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Review article

A review on Alzheimer's disease pathophysiology and its management: an update

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ABSTRACT

Alzheimer's disease acknowledged as progressive multifarious neurodegenerative disorder, is the leading cause of dementia in late adult life. Pathologically it is characterized by intracellular neurofibrillary tangles and extracellular amyloidal protein deposits contributing to senile plaques. Over the last two decades, advances in the field of pathogenesis have inspired the researchers for the investigation of novel pharmacological therapeutics centered more towards the pathophysiological events of the disease. Currently available treatments i.e. acetylcholinesterase inhibitors (rivastigmine, galantamine, donepezil) and N-methyl D-aspartate receptor antagonist (memantine) contribute minimal impact on the disease and target late aspects of the disease. These drugs decelerate the progression of the disease, provide symptomatic relief but fail to achieve a definite cure. While the neuropathological features of Alzheimer's disease are recognized but the intricacies of the mechanism have not been clearly defined. This lack of understanding regarding the pathogenic process may be the likely reason for the non-availability of effective treatment which can prevent onset and progression of the disease. Owing to the important progress in the field of pathophysiology in the last couple of years, new therapeutic targets are available that should render the underlying disease process to be tackled directly. In this review, authors will discusses the different aspects of pathophysiological mechanisms behind Alzheimer's disease and its management through conventional drug therapy, including modern investigational therapeutic strategies, recently completed and ongoing.

Contents

Abbreviations: AD, Alzheimer's disease; APP, amyloid precursor protein; ApoE, apolipoprotein E; ACh, acetylcholine; AChEs, acetylcholinesterase; AChEIs, acetylcholinesterase inhibitor; AChRs, acetylcholine receptors; Aβ, beta amyloid; CoQ, coenzyme Q; HSV, herpes simplex virus; NFTs, neurofibrillary tangles; NMDA, N-methyl D-aspartate; PD, Parkinson disease; PK, protein kinase; QS, quillaja saponaria; ROS, reactive oxygen species.

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Introduction

Alzheimer's disease (AD) is one of the most common neurodegenerative disease and accounts for more than 80% of dementia cases worldwide in elderly people. It leads to the progressive loss of mental, behavioral, functional decline and ability to learn [1].

Approximately 200,000 people younger than 65 years with AD comprise the younger onset AD population; 5 million are age 65 years or older. It is expected that by 2050, one new case of AD is expected to develop every 33 seconds, or nearly a million new cases per year, and the total estimated prevalence is expected to be 13.8 million [2].

Since the time of Dr. Alois Alzheimer, neuropathologists have identified amyloid plaques and NFTs in the autopsied brains of people with AD, suggesting that these pathologies cause the disease [3]. Amyloid plaques are extracellular deposits of Aβ in the brain parenchyma and in the cerebral blood vessels where it is known as congophilic angiopathy also known as cerebral amyloid angiopathy (CAA). NFTs composed largely of paired helical filaments with hyperphosphorylated tau proteins, neuronal and synaptic loss [1].

Currently and/or "only" approved treatments by US Food and Drug Administration (FDA), includes five drugs that are used to treat the cognitive manifestations of AD AChEIs–rivastigmine (Exelon), galantamine (Razadyne, Reminyl), tacrine (Cognex), and donepezil (Aricept) and NMDA receptor antagonist–memantine (Namenda) that target symptoms at its best [4]. Each drug acts in a different way to delay the breakdown of Ach (a chemical in the brain important for memory). AD is associated with inadequate levels of this important neurotransmitter. Tacrine (Cognex) is rarely prescribed due to its serious side effects (liver damage). In general, Reminyl, Exelon and Aricept are most effective when treatment is begun in the early stages. Memantine (Namenda) is the only drug shown to be effective for the later stages of the disease. They have all been shown to modestly slow the progression of cognitive symptoms and reduce problematic behaviors in some people, but at least half of the people who take these drugs do not respond to them. These present treatment strategies only delay the progression of symptoms associated with AD [5]. Much effort is being directed towards the discovery of disease-modifying therapies which can block the progression of the disease (i.e. clinical symptoms) and drugs targeting various molecular pathways. For development of disease modifying therapies complete knowledge about the various metabolic pathways is essential which includes production of Aβ from APP, *in vivo* clearance and pathophysiological events that leads to fibril formation and deposition into plaques [6]. The present article reviews the advance achieved recently in the field of pathogenesis of AD and also revealing possible new drug candidate targets. The most likely expected treatment strategies includes γ- and β-secretase inhibitors, Aβ vaccination, Cu–Zn chelators, cholesterol lowering drugs, statins and non-steroidal anti-inflammatory drugs (NSAIDs) [3].

