinguish between normal developmental changes and pathological findings. In epilepsy evaluations, EEG is often recorded during interictal periods, yet capturing a seizure during routine EEG monitoring can be challenging, potentially resulting in false-negative results (Loo et al. 2016). Moreover, EEG may have limited diagnostic utility in certain conditions, such as neurodegenerative disorders or psychiatric illnesses, where structural or functional imaging modalities like MRI, PET, or SPECT may provide more informative results. While EEG offers insights into broad cognitive processes, it lacks specificity for detailed cognitive functions, requiring additional functional imaging techniques like fMRI for tasks that specifically activate certain brain regions. Despite these limitations, EEG remains invaluable in neurology for its ability to capture real-time changes in brain activity. Integrating EEG findings with other diagnostic modalities and clinical information enhances its diagnostic accuracy and utility in managing patients with various neurological disorders.

13.7 Magnetoencephalography (MEG)

MEG is a noninvasive neuroimaging technique that measures magnetic fields produced by neuronal activity in the brain. Initially, for the first time, MEG signals were recorded in 1968 by physicist David Cohen at the University of Illinois. It provides high temporal resolution and is capable of capturing the millisecond-scale changes in brain activity. The principle underlying magnetoencephalography is based on the following: active neurons generate small electrical currents. These electrical currents produce associated magnetic field according to principle of electromagnetic induction, as described by Maxwell's equations. MEG measures magnetic field using highly sensitive sensors called superconducting quantum interference devices (SQUIDs) (Fig. 13.5). SQUIDs are capable of detecting extremely weak magnetic fields associated with neuronal activity (Clarke et al. 2007). MEG requires precise positioning of the sensors relative to the head. During recording, the subject's head is typically placed within a helmet-like structure containing the SQUID sensors. Magnetic field data in MEG enables researchers to capture dynamics of neuronal activity with precision down to the millisecond. The fusion of MEG and EEG offers a deeper knowledge about brain activity by using magnetic and electrical signals.

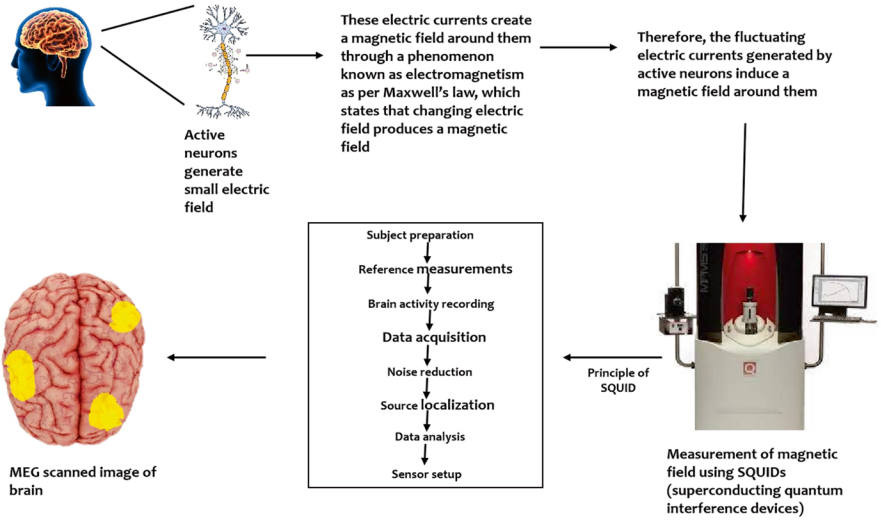

Fig. 13.5 Representation of MEG data collection as an noninvasive neuroimaging method to measure the magnetic fields produced by neuronal activity in the brain

13.7.1 Application in Diagnosis of Brain Disorder

- MEG analysis is part of presurgical planning for brain surgery, particularly in case of epilepsy. It helps identify eloquent areas of the brain, such as those involved in motor function or language processing to minimize risk of postsurgical functional deficits.
- This technique is utilized for functional brain mapping to identify and map areas of the brain associated with specific functions such as motor control, sensory processing, and language. This information is valuable for planning surgeries near critical brain regions.
- It is used in the investigation of various cognitive processes, including attention, memory, perception, and decision-making. MEG helps researchers to understand dynamic nature of neural activity during cognitive tasks.
- MEG is employed in research for neuropsychiatric disorders, such as schizophrenia, autism spectrum disorders, and attention-deficit/hyperactivity disorder (ADHD). It helps in studying aberrant neural activity patterns associated with these conditions (Hämäläinen et al. 1993).
- This technique is used in the evaluation of sensory processing disorders, providing insights into how the brain processes sensory information. It is particularly relevant in conditions where sensory integration is impaired (Kelloff et al. 2005).
- It can be used to assess the impact of strokes or traumatic brain injuries on brain function. It helps in understanding the reorganization of neural network following injury and aids in rehabilitation planning (Raichle 1983).

- MEG can evaluate movement disorders, including conditions like Parkinson's disease. It provides insights into the neural mechanism underlying motor control and movement.
- MEG has significant advantages, and thereby it is often used in combination with other neuroimaging techniques such as structural MRI and functional MRI to provide a more comprehensive assessment of both structural and functional aspects of the brain. The specific application of MEG depends on the clinical question and nature of the brain disorder being investigated.

13.7.2 Limitation of Diagnosis of Brain Disorder by MEG

MEG has limitations in spatial resolution, especially when compared to structural imaging techniques like magnetic resonance imaging (MRI). It is better at localizing the activity in the neocortex but cannot resolve localization in deeper brain structures. MEG is more sensitive to neocortical activity and may be less effective at capturing activity in subcortical structures (Attal and Schwartz 2013). One major limiting factor in MEG technique is its cost, and this may be the reason that this technique is not widely used for imaging as compared to other imaging tools. In MEG, it is hard to differentiate between overlapping signals from different regions in the brain. The interpretation of MEG data can be affected during recording when small errors in head positioning occur as it relies on complex mathematical models to estimate location and strength of neural sources (Wendel et al. 2009). The accuracy of these models depends on the assumptions made about the underlying neural activity, and errors in modeling can affect results. Due to the physics of magnetic fields, MEG has limitations in accurately localizing neural activity originating from deep brain structures. This can be a significant limitation for disorders primarily affecting subcortical regions. MEG is sensitive to environmental magnetic interference, such as metal objects or electrical devices in the vicinity (Hämäläinen et al. 1993). This sensitivity can lead to artifacts in the recordings and may require careful control of the recording environment. Structural imagining techniques such as MRI are frequently required to correlate and integrate functional findings with underlying anatomy. Despite these limitations, MEG is a wonderful tool for neurosciences research and clinical diagnosis, with certain types of brain disorders.

13.8 Magnetic Resonance Spectroscopy (MRS)

MRS is a noninvasive imaging technique that provides insights into the chemical composition of tissues by detecting the magnetic signals emitted by specific nuclei within molecules. It is a specialized form of MRI that focuses on the analysis of metabolites within tissues. MRS is based on the principles of nuclear magnetic resonance, a phenomenon observed when atomic nuclei with a magnetic moment are

exposed to a strong external magnetic field and radiofrequency pulses. MRS typically focuses on the detection of hydrogen nuclei (protons) in water and other molecules. Other nuclei such as carbon-13, phosphorus-31, and others can also be targeted depending on the specific application (Van den Thillart and Van Waarde 1996). The resonance frequencies of nuclei in different chemical environments vary, and, therefore, chemical shift due to a difference in resonance frequency between a specific nucleus and a reference standard provides information about the chemical environment of the nuclei (Hore 2015). MRS produces spectra that represent the distribution of resonating nuclei in the tissue. Peaks in the spectrum corresponds to specific metabolites, and their intensity reflects the concentration of those metabolites. Common metabolites studied in brain MRS include N-acetylaspartate (NAA), creatine (Cr), choline-containing compounds (Cho), myo-inositol (mI), and glutamate/glutamine (Glx) (McKiernan et al. 2023). Changes in the level of these metabolites can provide information about tissue health and pathology. MRS results can be analyzed with MRI to obtain spatial information. Volumes of interest (VOIs) are selected within tissues, and MRS is applied to analyze the chemical composition of those specific regions.

13.8.1 Application of MRS in the Diagnosis of Brain Disorder

- Tools like MRS are widely used for the assessment of metabolite concentrations in the brain region. Changes in metabolite ratios, such as elevated choline and reduced N-acetyl aspartate (NAA), can indicate the presence of abnormalities.
- MRS can investigate metabolic abnormalities in individuals with epilepsy. It helps identify changes in metabolite concentrations, such as alterations in gamma-aminobutyric acid (GABA) levels, which may be associated with epileptogenesis and contribute to a better understanding of the underlying mechanisms.
- In neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and multiple sclerosis, MRS can monitor altered metabolite ratio, such as decreased NAA, is associated with neuronal loss, and can serve as a potential biomarker for disease progression.
- MRS aids in diagnosis of inborn errors in metabolism, a group of genetic disorders affecting metabolic pathways. By detecting abnormal metabolite profiles, MRS contributes to the identification and characterization of these rare conditions (Kelloff et al. 2005).
- MRS is used to monitor treatment response in various brain disorders. Changes in metabolite concentration over time can provide insights into the effectiveness of therapeutic interventions, helping clinicians adjust treatment plans accordingly. MRS is useful in assessing white matter disorders, including leukodystrophies, and demyelinating diseases. It can detect changes in myelin-associated metabolites, contributing to the diagnosis and understanding of these conditions.
- In psychiatric research, MRS is employed to investigate neurochemical changes associated with conditions such as major depressive disorder, bipolar disorder,

and schizophrenia. Alterations in metabolite levels may provide insights into the neurobiology of these disorders.

- MRS can be used to assess metabolic changes in individuals with traumatic brain injury. It helps identify alterations in metabolite concentrations indicative of cellular damage and provides information on the severity of the injury. (Harris et al. 2012).
- It has applications in studying developmental disorders of the brain. It can detect metabolic abnormalities in regions associated with developmental delays, aiding in the characterization and understanding of these disorders (Gallamini et al. 2014).
- By providing additional biochemical information, MRS complements in conventional magnetic resonance imaging (MRI). The technique is particularly useful in cases where understanding the metabolic profile of tissues can enhance diagnostic accuracy and provide insights into disease mechanisms (Herholz and Heiss 2004).

13.8.2 Limitations of MRS in Diagnosis of Brain Disorder

MRS offers limited spatial resolution compared to conventional structural MRI, providing details about metabolite concentration in relatively large tissue volumes. Additionally, MRS encounters lower signal-to-noise ratio (SNR), particularly for metabolites with low concentrations, often necessitating longer acquisition times to enhance signals. Moreover, variations in tissue composition, such as the ratio of gray matter to white matter, can influence the metabolic profile obtained with MRS. Furthermore, MRS faces challenges in detecting and characterizing metabolic changes in deep brain structures due to limited spatial resolution and the orientation of magnetic fields. Data analysis of MRS necessitates consideration of factors such as choice of metabolite ratios and reference values, and misinterpretation of spectra can lead to inaccurate diagnostic conclusions (Wilson et al. 2019). Lastly, acquiring optimal MRS results often requires high-field MRI systems, which may not be universally accessible in clinical environments.

13.9 Diffusion Tensor Imaging (DTI)

Diffusion tensor imaging (DTI) is an advanced neuroimaging technique that provides insights into the microstructural organization of white matter in the brain. Unlike traditional magnetic resonance imaging (MRI), which primarily captures anatomical structures, DTI focuses on the movement of water molecules within tissues. Diffusion is initiated with the presence of a barrier, like cell membrane and axonal fibers, and exhibits directional movement. A directional diffusion pattern is utilized by DTI by representing the diffusion of water molecules as a tensor, a

mathematical framework that describes both the magnitude and direction of diffusion at every voxel (3D pixel) in the image (Rajan 2021). Fractional Anisotropy (FA) is the value of the scalar that is derived from a tensor and quantifies the degree of anisotropy or directionality of water diffusion. The higher the value of FA, the more organized and coherent white matter structures. DTI data is typically acquired using a series of diffusion-weighted images (DWIs) in different directions (Fig. 13.6). By analyzing the changes in signal intensity in these images, researchers can infer underlying diffusion properties (Park 2005). DTI allows the reconstruction of white matter tracts using a technique called tractography. This helps visualize and map pathways of major neural connections in the brain.

13.9.1 Applications of DTI in Diagnosis of Brain Disorder

- DTI is sensitive to changes in the microstructure of white matter. In conditions such as multiple sclerosis, traumatic brain injury, or white matter lesions, DTI can reveal disruptions in the normal organization of axonal fibers, helping to identify and locate abnormalities.
- DTI is useful to study neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, and Huntington's disease. It helps in assessing integrity of white matter tracts, revealing patterns of degeneration or atrophy, thereby contributing to early diagnosis and tracking disease progression (Andica et al. 2020).

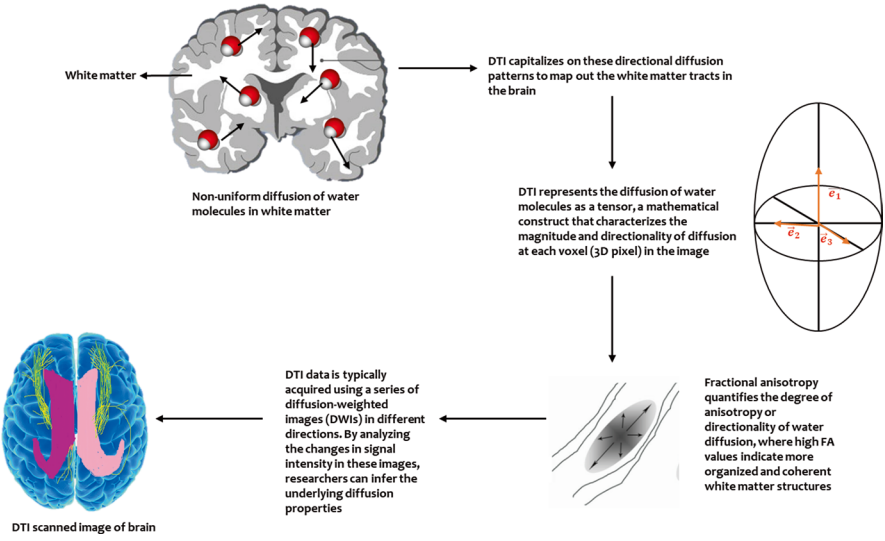

Fig. 13.6 Picture representation of DTI workflow, elaborating the process of capturing of anatomical structure by focusing on the movement of water molecules within tissues

- In epilepsy, DTI can be employed to investigate abnormalities in the structural connectivity of the brain. It aids in understanding the impact of seizures on white matter pathways and identifies potential regions responsible for seizure propagation.
- To explore structural connectivity alterations associated with conditions such as schizophrenia, bipolar disorder, and major depressive disorder, DTI provides valuable information about the neural circuits involved in these disorders (Wagner et al. 2015).
- Traumatic brain injury (TBI) often results in diffused axonal injury, affecting the microstructure of white matter. DTI is utilized to assess the extent and location of these injuries, helping in the diagnosis, prognosis, and monitoring recovery in individuals with TBI (Palacios et al. 2020).
- DTI is useful to study developmental disorders such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). It helps in understanding the connectivity differences in the developing brain and provides insights into the neural basis of these disorders.
- Following a stroke, DTI can be used to assess the impact on white matter tracts. It helps in understanding the extent of damage, predicting functional outcomes, and guiding rehabilitation strategies.

13.9.2 Limitations of DTI

DTI is a valuable technique in understanding brain connectivity and structural organization, yet it has notable limitations that affect its diagnostic accuracy and clinical utility. These limitations include susceptibility to artifacts, sensitivity to crossing fibers, and challenges in distinguishing different types of microstructural changes. To address some of these challenges, techniques like high-angular resolution diffusion imaging (HARDI) have been developed. One significant limitation of DTI is its susceptibility to motion artifacts, which can distort data and lead to errors in diffusion properties, particularly problematic in pediatric patients and individuals prone to restlessness (Peeters and Sunaert 2014). Additionally, DTI exhibits limited spatial resolution compared to other techniques, posing challenges in resolving small structures and characterizing intricate fiber patterns or distinguishing between adjacent white matter tracts.

Another challenge with DTI arises from areas with multiple fiber bundles, which can lead to inaccuracy in tractography. Furthermore, there are challenges in clinical translation, including the need for standardized protocols, data interpretation, and incorporation of DTI findings into regular clinical procedures.

13.10 HD-Transcranial Electrical Stimulation (HD-tES)

HD-tES is an advanced form of transcranial electrical stimulation (tES), specifically designed to provide precise and targeted neuromodulation. It involves application of weak electrical current to the scalp using an array of smaller electrodes arranged in a specific configuration. HD-tES is a neuromodulation technique that involves the application of a weak electrical current to specific areas of the scalp. It is an advanced form of transcranial electrical stimulation (tES) that utilizes an array of smaller electrodes for precise and targeted stimulation. HD-tES operates on the fundamental principles of transcranial electrical stimulation (tES) but introduces a higher degree of spatial precision (Guleyupoglu et al. 2013). The primary goal is to modulate neural activity in specific brain regions by applying a weak electrical current through the scalp HD-tES. HD-tES involves the use of an array of smaller electrodes arranged in a specific configuration on the scalp. This high-definition montage allows more focused and localized stimulation as compared to conventional tES, which typically uses larger electrodes (Fig. 13.7). The electrical current applied during HD-tES flows through the scalp and underlying brain tissue (Guleyupoglu et al. 2013). The configuration of electrodes determines density and distribution of the current. By using smaller electrodes in specific patterns, HD-tES aims to concentrate on the stimulation on targeted cortical areas (Fig. 13.7). One of the main principles of HD-tES is to achieve higher spatial resolution. The smaller electrodes and precise placement allows researchers and clinicians to target specific cortical areas with greater accuracy. This increased spatial precision is important when aiming to modulate neural activity in well-defined brain regions (Jeon et al. 2018). The high-definition electrode montage is designed to focus current density on the targeted brain region while minimizing the spread of current to surrounding areas. This spatial focusing is crucial for selectively influencing specific neural circuits. HD-tES often involves individualizing the electrode montage based on the specific brain region or network of interest. Researchers may tailor the electrode placement to achieve optimal effects for their experimental or clinical goals. In research, it is used to study brain function, cognition, and neural circuits. In clinical applications, it is explored as a potential therapeutic intervention for neuropsychiatric disorders,

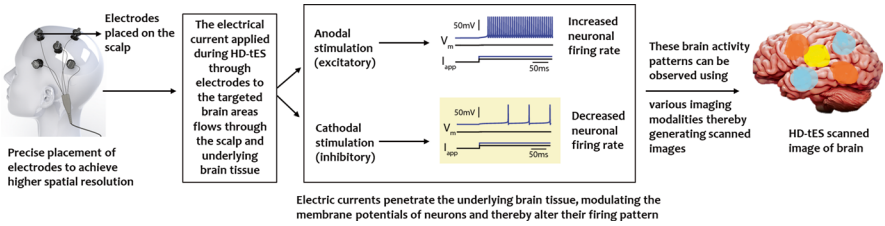

Fig. 13.7 Schematic representation of HD-tES depicting application of a weak electrical current to the scalp using an array of smaller electrodes arranged in a specific configuration and thereby generation of the scanned images for changes in brain based on the brain activity patterns observed by taking the neuronal firing rate into account

neurological conditions, and neurorehabilitation. Like other forms of transcranial electrical stimulation, safety considerations are crucial. HD-tES parameters should be within established safety guidelines to prevent adverse effects. Individual variability in response to stimulation is also taken into account. Overall, the principle of HD-tES revolves around achieving a more precise and targeted neuromodulation by using a high-definition electrode montage. This increased spatial resolution allows researchers and clinicians to explore the functional role of specific brain regions and develop therapeutic interventions (Huang et al. 2020).

13.10.1 Application of HD-tES

- It is used to study cognitive processes, sensory-motor functions, and neural circuitry. Even though it is not a diagnostic tool, these studies contribute to our understanding of brain function and may indirectly inform the understanding of brain disorders.
- HD-tES is useful for studies aiming to enhance cognitive functions such as memory, attention, and learning. Researchers investigate whether targeted stimulation of certain brain areas can lead to improvement in cognitive performance to provide insights into potential therapeutic applications.
- It is a potential tool in neurorehabilitation for individuals with neurological conditions or brain injuries. It is used to modulate neural activity in a way that may facilitate recovery of improved functional outcomes.
- It can be explored as a potential therapeutic intervention for various neuropsychiatric disorders, including depression, anxiety, and schizophrenia. Clinical trials are ongoing to assess its efficacy in alleviating symptoms and improving overall mental health. While these applications are more focused on treatment, they may indirectly contribute to diagnostic insights.
- In the context of therapeutic applications, HD-tES has the potential for individualized treatment approaches. Researchers and clinicians can tailor the electrode montage and stimulation parameters based on the specific needs of a patient. This customization is aimed at optimizing the effectiveness of neuromodulation (Ni et al. 2022).

13.10.2 Limitation of HD-tES

Diagnosis typically relies on neuroimaging and clinical assessments. It has the ability to modulate neural activity but does not yield specific insights into the structural or functional abnormalities. HD-tES also indues indirect effect on brain activity which is shown in result analysis but not necessarily specific to particular NDDs. This technique has the potential to alter neural excitability, but mechanisms concerning diverse brain disorders remain incompletely understood.

