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Reviews

Dendritic spines: Revisiting the physiological role

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ABSTRACT

Dendritic spines are small, thin, specialized protrusions from neuronal dendrites, primarily localized in the excitatory synapses. Sophisticated imaging techniques revealed that dendritic spines are complex structures consisting of a dense network of cytoskeletal, transmembrane and scaffolding molecules, and numerous surface receptors. Molecular signaling pathways, mainly Rho and Ras family small GTPases pathways that converge on actin cytoskeleton, regulate the spine morphology and dynamics bi-directionally during synaptic activity. During synaptic plasticity the number and shapes of dendritic spines undergo radical reorganizations. Long-term potentiation (LTP) induction promote spine head enlargement and the formation and stabilization of new spines. Long-term depression (LTD) results in their shrinkage and retraction. Reports indicate increased spine density in the pyramidal neurons of autism and Fragile X syndrome patients and reduced density in the temporal gyrus loci of schizophrenic patients. Post-mortem reports of Alzheimer's brains showed reduced spine number in the hippocampus and cortex. This review highlights the spine morphogenesis process, the activity-dependent structural plasticity and mechanisms by which synaptic activity sculpts the dendritic spines, the structural and functional changes in spines during learning and memory using LTP and LTD processes. It also discusses on spine status in neurodegenerative diseases and the impact of nootropics and neuroprotective agents on the functional restoration of dendritic spines.

1. Introduction

In 1888, Ramón Y Cajal, a neuroanatomist discovered the existence of thin protrusions emerging from the surface of certain neurons which he termed "Dendritic spines". Gray's (1959) electron microscopy study defined that dendritic spines are postsynaptic structures which play subtle functions in synaptic communications. Since dendritic spines comprise the most important parts of excitatory synapses (McKinney, 2010; Nimchinsky et al., 2002) their morphology and density is reported to play a crucial functional role in synaptic plasticity, and consequently, in the learning and memory processes. Synaptic development, maintenance and plasticity in both physiological and pathological conditions are frequently associated with abnormalities in the morphology and numbers of dendritic spines (Fiala et al., 2002). However, the exact molecular mechanisms involved in synaptic plasticity formation and role of dendritic spines remain a matter of debate. The mechanisms of synapse formation and the effects of therapeutic interventions in neural circuitry in neurological disorders have not been elaborated. In this review, the authors illustrate the major molecular mechanisms of dendritic spines in terms of the long-term potentiation (LTP) and long-term depression (LTD) processes; the fundamental variations in dendritic spines in acute and chronic neurological /

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neurodegenerative disorders; and the effects of neuroprotective and nootropic drugs on regulation of dendritic spines.

2. Dendritic spines morphogenesis

In the early postnatal stage, the dendrites are devoid of spines and synapses. During synaptogenesis, finger-like actin-rich protrusions called 'filopodia' emerge from dendrites and form synapses with adjacent axons (Portera and Yuste, 2001; Zhang and Benson, 2000; Ziv and Smith, 1996). Normally, filopodia measure 3-40 μm in length (García-López et al., 2010) and are highly mobile structures that extend or retract transiently to form synaptic contacts with adjacent dendritic shafts or to a new small protospine. Upon synaptic contact, these filaments morphologically transform into spines with functional synapses termed as protospines (Dailey and Smith, 1996; Portera-Cailliau et al., 2003). Later, the protospines undergo morphological changes and turn either into mushroom or thin dendritic spines (Majewska et al., 2006). The formation and maturation of spines fluctuates constantly depending upon the synaptic strength and activities (Hotulainen and Hoogenraad, 2010). However, not all the filopodia transform into spines (Ziv and Smith, 1996). Only a small percentage of filopodia (0.2%) stimulated during synaptic activity mature into spines (Majewska et al., 2006). Classically, dendritic spines consist of bulbous heads attached to the dendritic shafts by narrow necks (Nimchinsky et al., 2002; Rao et al., 1998). The size, shape and number of dendritic spines vary heterogeneously even within a single dendritic segment of a given neuron. The number of dendritic spines varies from 1 to 10 spines/um length of a dendrite depending on the type of neuron and the developmental stage (Calabrese et al., 2006). Dendritic spines in a matured brain are typically < 3 μm in length with a spherical head 0.5-1.5 μm in diameter which is connected to the parent dendrite by a thin neck (< 0.5 μm in diameter) (Phillips et al., 2015).