In this review, we discuss the supporting mechanisms of AD pathogenesis and progression. We also summarize the existing therapeutic strategies till date in correlation with the pathophysiological mechanisms for AD.

Pathophysiology of AD

With pathophysiology of AD, debate goes back to the Alzheimer's time 1907 when he observed the neuropathological features of the disease i.e. amyloidal plaques and hyperphosphorylated NFTs. Several hypotheses have been put forward on the basis of the various causative factors in order to explain this multifactorial disorder [7] such as the cholinergic hypothesis, Aβ hypothesis, tau hypothesis and inflammation hypothesis [6]. Recently it has been shown that the most commonly used Aβ hypotheses, prevailing for the last two decades, does not account for the complex pathophysiology of this incapacitating disease [8]. Recent studies have also highlighted the role of Aβ oligomers in synaptic impairment, suggesting that these are primarily the only one among several other signals that destroy the integrity of brain functions [1,8,9,14]. And formations of amyloid plaques that develop in the later age appear to be rather late event [9].

According to the amyloid cascade hypothesis, the APP 'is normally cleaved by α-secretase and aberrantly processed by

β- and γ-secretases (Fig. 1) resulting in an imbalance between production and clearance of Aβ peptide [10]. As a consequence, Aβ peptides spontaneously aggregate into soluble oligomers and coalesce to form fibrils insoluble beta-sheet conformation and are eventually deposited in diffuse senile plaques [8]. Some recent studies has shown that Aβ42 oligomers are produced by cooperative activities of both neurons and its associated astrocytes [9]. It has been observed that Aβ42 oligomers induce oxidative damage, promote tau hyperphosphorylation, results in toxic effects on synapses and mitochondria [6,7]. But the role of Aβ42 senile plaques cannot be ignored as Aβ42 plaques that are supposed to be appear during late stage attract microglia [11]. Microglial activation results in production and release of proinflammatory cytokines, including IL-1β, TNF-α, and IFN-γ. In turn, these cytokines stimulate the nearby astrocyte–neuron to produce further amounts of Aβ42 oligomers, thus activating more Aβ42 production and dispersal [9]. Oligodendroglia (OLGs) is also associated with neurons–astrocyte complex; Aβ oligomers also results in its destruction [12]. Aβ oligomers aggregates are considered to be responsible for the neuronal and vascular degeneration in AD brains [13]. It results in oxidative stress, a situation to which OLGs are particularly susceptible because their reduced glutathione (GSH) content is low and they have a high concentration of iron, thus presenting an impaired ability to scavenge oxygen radicals [14]. It has also been reported that Aβ42 oligomers possesses an increased capability for damaging cholesterol rich membranes, such as those found in OLGs and myelin [13,15].

Previous studies about the receptors pharmacology of Aβ have shown that Aβ42 monomers activate the neuroprotective signaling of insulin-like growth factor-1 receptor (IGF-1R), while Aβ42 oligomers target a host of neurons' and astrocytes' membrane receptors, such as the scavenger receptor for advanced glycation end products (RAGE), Frizzled receptor, insulin receptor, NMDA-glutamate receptor, p75 neurotrophin receptor (p75NTR), α7 nicotinic ACh receptor (α7nAChR), ApoE receptors, formyl peptide receptor-like 1 (FPRL1/2), cellular prion protein (PrPc) acting as an Aβ oligomer receptor, and the calcium-sensing receptor (CaSR) [16,17]. Removal of Aβ oligomers from the brain occurs by several pathways including proteolytic degradation by the proteases neprilysin and insulin degrading enzyme (IDE), uptake by astrocytes and microglia, passive flow into the cerebrospinal fluid and sequestration into the vascular compartment by soluble form of the low-density lipoprotein receptor related protein 1 (LRP1) [18,19]. The effect of NO on IDE-mediated degradation of Aβ has been studied and it has been shown that increased NO levels, which have been observed in AD, can decrease IDE enzymatic function, potentially resulting in increase in Aβ oligomers deposition in the brain and development of AD [20].