13.11 High-Resolution Magnetic Resonance Imaging (HR-MRI)

HR-MRI is used to obtain finer images of anatomical structures within the body compared to MRI. It is based on the same fundamental principle as standard nuclear magnetic resonance, but it is modified to achieve better spatial resolution. When a subject sample is placed in a strong magnetic field, atomic nuclei (hydrogen) get aligned with the magnetic field. Radiofrequency pulses are then applied to these nuclei, causing them to temporarily deviate from their alignment. When these nuclei return to their original alignment, they emit radiofrequency signals that can be detected and used to create images. Gradient coils are used to spatially encode the MRI signals (Boehm et al. 2003; Pradeep et al. 2022). HR-MRI often involves the use of high magnetic field (3T, 7T) to increase the signal-to-noise ratio and enhance the clarity of images, allowing improved visualization (Karamat et al. 2016). It employs specialized imaging sequences optimized for detailed anatomical imaging. Various sequences like T1-weighted, T2-weighted, and proton density-weighted sequences, in specific application, can enhance contrast, and resolute voxel size represents three-dimensional volume by each pixel in the image (Shaari et al. 2021).

HR-MRI decreases voxel size, leading to smaller and sharp image elements. Smaller voxel size enhances the visualization of fine structure within tissues. HR-MRI frequently uses parallel imaging technique to speed up and reduce the scan times (Sui et al. 2022). These methods use multiple receiver coils to capture data immediately and enhance both spatial and temporal resolution. The surface coils and muti-channel receiver system play a significant role in improving spatial resolution. Placing surface coil near the region of interest enhances the image quality of a small structure. Reconstruction algorithms are important for high- resolution images. They play a vital role in diminishing artifacts, enhancing image clarity, and improving the overall quality of the images. Application of HR-MRI is utilized in various clinical and research fields, including neuroimaging, musculoskeletal imaging, cardiac imaging, and vascular imaging (Belhocine et al. 2008). It is a valuable tool for detailed visualization of anatomical structures and pathological changes in small regions.

13.11.1 Application of HR-MRI

- It is used to assess neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and Huntington's disease. It allows visualization of subtle changes in brain structures, including the hippocampus, amygdala, and cortical atrophy associated with these disorders.
- In multiple sclerosis, HR-MRI aids in detecting and characterizing lesions in the brain and spinal cord. It helps in assessing the extent of demyelination and identifying lesions in specific anatomical regions, contributing to the diagnosis and monitoring of disease progression (Combes et al. 2022).

- For individuals with epilepsy, HR-MRI is used to identify structural abnormalities in the brain that may be contributing to seizures. It helps visualize malformations, tumors, and other lesions that can be targets for surgical intervention (Bernhardt et al. 2016).
- Combination of magnetic resonance angiography (MRA) and HR-MRI is used to assess vascular disorders such as arteriovenous malformations (AVMs), aneurysms, and vascular stenoses. It provides detailed images of the blood vessels and helps in planning interventions.
- Disorders affecting white matter, such as leukodystrophies and white matter demyelinating diseases, can be assessed using HR-MRI. It allows visualization of white matter tracts and helps identify abnormalities related to myelin integrity (Hajj-Ali and Calabrese 2020).
- HR-MRI is helpful in understanding structural changes in the brain of individuals with psychiatric disorders. It is used in research to investigate the neuroanatomical correlates of conditions such as schizophrenia, bipolar disorder, and major depressive disorder.
- Following traumatic brain injury, HR-MRI helps to visualize the extent of damage, identify contusions, and assess the impact on specific brain structure. It contributes to understand the relationship between injury and neurological deficits.
- HR-MRI is sensitive to small vessel changes, allowing detection of microvascular ischemia. This is particularly relevant in conditions like vascular dementia, where small vessel disease contributes to cognitive impairment (Jokinen et al. 2020).
- The detailed images provided by HR-MRI contribute to early and accurate diagnosis, enabling clinicians to tailor treatment plans for to for patients.

13.11.2 Limitation of HR-MRI

HR-MRI is a powerful diagnostic tool for various brain disorders but comes with certain limitations like increased scan time for higher spatial resolution, leading to patient discomfort. Additionally, we cannot achieve a single image of the entire tissue as it has a limited field of view. Therefore, multiple scanning and longer screening periods affect different regions of the brain and result in images being susceptible to various artifacts, such as motion artifacts, data misinterpretation, fine structure with false information, etc. Besides, the influence of image post-processing techniques on image quality and diagnostic consistency cannot be overlooked with the risk of overinterpretation (Cenek et al. 2018). Furthermore, HR-MRI primarily focuses on anatomical details and does not provide functional information. Combining with functional imaging modalities (MRI, PET) may offer a more comprehensive assessment in certain cases (Van der Kolk et al. 2013). On the other hand, cost and availability pose further constraints, as equipment requires higher field strength magnets and dedicated coils.

13.12 Conclusion

This chapter provides an overview of the diverse imaging techniques available for neurodegenerative disorders. With the advancements in imaging technology, we are now able to identify and monitor neurodegenerative disorders with greater precision and accuracy. The use of X-ray, single-photon systems, magnetic resonance, and ionizing and nonionizing radiation (radio waves) has significantly improved our understanding of the brain's cellular alterations associated with NDDs. These imaging methods are proven to be effective in better diagnostics and subsequently facilitating better treatment. Some of these methods provide detailed insights of anatomical alterations by structural imaging like MRI, CT scans, etc. Additionally, dynamic information like the metabolic activity of brain cells can be screened using PET, SPECT, etc. Recent developments in DTI and fMRI-based imaging have significantly improved NDD pathology. Using these methods we can now detect subtle microstructural changes associated with NDDs. However, there are certain limitations associated with the use of each imaging method and challenges due to the increased level of detail. However, the development in image post-processing and associating AI techniques will certainly improve the quality and diagnostic consistency. Therefore, integrating high-resolution structural imaging with functional imaging modalities will be a better approach for a comprehensive diagnosis of NDDs. Overall these multiple approaches and advancements in imaging methods will help in combating neurodegenerative disorders.

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Chapter 14
Novel Metabolic Biomarkers and Therapeutic Strategies in Neurodegenerative Diseases

Anurag Thapliyal, Shweta, and Shashank Kumar Maurya

Abstract Metabolic changes are a major cause of pathophysiological alterations in neurodegenerative diseases. Recent metabolic profiling studies have led to the identification of numbers of low-molecular-weight metabolites and their intermediates' association with neurodegenerative diseases. Further, neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), autism spectrum disorder (ASD), Huntington's disease (HD), and epilepsy display specific alterations in metabolic profiles, which can also be used as biomarkers. Targeting these metabolites could be a possible therapeutic strategy for the management of neurodegenerative diseases. Biomaterials can play an important role in managing neurodegenerative diseases. Numerous studies have shown potential of biomaterials such as exosomes, nanoparticles, hydrogels, carbon-based nanomaterials, nanofibers, and self-assembling peptides in the treatment of neurodegenerative diseases. Therefore, in the present chapter, we have tried to provide comprehensive understanding of metabolites as biomarkers for identification of NDDs and possible intervention in the management of disease using biomaterials.

Keywords Neurodegenerative diseases · Biomarkers · Metabolism · Biomaterial · Therapeutics

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14.1 Introduction

In brain-related disorders, neurodegeneration is the primary pathophysiological alteration (Merelli et al. 2013). Nerve degeneration, along with tissue damage, disorientation, altered personality, and other emerging symptoms that may accompany the disease's progression and ageing, is the hallmark of neurodegenerative diseases. In addition, they frequently result in a protracted period of neuronal inflammation and can cause irreversible damage. Most neurodegenerative disease therapies currently available only address the symptoms of the condition rather than its fundamental cause. Treatment plan formulation is significantly hampered by the complex aetiology and diverse disease histories of the majority of progressive neurodegenerative disorders. The exact causes of the onset and course of the most prevalent neurological disorders, including Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Alzheimer's disease (AD), are unknown. Additionally, each patient's disease course and severity are unique, making it more difficult to develop effective therapeutic strategies. These diseases have no known cure and are challenging to treat because, despite decades of research, the underlying molecular mechanisms remain poorly understood (Botas et al. 2015). Monitoring the course of the disease, assessing the efficacy of treatment approaches, and selecting appropriate interventions depend on early diagnosis. Further, to identify the processes underlying the complex behavioural or cognitive outcomes, biomarkers are required (Califf 2018). However, the process of identifying biomarkers as a diagnostic tool and a treatment response predictor for neurodegenerative disorders (NDDs) in children and adults is still quite challenging and time-consuming. Moreover, the pathologies of neurodegenerative disorders are complex. This has made the identification of biomarkers for diagnosis a difficult process.

Emerging metabolic profiling in the last few years has made the identification of biomarkers easier. The measurement of the complement of low-molecular-weight metabolites and their intermediates in unicellular to multicellular biological systems is known as metabolic profiling. Metabolic profiling shows the dynamic response to genetic modification (e.g. transgenic or viral), as well as physiological (e.g. gender), pathophysiological (e.g. disease morbidity) and/or developmental stimuli (e.g., ageing). There is abundant evidence suggesting an association between metabolic abnormalities and neurodegenerative diseases. Therefore, metabolic modulation is a potential therapeutic strategy for neurodegenerative disorders in both prevention and treatment. Several genes such as triggering receptors expressed on myeloid cells (TREM2), enzymes [cholesterol acyltransferase (ACAT1), carbonic anhydrase, phosphodiesterases (PDEs)], enzyme inhibitors (β- and γ-secretase inhibitors), metal ions (iron), proteins (erythropoietin), channels (TRPV1channel), and mitochondrial dysfunction could be potential metabolic therapeutic targets in NDDs. Triggering receptor expressed on myeloid cells 2 (TREM2) gene variants were found through genome-wide association studies (GWAS) and revealed a twofold to fourfold increase in the risk of developing AD (Qin et al. 2021). Genetic variations in the TREM2 gene disrupt the neuroinflammatory function of microglia

in inhibiting the disease's progression. Apart from its impact on microglial functions in tau and amyloid pathologies in AD, TREM2 can also be involved in metabolism and inflammatory responses. Thus, the involvement of microglia and TREM2 in the development of AD may lead to the development of new therapeutic approaches that target the immune system to affect AD pathogenesis (Li and Zhang 2021). Enzyme cholesterol acyltransferase (ACAT) is crucial for maintaining cholesterol homeostasis within cells (Rogers et al. 2015). In cell culture and mouse models, blocking ACAT activity, particularly ACAT1, has been proven beneficial in AD (Chang et al. 2021). Cyclic nucleotide phosphodiesterases (PDEs) are involved in NDDs and responsible for the breakdown of cyclic nucleotides, cyclic adenosine monophosphate (cAMP), and cyclic guanosine monophosphate (cGMP) (Bollen and Prickaerts 2012). Their inhibition tends to be an effective strategy in protecting against diseases like HD, PD, AD, and cognitive disorders (Bollen and Prickaerts 2012). Numerous studies have demonstrated the pathological mechanism of neurodegenerative diseases, such as Alzheimer's disease (AD), to be influenced by brain excessive levels of iron (Liu et al. 2018). Iron dyshomeostasis and ferroptosis could be possible targets for AD therapy (Zhang et al. 2022). Gene therapy-based novel approaches have several potential benefits over conventional therapy methods. Further, gene therapy may be utilized to repair or regenerate dopaminergic neurons lost during the progression of the disease or to treat circuit abnormalities in the basal ganglia linked to Parkinson's disease (Axelsen and Woldbye 2018). One of the main pathological events is the polymerization of Aβ into amyloid plaques, which is produced from amyloid precursor protein (APP) by sequential proteolytic cleavage by β- and γ-secretase. Since γ-secretase facilitates the ultimate cleavage that releases Aβ, it can be a possible drug target in AD treatment (Hur 2022). In the treatment of epilepsy, potential targets could be enzymes (carbonic anhydrase), proteins (erythropoietin), and channels (TRPV1channel; Zavala-Tecuapetla et al. 2020). Preclinical and clinical data demonstrate that all of these targets are effective in preventing seizures, exhibiting neuroprotective activity, and inhibiting the progression of epilepsy. One of the most recently discovered pathological processes in neurological disorders is mitochondrial dysfunction (Wu et al. 2019). The primary pathological characteristic of neurodegenerative diseases is the regulation of apoptosis by mitochondria. The apoptotic signalling in cases of mitochondrial dysfunction can be targeted (Wu et al. 2019).

Biomaterials are natural or synthetic, alive or lifeless substances, other than drugs, which can support, enhance, replace or interact with biological systems. These are of great importance in medical applications in augmentation or replacement of a natural function such as in cases of injury or degeneration and should possess some crucial properties such as biodegradability, bio-inertness, biocompatibility, functionality, and ability to be sterilized. Naturally derived biomaterials are mostly polymeric biomolecules having a lower rate of rejection, non-cytotoxicity, and ability to mimic the mechanical and biological function of the tissue to be restored (Doblado et al. 2021). Therefore they can act as scaffolds for cell adhesion, gaseous and nutrient exchange, and extracellular matrix (ECM) deposition. Synthetic biomaterials provide an alternative by being mechanically strong and

almost non-immunoreactive due to the absence of any biologically functional domains and providing better control over their physical and chemical properties. (Banigo et al. 2019). Biomaterials have been successful in several clinical applications such as nerve repair, neurite outgrowth, peripheral nerve regeneration, spinal cord injury, drug delivery, glioblastoma, cell adhesion and proliferation, severe burns, chondrocyte biosynthesis, bone surgery, implants and joint replacements, ligament reconstruction, rhinoplasty, intraocular lenses, heart valves, artificial arteries and veins, anti-cancer therapies, and periodontal treatment and pain relief (Wang et al. 2017). With inadequate effectiveness of symptomatic treatments and a dearth of disease-modifying therapies, innovative approaches such as exosomes, carbon-based nanomaterials, nanofibers, hydrogels, and self-assembling peptides are gaining significant attention in treatments of neurodegenerative and neurodevelopmental disorders. Therefore, the present chapter will discuss metabolic profiling, its potential in the identification of novel biomarkers, and possible therapeutic potential via targeting metabolites in neurodegenerative diseases.

14.2 Metabolic Profiling: Emerging Biomarkers for Predictive Testing in NDDs

Small molecules known as metabolites are present in all biological samples, including tissues, cells, and biofluids (blood, plasma, urine, cerebrospinal fluid, and serum). Metabolites can cross the blood-brain barrier (BBB), indicating that molecules in circulation could reflect biological processes occurring within the central nervous system (CNS). It is possible for circulating metabolites to be released as free molecules into the extracellular environment or to be contained inside extracellular vesicles. Metabolites can also shed light on the mechanisms underlying the onset and progression of diseases (Qiu et al. 2023).

The term "metabolome" refers to the quantitative and qualitative collection of all low-molecular-weight molecules that are involved in general metabolic reactions and necessary for a cell's growth, maintenance, and normal operation. Metabolome reflects the relationship between our genome and the environment. It comprises exogenous chemicals like environmental pollutants, medications, and toxins that are not naturally produced by an organism, as well as endogenous metabolites that are produced in an organism naturally, such as amino acids, nucleic acids, amines, sugars, fatty acids, vitamins, co-factors, and pigments. In order to detect and measure metabolites in biological samples, metabolomics uses analytical methods like nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry. Numerous tiny compounds, such as neurotransmitters, lipids, amino acids, and organic acids, can be detected using these methods (Belhaj et al. 2021) (Fig. 14.1).

For metabolomics research, the brain's inaccessibility and the energy required to maintain its essential functions present challenges (Ivanisevic and Siuzdak 2015). However, metabolic profiling has rendered insights into the potential roles various

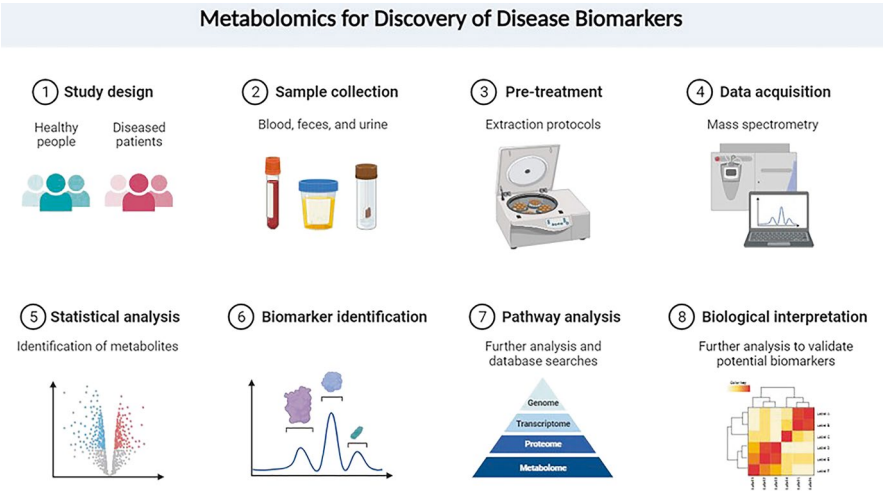

Fig. 14.1 Schematic diagram representing the utility of metabolomics in the identification of disease-specific biomarkers

metabolites could play in neurodegenerative and neurodevelopmental disorders including Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), epilepsy, Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and autism spectrum disorder (ASD).

14.2.1 Alzheimer's Disease

Alzheimer's disease (AD) is characterized by the build-up of tau tangles and amyloid-beta plaques. Metabolomic investigations have revealed modifications in the metabolism of tau and amyloid-beta, along with changes in oxidative stress, lipid metabolism, and neurotransmitter levels. Due to its complexity and heterogeneity, AD is a multifactorial disorder influenced by both genetic and environmental factors (Botas et al. 2015). According to recent research, the gut microbiota may even affect pathological characteristics of AD, such as beta-amyloid deposition and neuroinflammation (Yadav et al. 2023).

Cerebrospinal fluid (CSF) is typically used as the primary sample type in metabolomics research on AD. This biofluid transports nutrients and provides the CNS with mechanical protection. Because the CNS directly affects its composition, metabolic changes brought on by the disease can be more clearly demonstrated in CSF (Roche et al. 2008). The majority of the findings point to modifications in the biochemical pathways involved in energy metabolism, including sugars and amino acids connected to glucogenic and ketogenic energy metabolism. At the clinical stage of AD, glucose hypometabolism is thought to be a typical feature that

indicates a loss of neuronal functions. Glucose hypometabolism is also linked to ageing-related mitochondrial dysfunction and insulin resistance in the brain. Van der Velpen et al. reported modifications to the phosphocreatine degradation and tryptophan pathways. Tryptophan catabolites and amino acids have a particular association that implies a close connection to AD pathology (van der Velpen et al. 2019). There have also been reports of higher lactate levels in CSF samples of AD (Liguori et al. 2015). This falls in line with impaired mitochondrial functioning and glycolysis found in AD. Reduced pyruvate dehydrogenase complex activity and disturbed glycolysis may occur before mitochondrial dysfunction, which can then lead to elevated oxidative stress and molecular structural alterations that lead to deteriorating memory and cognition (Cunnane et al. 2011). Blood-based biomarkers have gained popularity due to the anticipated disruption of the blood-brain barrier with ageing and the increased metabolite exchange between tissues caused by AD (Lista et al. 2013). A transcriptome, metabolome, and lipidome analysis of plasma from 48 people with and without amyloid deposition respectively was carried out by Xicota et al. They identified several transcripts and metabolites associated with inflammation and fatty acid metabolism that are associated with amyloid deposition. The amyloid group had higher levels of medium-chain fatty acids (MCFA), such as octanoic, undecanoic, and hydroxyl-nonanoic acids, as well as 4-nitrophenol. AD is linked to brain glucose hypometabolism. Medium-chain triglycerides (MCT) are hydrolysed in the gut to produce MCFA, primarily decanoic and octanoic acids, which are metabolized to ketones in the liver (Xicota et al. 2019). Further, changes in the amount or composition of membrane lipids in the brain may cause AD. Sphingolipids have been discussed by Mielke as suitable biomarkers to track the advancement of AD and its treatment. Liposomal research has identified several intriguing compounds associated with AD, such as ceramides, phospholipids, and sphingolipids. Memory impairment, hippocampal volume loss, and the advancement of AD have all been related to ceramide levels in the serum and cerebrospinal fluid (Mielke and Lyketsos 2010). Moreover, ceramides have been linked in the past to atherosclerosis and insulin resistance in AD. In individuals with mild cognitive impairment (MCI), an early stage of AD, the levels of histidine and arginine are changed in both CSF and plasma/serum indicating that these two metabolites could serve as non-invasive biomarkers to track the progression of the disease (Xie et al. 2021). Metabolites such as arginine, valine, proline, serine, histidine, choline, creatine, and carnitine have been reported to be altered in metabolic studies using cerebrospinal fluid (CSF) samples from AD patients. Moreover, disruptions in the metabolism of methionine, tryptophan, and tyrosine have been noted, suggesting that these substances may be useful as biomarkers for AD diagnosis (Griffin and Bradshaw 2017). In a study by Milos et al., it was found that AD patients had lower levels of several amino acids and their derivatives such as proline, valine, glycine, succinic acid, serine, threonine, pyroglutamic acid, and glutamic acid than both the MCI group and the healthy controls (Milos et al. 2023).