Generally, dendritic spines are classified into 4 types on the basis of their morphology (Harris et al., 1992; Peters and Kaiserman-Abramof, 1970) as mentioned below (Fig. 1).

- Mushroom spines with a large head and a narrow neck (more stable).
- Thin spines with a smaller head and a narrow neck (less stable).
- Stubby spines without an obvious constriction between the head and the attachment to the shaft.
- Branched or cup-shaped spines with two heads attached to a single narrow neck.

3. Dendritic spines - ultrastructure

3.1. Main structural components of dendritic spines

Major components of dendritic spines include cytoskeleton structures (actin), cytoskeleton proteins, cell membrane receptors (NMDA, AMPA and metabotropic receptors), small GTPase and associated proteins, post-synaptic density (PSD) region, micro RNA, mRNA binding proteins, transcription factors, extra-cellular matrix and adhesion molecules (Fig. 2).

3.1.1. Actins

Actins are highly dynamic structures that act as the main cytoskeleton components of dendritic spines (Bosch and Hayashi, 2012; Koleske, 2013; Penzes and Rafalovich, 2012). Dendritic spines contain high levels of actin, approximately 6 times higher than dendritic shafts (Honkura et al., 2008). Actin exists either in a polymerized filamentous form (filamentous actin / F-actin) or as a soluble depolymerized monomeric form (globular actin / G-actin). In dendritic spines, F-actin forms the major proportion, whilst G-actin contributes to only about 12% of the total actin content (Honkura et al., 2008; Star et al., 2002). F-actin structure varies from branched filament networks to thick bundles of cross-linked filaments, which provide support and stability to dendrites (Blanchoin et al., 2014). Cross-talks between F- and G-actins allows morphological changes of dendritic spines during synaptic activities. These results suggest that mainly actin polymerization and/or depolymerization determines the motility, growth and shape of the dendritic spines during maturation process (Blanchoin et al., 2014; Pollard and Cooper, 2009). In fact, most of the morphological changes in spines are mediated by actin polymerization (Segal and Andersen, 2000).

3.1.2. Myosin

Myosin II, a hexameric polypeptide consists of 2 heavy chains and 2 pairs of regulatory light chains (Ryu et al., 2006a). Myosin IIB, the major non-muscle myosin II isoform found in brain binds and contracts actin filaments. It is essential for normal spine morphology and dynamics (Kawamoto and Adelstein, 1991; Ryu et al., 2006b; Vicente-Manzanares and Horwitz, 2010a). Recent mass spectrometry data show abundant presence of myosin heavy chain IIB in the post synaptic density (PSD) region of neurons in rats (Jordan et al., 2004; Peng et al., 2004). Loss-of-function experiments using both pharmacologic (blebbistatin, a small molecule inhibitor of myosin II) and genetic (myosin IIB-RNAi, hippocampal neurons transfected with a pSuper plasmid expressing small hairpin RNAs against rat myosin IIB) approaches led to depletion of mushroom-type spines and their replacement with irregular filopodia-like processes confirming the essential necessity of myosin IIB for spine morphology and normal motility (Ryu et al., 2006b). Short-term inhibition of myosin IIB activity induces immature filopodia-like spines and results in a corresponding disruption of LTP and memory acquisition (Rex et al., 2010; Ryu et al., 2006b).

The immunocytochemical localization of myosin IIB at synapses indicates its crucial role in shaping the dendritic spine head. Myosin IIB immunoreactivity is found to be more intense in the soma and proximal dendrites in immature rat hippocampal neurons vs. the immunoreactivity was more concentrated in the neck to the head of dendritic spines in the more mature neurons. Myosin IIB activity is regulated by phosphorylation on residues Thr18 and/or Ser19 in its regulatory light chain; simultaneous phosphorylation on both residues promotes maximal myosin ATPase activity and the formation of large actin bundles (Ikebe and Hartshorne, 1985; Vicente-Manzanares et al., 2009; Vicente-Manzanares and Horwitz, 2010b). Myosin IIB mediates