Recently it has been shown that there is a "contagion" like diffusion of Aβ42 oligomers and hyperphosphorylated tau oligomers *via* exocytosis (synapses) or exosomes to closely

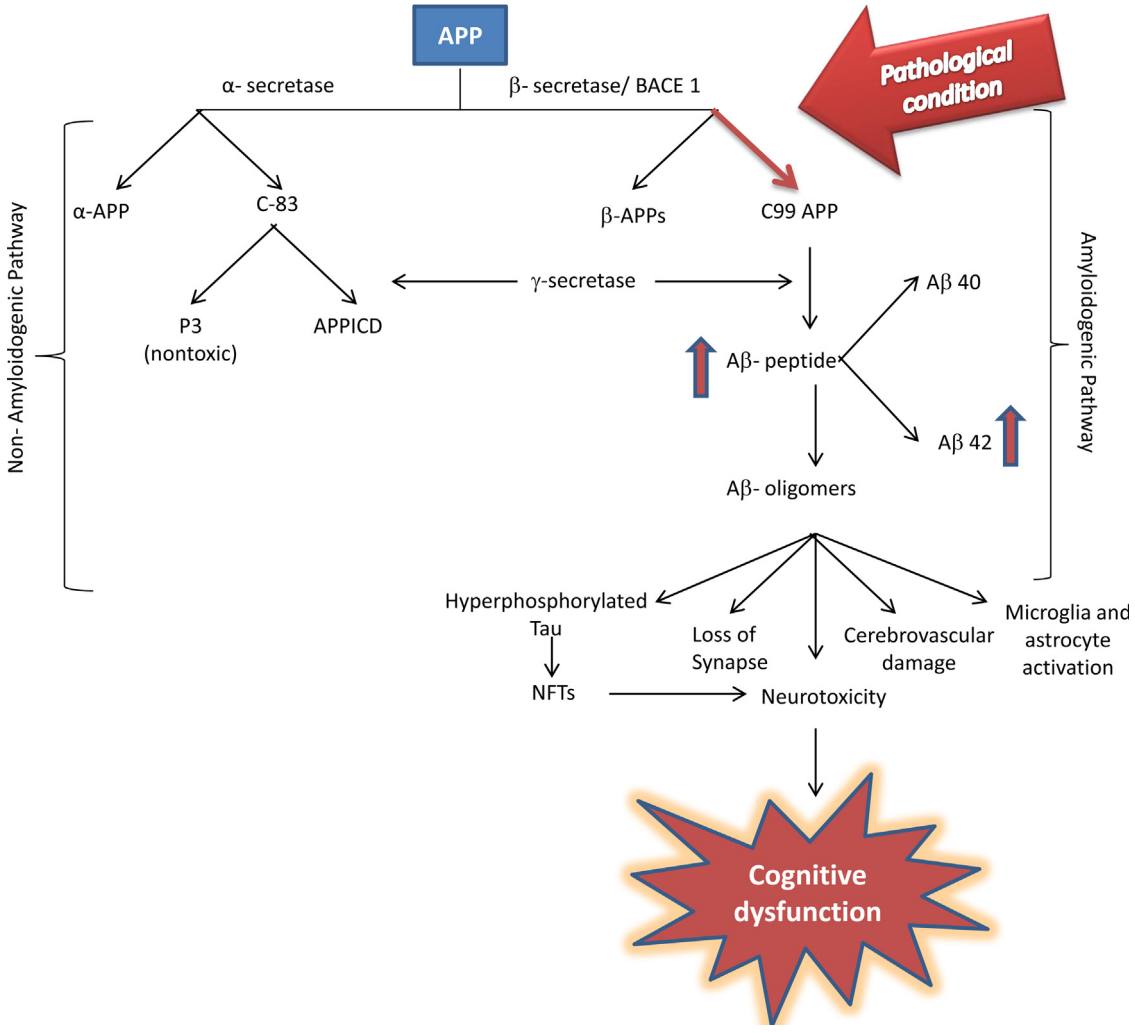

Fig. 1. Diagrammatic presentation of APP processing pathways.

associated target cells (astrocytes and oligodendrocytes), which in turn become producer cells of Aβ and tau oligomers [21]. Experimental evidence have shown that intracerebral (i.c.) administration of minute amounts of brain extract containing misfolded Aβ from patients with AD or from Aβ-APP transgenic (tg) mice induces cerebral β-amyloidosis and related pathologies in APP tg mice in a time- and concentration-dependent manner [21].