14.2.2 Parkinson's Disease

Parkinson's disease (PD) is the second-most prevalent neurodegenerative illness in the human population. Its incidence rises with age, similar to AD. One of the primary factors contributing to the disease's progression is dopamine depletion in the secondary basal ganglia, which leads to substantia nigra degeneration, though the precise mechanism underlying this illness is still unknown (Botas et al. 2015). There is extreme dopamine loss, which results in PD patients having less control over their movement patterns and exhibiting rigidity, sluggishness, tremors, and balance issues. Dopamine cell degeneration in PD is caused by several factors, including oxidative stress and excitotoxicity. As PD progresses, the level of urate has been reported to decrease. Urate can complex metallic ions, which lowers reactive oxygen species (ROS) and reactive nitrogen species (RNS), both of which can alter nucleic acids (Cipriani et al. 2010). Hatano et al. (2016) found that several metabolites, including biomolecules involved in purine metabolism, caffeine, and its derivatives, were only significantly reduced in the early stages of the disease in PD patients (Hatano et al. 2016). Caffeine may prevent PD by inhibiting adenosine A2A receptors, which control the release of neurotransmitters like glutamate and dopamine in the central nervous system (Palacios et al. 2012). Lower serum levels of ergothioneine have been reported in PD patients. Ergothioneine is a slowly metabolized antioxidant obtained through diet. It tends to build up in tissues over time and prevents tissue damage by lowering lipid peroxidation levels through s-nitrosoglutathione catabolism (Misiti et al. 2001). Recently, Yang et al. reported that ergothioneine can prevent the build-up of protein amyloid-β in mouse models suggesting that the onset of neurodegenerative diseases may be linked to a drop in serum ergothioneine levels. Furthermore, the heme metabolite biliverdin was reported to have a significantly higher level, and its metabolite, the antioxidant bilirubin, was considerably lower in PD patients (Jin et al. 2016). The quantity of ROS greatly controls the production of bilirubin, a reduced biliverdin product, and biliverdin, a product of oxygenation and reduction reactions of heme (Hatano et al. 2016). A bilirubin/biliverdin ratio may serve as a gauge for the level of reactive oxygen species (ROS) because early-stage PD patients show elevated bilirubin levels due to overexpression of oxidative enzymes, which may be a significant factor in the aetiology of PD. The findings of Hatano et al. are consistent with the theory put forth by Roede et al. that serum bilirubin levels may be correlated with the course of sporadic PD (Roede et al. 2013). The breakdown of heme into bilirubin/biliverdin, free iron, and carbon monoxide is carried out by heme oxygenases (HO), which may be involved in the pathomechanisms of neurodegenerative diseases. HO-1 was discovered to be significantly upregulated in PD-affected SNc astrocytes and was recognized as a Lewy body component through immunohistochemistry. Thus, a decrease in the ratio of bilirubin to biliverdin in the serum may indicate that HO is being overexpressed as a result of systemic oxidative stress (Hatano et al. 2016). Furthermore, in PD, alterations in the kynurenine pathway have been observed. It is estimated that 90% of tryptophan in the brain is metabolized in the kynurenine

pathway. While some of the intermediates, like kynurenic acid, are thought to be intrinsic neuroprotective substances because they primarily function as endogenous antagonists of ionotropic excitatory amino acid receptors, others, like quinolinic acid and 3-hydroxy kynurenine, are neurotoxic. Tryptophan depletion impedes the production of serotonin, a neurotransmitter, and stops T-cell proliferation (Mellor et al. 2003). According to LeWitt et al., one intriguing therapeutic approach involves the idea of inhibiting 3-hydroxykynurenine and stimulating tryptophan breakdown to produce kynurenic acid (Lewitt et al. 2013). Glutathione is another metabolite that combats the oxidative stress of metabolism. LeWitt et al. (2013) found that in post-mortem CSF samples from PD patients, there was an increase in 3-hydroxykynurenine levels and a decrease in glutathione levels. While 3-hydroxykynurenine is an excitotoxic metabolite, glutathione is an antioxidant metabolite that shields the brain from oxidative stress by lowering ROS (Lewitt et al. 2013). Amino acids, such as branched-chain amino acids (BCAAs) including ketoleucine, valine, and isoleucine, are in higher concentrations in the CSF of both PD animal models and patients. The maintenance of glutamate homeostasis, control over protein degradation, and brain energy metabolism all depend on BCAAs. Leucine is the source of up to 50% of all the α-amino groups in glutamate and glutamine. Using the neutral amino acid transporter on astrocytes, leucine enters the brain from the bloodstream more quickly than any other amino acid. After being converted by astrocytes into their corresponding ketoacids, BCAAs are released and subsequently absorbed by neurons. By converting ketoleucine back to leucine and consuming glutamate in the process, this functions as a crucial buffer for glutamate levels in neurons. These findings imply that the neuronal solute transport process may be impacted by the disturbance of BCAA homeostasis (Yudkoff 2017).

14.2.3 Multiple Sclerosis

Multiple sclerosis (MS) is a long-term neurological condition marked by inflammatory, neurodegenerative, autoimmune, and demyelinating processes. MS affects the CNS, and while it usually manifests as relapsing-remitting episodes of clinical deterioration interspersed with periods of remission, the majority of patients eventually experience irreversible neurological disabilities. A combination of techniques including CSF sampling, magnetic resonance imaging (MRI), and observation of nonspecific clinical symptoms is used to diagnose MS. Since these results are not unique to MS, particularly in the early stages of the illness, the diagnosis is typically made later and is frequently mistaken for other neuroinflammatory conditions. However, research indicates that early identification and, subsequently, early therapeutic intervention may lessen the detrimental effects of the disease and slow its progression. Because metabolic biomarkers may be used to help diagnose multiple sclerosis, metabolomic studies have become more and more important in the study of MS. The CSF serves as the primary biofluid source for metabolomics research in MS. Research has shown elevated levels of glucose, lactate, and other metabolites

such as acetone, choline, formate, myo-inositol, and threonate that are thought to be involved in energy metabolism. Comparing patients with MS to healthy controls also showed lower levels of acetate, mannose, citrate, and phenylalanine (Kim et al. 2017). The CSF of patients with MS differs from controls in terms of phenylalanine, tryptophan, and pyrimidine metabolism. Using a blood-based, untargeted approach, a clinical trial conducted in 2019 found 12 candidate metabolites in patients by searching for MS biomarkers. Some of these metabolites included laurate, phosphatidylcholine, pyroglutamate, acylcarnitine C14:1, and N-methylmaleimide. Furthermore, the authors discovered metabolites connected to oxidation, fatty acid metabolism, cellular membrane composition, and glutathione metabolism (Andersen et al. 2019). Further researchers extracted amino acids, polar lipids, acylcarnitines, and free carnitine using liquid chromatography-tandem mass spectrometry (LC-MS/MS) and discovered 30 tear lipid biomarkers including C12 and C14:1 in an MS patient pilot study. MS patients showed greater concentrations of Ser, His, Asp, C5OH/C4DC, C10:1, and C8:1, whereas lower concentrations of C12, C14:1, and C18:1OH were found in tear samples. The most significant lipidomic findings in tears are low concentrations of sphingomyelins in MS patients. Literature reporting low levels of sphingomyelin, an accumulation of neurotoxic ceramides in CSF, and reactive astrocytes in active lesions of patients with MS (Kim et al. 2012) is also consistent with this data. As demyelination and inflammation in the CNS are features of MS, studies on the metabolic pathways have brought attention to alterations in oxidative stress indicators, metabolites linked to inflammation, and lipid metabolism. Sphingosine-1-phosphate and ceramide species are examples of emerging biomarkers that show disease activity and treatment responses (van Kruining et al. 2020).

14.2.4 Epilepsy

One of the first neurological conditions to be identified was epilepsy, which is typified by frequent, unprovoked seizures. Untreated intractable epilepsy culminates in reactive gliosis and significant loss of hippocampal neurons. It involves the occurrence of epileptic seizures caused by aberrant neuronal discharges. One common problem with epilepsy patients is an insufficient response to anti-seizure medications. Patients and the healthcare system are severely burdened financially and socially as a result of these characteristics. Additionally, the type of epilepsy a patient has determines the medication that is best for controlling their seizures; therefore, a proper diagnosis is essential to maximizing treatment efficacy (Stafstrom and Carmant 2015). Cavus et al. initially examined extracellular glutamate in surgical tissue from patients' hippocampi and cortices with medically refractory epilepsy. The study aimed to gain insights into the energetic deficit in these tissues, and their findings raised the possibility that it would cause glutamate transporters and glutamate reuptake to function less effectively (Cavus et al. 2005). Comparing epilepsy patients with controls, the authors found a decrease in the concentrations of glucose, citrate, and lactate and an increase in the concentration of ketone bodies.

The authors hypothesized, based on their observations, that the rise in ketone bodies might be the body's attempt to trigger natural processes in epilepsy patients in order to maximize their energetic resources (Al Zweiri et al. 2010). Segers et al. analysed plasma samples in mice after induction of seizures and found altered metabolite concentrations including glutamate, methionine, lysine, citrulline, and histidine (Segers et al. 2020). Elevated levels of glutamate in serum were found after induction of seizures. Furthermore, certain monoamines such as dopamine and serotonin have been found to decrease in epileptic seizures. As a result, following a seizure, a decrease in the precursors of these neurotransmitters such as tryptophan, phenylalanine, and tyrosine is observed (Boguszewicz et al. 2019). Either a reduction in monoamine levels or excessive consumption may be the cause of this drop in precursor levels. GABA is an inhibitory neurotransmitter used as a substitute energy source for isoleucine and valine, and it can be found at lower levels in epileptic disorders. Other metabolites that are indirectly involved in a seizure include glycine, serine, threonine, methionine, creatine, proline, isoleucine, valine, arginine, and histamine. Furthermore, lower concentrations of asparagine, valine, arginine, and alanine have also been reported in studies on human hippocampal tissue or serum samples (Segers et al. 2020). According to Wang et al. blood matrix metalloproteinase-3 has also been found to be lower in epilepsy patients as compared to healthy controls (Wang et al. 2016). The role of circulating uridine in epilepsy has been observed. Uridine may protect against epilepsy (Zhao et al. 2006). Using MR, which is immune to residual confounding and reverse causality, it was discovered that elevated blood uridine levels were predictive of a higher risk of epilepsy. In a rat model of aminopyridine-induced epilepsy, Slézia et al. have reported an increased level of extracellular uridine, indicating that uridine may be involved in changes in neuronal activity related to epilepsy (Slézia et al. 2004). However, additional research is necessary to explore the underlying mechanisms because there are still gaps in our understanding of uridine's biofunction. Further, it has been proposed that two metabolites, myo-inositol and decanoylcarnitine, may protect against epilepsy (Segers et al. 2020). The concentrations of copper in epilepsy patients receiving antiepileptic medications are altered (Saghazadeh et al. 2017). Higher serum levels of zinc have been shown in epilepsy patients, which later on lowered upon treatment with anti-seizure drugs (Saghazadeh et al. 2015). Studies indicate that Zn administration, at least in those with reduced basal zinc supply/absorption, may be beneficial as an optimizing strategy for epilepsy (Doboszewska et al. 2019). In an effort to better understand the aberrant effects of anti-seizure medications on the developing foetus, the first metabolome-wide association study of these drugs was conducted in pregnant women. The researchers discovered changes in metabolites crucial for neurodevelopment and the health of mothers, such as a reduction in neurosteroids, progesterone, and 3β-androstanediol (Walker et al. 2019). Anti-seizure medications do not work for a sizable portion of epileptic patients, and it typically takes years before alternative therapies, like tissue resection surgery, are indicated. Furthermore, not all forms of epilepsy are candidates for the surgical approach. Consequently, research endeavouring to pinpoint biomarkers or even molecular patterns that may forecast medication reactions in epilepsy is highly

pertinent. The range of medications that epileptic patients take is a major concern when examining their metabolomes, as this is also the case for other neurological disorders. This becomes a significant confounding factor for research on biomarkers. Nevertheless, recent metabolomic studies on patients with epilepsy have not been able to distinguish between different types of seizures and drug responses.

14.2.5 Huntington's Disease

According to Saudou and Herbert, this rare neuropathology, which affects 5–10 subjects per 100,000 in the Caucasian population, is the cause of the decline in neurons involved in cognition and voluntary movements (Saudou and Humbert 2016). Moreover, HD impacts the immune system and metabolism, which results in a host of symptoms like weight loss, osteoporosis, cardiac failure, and behavioural changes like impulsivity, aggression, depression, and anxiety. HD typically strikes adults over 40, and its distinctive diagnosis delay impacts an entire family for many generations. The expansion of a repeating trinucleotide (CAG) in the HTT gene, which codes for the Huntington protein, is the cause of HD, which is inherited (Botas et al. 2015). However, the exact mechanisms underlying the progression of HD remain poorly understood. Even with a constant caloric intake, HD-gene carriers can experience significant weight loss, which is consistent with changes in energy metabolism that fuel the pathological process. Interestingly, the mechanisms underlying some of the metabolic abnormalities linked to HD have been thought to be promising targets for both developing biomarkers for tracking the disease and potential treatments. It is challenging to validate biomarkers for the clinical management of uncommon diseases like HD, despite advancements in analytical platforms for molecular analysis. To gain a better understanding of the relationship between metabolic abnormalities and pathogenesis, it is imperative to comprehend the metabolic pathways that are altered in HD. However, there is currently a dearth of comprehensive knowledge regarding the metabolites that contribute to these traits. Hersch et al. (2006) found that the serum levels of 8-hydroxydeoxyguanosine (8-OHdG), an oxidized derivative of deoxyguanosine, were elevated in HD patients. They used carnitine to lower the levels of 8-OHdG, indicating that this could be a potential treatment option (Hersch et al. 2006). However, different investigators have determined that 8-OHdG is not a useful biomarker for HD in its early stages (Ross et al. 2014). According to reports, branched-chain amino acids (BCAAs) are biomarkers of HD, and researchers have found that HD patients have reduced levels of isoleucine, leucine, and valine when compared to control plasma samples and postmortem human brain samples. In addition to being crucial for the movement of nitrogen between organs and tissues, BCAAs are also involved in the synthesis of CNS neurotransmitters (Sperringer et al. 2017). In the examined samples of postmortem human brain and CSF, metabolites like phenylalanine and tyrosine have decreased in HD patients. Aminoacyl-tRNA biosynthesis involves phenylalanine, isoleucine, valine, and leucine. Additionally, tyrosine may have an impact on

metabolism due to its binding to the wild-type HTT protein at the thyroid hormone receptor-α1, which is involved in the regulation of energy homeostasis. Because it can bind to the wild-type HTT protein, the thyroid hormone receptor-α1 is thus displayed as a specific biomarker of HD (Mastrokolias et al. 2016). Since isoleucine and valine are involved in aminoacyl-tRNA biosynthesis and because ribosomal frameshifting in HD causes an aminoacyl-tRNA depletion, the variation in metabolic profiles of isoleucine and valine in HD patients may be related to aminoacyl tRNA biosynthesis (Buhr et al. 2021).

14.2.6 Amyotrophic Lateral Sclerosis

The neurological condition known as amyotrophic lateral sclerosis (ALS), formerly called Lou Gehrig's disease, affects motor neurons in the brain and spinal cord that regulate breathing and voluntary muscle movement. When motor neurons deteriorate and die, they cease communicating with the muscles, resulting in weakening, twitching, and atrophy of the muscles. The brain eventually loses the capacity to initiate and regulate voluntary movements, including breathing, walking, talking, chewing, and other activities in individuals with ALS. Due to phenotypic heterogeneity, the diagnosis of this fatal and progressive condition is primarily made by clinical observation and may take some time. Approximately 10% of cases are familial, with the remaining 90% being sporadic. They can be inherited in an X-linked, autosomal dominant, or recessive pattern. Among the established pathophysiological mechanisms, ALS patients have been linked to oxidative stress, metabolic changes, such as altered glucose and lipid metabolism, and inadequate energy homeostasis in those with the superoxide dismutase 1 mutation (Zarei et al. 2015). Numerous metabolites such as higher levels of glucose in CSF and α-hydroxybutyrate in CSF and plasma have been found in ALS patients (Wuolikainen et al. 2016). Glutamate has consistently been found to be an important circulating metabolite in ALS patients. A glutamate excess may cause abnormal glutamate receptor activation, which in turn causes an excessive Ca2+ influx in the post-synaptic neuron, resulting in extreme neuronal firing (Le Gall et al. 2020). In ALS patients a significant decrease in asymmetric dimethylarginine (ADMA) in plasma has also been found. ADMA is involved in the synthesis of nitric oxide and the treatment of oxidative stress because it is an endogenous regulator of nitric oxide synthase (Wuolikainen et al. 2016). In patients with advanced ALS, there are abnormally high concentrations of glutamate and indoxyl sulphate, two known neurotoxicity markers. Similarly, advanced ALS patients have more substantial alterations in biochemical pathways linked to neuroinflammation than early ALS patients. Examples of these pathways include the ammonia recycling pathway, which includes the urea cycle and glutamine metabolism (Marino et al. 2022). Tyrosine, which is necessary for the synthesis of dopamine and adrenaline, is found in low concentrations (Daubner et al. 2011). This is consistent with general dysmetabolism in the biochemical pathways linked to the amine ligand-binding receptors, which may worsen the

neurotransmission deficit as ALS progresses. Although this is not easily seen in the CSF (Toczylowska et al. 2013), blood levels of acetate are elevated in ALS patients (Kumar et al. 2010). One important metabolite in the oxidation of fatty acids is acetate. Changes in circulating acetate may be caused by excess production via an increase in fatty acid oxidation, increased release from degenerating muscle cells, or other disruptions to mitochondrial membrane integrity. This is because acetate synthesis occurs before citric acid is formed in the Krebs cycle. These possible mechanisms fit the pathophysiology of ALS. Growth hormone (in CSF and blood) and gastric inhibitory peptide (in blood) have also been reported to be reduced in ALS patients (Saccà et al. 2012). On the other hand, ALS patients' saliva and blood exhibit elevated or dysregulated levels of hormones that support catabolism, such as cortisol and adiponectin (Ngo et al. 2015). Moreover, ALS patients' plasma or blood also has lower levels of ghrelin, a key appetite modulator (Czell et al. 2016). Given the severity of this illness, additional research aiming at identifying novel therapeutic targets, particularly through the use of metabolomics, may prove crucial to the care of ALS patients.

14.2.7 Autism Spectrum Disorder (ASD)

ASD is a group of neural development disorders that are defined by restricted and repetitive behaviours and difficulties in social interaction and communication. In a recent meta-analysis, cobalt, copper, selenium, iron, and zinc were analysed (Saghazadeh et al. 2015). Higher levels of copper were found indicating oxidative damage. It is a component of superoxide dismutase, which is linked to a reduction in defence against oxygen free radicals and the detoxification of free radicals. Iron deficiency was observed which points towards anaemia and emotional and behavioural problems. The brain's most prevalent transition metal, iron (Fe), is essential for several neurological processes, including the production of neurotransmitters, synaptic plasticity, neuronal myelination, mitochondrial activity, and electron transport. Thus, sufficient iron availability is required for neurodevelopmental processes. Furthermore, low levels of zinc were found in ASD patients indicating resistant and recurrent infection, mental retardation, and hyperactivity. Zinc is involved in primary metabolic pathways of macronutrients, nucleic acids, heme synthesis, and connective tissue. Cognitive development may be impacted by zinc deficiency. As a key excitatory molecule in the brain, glutamate metabolism changes can cause imbalances in the excitation/inhibition balance of neural networks, potentially resulting in symptoms resembling autism. Rangel-Huerta et al. (2019) report a comparable drop in plasma glutamate levels between the non-mental regression (ANR) and mental regression phenotype AR subgroups of ASD and the healthy kids. The metabolism of BCAAs was also observed to be potentially altered in ASD, as evidenced by the accumulation of various alpha-keto derivates, including 3-methyl-2-oxobutyrate, 3-methyl-2-oxovalerate, and 4-methyl-2-oxopentanoate. These accumulations suggest that these substances have a lower rate of TCA cycle

incorporation, which may have an impact on changes in anabolic processes and energy production. Compared to children in good health, tryptophan levels were significantly higher in both subgroups (ANR and AR). Additionally, the ANR group had higher levels of other tryptophan-associated metabolites, including kynurenine, 5-bromotryptophan, 3-indoxyl sulphate, indolelactate, and 6-hydroxyindole sulphate (Rangel-Huerta et al. 2019). Further, urine samples of children with ASD showed higher levels of hippurate, 3-(3-hydroxyphenyl)-3-hydroxypropionic acid (HPHPA), 3-hydroxyphenyl acetic acid (3HPA), 3-hydroxy hippuric acid (3HHA), indole-3-acetic acid, indolyl lactate, glycolic acid, tryptophan, and serotonin and lower melatonin levels (Liang et al. 2020a, b). This result was consistent with melatonin dysfunction, which causes patients with ASD to experience disruptions in their sleep-wake cycles (Wu et al. 2020). Disruption of the tryptophan kynurenine pathway has been shown in ASD, indicating that different neuroinflammatory states of ASD are associated with activation of the kynurenine (KYN) pathway (Bryn et al. 2018). In autism spectrum disorders, altered metabolites of the kynurenine pathway represent a novel potential biological diagnostic marker. The disruption of the tryptophan kynurenine pathway and the pathogenesis of autism have been linked to an increase in 7,8-dihydro neopterin and neopterin, which are markers of reactive oxygen species (Liang et al. 2020a; b). Children with ASD also showed higher levels of these two metabolites in their urine (Liang et al. 2020a, b). The elevated levels of creatinine and decreased levels of creatine in the urine of female children with ASD also suggested abnormalities in arginine metabolism (Xiong et al. 2019). Children with low communication scores had lower blood levels of the tyrosine intermediate N-formylphenylalanine than children with normal scores (Kelly et al. 2016). Additionally, patients with ASD were found to have altered branched-chain amino acid (BCAA) metabolism, as evidenced by elevated blood levels of alpha-keto derivatives from BCAA catabolism (Rangel-Huerta et al. 2019). Children with ASD have been shown to have elevated ratios of particular amino acids, including glutamine, glycine, and ornithine, when combined with BCAA (Smith et al. 2019). The branched-chain ketoacid dehydrogenase kinase enzyme deficit was thought to be the source of these abnormalities (Smith et al. 2019). Research employing diagnostic methods has suggested that the detected changes in metabolism could contribute to a deeper comprehension of the processes that either initiated or exacerbated an illness. However, understanding how disease-modifying metabolic pathways affect physiology, among other things, can help identify new targets for treatment (Wilkins and Trushina 2018). Identifying the mechanisms and errors in the biochemical pathways underlying each of the neurodegenerative diseases may be aided by the biomarkers reviewed in this article. It is imperative to emphasize that numerous constraints need to be addressed to utilize metabolomics for research purposes that will be beneficial in terms of diagnosis. Furthermore, the precise disease-specific identification of prognostic and diagnostic biomarkers will contribute significantly to the provision of important information regarding the course of treatment, the therapy's response, and associated variations in the disease's mechanism (Fig. 14.2).