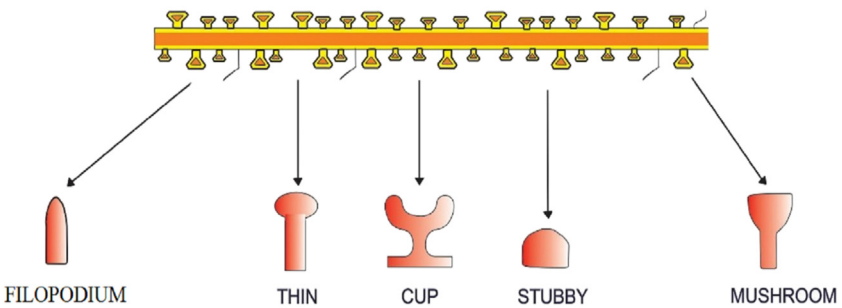

Fig. 1. Types of spines based on shapes. Filopodium – thin elongated protrusions; Thin spines – small head connected to the dendritic shaft by a narrow neck; Cup spines – two small heads connected to the dendritic shaft by a short neck; Mushroom spines - large head connected to the dendritic shaft by a narrow neck; Stubby spines – Short bulbous structure with no distinction of head and neck

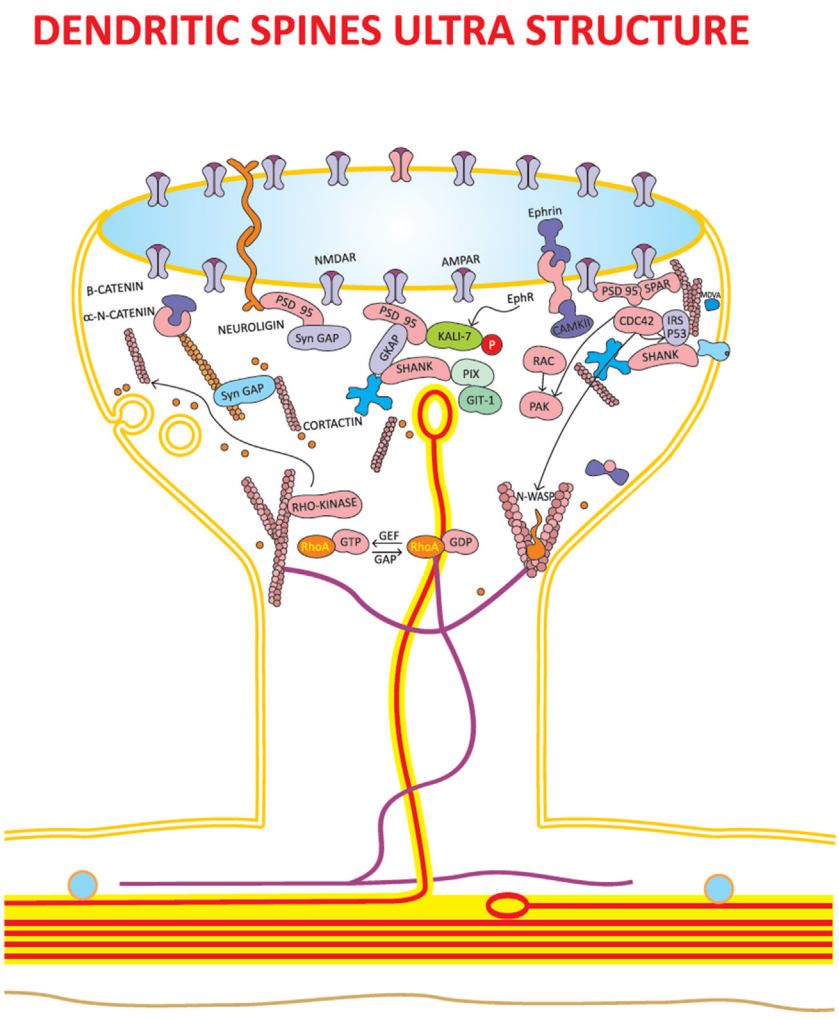

Fig. 2. Major components of dendritic spines. Synaptic activation (via AMPA and NMDA receptors by glutamate) alters structural molecule like PSD-95 which in turn stimulates RhoGTPases, or protein kinases signals. RhoA, Rnd1, Rac1 and Cdc42 are main regulators of dendritic spine morphology and synapse strengths.

and regulates the emergence of filopodia from the dendritic shaft, spine elongation, and maturation into mushroom spines indicating its role as main coordinator during the different stages of spine development (Yuste and Bonhoeffer, 2004).