The important consequence of the astrocyte–neuron interconnections is the astrocytes abilities to promote or reduce neurotransmitters release into the synapses they envelop with the Ca^{2+} they respectively let out or take up during their Ca^{2+} waves [12]. When neurons Aβ42 production exceeds the safe limit, toxic Aβ42 oligomers start spilling out of the neurons and onto their enveloping astrocytes both cell types being empowered with Aβ42 oligomer-binding receptors besides accumulating or dispersing in the extracellular surrounding [9]. Because of the intimate physical and functional interdigitations in the neurons client group, the Aβ42 oligomers releases by the neuron can directly bind to the α-7nAChRs of its partner astrocytes [22]. The signals from these receptors induce the astrocytes to exocytose the glutamate they have been taking up from the neuronal synapses [22]. The discharged glutamate activates the extrasynaptic NMDARs of the astrocytes' partner neurons [20,22]. The resulting signals trigger Ca^{2+} surges evoking a cascade of events, including dysfunctional mitochondria pumping out ROS, which inflict an oxidative damage, caspase 3 activation, tau hyperphosphorylation, excess production of NO, ROS and VEG-F thereby destroying dendritic spines and neuronal synapses and severing communications within the astrocyte's neurons and beyond [22]. Armato and others have shown that CaSRs (present on the cell membranes of astrocytes and neurons on which Aβ42 oligomers binds) selective allosteric antagonist (calcilytic) NPS 2143 specifically stops the excess release of endogenous Aβ42 from the Aβ25–35-exposed human astrocytes and neurons [17,22].

Management of AD

The currently available treatment strategies include AChEIs and NMDA receptor antagonists [23]. In order to modify the disease process novel strategies have been developed. In this regard major developing is targeted to the Aβ and tau based therapeutics, which is a major key to unlock this disease in the near future [1,6]. In this paper we highlight the currently approved treatment along with some disease modifying therapeutic drug targets.

Various therapeutic drug targets in AD

Targeting Aβ protein (anti-amyloid approach)

The anti-amyloid therapeutics targets several aspects of APP metabolism [24].

Targeting amyloid transport

It is reported that with age, LRP expression decreases, impairing Aβ oligomers efflux contributing to prolonged there stay in the brain [25]. Antibodies against LRP reduce Aβ oligomers efflux from the brain so, this can be targeted as a potential treatment strategy in AD [26]. Previously reported that Aβ oligomers binds to receptor for RAGE (multiligand receptor) with high affinity at the blood brain barrier and facilitates there entry into CNS and contribute to increased CNS entry, inflammation and neuronal death [27].

Modulation of secretase enzymes

It has been reported that the activity of α-secretase is regulated by cell surface receptors (muscarinic/GABA agonists) and activation of signaling cascades like PKC. Bryostatin 1 which is a potent PKC activator and an anti-cancer agent was investigated; the drug is currently in phase II clinical trials. Other possibility of targeting APP processing is β-secretase [28]. GRL-8234 is also a β-secretase inhibitor that has shown positive results in preclinical studies [29].

Targeting amyloid aggregation

Tramiprosate, a glycosaminoglycan, binds to monomeric Aβ and preventing its oligomerization and aggregation. The drug is in phase II trial [30]. ELND005 (Scyllo-Inositol) has also studied for its anti-oligomerization properties as this compound effectively decreased insoluble Aβ oligomers and reversed cognitive decline in transgenic mice [31]. It is recently in phase II trial. Colostrinin (CLN) or proline rich polypeptide complex and was isolated first from ovine colostrum. It has strong immunoregulatory properties besides which it affects learning, memory and cognitive functioning. Colostrinin prominently inhibit the aggregation of Aβ peptides and dissolve pre-formed fibrils [32].

Targeting amyloid clearance

In AD the levels of Aβ oligomers degrading enzymes decline which may bestow to Aβ accumulation [18]. Experimental evidence suggests that inhibitors of plasminogen activator inhibitor 1 decrease the plasma and brain Aβ oligomers levels in transgenic animals [33]. Previous studies have shown that the peptide hormone somatostatin regulates Aβ oligomers clearance through activation of neprilysin [34].

Amyloid based vaccination therapy

Amyloid based immunotherapy means vaccination of the individuals with Aβ oligomers which in turn induces an immune response that causes inhibition of Aβ oligomers aggregation and its clearance from the body [35]. In 2001 first clinical trial was started sponsored by Elan and Wyeth with active immunization, consisting of aggregated synthetic Aβ42 peptide delivered in QS21 adjuvant [24]. From these studies it has been reported that treatment with Aβ42 peptide generated anti-Aβ antibodies, reducing cerebrospinal levels of tau and reported a slower cognitive decline [36]. APPswe/PS1dE9 vaccine evaluated for its therapeutic immunization potential in double transgenic mice an animal models with AD-like pathology [37].