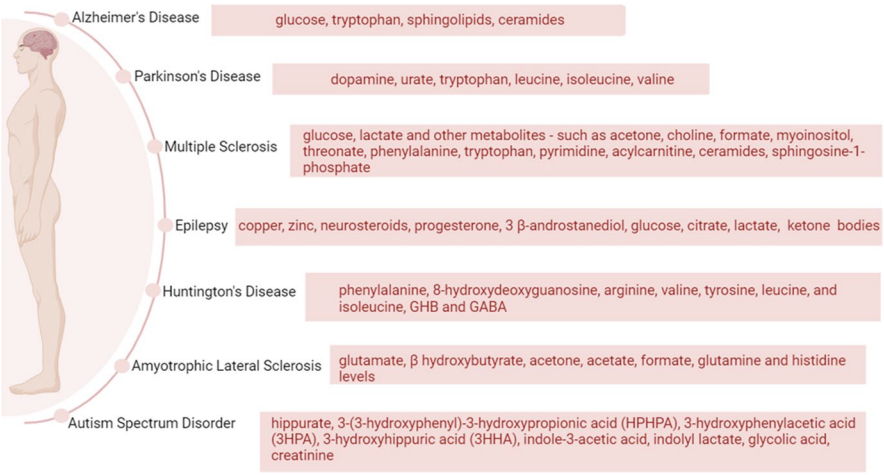

Fig. 14.2 Diagrammatic representation showing altered metabolites in neurodegenerative and neurodevelopmental disorders

14.3 Symptomatic Treatments of NDDs

Treatment for neurodegenerative diseases is primarily symptomatic such as dopaminergic treatment for PD, anti-amyloid antibody for AD, anti-chorea drugs for HD, glutamate antagonists in ALS, anti-convulsants in epilepsy, behavioural therapies for ASD and ADHD, anti-inflammatory and analgesic medications for neuronal infections and pain, cholinesterase inhibitors for cognitive impairments, antipsychotic medications for dementia, and so on. In this section, we will be dealing with ongoing symptomatic treatments in the management of NDDs.

One way that AD damages the brain is by lowering acetylcholine levels, a chemical messenger essential for cognition, judgement, memory, and attentiveness. By stopping acetylcholine from being broken down in the brain, cholinesterase inhibitors increase the quantity of acetylcholine that is available to nerve cells. Drugs such as galantamine (Razadyne), rivastigmine (Exelon), and donepezil (Aricept) aid in raising acetylcholine levels, which are frequently low in Alzheimer's patients (Cummings et al. 2010). These medications may lessen behavioural problems and enhance cognitive performance. Memantine (Namenda), an antagonist for N-methyl-D-aspartate (NMDA) receptor, alleviates problems related to cognition and function by regulating the activity of glutamate (Areosa et al. 2005). Aducanumab is a human immunoglobulin gamma 1 (IgG1) monoclonal antibody which works by binding aggregated soluble oligomers and insoluble fibrils of Aβ plaques. Aducanumab's higher selectivity for aggregated Aβ forms reduces Aβ plaques in the brain (Sevigny et al. 2016), and lecanemab is a humanized monoclonal antibody that has a strong affinity for soluble Aβ protofibrils. Lecanemab is thought to target the most hazardous pathologic amyloid species since it has a high selectivity for soluble aggregated species of Aβ relative to monomeric amyloid and a modest preference for fibrillar

amyloid. It prevents amyloid plaques in the brain from aggregating (van Dyck et al. 2023). Brexpiprazole is a typical anti-psychotic drug used to improve agitation in Alzheimer's dementia (Grossberg et al. 2023).

Currently, no medication can cure PD, although there are treatments that can provide significant symptomatic alleviation of the motor symptoms. Levodopa, a naturally occurring amino acid that is metabolized to dopamine in the brain, is considered the most effective drug available for PD. Further, carbidopa is added to levodopa formulations which lower peripheral conversion of L-dopa to dopamine, lessen gastrointestinal side effects, and improve levodopa bioavailability in the CNS (Deleu et al. 2002). Carbidopa, also known as 1-α-methyldopa hydrazine, functions by permanently attaching to pyridoxal 5′-phosphate (PLP) and preventing the PLP-dependent enzyme l-aromatic amino acid decarboxylase (AADC). 5-Hydroxytryptophan is converted to serotonin by AACD, while L-dopa is converted to dopamine. The best medication now available to treat PD motor symptoms is carbidopa-levodopa treatment. Anti-cholinergic drugs were the first to be developed to treat PD symptoms, and they are still widely used today, both as stand-alone treatments and as components of combination therapy. They are often thought to have a less desirable side effect profile than other anti-parkinsonian medicines, particularly in terms of neuropsychiatric and cognitive adverse effects. They are reported to be more effective at treating tremors than other parkinsonian symptoms. Trihexyphenidyl (Artane) and other medications may be used to treat tremors and dystonia (involuntary muscular contractions) in PD (Jankovic 2008). Dopamine agonists, such as pramipexole (Mirapex) and ropinirole (Requip), work in the brain similarly to dopamine and relieve motor symptoms (LeWitt 2008). Monoamine oxidase (MAO), a riboflavin protein, is present on the outer membrane of mitochondria. It causes the oxidative deamination of monoamine neurotransmitters such as dopamine, norepinephrine, phenethylamine, and 5-hydroxytryptamine as well as tyramine. MAO-B drugs such as safinamide, rasagiline, and selegiline selectively increase dopamine levels in synaptic clefts by inhibiting MAO-B activity in the brain, preventing dopamine catabolism, and improving dopamine signalling (Alborghetti and Nicoletti 2019). In addition to carbidopa-levodopa therapy, a class of medications known as catechol-O-methyl transferase (COMT) blockers is used to treat PD symptoms. COMT inhibitors can improve the efficacy of carbidopa-levodopa therapy. COMT is a natural enzyme. When a person takes levodopa, COMT can deactivate it before it reaches the central nervous system. COMT inhibitors such as entacapone (Comtan) and tolcapone (Tasmar) extend the effects of levodopa by obstructing its breakdown. COMT inhibitors may help to minimize the motor fluctuations found in many persons with PD (Fabbri et al. 2022). For restless legs syndrome, dopamine agonists like ropinirole are the first line of treatment; bromocriptine is used to treat neuroleptic malignant syndrome. In order to treat dopamine antagonist-induced hyperprolactinaemia, dopamine agonists are also administered (Choi and Horner 2023).

Symptomatic treatment continues to be the mainstay of medical management since there are no neuroprotective medications that effectively slow Huntington disease's (HD) progression. The numerous symptoms of HD have been addressed by

several drug classes. Anti-parkinsonian drugs, such as levodopa, dopamine agonists, and amantadine, may be effective for people with the akinetic form of HD (Westphal variant). They lead to improvement in motor function and depressive symptoms (Low et al. 1974). Chorea is a movement disease characterized by sudden, unintentional, and uncontrollable jerky movements of the arms, legs, and facial muscles due to the overactivity of dopamine in brain areas that control the movement. Tetrabenazine, amantadine, or riluzole is prescribed for the treatment of chorea (Armstrong et al. 2012). These medications, however, do not influence the course of the disease. Citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), and sertraline (Zoloft) medications help in the treatment of obsessive-compulsive disorder that arises in the course of HD (Pla et al. 2014). Anti-convulsants such as divalproex (Depakote), carbamazepine (Tegretol, Carbatrol, Epitol, and others) and lamotrigine (Lamictal) are mood-stabilizing medicines that can help prevent the highs and lows associated with bipolar disease (Pla et al. 2014). Olanzapine (Zyprexa) and quetiapine (Seroquel) reduce agitation, violent outbursts, and other symptoms of mood disorders or psychosis (Andriessen et al. 2022).

There are certain medications that alleviate the symptoms of ALS including glutamate antagonists. Riluzole is used for the treatment of ALS. It acts by decreasing glutamate release, a neurotransmitter that can contribute to motor neuron injury. Riluzole inhibits the release of glutamate from presynaptic terminals while promoting the absorption of glutamate extracellularly. Additionally, the drug maintains voltage-dependent sodium channels in an inactive state and suppresses reactions mediated by N-methyl-D-aspartate receptors. Riluzole also inhibits some of glutamic acid's post-synaptic actions via non-competitive inhibition of N-methyl-D-aspartate (NMDA) receptors. Riluzole possesses neuroprotective, sedative, and anti-convulsant effects in vivo (Doble 1996). Edaravone is another ALS drug. It is an antioxidant that may help minimize oxidative stress and halt the symptoms of diseases (Abe et al. 2014). Most patients develop chronic respiratory insufficiency during the disease due to gradual weakness of the diaphragm and auxiliary respiratory muscles. Respiratory issues in ALS often develop slowly; consequently, abrupt deterioration should prompt diagnostic testing to rule out consequences such as atelectasis, pneumonia, or pulmonary embolism. Non-invasive ventilation (NIV) is the provision of ventilatory support via the upper airways without the use of invasive artificial airways such as endotracheal tubes or tracheostomy. NIV has emerged as a critical component of ALS treatment (Dorst et al. 2017). Sodium phenylbutyrate-taurursodiol (Relyvrio) approved by the FDA in 2022 has been shown to delay the pace of functional deterioration in persons with ALS by roughly 25%. It may also help people with ALS live an extra 6 months (Aschenbrenner 2023).

Different types of drugs are available to treat symptoms related to MS which are discussed in this section. Diazepam (Valium) is used to relax muscles (From and Heltberg 1975). The most often used antispastic medicines orally are tizanidine and baclofen (Orsnes et al. 2000), both of which reduce "spinal spasticity" significantly. Neurogenic bladder dysfunction (NBD) can occur in up to 80% of MS patients and significantly reduces quality of life. Oxybutynin and tolterodine have been shown to lessen incontinence and urgency in overactive bladder patients (Chancellor et al.

2001). Gabapentin and pregabalin are medications used to treat neuropathic pain (Dworkin et al. 2003). Up to 70% of people with chronic MS have dysfunctional cognitive functions. Implicit function and speech are rarely impacted, but attentional domains, memory, executive functions—particularly "multitasking" skills—and constructive visual skills are the most commonly affected areas. Cholinesterase inhibitors such as physostigmine and donepezil, as well as 4-AP and amantadine, have been examined for their influence on cognitive impairment in MS (Henze et al. 2006). People with MS develop exhaustion; the medications amantadine and modafinil are used to treat these symptoms they act as neurostimulants. Pregabalin and gabapentin work by reducing calcium influx and the subsequent release of excitatory neurotransmitters. Dimethyl fumarate (Tecfidera), diroximel fumarate (Vumerity), monomethyl fumarate (Bafiertam), ozanimod (Zeposia), and ponesimod (Ponvory) are generally prescribed to reduce the relapse rate in MS (Henze et al. 2006). They cause the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathways to be activated. This mechanism is activated in cells in response to oxidative stress and helps in the reduction of relapse rate. Inhibitors of serotonin-norepinephrine reuptake and selective serotonin reuptake inhibitors (SSRIs) (SNRIs): These medications are used to treat mood disorders (Feinstein et al. 2014). SSRIs work by blocking serotonin reuptake and thereby enhancing serotonin activity; hence they help in reducing anxiety and depression.

Multiple approaches can be used to treat epilepsy. Medication is usually required to control seizures and treat epilepsy; these regularly prescribed medications are known as anti-convulsants. Phenytoin is used in the management and treatment of epilepsy, generalized tonic-clonic seizures, complex partial seizures, and status epilepticus by stabilizing voltage-gated sodium channels in neurons. Valproic acid has a broad spectrum of activity and is used for various seizure types. It is concerned with the pre- and post-synaptic regulation of GABAergic transmission. VPA promotes the inhibitory activity of gamma-aminobutyric acid (GABA) using both pre- and post-synaptic pathways, increasing synaptic GABA availability and facilitating GABA-mediated responses (Romoli et al. 2019). Epilepsy surgery refers to the many types of brain surgery (also known as neurosurgery) that some people with epilepsy undergo to halt or minimize their seizures. There are various types of epilepsy surgery. One type of surgery includes removing a specific area of the brain presumed to be the source of the seizures. Another method is to isolate the area of the brain that is triggering the seizures from the rest of the brain (Bromfield et al. 2006). Lamotrigine is used to treat partial seizures, primary generalized tonic-clonic seizures, the maintenance of bipolar I illness, and Lennox-Gastaut syndrome. Lamotrigine binds to and inhibits voltage-gated sodium channels, thereby stabilizing presynaptic neuronal membranes and inhibiting presynaptic glutamate and aspartate release (Marson et al. 2007). Topiramate is a medication that is used to treat seizures in both adults and children. Topiramate inhibits voltage-gated sodium channels, which most likely results in seizures with persistent depolarization control (Marson et al. 2007). In order to stop seizures, a vagus nerve stimulator device is surgically inserted beneath the skin on the chest and electrically stimulates the nerve that passes through the neck. Regular, mild electrical energy pulses sent to the

brain through the vagus nerve are helpful to prevent or minimize seizures (Krahl 2012). Carbamazepine is commonly prescribed for focal seizures and generalized tonic-clonic seizures. Through the reduction of high-frequency repeated firing of action potentials and influence on synaptic transmission, it enhances sodium channel inactivation. Clobazam is a benzodiazepine anti-convulsant. It has been demonstrated to be an effective anti-convulsant in previously untreated children with focal seizures, with efficacy comparable to phenytoin or carbamazepine. Clobazam is also effective as an adjunct treatment for refractory focal epilepsy in both children and adults (Arya et al. 2018). Oxcarbazepine medication is used to treat focal seizures. This suppresses high-frequency repeated neuronal activity via binding to sodium channels. Oxcarbazepine also prevents glutamate release (Preuss et al. 2023).

There is no cure for autism spectrum disorder, and no medication is currently available to treat it. However, some medications can assist with linked symptoms such as depression, seizures, sleeplessness, and difficulty concentrating. Medication is most effective when paired with behavioural therapy. Because the efficacy of medications in treating the core symptoms of autism has not been proved, they are largely used to treat related symptoms of autism spectrum disorder, i.e. irritability, aggression, self-injurious behaviours, anxiety, hyperactivity, impulsivity, inattention, and sleeplessness are some of targeted related symptoms. Olanzapine, lurasidone, quetiapine, ziprasidone, and paliperidone are some of the drugs used to treat irritability in autism disease patients. Acute haloperidol administration has been proven to benefit hyperactivity, temper tantrums, withdrawal, stereotyped behaviours, and enhancing learning on discrimination (Campbell et al. 1982). Applied behaviour analysis (ABA) is a treatment that is based on learning and operant conditioning ideas. It consists of particular intervention goals combined with positive reinforcement (verbal praise, tokens, or culinary incentives), with repetition of learning trials being a significant component. Pivotal response treatment (PRT) is based on applied behaviour analysis (ABA) concepts. Instead of focusing on a single behaviour, the PRT therapist focuses on "pivotal" areas of a child's development. PRT generates improvements in other aspects of social skills, communication, behaviour, and learning by focusing on critical areas (Koegel et al. 1999). Venlafaxine, mirtazapine, and clomipramine are some of the other antidepressants. Divalproex sodium may be beneficial for patients with ASD, especially those who also exhibit impulsivity, aggression, and affective instability, as well as those who have a history of seizures or aberrant EEG readings (Hollander et al. 2001). Risperidone showed long-term efficacy and tolerance in the treatment of children with autism who exhibit tantrums, hostility, and/or self-injurious behaviour. Risperidone's mode of action is associated with its affinity for the 5-HT_2A serotonin receptor and the dopamine D2 receptor, in addition to binding to α_1 e α_2 adrenergic and H1-histaminergic receptors. Risperidone binds by inhibiting D2 and 5-HT_2A receptors, as well as antagonists of adrenergic α_1 e α_2 and histamine H1 receptors. Aripiprazole is a partial agonist of the D2 (dopamine), D3, and 5-HT_{1A} (serotonin) receptors. It also acts as a 5-HT_2A receptor antagonist. It has a high affinity for D2, D3, 5-HT1A, and 5-HT2A receptors (Gründer et al. 2006). Aripiprazole is beneficial in the treatment of irritability associated with autism in children and

adolescents. It works as an anti-psychotic by inhibiting dopamine D2 receptors in the brain. Selective serotonin reuptake inhibitors (SSRIs) raise serotonin levels in the brain, which helps improve mood and anxiety. SSRIs include the drugs fluoxetine (Prozac), sertraline (Zoloft), fluvoxamine (Luvox), and citalopram (King et al. 2009; Liang et al. 2022).

Attention-deficit hyperactivity disorder (ADHD) therapies often include medication, education, skill training, and psychological counselling. Often, a combination of these is the most effective treatment. Behavioural treatment can also aid in the management of ADHD symptoms by encouraging positive adjustments and boosting self-control and self-esteem. Behavioural treatment for ADHD entails recognizing harmful behaviours and attempting to replace them with beneficial ones. According to research, behavioural therapy is an effective strategy to manage ADHD symptoms in children, teenagers, and adults (Pfiffner and Haack 2014). Parental behavioural training teaches parents how to reward positive behaviours, set clear expectations, and manage challenging behaviours. Teachers use behavioural classroom interventions to encourage positive behaviour and academic success in the classroom. Individual counselling includes offering assistance with emotional and social difficulties connected with ADHD (Pfiffner and Haack 2014). Medications can assist with many of the symptoms of ADHD, but they do not cure it. Stimulants can help with ADHD symptoms like short attention span, impulsive behaviour, and hyperactivity. These medications help roughly 70% of adults and 70–80% of children with ADHD symptoms. They have been shown to lessen interruptions, fidgeting, and other hyperactive symptoms. Stimulants, such as methylphenidate or amphetamine-containing drugs, are the most usually recommended treatments for ADHD. Methylphenidate is the most commonly prescribed psychostimulant. Treatment with psychostimulants results in behavioural changes such as sustained attention, impulse and reduction of task-irrelevant activity, and emotional control reduction of noisy and disruptive behaviour and aggression (O'Driscoll et al. 2005). Methylphenidate inhibits the reuptake of two neurotransmitters in presynaptic neurons: norepinephrine (NE) and dopamine. It specifically blocks these neurotransmitter transporters, which causes dopamine and NE levels in the synaptic cleft to rise. This causes the central nervous system to experience its well-known stimulating effect. Amphetamine is a CNS stimulant that works by boosting the levels of dopamine, norepinephrine, and serotonin (to a lesser extent) in the synaptic cleft (Martin and Le 2023). It reduces the severity of symptoms of ADHD (Fig. 14.3).

14.4 Potential Metabolic Targets and Therapeutic Interventions in NDDs

Severe metabolic anomalies are present in neurodegenerative diseases. There is currently no known cure for these diseases. However, approaches employing metabolic targets could be proven beneficial in protecting against these diseases.