3.1.3. GTPases

The Rho family of small GTPases (particularly RhoA, Rnd1, Rac1 and Cdc42) are the main regulators of actin and have a profound influence on spine morphogenesis (Ishikawa et al., 2003; Newey et al., 2005). The Ras family of GTPases and their downstream MAP kinase signaling pathways also regulate spine morphogenesis. A major postsynaptic inhibitor of Ras signaling is SynGAP (synaptic Ras GAP), which is enriched in PSD. Even though both Rap GTPases and Ras exhibit a close relationship in synaptic plasticity, they play opposite roles. Ras promotes long term potentiation (LTP), while Rap1 and Rap2 mediate long term depression (LTD) and depotentiation, respectively (Zhu et al., 2005). In contrast to RasGAP and SynGAP, the postsynaptic RapGAP SPAR (spine associated RapGAP) enhances spine growth (Pak et al., 2001; Pak and Sheng, 2003). Ras and Rap act antagonistically in PSD matrices to regulate the spine morphology and synapse strengths.

3.1.4. PSD region

In the adult mouse neocortex, the majority (almost 96%) of dendritic spines are characterized by large complex electron-dense structures defined as PSD that mark synaptic contacts (Arellano et al., 2007). Within the PSD matrix, synaptic vesicles comprising the excitatory neurotransmitter - glutamate and its receptors - α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), *N*-methyl-D-aspartate (NMDA) and metabotropic glutamate receptors are established (Calabrese et al., 2006; Kennedy, 2000; Nimchinsky et al., 2002). AMPA receptors are found at the edges of PSD while NMDA receptors are located centrally within the PSD (Kharazia and Weinberg, 1997). Morphological alterations of dendritic spines mainly depend on NMDA receptor's activation and contribute to the formation of new synapses during LTP induction and the regression of existing synapses during LTD induction (Matsuzaki et al., 2004; Park et al., 2006; Zhou et al., 2004).

The PSD surfaces range from small discs to large irregular shapes that can be perforated by electron lucent regions (Bourne and Harris, 2008). A recent protein analysis of PSD revealed numerous properties such as actin binding and cytoskeletal proteins (actin, N-catenin, Arp2/3, calponin, cortactin, cofilin, drebrin, myosin IIB, myosin VI, neurabin I, neurabin II, spinophilin, profilin I/II, synaptopodin and SPIN90); small GTP-ases (ARF6, Cdc42, Rac1, Rap1, Rap2, Rem2, RhoA, Rif and Rnd) and associated proteins (Rho-GEF: ARHGEF6/PIX, ARHGEF7/PIX, Dock180, GEFT, kalirin-7, Lfc/GEF-H1, Tiam1, Vav and Rho-GAP: alpha1chimerin, oligophrenin1, p190RhoGAP, p250GAP, RhoGAP2, SrGAP2); cell surface receptors (beta2-nAChR, GABBAR, GluA2, GluN1, GluN2B, Npn-2, NgR1, PGC-1); adhesion molecules (alpha3-integrin, alpha5-integrin, arcadlin, DSCAM, N-cadherin, neuroligins (1,2,3,4), syndecan-2, telencephalin, APP, vezatin); receptor tyrosine kinases (EphB1/2/3, EphA4/ephrin-A3, ErbB2/B4, p75NTR, TrkB); other

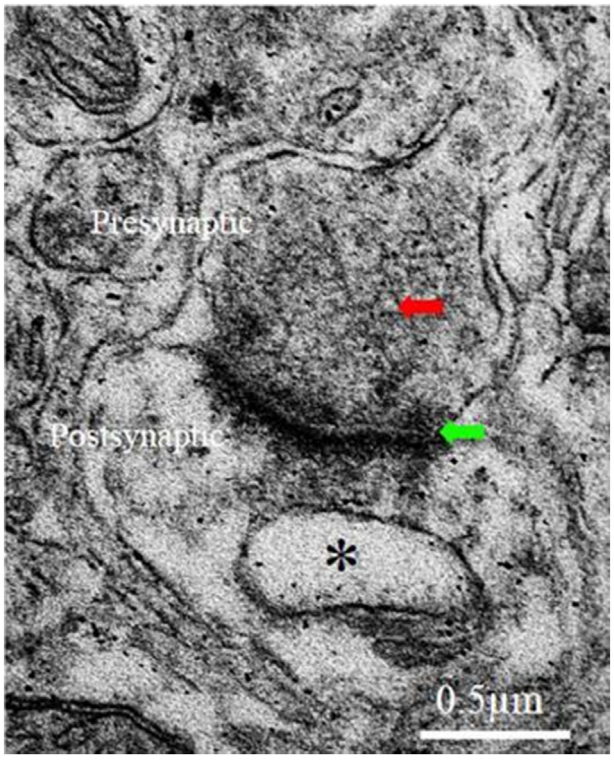

Fig. 3. Transmission electron microscopy of a dendritic spine (magnification 50 × 10^3 times). Red arrow denotes presynaptic density which contains vesicles; Green arrow denotes postsynaptic density and star denotes spine apparatus (Maiti et al., 2015, reproduced with permission from Hiroyuki Kamiguchi, Editor Neuroscience Research journal)