Targeting tau protein

Tau protein normally synthesized by neuronal cells in order to stabilize the microtubules for proper functioning of the neurons, particularly axonal morphology, growth, and polarity [38]. So, targeting tau protein may prove to be better therapeutic intervention.

Inhibition of tau phosphorylation

Glycogen synthase kinase 3 (GSK3), one of the primary enzymes involved in tau phosphorylation, is targeted. It is reported experimentally that lithium and valproate have inhibitory actions on GSK3 and when administered they reduce tau pathology [39]. Currently tideglusib (NP031112) an irreversible inhibitor of GSK3β, recently completed phase IIb trials (NCT01350362) [1].

Targeting microtubule stabilization

Microtubule stabilizer paclitaxel is known to improve fast axonal transport, microtubule density and motor function in experimental model of AD [40]. Epothilone D a microtubule stabilizing compound known for its blood brain barrier clearance has been reported to show significant amelioration in microtubule pathology [41]. Some neuropeptides like NAP (NAPVSIPQ) and D-SAL (SALLRSIPA) are available that boasts microtubule stabilization effects [42].

Blocking tau oligomerization

Some drugs like astemizole, lansoprazole [43] show a strong affinity for tau protein, therefore, indirectly reduce tau–tau interaction [44]. The dye methylene blue (methylthioninium chloride) has also known to prevent tau interactions, it also inhibiting Aβ aggregation [45], improving electron transport, decreasing oxidative stress, prevent mitochondrial damage, regulate autophagy and inhibition of AChEs [44,46].

Enhancing tau degradation

It is well documented that, heat shock protein 90 (Hsp 90), a chaperone involved in folding the denatured proteins, seems to play a role in preventing tau degradation. Curcumin with wide varieties of action has also known to inhibit Hsp 90 [47]. It has been investigated that curcumin treatment decreases the tau pathology in tau transgenic mice by suppressing tangle formation as well as promoting dissolution of already formed tangles [48].

Tau based vaccination therapy

Another approach is tau based immunotherapy to promote immunological clearance of tau tangles [11]. Recent active immunization studies have raised the possibility of modulating tau pathology by activating the immune system. JNPL3 mouse P301S tauopathy model for passive immunotherapy is effective at preventing the intracellular tau pathology and associated symptoms, although the exact mechanism remains uncertain [49].

Targeting intracellular signaling cascades

Modulation of intracellular signaling cascades can also be targeted as a therapeutic intervention in AD. As Aβ oligomers activate various intracellular pathways, so drugs that interrupt these signaling pathways could be useful in AD [50]. It has been reported that inhibitors of phosphodiestrase (PDE) provides significant benefit in experimental models. Recently reported that, rolipram is a PDE-4 selective inhibitor that effectively reversed memory and cognitive deficits in Aβ treated mice [51]; sildenafil, a PDE-5 inhibitor also produced similar results [50]. Recently cilostazol have been discovered, it inhibits PDE-3 activity and its administration protected transgenic mice from Aβ oligomer mediated damage, decreased Aβ accumulation and tau phosphorylation [52]. Some PDE inhibitors that are in preclinical stages of development include AVE-8112, BCA-909, and THPP-1 [53]. It has been experimentally proved that inhibition of phospholipase A2 protects rats from cognitive deficits and decreases the levels of total tau in brain [54]. Recently rilapladib, an oral inhibitor of lipoprotein associated phospholipase A2, have investigated currently in phase II trials (NCT01428453) [55].

Modulating levels of neurotransmitter

Acetylcholinesterase inhibitors (AChEIs)

There are four AChEIs approved by the U.S. FDA for the treatment of AD i.e. tacrine, donepezil, rivastigmine, and galantamine [56]. AChEIs enhance cholinergic neurotransmission through inhibition of enzyme AChEs, thus decreasing the breakdown of ACh. In the past couple of years, novel AChEI molecule Memogain (GLN-1062), pro-drug of benzoyl ester of galantamine is available as intranasal formulation [57]. Other novel molecule includes Huperizine A, which is a natural alkaloid isolated from the Chinese moss shrub (Huperzia serrata), an AChEI and have also action with modest effects on APP metabolism and neuroprotection [58]. It has been reported that M1 agonists seems to play their role in APP processing and thus indirectly on other processes such as tau phosphorylation because studies have shown that removal of M1 AChRs lead to increased Aβ oligomers generation. AF102B, an M1 partial agonist, significantly lowered CSF Aβ levels in AD patients. AF150(S) and AF267B have also shown promising results in the preclinical setup [59]. ANAVEX 2-73 is a mixed muscarinic/σ1 agonist and is currently in phase I/IIa trials [60]. A few recent studies highlight the use of the metabolite of nicotine "cotinine" in cognitive enhancing potential this compound is a positive allosteric modulator of α7 nicotinic AChRs [61].