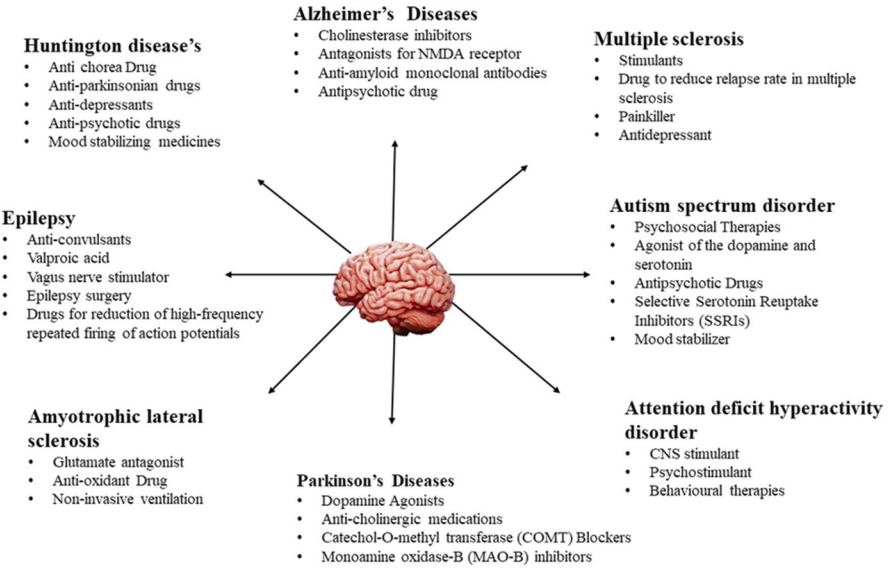

Fig. 14.3 Schematic representation of symptomatic treatment of neurodegenerative diseases

14.4.1 Triggering Receptor Expressed on Myeloid Cells 2 (TREM2)

Triggering receptor expressed on myeloid cells 2 (TREM2) is a single-pass transmembrane receptor whose expression is restricted to microglia in the brain and macrophages in the peripheral regions. This receptor is important in the maintenance of microglial metabolic fitness under stress conditions, and it facilitates the acquisition of disease-associated microglia (DAM) profile (Ulland and Colonna 2018). In recent investigations, TREM2 has been recognized as a risk factor associated with AD. TREM2 maintains cellular energetic and biosynthetic metabolism during AD, enabling microglial responses (Li et al. 2023). In AD patients as well as mouse models, defected TREM2 leads to impairment in mTOR signalling and enhancement of AMPK activation in microglia which results in increased autophagy and low ATP levels, ultimately leading to exacerbation of AD neuropathology (Ulland and Colonna 2018). Hence, TREM2 is a potential metabolic therapeutic target (Li and Zhang 2021).

14.4.2 Acyl-CoA Cholesterol-Acyltransferase (ACAT1)

ACAT, also referred to as sterol O-acyltransferase, is an enzyme that is crucial for regulating the cholesterol homeostasis in cells (Chang et al. 2009). Abnormally high levels of cholesterol, particularly free (unesterified) cholesterol, have detrimental effects (Tabas 2002). ACAT prevents excessive accumulation of free cholesterol at cellular membranes by converting it into cholesteryl esters (Chang et al. 2009). Cholesteryl esters are found as cytoplasmic lipid droplets in the majority of cell types. The lipoprotein known as chylomicrons, which transports cholesterol in the blood, contains cholesteryl esters as one of its core lipid moieties in the small intestine (Feingold 2021). Cholesterol metabolism is linked with AD at several stages (Shibuya et al. 2015). According to recent studies in mouse models, inhibiting ACAT1 is beneficial in AD (Shibuya et al. 2015).

14.4.3 Phosphodiesterases (PDEs)

PDEs (cyclic nucleotide phosphodiesterases) are a class of enzymes that regulate the rate of cAMP and cGMP hydrolysis. As a result, these enzymes play an important role in the regulation of signals mediated by these second messengers (Bender and Beavo 2006). In various animal models of AD, it has been demonstrated that certain phosphodiesterase (PDE) inhibitors enhance memory function. By increasing cAMP and/or cGMP levels, PDE inhibitors control signalling pathways. This may eventually promote gene transcription by triggering the cAMP response element-binding (CREB) (Scott Bitner 2012). CREB is a cellular transcription factor that binds to cAMP response elements (CRE) in DNA, altering the transcription of downstream genes involved in neural plasticity and neuroprotection (Scott Bitner 2012). The most consistent markers of PDE inhibitor activity are increase in cAMP and/or cGMP levels (Delhaye and Bardoni 2021). Increased levels of cAMP and/or cGMP in the endothelial cells of brain vessels and/or neurons have been proposed to be the mechanism by which PDE inhibitors affect cognition or the pathophysiological mechanisms of AD (Sheng et al. 2022). In animal models of AD, rolipram, a specific PDE4 inhibitor, was the first drug to successfully improve cognitive deficits. PDE5 inhibitors have also been demonstrated to successfully restore memory function (Liu et al. 2019). Therefore, in both AD and non-AD animal models, inhibitors of other members of the PDE family may also enhance memory function. The data supports the use of PDE inhibitors as cognitive enhancers in AD (Rose et al. 2005). PDE1B and PDE10 have been extensively studied in Huntington's and Parkinson's diseases due to their high abundance in striatal neurons (Bollen and Prickaerts 2012).

14.4.4 Iron and Ferroptosis

Iron is essential for brain development, neurogenesis, cognitive functions, and normal physiological functions such as mitochondrial respiration, myelin synthesis, neurotransmitter synthesis and metabolism (Belaidi and Bush 2016). Brain regions (substantia nigra, putamen, globus pallidus, caudate nucleus) that have been associated with neurodegenerative disorders have shown progressive accumulation of iron. Dysregulation of iron metabolism can lead to cellular damage and oxidative stress (Berg and Youdim 2006). Ferroptosis is a type of cell death caused by iron metabolism, amino acid metabolism, and lipid metabolism, all of which affect iron ion accumulation (Zhao et al. 2023). Iron is required as a redox metal in a variety of physiological functions. Ferroptosis has been found to play a crucial role in the AD pathogenesis. Disruption of iron homeostasis leads to the formation of senile plaques (SP) and neurofibrillary tangles (NFTs). Ferroptosis features, such as abnormal iron accumulation, glutamate excitotoxicity, and lipid peroxidation accumulation, can be found in the brain tissues of AD patients and mouse models (Lyras et al. 1997). Since AD and Aβ have a strong correlation, lowering Aβ levels in the brain should be beneficial for treating AD (Arendash et al. 2009). The Aβ peptide is released from APP through endoproteolytic cleavage by two proteases known as β- and γ-secretase. A potential strategy would be to block the enzymes responsible for producing Aβ (Vassar 2004).

14.4.5 γ-Secretase and β-Secretase Inhibitors

γ-Secretase is a pivotal enzyme responsible for the formation of beta-amyloid [Aβ peptides [$A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$], from amyloid precursor protein (APP). Inhibiting γ-secretase is one of the potential therapeutic targets (D'Onofrio et al. 2012). Preclinical studies in rodent models have shown γ-secretase inhibitors can reduce Aβ. However, γ-secretase inhibitors also cause abnormalities in the gastrointestinal tract, thymus, and spleen in rodents (Barten et al. 2006). This significant toxicity in experimental animals and humans is due to the inhibition of notch cleavage, a transmembrane receptor which is responsible for cell communication and determination (Panza et al. 2011). This could explain why treatments based on this pathway have failed in various clinical trials to date. Semagacestat (LY-450139), a γ-secretase inhibitor, for instance, in phase 3 trials failed to improve cognitive abilities, and in patients receiving higher doses, it worsened cognitive functioning and increased the risk of infections and skin cancer (Doody et al. 2013). The phase 3 trial of another γ-secretase modulator, tarenflurbil, was terminated due to poor penetration in the brain (Imbimbo 2009). Avagacestat (BMS-708163), an oral γ-secretase inhibitor, when compared to the control group, was associated with several side effects, including skin cancer, renal dysfunction, and brain atrophy (Coric et al. 2015). In order to overcome the previous limitations, new notch-sparing γ-secretase inhibitors

are being developed. One of the main therapeutic targets for Alzheimer's disease (AD) is the β-secretase BACE1 (β-site APP cleaving enzyme) (McDade et al. 2021). Presently, inhibitors of BACE1 are being investigated for their ability to reduce Aβ concentrations in the brain and to both treat and prevent AD (Yan and Vassar 2014). Presently two β-secretase inhibitor drugs elenbecestat (E2609) and umibecestat (CNP520) are under phase 2 and phase 3 clinical trials, respectively (Cummings et al. 2019).

14.4.6 Carbonic Anhydrase

Carbonic anhydrases (CAs) belong to ubiquitously expressed metalloenzymes that catalyse the reversible hydration/dehydration of CO_2/HCO_3 (Ciccone et al. 2021). They play a vital role in pH balance of tissues by catalysing the reversible hydration of carbon dioxide (CO_2) and dehydration of bicarbonate (HCO_3^-) in a two-step reaction (Boone et al. 2014). The correlation between neuronal excitability and γ-aminobutyric acid (GABA)ergic depolarization is well understood. Carbonic anhydrase membrane-permeable inhibitors can inhibit HCO_3-dependent depolarization (Bruno et al. 2016). The inhibition of CAs has pharmacologic applications for many neurological diseases. Several clinical and experimental studies have demonstrated the anti-convulsant effects of carbonic anhydrase inhibitors including acetazolamide (Szaflarski et al. 2016), methazolamide (Rauh and Gray 1968), topiramate (Shank et al. 1994), and zonisamide (Wilensky et al. 1985). In epilepsy, carbonic anhydrase II, VII, and XIV isoforms are implicated, and these isoforms are used as anti-convulsants in epilepsy treatment (Ciccone et al. 2021). The carbonic anhydrase VII isoform expressed mainly in the cortex, hippocampus, and thalamus of the brain is involved in neuronal excitation through promoting GABAergic excitation induced by bicarbonate during GABA receptor activation (Halmi et al. 2006).

14.4.7 Erythropoietin (EPO)

Erythropoietin is a 34-kDa glycoprotein hormone that facilitates red blood cell synthesis under hypoxic conditions (Jelkmann 2004). Both in vitro and in vivo (Brines et al. 2000; Buemi et al. 2002) studies have demonstrated that EPO exerts neuroprotective effects in neurological disorders by ameliorating the process of neurogenesis. Erythropoietin (EPO) protects neurons and astrocytes by diminishing molecules that cause harm to tissue, including glutamate, reactive oxygen species, inflammatory cytokines, and other damaging molecules (Chu et al. 2008). In a chemically induced animal model of epilepsy, EPO has been able to protect against blood-brain barrier (BBB) disruption (Uzüm et al. 2006), reduce the severity of seizures and prevent abnormal neurogenesis (Kondo et al. 2009), inhibit proinflammatory markers (Bahçekapılı et al. 2014), and prolong seizure latency (Kapucu et al. 2020).

According to Sanchez et al. (2009), increased receptor expression in neurons is necessary for erythropoietin to exhibit neuroprotective effects. Ott et al. (2015) reported the upregulation of erythropoietin receptors in the hippocampus of drug-resistant epileptic patients. Therefore, it is suggested that synthesizing EPO-derived mimetic peptides could be used as a therapeutic target for the treatment of both drug-resistant and epileptic seizures.

14.4.8 Transient Receptor Potential Vanilloid Type 1 (TRPV1)

Transient receptor potential vanilloid type 1 (TRPV1) belongs to the vanilloid TRP family, and it is a ligand-gated, nonselective cation channel. Hippocampal neurons with accumulated calcium ions are the major contributors to epilepsy aetiology. In the hippocampus, TRPV1 is a calcium-permeable channel that mediates epilepsy (Nazıroğlu 2015). TRPV1 is expressed in brain regions associated with epilepsy, including the dentate gyrus of the hippocampal region and the CA1 area (Nazıroğlu 2015). In *TRPV1* knockout mice, a decrease in duration of seizure, seizure severity, seizure susceptibility and delayed seizure latency were observed (Huang et al. 2015). In vitro studies in mice showed that capsazepine (CPZ), a TRPV1 antagonist, showed suppressed epileptiform activity in hippocampal slices, whereas capsaicin, a TRPV1 agonist, enhanced epileptiform activity (Gonzalez-Reyes et al. 2013). Therefore, TRPV1 inhibition in the hippocampal region could be a novel target for preventing epileptic seizures.

14.4.9 Disease-Modifying Therapies (DMTs)

The first line of DMTs include interferons, glatiramer acetate, teriflunomide, and dimethyl fumarate (DMF). Interferon therapy involving INFβ-1a and INFβ-1b inhibits T-cell proliferation, leukocyte migration across the BBB, and shift of cytokines from pro-inflammatory to anti-inflammatory (Dhib-Jalbut and Marks 2010). Glatiramer acetate is the combination of four myelin basic proteins (MBP) resembling polypeptides. It exhibits a strong affinity to MHC molecules and inhibits the T-cell response against several myelin proteins; therefore, it has been a promising drug in preventing experimental autoimmune encephalomyelitis (EAE) by reducing the activity of monocytes and dendritic cells and enhancing the secretion of neurotrophic factors such as brain-derived neurotrophic factor (Schrempf and Ziemssen 2007). Teriflunomide is a dihydroorotate dehydrogenase (DHODH) inhibitor which reversibly blocks DHODH, a mitochondrial enzyme essential for de novo pyrimidine synthesis, and hence reduces the proliferation of lymphocytes in blood (Papadopoulou et al. 2012). Finally, DMF supposedly activates the nuclear factor erythroid-2-related factor 2 (Nrf2) pathway which is implicated in the transcriptional activation of antioxidant and anti-inflammatory genes (Linker and Gold 2013).

The second lines of DMTs are sphingosine 1-phosphate receptors (SP1R) and monoclonal antibodies. Fingolimod strongly binds to the SP1R after phosphorylation and induces its internalization and degradation in different cells including lymphocytes which prevents movement of autoreactive T lymphocytes to CNS and subsequent demyelination (Kappos et al. 2000). Natalizumab is an anti-α1-integrin monoclonal antibody which prevents extravasation of activated inflammatory leukocytes in CNS (Polman et al. 2006). Alemtuzumab is an anti-CD52 monoclonal antibody which induces antibody-dependent cellular cytotoxicity and complement-mediated lysis of T and B lymphocytes (Brown and Coles 2013).

14.4.10 Mitochondrial Dysfunction

The main cause of ageing and the most significant risk factor for neurodegenerative diseases is oxidative stress and mutations in mitochondrial DNA (Guo et al. 2013). Specific interactions between neurodegenerative disease-associated proteins and mitochondria have been discovered recently, and APP, Aβ, presenilin, α-synuclein, parkin, DJ-1, PINK1, LRRK2, HTRA2, SOD1, and huntingtin are found within the mitochondria (Guo et al. 2013). Lastly, intriguing new prospects for therapeutic targets are laid out by the interaction of mitochondria with specific disease-related proteins. For instance, in HD, p53 reduction protects against mutant huntingtin. However, only a small portion of cases of AD, PD, and ALS are genetic; therefore, it is necessary to ascertain the significance of mitochondrial interactions with these proteins for sporadic cases (Lin and Beal 2006).

14.4.11 Gene Therapy

In order to treat a disease by genetically altering populations of cells that are either directly functionally impaired or capable of alleviating disease symptoms, gene therapy is a rapidly developing genome editing technology (Coune et al. 2012). The technique is based on introducing DNA, RNA, antisense oligonucleotides, or enzymes that incorporate DNA or RNA into target cells via a vector to control the expression of certain genes (Haggerty et al. 2020). A growing body of clinical research on the use of viral vector-based gene therapy approaches for PD has been made possible by studies on animal models that demonstrated the safety and effectiveness of two families of viral vectors, lentiviruses (LVs) and adeno-associated viruses (AAVs), which are known for their minimal immunogenicity and long-lasting gene expression in neurons (Wong et al. 2006). AAVs have been extensively employed as vectors for disorders affecting the central nervous system (CNS) (Cearley and Wolfe 2007). Four primary targeted approaches have been the focus of gene therapy clinical trials in PD: (1) regaining dopamine synthesis, (2) neuroprotection, (3) genetic neuromodulation, and (4) addressing pathogenic variants

specific to the disease (Merola et al. 2020). Recent phase I and II clinical trials investigating AAV-based gene therapy for PD have produced promising results (Kaplitt et al. 2007). Patients with PD have successfully received neurturin (AAV2-NRTN) or glial cell line-derived neurotrophic factor (AAV2-GDNF) through two neurotrophic factor gene therapies delivered via AAV2 vectors (Lin et al. 1993).

14.5 Biomaterials: Developing Innovative Approaches to Treat NDDs

Neurodegenerative disorders can be considered as the second-most deadly group of diseases after cardiovascular disorders, and none of these diseases are curable. The currently available treatments only alleviate symptoms or retard the disease progression; hence there is a dire need for novel regenerative treatments crucial for functional recovery. Biomaterials have revolutionized the treatments of NDs mainly by regeneration of nervous tissue, drug delivery, and targeting. They have been successful in supporting the cells by providing scaffolds and allowing them to grow, proliferate, and regenerate (Wang et al. 2017). Current drug delivery systems targeting the brain face certain difficulties leading to inadequate therapeutic levels of drugs and therefore challenges in the prevention or reversal of neurodegenerative disorders. The foremost among them is the blood-brain barrier (BBB). BBB is a complex, highly selectively permeable barrier in the brain containing tight junctions and several efflux transporters, which prevents entry of therapeutic drugs. Therefore, it is imperative to develop novel targeting approaches which enhance the efficiency of drug delivery in the brain. Construction of biocompatible biomaterials is one such approach which can be used as drug delivery agents and act as scaffolds for cell adhesion and proliferation. Some of the well-studied biomaterials for neurodegenerative disorders are extracellular vesicles, carbon-based nanomaterials, hydrogels, nanofibers, nanoparticles, and self-assembling peptides.

14.5.1 Extracellular Vesicles

Extracellular vesicles also known as exosomes are lipid bilayered, containing transmembrane proteins and cytosolic proteins or RNA in the lumen. Extracellular vesicles can be microvesicles (50–1000 nm), which are a result of outward vesiculation of the plasma membrane, or exosomes (30–150 nm) which are synthesized in endosomal network and get secreted after fusion of multi-vesicular bodies with the membrane and apoptotic bodies, among which exosomes are best characterized. Exosomes are secreted by all types of cells as a medium of short- and long-range communication and can efficiently transport DNA, RNA, proteins, and miRNAs and regulate the physiology of the target cells (Kumar et al. 2020). They can transfer

the components between the central nervous system and systemic circulation by their ability to cross the blood-brain barrier. These properties of exosomes have enabled them as excellent drug delivery systems in neurodegenerative disorders. Exosomes derived from stem cells, especially mesenchymal stem cells, are being extensively experimented with in treatments of neurodegenerative disorders.

EVs from neprilysin (NEP) gene-modified human umbilical cord-derived MSCs (hUC-MSCs) have been shown to enhance memory, neurogenesis, and anti-inflammatory properties in AD mice models. Neprilysin (NEP) is the main cleavage enzyme of β-amyloid involved in AD pathology (Jeong et al. 2021). Intranasal administration of cytokine-primed human bone marrow MSCs (hBM-MSCs) derived EVs has shown enhanced neuroimmunomodulatory effects by enhancing anti-inflammatory phenotype of microglia and reducing microglia activation in 3xTg AD mice (Losurdo et al. 2020). Hypoxia-preconditioned mBM-MSCs release miR-21-enriched exosomes in the brain of APP/PS1 AD mice. These mice showed enhanced memory and cognition, expression of synapsin 1, and growth-associated protein 43, lower levels of amyloid plaques, and expression of Gfap and Iba1 (Cui et al. 2018). 6-Hydroxy dopamine (6-OHDA)-induced apoptosis of dopaminergic neurons was reduced by treatment with human dental pulp-derived MSCs (hDP-MSCs) (Jarmalavičiūtė et al. 2015). Ex vivo loading of catalase in macrophage-derived EVs and their intranasal administration show reduced inflammatory activity of microglia and enhanced survival of DA neurons in *SNpc* of 6-OHDA-intoxicated PD mice (Haney et al. 2015). Dopamine-loaded blood exosomes have been found to efficiently deliver dopamine to the brain, increase by >15-fold, and reduce systemic toxicity of free dopamine intravenous administration (Qu et al. 2018b). Serum-extracted exosomes from young and environmentally stimulated rats were enriched in miR-219, and induced oligodendrocyte maturation and proliferation and nasal administration of these exosomes promoted remyelination in lysolecithin-induced demyelination (Pusic and Kraig 2014). A covalently conjugated aptamer-exosome complex has also shown oligodendroglia proliferation and reduced inflammatory response and hence lower demyelination in female C57BL/6 mice (Hosseini Shamili et al. 2019). EVs from placenta-derived MSCs (hP-MSCs) reclaim motor dysfunction and demyelination in EAE mice (Clark et al. 2019). Adipose-derived MSCs (A-MSCs) exosomes have been shown to reduce mHtt aggregates in R6/2 HD mice neurons in vitro (Lee et al. 2016). Silencing of Htt mRNA and HTT protein has been achieved by loading siRNA into U87 glioblastoma-derived exosomes in primary cortical neurons of FVB/NJ mice (Didiot et al. 2016). ALS-mouse plasma-induced damage to the mice brain endothelial cells was reduced in vitro by human bone marrow-derived endothelial progenitor cell-secreted exosomes indicating their potential to repair the blood-CNS barrier in ALS (Garbuzova-Davis et al. 2020). Exosomes derived from mA-MSCs were able to rescue the NSC-34 cells overexpressing hSOD1 (G93A, G37R, A4V) subjected to H_2O_2-induced oxidative stress (Bonafede et al. 2016). Young mice subjected to pilocarpine-induced status epilepticus (SE) showed a reduction in GABAergic neuron apoptosis and inflammation in the hippocampus (Long et al. 2017). MSC-derived exosomes have also been shown to reduce SE-induced reactive astrogliosis and enhance memory and learning (Xian

et al. 2019). Intranasal administration of human iPSCs-neuronal stem cell-derived EVs reduced the elevated levels of inflammatory cytokines, e.g. TNFα, IL-1β, IFN-γ, etc., in the hippocampus of SE mice (Upadhya et al. 2020).