kinases (PAK, PAK1, PAK3, CaMKII, CaMKII-alpha, CDKL5, DCLK1, DGKf, LIMK-1, MARK4); post synaptic scaffold proteins (G-protein coupled receptor kinase-interacting protein 1, PSD-95, Homer1a, Homer1b, intersectin-s, PSD95, SAP102, TANC1/2, PAR-3, PAR-6 and Shank1,2,3) and adaptor proteins (afadin, IRSp53, numb); and micro RNA, mRNA binding proteins, and other transcription factors that are involved in various signaling cascades in dendritic spines during synaptic plasticity (Husi et al., 2000; Maiti et al., 2015; Walikonis et al., 2000). The scaffold protein - PSD-95, found closely in the postsynaptic membrane zone interacts directly with several NMDA receptor subunits (Fujita and Kurachi, 2000; Kim and Sheng, 2004), membrane proteins and many cytoplasmic signaling molecules and thus it (PSD-95) facilitates signal conduction in PSD (von Bohlen Halbach, 2009) (Fig. 3).

3.1.5. Other cellular organelles in dendritic spines

Myosin II, a hexameric polypeptide, consists of 2 heavy chains and 2 pairs of regulatory light chains (Ryu et al., 2006a). Myosin IIB is the major non-muscle myosin II isoform found in the brain. It binds and contracts actin filaments and is essential for normal spine morphology and dynamics (Kawamoto and Adelstein, 1991; Ryu et al., 2006a; Vicente-Manzanares et al., 2009). Recent mass spectrometry data shows an abundant presence of myosin - heavy chain IIB in the PSD region of neurons in rats (Jordan et al., 2004; Peng et al., 2004). Some forms of smooth endoplasmic reticulum are found in the spines of hippocampal CA1 and Purkinje neurons (Spacek and Harris, 1997), while in few larger spines, endoplasmic reticulum transforms itself into a specialized organelle called *'spine apparatus'* (Gray and Guillery, 1963). Endocytic machineries located within specialized subdomains have also been noted in spines (Rácz et al., 2004; Song and Huganir, 2002). Stimulation of the synapses translocate mitochondria into spines; further the number and functions of mitochondria determine the spine morphogenesis in dendrites (Li et al., 2004). Additionally, polyribosomes and protein translational machineries are rooted at the base of spines (Ostroff et al., 2002). Such specialized molecular assemblies determine the shape and function of the spine and facilitate the postsynaptic neurons to biochemically respond to glutamate or other transmembrane signals (Hering and Sheng, 2001; Smart and Halpain, 2000; Zhang and Benson, 2001).

3.2. Molecular mechanisms involved in dendritic spines morphogenesis

New outgrowth of dendritic spines or changes in existing spine morphology during LTP mostly results from the modulation of actin filaments (Fukazawa et al., 2003; Kim and Lisman, 1999; Lin et al., 2005; Okamoto et al., 2004; Ouyang et al., 2005). Actin polymerization can be regulated directly by actin-binding proteins (mainly cofilin and profilin) which in turn are controlled by many upstream signaling pathways (particularly PAK kinase, LIM kinase, calcineurin phosphatase and slingshot phosphatase) involved in synaptic activity (Chen et al., 2007; Halpain et al., 1998; Meng et al., 2002). Several studies reveal that Arp2/3 complex stimulates the nucleation of new actin filaments and the formation of branches (Matsuzaki et al., 2004; Nägerl et al., 2004; Okamoto et al., 2004).

LTP causes an early transient phase of actin depolymerization which allows for structural plasticity and motility leading to new spine formation or changes in spine morphology, followed by subsequent polymerization of F-actin. The above-mentioned changes in-turn result in the long-term stabilization of these dendritic changes and consolidation of LTP (Ouyang et al., 2005). Actin-stabilizing proteins such as phosphorylated-cofilin (Gohla and Bokoch, 2002), profilin (Ackermann and Matus, 2003) and gelsolin (Star et al., 2002) are translocated to the spine heads by LTP-mediated NMDA receptor activation (Okamoto et al., 2004).