Modulation of GABAergic neurons

In neurodegeneration if we consider neurons of hippocampal region, than earliest to be affected are the cholinergic neurons followed by the glutamatergic neurons; for unknown reasons there is relative sparing of GABAergic neurons [62]. Some studies have reported that when chronic growth factor deprivation occurs, the GABA transmission changes from inhibitory to excitatory stimulus. GABAergic drugs are currently being tried for their cognitive enhancing potential [63]. SGS742 is a GABAB antagonist that showed promising results in preclinical and phase I studies and currently it is in phase II trial stage. Etazolate, a pharmacological modulator of GABAA receptor is also neuroprotective. It also activates α-secretase and inhibits phosphodiestrase (PDE)-4 activities [64].

NMDA receptor antagonism

Glutamatergic neurons regulate synaptic plasticity, neuronal growth and differentiation, cognition, learning and memory [65]. Memantine is an uncompetitive NMDA antagonist, blocks the receptor by trapping it in open conformation. Experimental evidences show that memantine treatment improves spatial learning in animal models of AD, protects neurons from Aβ induced toxicity, decreases apoptosis, free radical mediated damage and restored synaptic degeneration [66]. Currently memantine is the only drug approved for clinical use in moderate to severe AD in USA and Europe [67]. The involvement of cholinergic neurons probably occurs early in the disease but, damage to glutamatergic system and excitotoxic degeneration occurs late in the course of disease [68]. A current trial of memantine and donepezil combination in moderate to severe stages of AD is ongoing (NCT00866060). ADS-8704 (Adamas pharmaceuticals) is currently in phase III trials [67].

Modulation of serotonin receptor

The areas of the brain concerned with learning and memory show high concentrations of 5-HT1A, 5-HT4, 5-HT6 and 5-HT7 receptors. A large number of compounds with serotonomimetic property (monoamine oxidase inhibitors and selective serotonin reuptake inhibitors) are already in clinical use and are used in AD as monotherapy or along with AChEI for their cognitive enhancing capacities [69]. Number of novel ligands with agonistic or antagonistic properties targeting different 5-HT receptors is available (5-HT1A, 5-HT4 and 5-HT6) [70]. A 5-HT1A antagonist lecozotan is in phase II trials (NCT00151333) [71]. A number of 5-HT4 agonistic compounds like PRX-03140, Velusetrag, TD-8954, RQ-00000009, SUVN-D1003019 and SUVN-1004028 have shown cognitive benefits in preclinical studies with potential effects on amyloid processing. SB-742457, a novel 5-HT6 agonist has also shown positive results in phase II trials as a monotherapy and combination with donepezil [72]. Interestingly, 5-HT6 antagonists like Ro-4368554, SB-258585 and SB-399885 have also shown cognition enhancing properties in preclinical studies [73].

Histaminergic modulators

Brain regions which are involved in sleep–wake regulation and cognitive functions the histamine receptor (H_3) expression is high [74]. Activation of this receptor inhibits histamine release in the brain but its selective antagonism enhances the release of various

neurotransmitters including acetylcholine, GABA, dopamine and nor adrenaline [75]. Preclinical studies have shown cognition enhancing properties for novel H3 antagonists, including BF2.649, PF-03654746, GSK189254, MK-0249, JNJ-17216498, and ABT-288 [76]. PF-03654746 has completed a phase I trial, but the results are not available (NCT01028911). ABT-288 was safe and well tolerated in healthy adults [77]; the compound recently completed its phase II trial (NCT01018875). A small pilot trial with selective H3 antagonist GSK239512 also showed excellent safety profile with positive effects on attention and memory [78].

Modulation of adenosine receptor

Recently it has been investigated the role of adenosine as neuromodulator and in neurodegenerative disorders. Adenosine receptors, especially adenosine 2A play pivotal roles in modulation of neuronal function, linking the system to AD related cognitive deficits. *In vivo* studies have shown neuroprotective value for SCH58261, an adenosine 2A blocker [79].

Targeting mitochondrial dysfunction

Aβ accumulation inhibits certain mitochondrial import channels, thereby decreasing complex IV activity and increasing ROS production [80]. The increased mitochondrial ROS production will further induce mitochondrial dysfunction, finally leading to cell death [81].