Intranasal administration of exosomes from A-MSCs improved the behavioural deficits in BTBR and Shank3 (Δ22q13.3 and insG3680) models of ASD (Geffen et al. 2020). hUC-MSC exosomes improve repetitive behaviours, sociability defects, and neuroinflammation in valproic acid-induced ASD in mice (Liang et al. 2020a, b).

14.5.2 Carbon-Based Nanomaterials

Neurons are the only major cells, apart from muscles, with the ability to generate and conduct an action potential and respond to electric stimuli. This property is majorly imparted by voltage-gated channels. These voltage-gated channels can be modulated by extrinsic electrical stimulation, hence influencing neuronal functions such as conduction, migration, and proliferation. This makes electric stimulation a novel and promising approach in regenerative therapies. Therefore, carbon and its allotropes provide suitable physical and chemical properties like thermal and electrical conductivity, which make them a promising candidate in tissue regeneration and nanomedicine. Three principal forms of carbon-based nanomaterials include fullerenes (C60), carbon nanotubes, and graphene.

Buckminsterfullerene is the third allotrope of carbon and has a cage-like spherical structure consisting of 60 sp^2 carbons. Fullerenes are zero-dimensional carbon-based nanomaterials shown to have effective antioxidant properties during oxidative stress. The antioxidant properties are owed to the unique structure of fullerenes which assists in scavenging several free radicals at once, by a single molecule, making it a "radical sponge" (Masoudi Asil et al. 2020). Hydrophobic fullerenes can also bind to KLVFFAE peptides which are the core hydrophobic fragments of β-amyloid and inhibit the formation of β-sheets. A polyhydroxylated fullerene derivative, C60(OH)24 has been found protective against 1-methyl 4-phenylpyridinium (MPP1)-induced acute cellular PD (Masoudi Asil et al. 2020). However, fullerenes lack solubility in most biological environments leading to the development of more sophisticated systems such as carbon nanotubes (CNTs) (Da Ros 2008).

Carbon nanotubes are one-dimensional carbon-based nanomaterials having single or multi-walled, hollow, cylindrical structures possessing exceptional physical, electrical, optical, and tunable physical properties. These are synthesized by chemical vapour deposition or arc discharge of graphite (Cha et al. 2013). In biomedical settings, CNTs are renowned for their mechanical strength, electrical conductivity, and optical properties which make them a widespread candidate in drug delivery systems, reinforcing scaffolds in tissue engineering, and biosensing (Ajitha et al. 2018). Single-walled carbon nanotubes (SWNTs) effectively deplete $A\beta_{1\text{-}40}$ peptides by adsorbing them on their surface or preventing the formation of amyloid plaques by directing the production of β-sheet rich non-amyloid plaques (Lin et al. 2016).

SWNTs loaded with dopamine show target specificity, high drug loading, and pH-responsive unloading in the PD mice model (Senthilkumar et al. 2007). Conjugation of riluzole with acid-oxidized multi-walled carbon nanotubes (MWCNTs) has been proven to be non-cytotoxic and enhance the efficacy of the drug action in ALS (Chigumbu 2012). Carbon nanotubes and nanofibers of a diameter of 1 mm can be used in deep brain stimulations in epilepsy patients (Fraczek-Szczypta 2014).

Graphene forms a two-dimensional single-layered sheet-like honeycomb lattice and exhibits electrochemical and thermal properties. It can be extracted from the mechanical exfoliation of pyrolytic graphite. The physicochemical, electrical, thermal, and optical activities depend on the number of layers a sheet of graphene has. Exploitation of graphene in biomedical applications has been limited due to its hydrophobicity which causes it to form aggregates in an aqueous environment and hence unstable and lacking functional groups. Therefore, graphene can be oxidized in acidic conditions to form graphene oxide (GO). GO offers several advantages as it easily disperses in water, and the presence of functional groups allows chemical functionalization (Gao 2015). The success of GO in medicine has been exemplified in drug delivery, biosensing, and scaffold function (Zhang et al. 2010).

Graphene oxide covered with the GPE neuroprotective peptide decreases kinetic reaction, hence preventing amyloid fibrillation (Mahmoudi et al. 2012). GO sheets and quantum dots sequester α-synuclein monomers and disrupt their inter-filament assembly (Ghaeidamini et al. 2020). GO has also been found to enhance ubiquitination and degradation of mutant huntingtin (mHtt) by directly translocating mHtt to autophagosomes. GO-based scaffolds can be used in neural regeneration in epilepsy (Reddy et al. 2018).

14.5.3 Hydrogels

Hydrogels are soft, polymeric, and three-dimensional structures that possess biomimetic properties of the extracellular matrix. They offer several advantages of being biodegradable, biocompatible, porous, water-retentive, and least immunoreactive which makes them excellent transporters of gases, nutrients, and soluble factors. Hydrogels can be cross-linked by various interactions such as covalent bonds, hydrogen bonds, ionic bonds, hydrophobic interactions, affinity interactions, physical entanglements, or a combination of two or more of these interactions. Based on molecular interactions, these can be chemical hydrogels if the major bonds participating in cross-linking are covalent and can be neutral (agarose), anionic (hyaluronic acid), cationic (chitosan), or ampholytic (gelatin) or physical hydrogels which include hydrogen bonds, ionic bonds, or physical entanglement of chains. Hydrogels can be synthesized by free radical polymerization where free radicals perform the polymerization of one or more monomers with a multifunctional monomer in the absence of oxygen. Another method for hydrogel synthesis is cross-linking of linear or branched, multiple bi-functional, or multifunctional reactive

polymers using linking agents such as the Michael addition (Peppas and Hoffman 2020).

Numerous different types of hydrogels have found their applications in neurodegeneration and tissue engineering. These hydrogels sometimes act as scaffoldings for supporting and regenerating of tissue on their own, or cells can be encapsulated in hydrogels and implanted in the degenerated tissue, for example, striatal medium spiny neurons were generated using hPSCs encapsulated in PNIPAAm-PEG 3D hydrogel in transgenic mouse model of HD and slowed disease progression, enhanced motor function, and improved survival (Adil et al. 2018). Dendritic cells encapsulated in poly(ethylene glycol) hydrogel transplanted to the cervical lymph nodes effectively attenuated paralysis in experimental autoimmune encephalomyelitis (EAE) MS mice (Thomas et al. 2021).

Hydrogels can also be composited with therapeutic compounds or drugs and act as carriers. Curcumin is a renowned polyphenol that has neuroprotective, anti-inflammatory, and antioxidant functions but has the disadvantages of being hydrophobic, poorly permeable, and less bioavailable. Curcumin encapsulated in self-assembling β-hairpin peptide hydrogel has been shown to release sustained concentrations of curcumin-inducing caspase 3-mediated apoptosis in medulloblastoma cells (Altunbas et al. 2011). Human nerve growth factor (NGF)-loaded PLGA microspheres have also shown survival of cholinergic neurons, spatial learning, and memory in the AD rat model (Gu et al. 2009). Collagen hydrogel loaded with glia-derived neurotrophic factor (GDNF) can deliver the factor in the brain and protect DA neurons in *substantia nigra* from rotenone-induced cell death. A dextran dialdehyde-gelatin cross-linked hydrogel loaded with dopamine has been shown to alleviate contralateral rotational behaviour in hemiparkinsonian rat models (Senthilkumar et al. 2007). VEGF-containing alginate hydrogel system prevents quinolinic acid-induced striatal neuronal loss in rat models of HD (Emerich et al. 2010). Alginate-chitosan-PLGA colloidal hydrogel has been used to deliver the Ac-PLP-BPI-NH_2-2 peptide to reduce EAE symptoms in MS mice (Büyüktimkin et al. 2012). A 3D motor unit formed in a collagen/matrigel microfluidic device co-culturing human iPSC-derived skeletal muscle fibres with iPSC-derived motor neuron spheroids from a sporadic ALS patient can produce functional NMJs and replicate pathological conditions of ALS. It was also shown that bosutinib and rapamycin enhanced neuronal survival and muscle contractions (Osaki et al. 2018). Local adenosine deficiency in the brain has been implicated in epileptogenesis; hence sustained focal release of adenosine-affected brain area can reduce seizure severity. Silk fibroin scaffolds embedded with adenosine-containing microspheres can provide a delay in seizure acquisition in rat models of kindling epileptogenesis (Wilz et al. 2008).

14.5.4 Nanofibers

Nanofibers are nanoscale structures that can be manufactured using various materials such as carbon, polymers, and semiconductors. These are a special kind of nanomaterials because they can be arranged into porous fibre designs that are helpful in a variety of applications, much like biological tissues in their native state. For example, an axon is a bundle of minuscule fibres in the brain that have supporting cells wrapped around them. Furthermore, the structure of collagen fibres and capillaries resembles a fascicle, which is crucial for both contact guidance in signal transmission and neuronal survival and function. In the realm of biomedicine, nanofibers are of interest for several reasons. First, nanofibers have far more surface area and surface energy than bulk materials, which enables improved adhesion with medications, proteins, and cells. Numerous in vitro studies on nanofibrous wound dressings, tissue engineering scaffolds, and drug carriers have demonstrated that they can perform better than their micro- or macro-metric-scale counterparts. Second, it is possible to greatly alter the features of nanofiber assemblies, such as flexibility. Electrospun polymers come in a variety of forms to meet a variety of needs. Additionally, nanofiber assemblies can have extremely high porosity while maintaining a large surface area as compared to bulk materials, which is advantageous for cell activities (Chen et al. 2016).

Nanofibers can be synthesized by three methods: electrospinning, phase separation, and self-assembly. Electrospinning produces fibres in the range of 50–1000 nm or greater. Electrospun chitosan nanofibers (CNfib) having a diameter of less than 150 nm incorporating donepezil hydrochloride have shown quick drug release in AD rat model (Anjireddy and Karpagam 2017). Electrospun nanofibrous PLLA scaffolds can provide an excellent substratum for the growth and differentiation of human eye trabecular meshwork (TM)-derived mesenchymal stem cells (MSCs) into dopaminergic neurons (Jamali et al. 2017). Zein is an amphiphilic prolamine protein found in maize. Its biocompatibility, non-toxicity, and easy availability make it a preferred candidate for drug delivery. Electrospun zein fibres loaded with levodopa show sustained release and increase their bioavailability in blood (Ansari et al. 2019).

Phase separation yields a nanofibrous matrix that mimics the collagen in a natural extracellular matrix where the fibres range from 50 to 500 nm. Self-assembly of nanofibers often involves small amphiphilic peptides which undergo nucleation in solution and eventually grow into high-ordered nanofibers with ageing. A bioactive sequence can also be incorporated in the PA to mimic any ECM protein matrix, e.g. a PA containing GVKGDKGNPGWPGAP sequence closely resembles collagen α1 (IV) sequence, and it can readily self-assemble generating a triple helical conformation at the liquid-air interface (Berndt et al. 1995). Despite having widespread use, biomimetic properties, and several advantages, the prevalent use of nanofibers is limited due to their small size which makes handling cumbersome, controlling the length and size, and insufficient testing measures to test the tensile strength of fibres.

14.5.5 Nanoparticles

Nanoparticles can be defined as solid particles or particles dispersed in solution between the size range of 1 and 100 nm. These are the most widely applied biomaterials owing to their exceptional properties like small size, large surface, and surface/volume ratio. The peculiar physical properties of nanoparticles lead to their different behaviour from other bulk materials. Sustained drug release, restricted targeting to specific tissues/organs, easily modulated physical characteristics, and a range of routes of administration make nanoparticles an outstanding candidate for the improvement of pharmacokinetic and pharmacodynamic properties of therapeutic agents such as nucleic acids, peptides, proteins, or drugs (Silva Adaya et al. 2017).

Nanoparticles can be fabricated using numerous biomaterials such as ceramics, metals, oxides, salts, proteins, polysaccharides, lipids, and synthetic polymers and find use in nanoelectronics, catalysis, drug delivery, and separation technology. Each type of the raw material of the nanoparticles imparts a certain function to them. Silica NPs provide a larger surface area, porous matrix, and good compatibility, and mesoporous silica NPs ranging from 2 to 50 nm are the most frequently used in drug delivery. Metal NPs are another kind of nanoparticle that has been thoroughly studied and used in biology and medicine due to their regulated geometric, optical, and surface chemical properties. Cerium oxide and silver nanoparticles exhibit degradation of β-amyloid and possess anti-Alzheimer potential (Youssif et al. 2019). Pt-Cu nanoparticles mimic catalase and superoxide dismutase activity and have been shown to scavenge reactive oxygen species, hence preventing intercellular transmission of α-synuclein fibrils and cell death in PD (Liu et al. 2021). Selenium nanoparticles reduced neuronal loss, oxidative stress, and behavioural dysfunction in the transgenic HD model of *Caenorhabditis elegans* (Cong et al. 2019). Cerium oxide nanoparticles have been shown to penetrate the brain, reduce ROS and RNS levels, and improve motor deficits in mice with MS and ALS (Heckman et al. 2013; DeCoteau et al. 2016). Gold NPs have been used to induce differentiation of $FoxP3^+$ T_{reg} cells which suppress the development of EAE in MS rats (Yeste et al. 2012). Protein NPs are made up of biological components that carry both large and small molecules. They have been utilized as drug carriers in several cancer treatments. Modified protein NPs in colloidal drug carrier systems enable selective drug targeting, thereby lowering drug toxicity. Using protein materials in vivo, which have many advantages over colloidal carriers like liposomes and cell ghosts, prevents enzymatic degradation. It has been noted that protein NPs have the potential to be used as adjuvants for vaccines as well as drug delivery systems for parenteral, peroral, and ocular administration (Herrera Estrada and Champion 2015). Lipid NPs, called liposomes, are made up of phospholipid mono- or bilayer applied in the transport of drugs, nucleotides, and proteins. Being amphipathic, these are nonimmunogenic, nontoxic, as well as water soluble. Two non-phospholipid lipid NPs, solid lipid NPs (SLNPs) and nanostructured lipid carriers (NLCs), have been extensively used in cancer therapy (Silva Adaya et al. 2017). Resveratrol is an anti-amyloidogenic polyphenol that prevents the amyloidogenic cleavage of APP. It

has been shown that nasal administration of resveratrol encapsulated in a nanostructured lipid carrier made of gellan gum and xanthan gum enhances memory function in scopolamine-induced amnesia (Rajput et al. 2018). N-3,4-bis(pivaloyloxy)-dopamine (BPA)-loaded liposomes functionalized with a 29 amino acid peptide (RVG29-lip) derived from rabies virus glycoprotein have shown enhanced uptake at BBB and selective distribution in the brain, striatum, and *substantia nigra* improving symptoms of PD (Qu et al. 2018a). Rosmarinic acid-loaded solid lipid nanoparticles improved behavioural deficits and oxidative stress in 3-nitro propionic acid-induced HD rats (Bhatt et al. 2015). Intravenous injection of 500-nm negatively charged diamond microparticles has been shown to induce caspase 3-dependent apoptosis of inflammatory monocytes in MS (Getts et al. 2014). Minocycline-loaded liposomes modified with LPS targeted microglia of $SOD1^{G93A}$ mice model of ALS and showed significant delay in disease progression (Wiley et al. 2012). Poly(lactide-coglycolide), poly(lactic acid), poly(e-caprolactone), chitosan, and poly(alkyl cyanoacrylates) are some polymeric biomaterials that have been used to construct nanoparticles. These NPs are easy to synthesize, are less expensive, and have higher biocompatibility and biodegradability, and their composition can be varied to a much greater extent. However, many polymeric NPs are toxic; hence their cytotoxicity must be enhanced before their clinical application (Lecároz et al. 2006). Phenytoin is an anti-convulsant medication, but its lower concentrations in the brain due to BBB lead to its resistance. This resistance is a result of P-glycoproteins present in the BBB. Pluronic P85-coated phenytoin PBCA nanoparticles could overcome the P-gp in BBB and enhance its concentration in brain of lithium-pilocarpine-induced epilepsy in rats (Fang et al. 2016).

14.5.6 Self-Assembling Peptides

Self-assembling peptides (SAPs) can self-assemble and get organized into complex nanofibrous structures starting from simple peptide monomers. Self-assembly of peptides involves various forces including hydrophobic interactions, hydrogen bonds, and electrostatic interactions which lead to the formation of tubes, rods, or sheet-like nanostructures (Liao et al. 2016). The morphology, size, and accessibility of the active surface area determine the physicochemical and biochemical activities of these assemblies. The properties of self-assembled structures can be altered by altering the pH, temperature, ionic strength, enzymatic triggers, or assembling rate. SAP systems such as peptide amphiphiles (PAs) as described above, aromatic N-terminally capped peptides, and proline-containing oligopeptides have been explored in neural regeneration. Specific bioactive sequences can also be integrated into the SAP systems to impart the biomimetic property of a specific ECM protein in the resulting matrix. For example, the GVKGDKGNPGWPGAP sequence resembles collagen α1 type IV which when self-assembled forms a collagen-like matrix (Berndt et al. 1995). Specific sequences SKPPGTSS, PFSSTKT, and RGDS have been found to enhance neuronal growth, differentiation, proliferation, and

migration (Koutsopoulos and Zhang 2013). Injection of self-assembling peptide amphiphile IKVAV which is a laminin epitope forms a three-dimensional network of nanofibers in the hippocampus and results in enhanced neurogenesis and improved cognitive impairment (Yang et al. 2013). Designer self-assembling peptide containing YIGSR laminin domain enhances survival and differentiation of neuronal stem cells transplanted at the site of degeneration in $A\beta_{1\text{-}40}$ rat model (Cui et al. 2016). Heparan sulphate and laminin mimicking self-assembling peptide amphiphiles along with 6-OHDA injections reduce striatal injury and enhance functional recovery with significantly reduced contralateral forelimb akinesia and asymmetry in PD rats (Sever et al. 2016).

Numerous different types of SAP systems can be created by selecting different building blocks such as dipeptides, surfactant-like peptides (SLPs), bolaamphiphilic peptides, cyclic peptides, and ionic-complementary SAPs. Dipeptides are the simplest building blocks of SAP systems. FF peptide is crucial in the recognition of the β-amyloid plaques in AD, and it can self-assemble into higher-ordered structures of nanoscale order (Reches and Gazit 2003). Surfactant-like peptides (SLPs) contain amphiphilic structures with one of two hydrophilic residues at the head and a long hydrophobic residue tail; hence these can dissolve both in organic solvents and water. When dissolved in water they reduce their surface tension and form lipid micelle-like structures; in this way, they can form nanotubes or nanovesicles. Ac-AAAAAAD (A6D), Ac-VVVVVVD (V6D), and Ac-AAAAAAK (A6K) have an N-terminal acetylated end which has no charge, followed by a tail of hydrophobic amino acid residues and a negatively or positively charged head (Zhao 2009). Modified SLPs containing both hydrophobic ends connected by a hydrophobic stalk are known as bolaamphiphilic peptides. The presence of the same or opposite charges at the ends can form a symmetric or asymmetric bolaamphiphilic peptide. The presence of two charged ends makes the peptide multifunctional and helps it to interact with different moieties like nucleotides or other proteins and assemble into vesicles. KAAAAK (KA4K), KAAAAAAK (KA6K), and RAAAAAAR (RA6R) can assemble into fibrous form, whereas EFLLLLFE (EFL4FE) forms peptide nanotubes (da Silva et al. 2015). The ionic-complementary SAPs contain alternating arrangements of positive and negative charges. These patterns determine the structural properties of the peptide, e.g. the −−++−−++ pattern shows the α-helical structure, and − + − + shows the β-strand structure (Lee et al. 2019). In cyclic peptides, the amino acids are stacked together to form a cylindrical structure with peptide backbone inside and side chains outside. The intermolecular hydrogen bonds between each amino acid stabilize the structure. The properties of the external surface can be manipulated by the choice of type and number of amino acids. Cyclic peptides form stable conformations as opposed to linear peptides (Choi et al. 2012). Self-assembling amyloid-like β-sheet peptides are also being investigated as potential vaccine candidates due to their biocompatibility and biodegradability. Unlike monomeric peptides, these assemblies are immunogenic, stable, and resistant to proteolysis and can generate stronger immune responses against AD (Al-Halifa et al. 2019).