It is well reported that CoQ10 administration has potential neuroprotective effects including suppression of ROS production, minimized ROS injury and stabilization of mitochondrial function [82]. Idebenone, a water-soluble analog of ubiquinone has also been reported to show some dose dependent beneficial effects on cognition and disease progression for up to 2 years [83]. Methylene blue also seems to serve as an alternative electron carrier; bypassing complex I/III blockage thus may provide neuroprotection in AD [84]. Lipoic acid in combination with vitamin E and C has been tried and it was observed that oxidative stress decreased [85]. Currently lipoic acid and omega-3-fatty acids combination therapy is in phase I/II trials (NCT01780974, NCT01058941). Szeto-Schiller peptide (SS-31) is also a novel mitochondrial targeted ROS scavenger therapy [86].

Targeting oxidative stress

ROS attack many key molecules including enzymes, membrane lipids and DNA and hence leads to cell death. Some natural antioxidants including vitamins (E, C, and carotenoids), phytochemicals and synthetic compounds provide protection in AD [87]. A phase III trial combining vitamin E with memantine was completed recently, and the results will be awaited [88]. A phase III trial of vitamin E and selenium is currently ongoing (NCT00040378). Some ubiquitous antioxidants like flavonoids, rutin and carotenoids have also shown neuroprotective effect in experimental models of AD [89]. Melatonin (NCT00940589) is another potent antioxidant currently in phase II trial. Recently novel melatonin agonist Neu-P11 that has attenuated neuronal loss and improved memory performance in rats has been discovered [90].

Anti-inflammatory therapy

To tackle neuroinflammation associated with disease process NSAIDs are used and they exert beneficial effects via variety of mechanisms apart from their cyclooxygenase (COX) inhibition like maintaining Ca^{2+} homeostasis, targeting γ-secretase, Rho-GTPases, and PPAR [91]. Through Rho-GTPases pathway, NSAIDs manage various phenomena associated with AD including axon growth, tau phosphorylation, and astrocyte motility [92]. Preclinical studies show that administration of SC-560, a COX-1 selective inhibitor, in triple transgenic mice has reduced inflammation, neuropathology and improved cognitive performance [93].

Other pharmacotherapeutic strategies

Cholesterol lowering drugs

It has been well documented that the statins shows its pleiotropic effects and dose-dependent beneficial effects on cognition, memory and neuroprotection [94]. Statins are also known to protect primary cortical neurons from glutamate toxicity [95]. Some studies have shown that low dose statins prevent aberrant neuronal entry into mitosis, activate anti-apoptotic pathways and suppresses inflammation but not at higher dose [96].

Neuroprotective gonadotropin hormones

Various hormones are known for their neuroprotective properties like testosterone, estrogen and progesterone. It is well reported that their levels decreases with ageing and luteinizing hormone (LH), supports the disease process, but the concentrations increase with aging [97]. Studies have shown that prior use of HRT (hormone replacement therapy) decreases the risk of AD in women, but current use is not useful unless used more than 10 years. Another recent study shows that low dose estrogen therapy decreases the risk of AD [98]. Similarly male hormone testosterone has known to significantly improve cognition in males and quality of life showing protective as well as therapeutic effects [99]. The primary female hormone estrogen and the primary male hormone testosterone have numerous protective effects in the brain relevant to the prevention of AD such as the promotion of neuron viability, reduction of Aβ accumulation and alleviation of tau hyperphosphorylation. Complications are associated with estrogen-based hormone therapy such as the inclusion of a progestrogen, hormone responsiveness with age, and natural *vs*. synthetic hormones [100].

Neurogenesis

Cholinergic neurons are nerve growth factor (NGF) sensitive and dependent; so neurotrophic factors administration is tried to maintain neurogenesis and cell survival in neurodegenerative disorders. Preclinical studies have shown beneficial results when treated with neurotrophic factors [101]. Cerebrolysin® (Ever Neuro Pharma) is a porcine derived peptide that possesses neurotropic properties, and has gained attention recently in several randomized trials. It has been reported that the combination therapy of AChEI and cerebrolysin has synergistic effects in AD [102].

Epigenesis

Epigenetics are thought to be one of the most needed reasons to the beginning of the pathophysiological events. Epigenetic modifications include DNA methylation and histone modifications. For targeting AD, drugs that alter the DNA methylation and histone acetylation could hold the key to the treatment [103]. In AD, there is disturbance of methylation homeostasis occurs which in turn result in the deficiency of one of the vitamins. Some clinical studies have shown positive results when vitamins B was given in AD [104].

Caspase inhibitors

As discussed in the previous reviews about the role of caspase, enzymes of cysteine family of proteases, in the apoptotic pathways [105]. Caspase inhibitors, both selective and non-selective have shown neuroprotective benefits in preclinical studies [106] but their feasibility as therapeutics in clinical studies is yet to come.

Modulators of NOS

Nitric oxide (NO) performs multiple roles in CNS function like maintaining cognitive function, neurotransmitter secretion, sleep wake cycle, appetite control body temperature homeostasis and neuroprotection [107]. It has been well documented that NO seems to protect the neurons from excitotoxicity through its effect on NMDA receptors as well as caspase inhibition [108]. As very well documented that central mediators of microglial stress response is NO. It is implied in regulation of vascular integrity, neurotransmission and neuroinflammation. NOS are required for the synthesis of NO and there are three isoforms of NOS–iNOS, eNOS and nNOS. Out of these three isoforms iNOS is expressed in glial cells as response to pro-inflammatory cytokines. In AD there is activation of microglia which in turn activates iNOS that results in excess NO release by microglial cells consequently results in immunomodulation and neuronal damage and AD [108].

Nucleic acid drugs

It is a new approach for treatment of neurodegenerative diseases include plasmid DNA (pDNA) or antisense oligodeoxynucleotides such as nuclear factor k-B (NF-kB) decoy based options. Currently they are in preclinical studies and early phases of clinical trials. Another strategy is to provide neurotrophic factors using naked pDNA incorporated with the genes of neurotrophic factors. pDNA can also be used as a DNA vaccine since the molecule is immunogenic thus stimulates the dendritic cells and promotes a T-cell response [109].

Multi-target directed ligands

The compounds with several potential targets (multi-target directed ligand) for the complexity of the mechanisms involved in AD interact with different mechanisms, therefore, provide symptomatic and disease modifying benefits; for example, compounds with dual AChE and BACE inhibition or AChEIs with antioxidant properties [110]. Ladostigil (TV3326) [(N-propargyl-(3R) aminoindan-5yl)-ethyl methyl carbamate], a multifunctional compound, acts by blocking AChE, and hence increase cholinergic neurotransmission; with the inhibitory effect on monoamine oxidase (MAO)-A and B. It decreases amyloidogenic APP processing. It offers neuroprotective and neurorestorative activities and decreases apoptosis. Ladostigil combines the neuroprotective effects of the antiparkinson drug rasagiline, a selective MAO-B inhibitor, with the cholinesterase (ChE) inhibitory activity of rivastigmine in a single molecule, as a potential treatment for AD and Lewy Body disease [111].

Conclusion

In this paper we learn more detail about the pathophysiology and disease progression of AD and an insight into the potential therapeutic targets. Despite of the bulk of knowledge regarding this complex disease, only a fistful options are available for its management. Currently available drugs (AChEIs and memantine) for the treatment unfortunately target symptoms only and not the cause of the disease. So, the hope is now raised for the novel therapies that act at the root of the disease process and will be able to stop the progressive accumulation of Aβ. Targeting Aβ production *via* inhibition of β-secretase, though a promising approach, but at present only few compound have been tested and undergone clinical trials.

Another enzyme involved in Aβ oligomers production i.e. γ-secretase can also be targeted but risk of toxicity associated with inhibition is hindering the use of such compounds for the treatment of AD patients.

By contrast, the vaccination approach remains promising approach as a result of behavioral improvements observed in mice and the possibility that the amyloid accumulated in the preclinical stages of the disease can be cleared following Aβ vaccination. Vaccination supposed to stimulate endogenous removal of Aβ oligomers and tau oligomers hence is another attractive option. Some novel approaches are also available such as DNA vaccination, NOS modulation, or caspase inhibition that is still to be studied.

It has been reported that results of some non-targeted approaches such as anti-inflammatory therapy, metal chelation, antioxidant supplementation, epigenetic modifications are more harmful so it is difficult to say that whether there proper usage will improve clinical outcomes or not. If the failed anti-amyloid and antioxidant trials taken into consideration then that make us to think where we have gone wrong? Reasons may be due to failure of compound, of experimental design, failure to include biomarkers in trials, incomplete reporting of data, population heterogeneity, inappropriate dosage, inappropriate timing-antioxidant therapy may be helpful in early stages of the disease not in the late stages and last but not the least i.e. incomplete understanding of the drug's pharmacokinetics and bioavailability.

As reviewed in this paper, several promising clinical trials are ongoing, which may provide new drug target and that may be helpful in solving complex AD puzzle.

Conflict of interest

None declared.

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