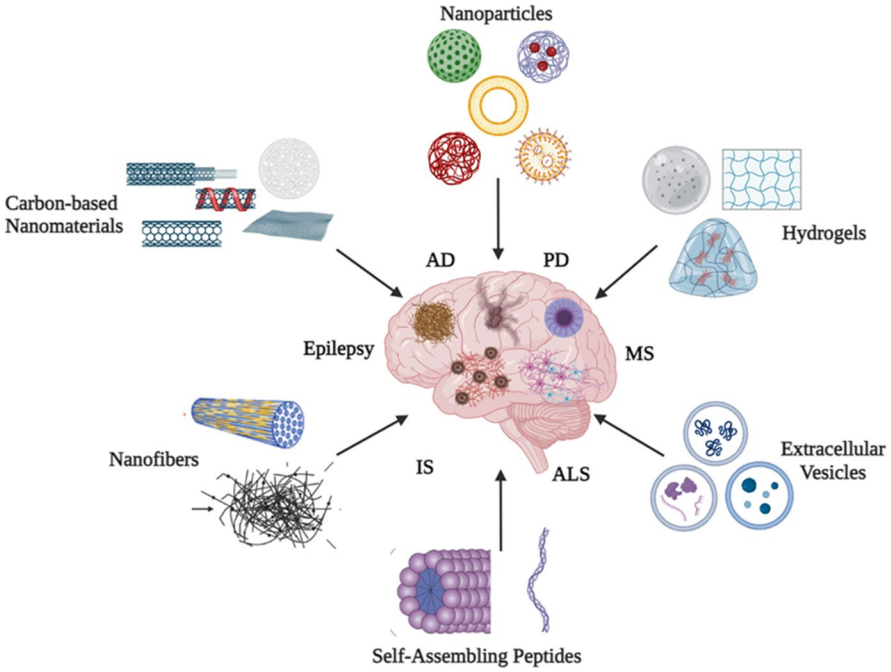

Fig. 14.4 Diagrammatic representation showing the involvement of different biomaterials in treatment of neurodegenerative diseases

Most interventions for ASD include cognitive-behavioural therapy, speech therapy, parental training, or applied behavioural analysis. However, the use of a few psychotropic drugs such as risperidone and aripiprazole in the symptomatic treatment of ASD is approved (Jobski et al. 2017). No biomaterial-based interventions in ASD have been studied so far as there is a dearth of sufficient understanding about the genetics, heterogeneity, and aetiology of the disorder. The pathophysiology of ASD is being deciphered using novel techniques like HTP sequencing, use of patient-derived iPSCs, and linkage and association studies (Ghosh et al. 2013). These studies will pave the way for novel therapeutic targets for pharmacological developments in treating ASD (Fig. 14.4).

14.6 Conclusion

Metabolic alterations play a key role in the development and progression of neurodegenerative diseases. Using advance technology, the identification of small molecules as indicative of disease development and progression will ease diagnosis and provide clues for early intervention in combating neurodegeneration. At the same time, the identification and targeting of key metabolic proteins may provide better

management of disease conditions. Thus, metabolic biomarkers will revolutionize the diagnosis and therapeutic strategies in neurodegenerative diseases.

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Chapter 15
Phytochemicals: Promising Alternatives for Metabolic Regulation in Neurodegenerative Diseases

Anand Kar and Sunanda Panda

Abstract Neurodegenerative diseases (NDDs) are the disorders which involve the degeneration of neurons, particularly present in the central nervous system (CNS). Despite the significant efforts and understanding of the major pathways involved in the NDDs, there is no cure of these debilitating diseases. Presently, for the treatment of NDDs, some conventional drugs are available, but they are very expensive and in addition exhibit side effects. Since plant-based drugs are believed to be effective and relatively safe with strong antioxidant property, free radical scavenging, and anti-inflammatory abilities with least side effects, several groups are working to find out suitable bioactive compounds for the treatment of different NDDs such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and multiple sclerosis (MS). These diseases usually result from altered energy homeostasis, metabolic defects, inflammation, and ultimately from neuronal death. More than 15 phytochemicals have been reported to ameliorate the common NDDs. As per the published literature, most of the effective phytochemicals have high anti-oxidative and anti-inflammatory properties. In this chapter, we have discussed the potential role of some bioactive compounds as critical phytochemicals for the treatment of NDDs with respect to their regulating properties and the mechanism of actions through different signalling pathways.

Keywords Neurodegenerative diseases · Phytochemical · Metabolic regulation · Oxidative stress

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15.1 Introduction

Neurodegenerative diseases (NDDs) are a group of neurological disorders that adversely affect lives of people through the progressive loss of neurons, mainly in the central nervous system (CNS). The loss of neurons, which cannot efficiently renew themselves due to their altered nature, results in breakdown of the function of neural networks of communication leading to impaired memory, cognition, behavior, sensory, and/or motor functions. According to the World Federation of Neurology, more than one billion people have been impacted by neurological disorders worldwide. In fact, aging is one of the major factors for NDDs, and many old people are suffering from Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease(HD), multiple sclerosis (MS), dementia, and various other neural abnormalities. According to the Alzheimer's Association (2015), AD is the most prevalent NDD with an incidence of 5.7 million Americans having Alzheimer's dementia in the United States. With the increase in life expectancy, the prevalence of age-related disorders including NDDs is rising, and AD is expected to be 13.8 million by the mid-century. These diseases are usually due to the slow loss of a group of neurons that are particularly sensitive.

Alzheimer's disease is characterized by progressive degeneration in the brain, particularly affecting cholinergic neurons, with the pathological hallmark being amyloid-β and tau fibrillary tangles. AD is commonly characterized by the deposition of extracellular Aβ plaques and intracellular neurofibrillary tangles (NFTs) composed of tau aggregates, leading to progressive memory loss (Sehar et al. 2022). The second most common neurodegenerative disease is Parkinson's disease, and its prevalence is likely to be double over the next 30 years (Tolosa et al. 2021). Parkinson's disease is a progressive neural disorder that affects the parts of the body controlled by the nerves. Symptoms include mainly the tremors that become worse over the time. The disorder may also cause stiffness or slowness in the movement. A global estimate in 2019 showed over 8.5 million individuals with PD. Huntington's disease, also known as Huntington's chorea, is an incurable neurodegenerative disease that is mostly inherited. This is manifested by a general lack of coordination and an unsteady gait and often showing a hyperkinetic movement disorder known as chorea. In advanced stage of the disease, uncoordinated, involuntary body movements of chorea become more significant. Although rare, HD is the most common single-gene neurodegenerative disorder, affecting about 15,000–30,000 people in the United States. Multiple sclerosis affects function in cognitive, emotional, motor, sensory, or visual areas and occurs as a result of a person's immune system attacking their brain and spinal cord. More than 1.8 million people are believed to have MS worldwide. As the life expectancy is increasing along with the drastic change in lifestyle, these common neural diseases are increasing day by day.

Despite a recent report indicating a complex dysregulated signalling pathway behind neurodegeneration, the exact mechanism is yet not clear. Of those dysregulated pathways, oxidative stress, inflammation, apoptosis, and autophagy are known to play critical destructive roles toward neurodegeneration (Wang et al. 2020). In

fact, oxidative and inflammatory mediators play major roles in the progression of neuronal dysfunction as oxidative stress leads to accumulation of damaged mitochondria as well as the aggregation of abnormal proteins (Olufunmilayo et al. 2023). Regulation of oxidative stress, cytokine/chemokine release, and other destructive molecules may benefit treating multiple NDDs. Thus, there is a crucial need to develop effective and multi-target agents to target multiple dysregulated pathways and to understand the mechanisms involved in NDDs. Moreover, the drugs that are available in the market offer only symptomatic relief with improvement in the daily functions to some extent. Obviously, there is a need of finding out suitable plant-derived bioactive compounds that are considered to be safe and effective. Natural products are believed to exert beneficial effects on various NDDs by targeting different signalling pathways, including oxidative stress, inflammation, apoptosis, and some other cellular and molecular mechanisms. They also downregulate inflammatory cytokine/chemokine release and enhance antioxidative performance by preventing mitochondrial damage and neutralizing free radicals (Moratilla-Rivera et al. 2023). Obviously we cannot ignore the efficacy of phytochemicals in combating Alzheimer's disease, Parkinson's disease, Huntington's disease, brain/spinal cord damages, depression, and other neural dysfunctions. This chapter focuses on the role of phytochemicals in the regulation of neurodegeneration through different signalling pathways.

15.2 Oxidative Stress and Inflammation in NDDs

Neurodegenerative disorders are characterized by metabolic disorders, mitochondrial dysfunction, and subsequently oxidative stress, inflammation, and apoptosis that contribute to neuronal cytotoxicity and degeneration. Oxidative stress occurs from the imbalance between reactive oxygen species (ROS) and/or nitrogen species (RONS) produced and the cellular antioxidants. Reactive oxygen and nitrogen species play an important role in aging as well as in age-related diseases. In fact, the exacerbated oxidative stress, mitochondrial dysfunction, and chronic neuroinflammation are believed to be common pathological mechanisms underlying neurodegeneration.

The main factor that contributes to brain oxidative stress is mitochondrial dysfunction affecting the nervous system more severely than other tissues causing or worsening diseases, thus playing a role in the biological deterioration in aging. Furthermore, the mitochondrial energy supply is associated with the production of highly reactive ROS. Approximately 95% of the molecular oxygen is metabolized within the mitochondria by the electron transport chain so that mitochondria are highly exposed to oxidative stress which may damage the neurons. Oxygen radicals created during respiration induce mitochondrial dysfunction which accelerates the production of more deleterious species of oxygen. Therefore, in neurodegenerative disorders, mitochondrial dysfunction and oxidative stress are considered to be the main causes of disease progression (Tritschler et al. 1994).

In different NDDs, mitochondria are targeted by specific hallmarks, contributing to oxidative stress. Amyloid-beta (A-beta), the prominent hallmark of AD, is known to induce oxidative stress causing mitochondrial dysfunction through alteration of its membrane potential. Similarly, Aβ42 binds copper(I) ion forming Aβ42-Cu+ complex that helps in generating H_2O_2 and the free radicals (Cheignon et al. 2018). These Cu+-Aβ42 oligomer complexes are highly cytotoxic. In PD, the misfolding and aggregation of α-synuclein (α-syn) as a casual factor in the pathogenesis are also known. The α-syn dysfunction-induced degeneration of the dopaminergic neurons leads to mitochondrial dysfunction and enhances oxidative stress (Sohrabi et al. 2023). Oxidative stress is also involved in the degeneration of dopaminergic neurons in Parkinson's disease. The generation of ROS can also be through the metabolism of dopamine itself. In PD some gene products such as DJ-1, PINK1, parkin, alpha-synuclein, and LRRK2 also affect the mitochondrial function leading to excess production of ROS. In HD, mitochondrial failure is found involved in neurodegeneration and increased levels of oxidative stress (Teleanu et al. 2022). HD is a protein-misfolding disease, in which the mutant huntingtin (mHtt) protein, often called huntingtin, disrupts the normal biological functions by interacting with other proteins. The protein misfolding generated by ROS leads to the formation of bodies that are collected next to the axons and dendrites of neurons, disrupting the neural transmission (Alqahtani et al. 2023). In multiple sclerosis also oxidative stress appears to play a key role, although sufficient clinical data are not available.

15.3 Role of Pro-Inflammatory Cytokines

Inflammation of neural tissues is a common manifestation of most neurodegenerative diseases. Two types of glial cells, microglia and astrocytes, are primarily involved in the inflammatory responses in the central nervous system (CNS). In fact, the process of neuro-inflammation is attributed to the activation of microglia and astrocytes in the brain followed by tau formation, synaptic damage, and neuronal loss.

AD, the most common form of dementia, is pathologically characterized by extracellular accumulation of amyloid-beta (Aβ)-containing plaques. Here also neuro-inflammation contributes to its pathogenesis and possibly triggers the progression of this disease. Dysfunctions of microglia and astrocytic metabolism result in the accumulation of Aβ activating these two neural cells to release neuroinflammatory mediators that promote neurodegeneration. The activated microglia migrate, proliferate, phagocytize, present the antigen to T cells, and release various oxidants, TNF-α, inducible nitric oxide synthase (iNOS), ROS, cyclooxygenase (COX-1 and COX-2), and several neurotoxic compounds causing dysfunction of neurons and their death, ultimately leading to permanent brain damage (Zeng et al. 2023). Neurotoxic molecules are released for an extended period in chronic neuroinflammation and cause prolonged neurodegeneration. Numerous pathways like NF-κB, p38 MAPK, Akt/mTOR, caspase, nitric oxide, and COX are known to be

involved in triggering brain immune cells, astrocytes, and microglia to secrete inflammatory cytokines such as TNF-α, IFN-γ, interleukins (IL-1β, IL-6, IL-18), and chemokines to participate in neurodegeneration (Thakur et al. 2023; Sastre et al. 2006).

The pathophysiology of PD is also due to chronic neuro-inflammation as here also activated glial cells release pro-inflammatory and neurotoxic factors that induce neural damage and subsequent neurodegeneration (Miyazaki and Asanuma 2020). In MPTP-injected PD models, it was observed that the microglial activation increased the levels of pro-inflammatory cytokines, TNF-α, IL-1β, and IL-6, and NF-κB signalling in astrocytes caused neuro-inflammation and neuronal loss (Hammond et al. 2020). MS, a severely debilitating disease, is also characterized by progressive degeneration of motor neurons. In this disease too, astrocyte and microglia activation has been well characterized, as microglial release of inflammatory factors serves as trigger for activated neurotoxic astrocytes.

All these findings do suggest that the inhibition of pro-inflammatory mediators would be an effective therapeutic intervention to mitigate the progression and/or amelioration of neurodegenerative diseases.

15.4 Properties and Mode of Action of Natural Compounds (Table 15.1)

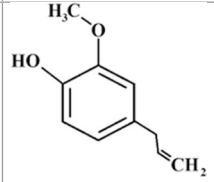
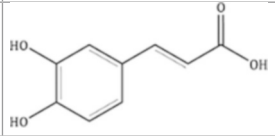
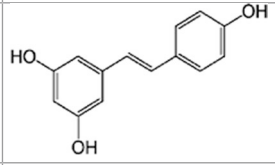
As discussed in previous sections, substantial evidences have now proved that neurodegenerative disorders are characterized by mitochondrial dysfunction and subsequently oxidative stress, inflammation, and apoptosis that contribute to neuronal cytotoxicity and degeneration. Scientists have tried from time to time to counteract these deleterious processes by different agents/drugs. Some phytochemicals have now been found to prevent and manage NDDs by playing protective roles in oxidative stress, neuro-inflammation, and prevention of neuropathies (Tavan et al. 2024). Therefore, in the following section we have enlisted various classes of key phytochemicals that were found to act as protective agents in neuronal disorders.

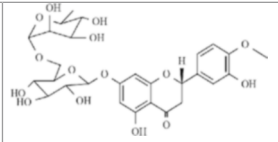
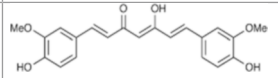
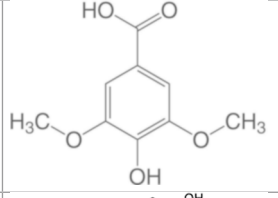
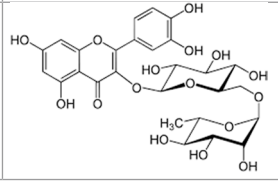
15.4.1 Eugenol

Eugenol (EUG), the phenolic compound, comprised of 4-allyl-1-hydroxy-2--methoxy benzene, is commonly found in clove, cinnamon, basil, and nutmeg essential oil. It is known as a powerful antioxidant and anti-inflammatory agent, apart from working as a local anesthesia and pain reliever. This compound works for countering the pathological conditions of AD and PD (Phukan et al. 2023).

Eugenol is also a potential phytoconstituent that suppresses the neuroinflammatory processes induced by epileptic seizures through inhibition of NF-κB activation

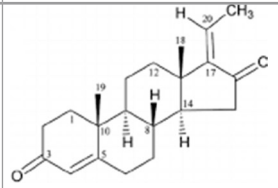
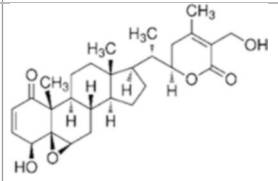
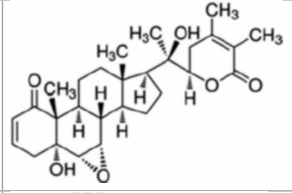
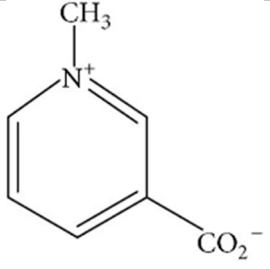
Table 15.1 Phytochemicals, their structure, and the primary mode of actions in the regulation of neurodegenerative diseases

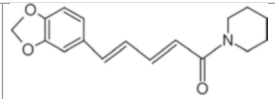
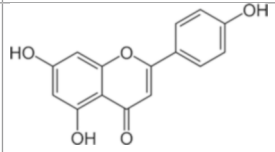
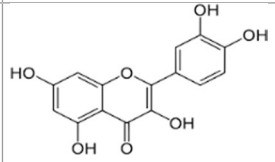
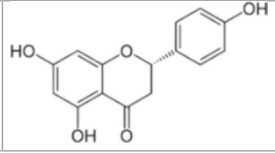
Compounds	In vitro/in vivo (model)	Mode of action(s)	References	Structure
Eugenol	In vivo: rat traumatic SCI model	↓ Oxidative stress ↓ NF-κB and MAPK signaling pathway	Zhu et al. (2023)	
	In vivo: 5xFAD; mouse model	↓ Necroptosis activation ↑ Microglial phagocytosis ↓ Neuronal cell loss ↓ Aβ deposition	Jung et al. (2023)	
Caffeic acid	In vivo: rat, Aβ-induced AD mice	↓ Oxidative stress ↑ Nrf2 and HO-1 expressions ↓ Expression of Aβ and BACE-1	Khan et al. (2023)	
	In vitro and in vivo PC12 and SH-SY5Y cell line mice	↓PHD2 enzyme activity	Guo et al. (2022)	
Resveratrol	In vivo: rat	↓ PHD2 enzyme activity ↑ SIRT1 and p-AMPK expression	Wan et al. (2016)	
	In vitro: TM4 Cells	↑ Activates (Nrf2) to protect cells via (PI3K)/ Akt protein kinase B signalling pathway	Xu et al. (2022)	

Hesperetin	In vivo LPS-induced mouse and in vitro HT-22 cells	↑ Akt/Nrf2, ↓ ROS, ↓ LPO ↓ NF-κB and MAPK signalling pathways	Cho (2006) and Muhammad et al. (2019)	
Curcumin	In vivo: mouse TBI model	↑ Nrf2-ARE signaling ↓ Inflammatory cytokines and ↑ TGF and IL-10	Garodia et al. (2023) and Moratilla-Rivera et al. (2023)	
Chlorogenic acid	In vivo: APP/PS1 mouse In vivo*:* rats	↑ Activation of the mTOR/TFEB signalling pathway AMPK/sirtuin 1/PGC-1α-mediated mitochondrial biogenesis	Gao et al. (2020) and Pai et al. (2023)	
Syringic acid	In vitro cerebro-cortical slices In vitro: *U*-251MG cells	↑ PI3K/Akt/GSK-3β signalling pathway ↓ Matrix metalloproteinases	Li et al. (2023) and Khatun et al. (2023)	
Rutin	In vivo: mouse	↓ Tau aggregation and modulation of the signalling pathways of MAPK, NF-kβ, and TLR, and further ↓ Aβ genesis and tau hyperphosphorylation	Wang et al. (2023)	

(continued)

Table 15.1 (continued)

Compounds	In vitro/in vivo (model)	Mode of action(s)	References	Structure
Z-Guggulsterone	In vivo: APPswe/PS1dE9 mouse	↓ Activated TLR4/NF-κB signalling and CREB/BDNF signalling pathways	Liu et al. (2020)	
Withaferin A	In vivo mouse model of FTLD	↓ NF-κB activity; alleviates TAR DNA-binding protein-43; ↓ Aβ production and NF-κB-mediated neuro-inflammation	Kumar et al. (2021)	
Withanolide A	In vitro: neuronal cells	↑ Glutathione biosynthesis by upregulating GCLC level through Nrf2 pathway ↓ Pro-inflammatory factors	Das et al. (2021)	
Trigonelline	In vitro: hippocampal neurons	↓ TNF-α, IL-6, and IL-1β and activation of PI3K/Akt signaling pathway	Qiu et al. (2020)	

Piperine	In vitro: SH-SY5Y cells	↓ Apoptosis, oxidative stress, and neuro-inflammation, partly via suppression of Keap1-Nrf 2 complex	Yang et al. (2021)	
Apigenin	In vivo rat AD model	↓ BACE1 and GSK-3β and hyperphosphorylation of tau protein	Zhang et al. (2014)	
Quercetin	APPswe / PS1De9 transgenic mouse model In vitro: HT22 cells	↓ Mitochondrial dysfunction via the activation of AMP-activated protein kinase (AMPK)	Wang et al. (2014)	
Naringenin	In vivo: rat AD model	↓ Aβ-induced cyclooxygenase-2, Bax activation, and Bcl-2, CREB, BDNF, and TrkB inhibition	Choi et al. (2023)	

Downward arrow indicates inhibition, whereas upward arrow indicates stimulation

and the formation of the NLRP3 inflammasome in the hippocampus after status epilepticus (Zhu et al. 2023).

Recent reports indicate that eugenol treatment effectively mitigates cognitive impairments in 5 × FAD mice inhibiting necroptosis activation and increasing microglial phagocytosis resulting in reduction of neuronal cell loss and amyloid-beta (Aβ) deposition (Jung et al. 2023).

15.4.2 Caffeic Acid

Caffeic acid (CA) is one of the most common phenolic acids, found in fruits, tea, coffee, oil, and spices. CA is a well-known potent protective agent for the treatment and prevention of neurodegenerative diseases. A recent finding indicated that the protective mechanisms of CA against oxidative stress and ferroptosis in permanent cerebral ischemia is mediated through the Nrf2 signalling pathway, suggesting that CA may act as a potential therapeutic agent for alleviating cerebral ischemia-induced brain injury (Li et al. 2024b).

In AD mice, CA enhanced synaptic markers and decreased the Aβ and BACE-1 expression indicating that its administration reduces ROS and LPO levels and thereby improves spatial learning, memory, and cognitive abilities (Khan et al. 2023). In an in vitro study of PC12 and SH-SY5Y cell line, CA inhibited prolyl hydroxylase-2 (PHD2) enzyme activity which then activated the hypoxia-associated transcription factor and hypoxia-inducible factor (HIF) leading to neuroprotection (Guo et al. 2022).

15.4.3 Resveratrol

Resveratrol (RV) is a well-known polyphenolic compound present in various plants including grape, peanut, berry fruits, and red wine. It is quite famous for its association with several health benefits including the neuroprotective and antiaging actions (Zhou et al. 2021). Its neuroprotective effect is thought to be mediated by improving the brain antioxidants and monoamine levels and by HPA axis dysregulation, thus improving MD-induced depression like behavior in Wistar rats (Shukla et al. 2024). It is also reported to regulate neuroprotective signalling pathways implicated in neurotrophin-mediated activation of tropomyosin receptor kinase (Trk) and p75 neurotrophin receptor (p75NTR) (Ayaz et al. 2024).

It is further known to play an important role in promotion of non-amyloidogenic cleavage of the amyloid precursor protein, enhancing the clearance of amyloid-beta-peptides and thus reducing the neuronal damage. Accumulation of Aβ decreases the level of SIRT1 in neurons that is restored by resveratrol, thereby protecting from neurotoxicity (Wan et al. 2016).

RV treatment is reported to prevent the increase in AChE in the cerebral cortex and the levels of ROS and TBARS in brain tissues but to improve the serum catalase enzyme activity and thus prevents brain damage resulting from hypothyroidism (de Souza Cardoso et al. 2021).

Another possible mechanism of its neuroprotection is by inhibiting phosphodiesterase (PDEs) level and regulating the cAMP/AMPK/SIRT1 pathway, which reduces ATP energy consumption during ischemia (Hammond et al. 2020). Resveratrol can activate nuclear factor erythroid 2-related factor (Nrf2) to protect cells through the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signalling pathway (Xu et al. 2022).

15.4.4 Hesperetin

The citrus flavonoid hesperetin (HPT), an aglycone of hesperidin, is found commonly in orange, mandarin, and lemon. Literature has demonstrated that HPT exhibits numerous biological properties including anti-inflammatory, free radical scavenging, neuroprotective, anxiolytic, antidepressant, antinociceptive, and anticonvulsant effects (Roohbakhsh et al. 2014).

Hesperetin counteracts LPS-induced inflammation in animals and cognitive deficits in rodents by modulating cell signalling NF-κB pathway (Decandia et al. 2023). Similarly, transcription factors, Nrf-2 and HO-1, are the main cellular components that regulate antioxidant and cytoprotective genes and are downregulated in neurodegenerative disorders. Elevated LPO and ROS and the reduced expression of Nrf-2 and HO-1 were significantly regulated by hesperetin, supporting the hypothesis that it has potential antioxidant effects (Cho 2006). A preclinical study suggests that hesperetin confers neuroprotection by downregulating the TLR4/NF-κB signalling pathway against lipopolysaccharide (LPS)-induced neuro-inflammation. It also reduces the protein expression level of TNF-α and IL-1β cytokines, and this protective effect is thought to be mediated by NF-κB and MAPK signalling pathways (Muhammad et al. 2019).

15.4.5 Curcumin

Curcumin (CUR) is a bright yellow chemical present in plants of the Curcuma *longa* species. It is the principal curcuminoid that is considered to be a powerful antioxidant that has received much attention for its therapeutic properties for a wide range of diseases. This is also known to slow down the progression of neurodegenerative diseases including AD, HD, and PD (Garodia et al. 2023). In vitro, in vivo, and clinical studies considering curcumin on NDDs revealed that curcumin modulates important signalling pathways that regulate neuro-inflammation. For example, curcumin and its derivatives have been found to regulate different pathways such as

Akt/mTOR NF-κB, β-catenin, NLRP3 inflammasome, BDNF/TrkB, Nrf2, IL-6/STAT3 inflammatory, and DNA repair pathways. It has also been found to down-regulate inflammatory cytokines including IL-6, IL-1, TNF-α, IL-13, IL-17, and IL-23 and upregulate anti-inflammatory molecules such as TGF and IL-10 (Garodia et al. 2023). A novel formulation of curcumin, CurcuWIN® ameliorated TBI, works through reduction in glial activation, NF-κB, and the reduction of inflammatory cytokines, IL-1β, and IL-6, other than increasing BDNF, GAP-43, ICAM-1, and Nrf2 expression (Sakul et al. 2024).

Moreover, evidence is there for enhancing antioxidant activity by curcumin through the inhibition of Nrf2 and so the protection from neural damage (Moratilla-Rivera et al. 2023).

15.4.6 Chlorogenic Acid

Chlorogenic acid (CGA), an ester formed from caffeic acid and L-quinic acid, is commonly found in coffee, honeysuckle, betel, and grapes. This phenolic compound is known for its potential as antioxidant and neuroprotector. CGA has been found to act as an anti-PD agent that acts through activation of PI3K/Akt signalling pathway and inhibition of the ERK signalling pathway, thereby alleviating neuronal degeneration and preventing neuronal death in in vitro treatment of SH-SY5Y cells (Zhang et al. 2023).

The marked neuroprotective potential of CGA against kainic acid-induced neurotoxicity and seizures could be through the prevention of glutamate increase and preservation of AMPK/sirtuin 1/PGC-1α-mediated mitochondrial biogenesis and PINK1/Parkin-induced mitophagy to maintain adequate mitochondrial homeostasis and function (Pai et al. 2023). In a cognitive deficit model of APP/PS1 mice, CGA suppressed autophagosome production and enhanced autophagy flux in SH-SY5Y cells induced by $A\beta_{25-35}$. This was accompanied by upregulated cathepsin D protein expression that alleviated cognitive impairments in APP/PS1 mice via enhanced activation of the mTOR/TFEB signalling pathway (Pai et al. 2023).

15.4.7 Syringic Acid

Syringic acid (SA) or 4 hydroxy-3,5-dimethoxybenzoic acid is a major active phenolic compound which is distributed widely in fruits, vegetables, medicinal herbs, and some dietary plants. It has been indicated that SA treatment may help in improving neurological dysfunction and behavioral impairments with its antioxidative, chemoprotective, antiangiogenic, anti-glycating, antiproliferative, antihyperglycemic/antidiabetic, anti-endotoxic, antimicrobial, anti-inflammatory, antidepressant, and perithyroidal properties (Ogut et al. 2022). Its neuroprotective action has also been claimed in brain malignancy as has been seen in *U*-251MG cells through the inhibition of matrix metalloproteinase expression (Li et al. 2023). Now it is well

understood that SA reduces malondialdehyde and enhances the antioxidants such as glutathione, superoxide dismutase (SOD), and total thiol in mice (Khatun et al. 2023). It also acted against glutamate-induced damage and presented antidepressant-like and neuroprotective effects via PI3K/Akt/GSK-3β pathway (Dalmagro et al. 2019).

15.4.8 Rutin

Rutin is a naturally occurring flavonoid in many foods, especially buckwheat, apricot, cherry, grape, plum, and orange. It possesses a wide range of medicinal values including reduction of capillary fragility in some hemorrhagic diseases, in hypertension in humans, and in varicose veins, bruising, or hemorrhoids. It is also known to exhibit numerous neuronal health-promoting effects in both in vivo and in vitro studies. In an in vitro study, the inhibition of $A\beta_{1-42}$ fibrillogenesis was observed in the presence of rutin (Asti et al. 2024). Its antiapoptotic, antioxidative, and anti-inflammatory properties prevent the neuronal or glial cells from injury or death, minimize oxidative damage, and inhibit the production of pro-inflammatory cytokines by modulating typical signalling pathways of MAPK, NF-kβ, and TLR, further reducing Aβ genesis and tau hyperphosphorylation (Wang et al. 2023). Another finding also indicated that rutin consumption may help in preventing Huntington's disease through the IGF1 (IIS) signalling pathway and autophagy activity (Cordeiro et al. 2020).

15.4.9 Z-Guggulsterone

Z-Guggulsterone (Z-GS) is a natural steroid, usually extracted from *Commiphora mukul*, and has anti-inflammatory effects both in vivo and in vitro. It ameliorates memory impairment mainly through the activation of the CREB-BDNF signalling pathway, thereby exhibiting memory-improving effects (Liu et al. 2022). Its treatment significantly decreases cerebral amyloid-β level and plaque burden through inhibition of amyloid precursor protein (APP) processing by reducing beta-site APP cleaving enzyme 1 (BACE1) expression and markedly alleviates neuro-inflammation and reduces synaptic defects in the APPswe/PS1dE9 mice through the inhibition of the activated TLR4/NF-κB signalling and CREB/BDNF signalling pathways (Liu et al. 2020).

15.4.10 Withaferin A

Withaferin A (WA) is a steroidal lactone glycowithanolide, a secondary metabolite with several therapeutic properties, including antioxidant, anti-inflammatory, antibacterial, antistress, antidiabetic, antipyretic, cardioprotective, anticancer activities,

and neuroprotective effects. Usually, it is derived from *Withania somnifera* (Ashwagandha) and *Acnistus breviflorus* (Gallinero) through the mevalonate and non-mevalonate pathways. In AD, the neuroprotective potential of WA is mediated by the reduction of beta-amyloid plaque aggregation, accumulation of tau protein, regulation of heat shock proteins, and inhibition of oxidative and inflammatory constituents. WA induces autophagy, reduces TDP-43 proteinopathy, and improves cognitive function in transgenic mice of mutant TDP-43 model, by targeting critical inflammatory pathways like NF-κB and nuclear erythroid 2-related factor 2 signalling (Kumar et al. 2021).

WA also inhibits Aβ production in microglial and SH-SY5Y cells overexpressing amyloid precursor protein (SH-APP cells) and suppresses NF-κB-mediated neuroinflammation (Das et al. 2021).

15.4.11 Withanolide A (WL-A)

Withanolide A is a steroid from *Withania somnifera*, known as Indian ginseng, and is a major component of *Withania* root. It is primarily known for its ameliorative effects in epilepsy, depression, arthritis, and diabetes and in the improvement of memory. It is also known to reduce neurodegeneration by restoring hypoxia-induced glutathione depletion in the hippocampus. Further, withanolide A increases glutathione biosynthesis in neuronal cells by upregulating GCLC level through the Nrf2 pathway in a corticosterone-dependent manner (Baitharu et al. 2014). WL-A also exerts neuroprotective activity in Alzheimer's and other neural diseases by inhibiting neuro-inflammation in the hippocampus after pilocarpine-induced status epilepticus (Zhu et al. 2020).

15.4.12 Trigonelline

Trigonelline (TG), a pyridine alkaloid, is often isolated from *Trigonella foenum-graecum* (Fabaceae). However, the common foods containing trigonelline include barley, cantaloupe, corn, onions, peas, soybeans, and tomatoes. TG is also found in coffee, fish, mussels, and crustaceans. Part of niacin consumed is also converted to trigonelline. Trigonelline is not only hypoglycemic but also hypolipidemic, neuroprotective, antimigraine, sedative, memory improving, antibacterial, antiviral, and antitumor in nature. Apart from known antihyperglycemic property, it has shown protective effects against many neurologic diseases including Alzheimer's disease, Parkinson's disease, stroke, and depression (Liang et al. 2023). Hippocampal neuronal injury induced by oxygen-glucose deprivation/reperfusion and the protection is through increasing the activity of PI3K/Akt signalling pathway and is believed to be the major reason for protective effects of trigonelline (Qiu et al. 2020).

15.4.13 Piperine

Piperine (PIP) is an alkaloid isolated primarily from black pepper (*Piper nigrum*), one of the most widely used spices. It is also found in long pepper (*Piper longum*) and in the fruits of other piper species. Piperine provides several health benefits such as anti-inflammatory effects and reduction of hepatic steatosis. It also helps in reduction of insulin resistance. Piperine, used in traditional medicine, has demonstrated anti-inflammatory and antioxidant properties. It can penetrate the blood-brain barrier (BBB), attenuates β-amyloid or oxidative stress-induced neuronal cell damage and death, and improves depression-like behavior and cognitive impairment (Roshanbakhsh et al. 2020). HJ105, a piperine derivative, exerts neuroprotective effects in SH-SY5Y cells induced by $A\beta_{1-42}$ as well as in experimental rats with AD by decreasing apoptosis, oxidative stress, and neuro-inflammation, partly via suppression of Keap1-Nrf2 complex generation (Yang et al. 2021).

15.4.14 Apigenin

Apigenin (APG) is a bioactive flavonoid present in edible vegetables and fruits, including parsley, onion, broccoli, chamomile, celery, spinach, guava, and juniper berries. A recent report indicates that apigenin has the unique ability to cross the blood-brain barrier, and its antioxidative, anti-inflammatory, neurogenic, and neuroprotective effects have made this flavonoid a great option for the treatment of neurodegenerative disorders (Lotfi and Rassouli 2024). In a rat model of AD, apigenin (50 mg/kg) significantly reduced the hyperphosphorylation of tau levels in the hippocampus, decreasing the expression of GSK-3β, suppressing BACE1 expression, and supporting an anti-amyloidogenic activity. Also in human THP-1 monotypic cells, it inhibits the production of IL-6 and IL-1β by modulating the MAPK/ERK and PI3-K/Akt signal transduction pathways associated with neuronal survival blocking (Zhang et al. 2014).

15.4.15 Quercetin

Quercetin (QCT) is found particularly in citrus fruits, apples, tea, and red wine. Olive oil is also high in quercetin and other flavonoids.

Quercetin is a flavonoid that is found commonly in daily diets predominantly in citrus fruits grapes, dark cherries, blueberries, blackberries, bilberries apples, and some vegetables including onions, parsley, and sage. QCT has notable pharmacological effects and promising therapeutic potential. Quercetin, naturally within the safe dose range, exhibits antioxidant, antiapoptotic, and anti-inflammatory properties and plays an important role in the treatment of aging-related diseases.

Glucose-modified QU liposome (QU-Glu-Lip) was found to attenuate H_2O_2-induced oxidative damage to PC12 and effectively exerted the antioxidative and neuroprotection effects (Chen et al. 2024). Sirtuin 1 (SIRT1), a member of NAD^+-dependent deacetylase enzyme family, was extensively explored as a potential therapeutic target for attenuating aging-related diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease. Its neuroprotective effects against chronic aging-related diseases could also be through the regulation of cellular senescence and processes such as SIRT1/Keap1/Nrf2/HO-1 and PI3K/Akt/GSK-3β-mediated oxidative stress and inflammatory response or through SIRT1/PGC1α/eIF2α/ATF4/CHOP-mediated mitochondrial damage and SIRT1/FoxO-mediated autophagy (Cui et al. 2022). Quercetin was further found to improve the cognitive function in the APPswe/PS1De9 transgenic mice model during chronic AD, by reducing mitochondrial dysfunction via the activation of AMP-activated protein kinase (AMPK) (Wang et al. 2014).

15.4.16 Naringenin

Naringenin (NAR), a trihydroxy-flavanone, is primarily found in citrus fruits, sour orange, tart cherries, tomatoes, and Greek oregano. Little amount of NAR is also found in bergamot, cocoa, water mint, *Drynaria*, and in beans. This flavanone glycoside is attributed to the bitterness of its sources. Another ingredient in citrus fruit, aka naringin, also shows most properties similar to naringenin. Both the polyphenols are considered therapeutically important for regulating cancer and neurodegenerative disorders. Naringenin is believed to be a promising option for treating neuro-inflammation in aging and declining brain function. It probably brings its neuroprotective effect in hypoxic-ischemic brain damage (HIBD) by activating the PI3K/AKT pathway to inhibit apoptosis (Li et al. 2024a). The effects of pre- and post-naringenin supplementation on a rotenone-induced PD model showed that motor and non-motor impairments are considerably reduced by naringenin supplementation through increased antioxidant enzyme activities and restoring the changes in neurotransmitter levels (Madiha et al. 2023). Naringin has therapeutic potential to reduce neuronal inflammation and apoptosis induced by Aβ-related BDNF/TrkB/CREB, as it attenuates the Aβ-induced cyclooxygenase-2, Bax activation, and Bcl-2, CREB, BDNF, and TrkB (Choi et al. 2023).

15.5 Pleiotropic Bioactive Components in the Management of NDDs

Other than the discussed neuroprotection potential, most of the aforesaid bioactive compounds exhibit pleiotropic effects as they act primarily through their antioxidative and anti-inflammatory activities. Besides regulating NDDs, these bioactive

compounds are able to exhibit beneficial effects on thyroid diseases, diabetes mellitus, cancer, hepatic disorder, and cardiovascular diseases (Panda and Kar 2003, 2007, 2014; Panda et al. 2012, 2013, 2020, 2021 ,Sunhre et al. 2020, Kar et al. 2023).

In fact, multiple cellular and molecular pathways have been involved for their roles on different chronic disorders, showing their pleiotropic nature and beneficial role against different diseases, mainly related to metabolic disorders or inflammation. One mechanism of action common for all is the inhibition of tissue peroxidation and enhancement of antioxidants such as SOD, CAT, and GSH. For the antioxidative or free radical scavenging activities, Nrf2 is the primary regulator of cellular resistance to oxidants. It regulates the basal and induced expression of different antioxidant response element-dependent genes to mitigate the pathophysiological outcomes of exposure to oxidants.

In case of anti-inflammatory response, it was observed that most phytochemicals act by inhibiting major inflammatory cytokines including interleukin (IL)-1,IL-4, IL-6, IL-10, IL-11, and IL-13 and the tumor necrosis factor-alpha and IL-18 that function as pro-inflammatory cytokines. Some compounds also inhibit NF-κB, the main mediator of the priming signal of NLRP3 inflammasome activation that acts by inducing the transcriptional expression of NLRP3. These pathways are common for most bioactive compounds including, eugenol, quercetin, and resveratrol.

15.6 New Hope and Challenges in the Treatment of NDDs

Although a good deal of research work has been done on the understanding and treatment of NDDS, there are a lot more to be explored, and new hope is always there. The hope for novel therapeutics depends on new knowledge that can reveal the exact mechanism of neuronal dysfunction and death. At this stage, the main etiology of most of these diseases and the exact nature of neuronal cell death and the pathological processes are poorly understood. Despite significant advances in pharmacological benefits, the known active components are still far from their clinical application as most of them have failed to produce best effective results for many reasons, including the substantial neuronal damage, caused by the accumulation of the diseased proteins like amyloid-β (Aβ) peptide and tau protein abnormalities, deleterious adverse effects of drugs, and inadequate design of clinical trials. New molecular targets, biomarkers, diagnostic techniques, and alternative nonpharmacological approaches are required to detect and treat early pathological events. New hope was spread for immunotherapy for the most prevalent neural disorder, AD using antibodies against A-beta plaques, and some antibodies against fibrillary tangles. However, the side effects of these antibodies are the major concern that throws a big challenge for drug companies. The use of stem cell therapy and gene therapy, along with pharmaceuticals and judicious lifestyle adjustments, holds promise for the prevention and/or cure of neurodegenerative disorders. Even the proper drug delivery is also a problem, although the use of nanoparticles is being advocated (Rafe 2024).

15.7 Conclusion

In the pharmaceutical industries, isolated and well-characterized plant compounds are the main sources for drug synthesis. In last two to three decades, there is a rapid increase in the research activities on therapeutic drugs using naturally occurring phytochemicals from plants for the prevention and treatment of different diseases including neural disorders. A good number of compounds have been screened and claimed for their efficacy. Many phytochemicals, mostly phenolic compounds, have been shown to attenuate neurodegenerative diseases. However, on their side effects and mechanism of actions, significant research is warranted. We suggest that the compounds discussed in this chapter may be investigated by proper preclinical trials in detail with respect to their long-term efficacy, mechanism, and side effect, if any. Once thoroughly tested, then they should be clinically tried and released in the market for their therapeutic use to improve the quality of patient's life suffering from these debilitating neurodegenerative diseases.

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