As the major function of spines is to compartmentalize the chemical changes within the individual synapses, the length and diameter of the neck of the spine influence the degree and dynamics of postsynaptic intracellular Ca2+ elevation, which is mediated by NMDA receptor activation. Small spines show greater increases in Ca2+ owing to reduced leaks through the thinner spine neck (Matsuzaki et al., 2004; Noguchi et al., 2005). The enlargement of the spine head largely depends upon the strength of synaptic stimuli. This is presumably related to higher levels of AMPA-type glutamate receptors in the larger spines (Kasai et al., 2003a; Matsuzaki et al., 2001).

With the maturation of synapses, the stimulation of NMDA receptors promotes actin mobilization to nascent synaptic sites leading to the emergence of new motile filopodia. The acquisition of AMPA receptors (Shi et al., 1999) and recruitment of adhesion molecules to synaptic junctions (Bozdagi et al., 2000) suppresses the motility of actin and stabilizes the morphology of spine (Matus, 2000). In dissociated hippocampal cells, the blockage of the neuronal activity by tetrodotoxin decreases the number of spines or leads to the emergence of filopodia (Kang et al., 2009; McKinney et al., 1999; Verpelli et al., 2010). Furthermore, blocking the AMPA receptor by NBQX results in spine loss (Kang et al., 2009; McKinney et al., 1999). Blocking NMDA receptors by AP5 (selective NMDAr antagonist) leads to the appearance of filopodia-like processes without reducing the density of total dendritic spines, indicating different roles for the two types of receptors in the maintenance and maturation of spines (McKinney et al., 1999). Loss-of-function experiments via both pharmacologic (blebbistatin, a small molecule inhibitor of myosin II) and genetic (myosin IIB-RNAi, hippocampal neurons transfected with a pSuper plasmid expressing small hairpin RNAs against rat myosin IIB) approaches led to depletion of mushroom-type spines and their replacement with irregular filopodia-like processes confirming the necessity of myosin IIB for spine morphology and normal motility (Ryu et al., 2006a).

4. Advanced methods for studying dendritic spines morphology and dynamics

Dendritic spines, the fundamental units of synaptic activity undergo various structural aberrations in a variety of neurological diseases. An accurate and unbiased structural characterization of dendritic spines are vital for the understanding of their involvement in the development of neural circuitry, synaptic activity and synaptic failure in neurological diseases (Fiala et al., 2002; Maiti et al., 2015). The most commonly used methods are Golgi-Cox or fluorescent dye staining in post-mortem brain tissues. Fortunately, recent technological advances in microscopy, molecular biology, computational biology, immune-labeling techniques, and protein and genetic engineering have now made imaging dendritic spine dynamics in the living brain not a distinct reality (Mancuso et al., 2013).

4.1. Golgi staining and fluorescent-labeling methods

In classical staining techniques, thick sections of post-mortem brain tissues are immersed in a solution containing potassium chromate and dichromate and chloride salts of heavy metals (silver or mercury) for several weeks. After procedures such as the dehydration of the tissue and clearing, these Golgi-impregnated tissues are mounted on microscope slides and viewed under bright field microscopy to study the structure of individual dendritic spines and dendritic arborizations (Gipson and Olive, 2017). Main advantages of staining (Golgi, Golgi-Cox and rapid or modified) methods are less costs, and clear images of the entire neuron. The procedure is also time efficient and the samples are resistant to fading or photobleaching over time. Major disadvantages of these staining techniques include limited capacity to determine the neurochemical phenotypes of impregnated neurons, inconsistent specificity, overlapping and out-of-focus dendritic segments. Staining methods cannot be applied to visualize the cultured living neurons, and this may cause underestimation of spine numbers due to the two-dimensional nature of the obtained images (Gipson and Olive, 2017). These disadvantages have been overcome by the development of fluorescent Golgi stains (Koyama and Tohyama, 2013), confocal laser scanning microscopy (Tredici et al., 1993), and immunofluorescence procedures that allow the identification of labeled neurons (Pinto et al., 2012; Spiga et al., 2011). Following their labeling with fluorescent dyes, images are taken on a confocal laser scanning microscope and serial images obtained are processed for three-dimensional reconstruction, and then, the density and morphology of dendritic spines is assessed. Other fluorescent labeling methods include the use of various commercially available tracer dyes, fluorochrome-labeled antibodies, and genetically encoded fluorescent proteins such as green fluorescent protein (GFP) or yellow fluorescent protein (YFP) (Malinow et al., 2010; Staffend and Meisel, 2011). Among these methods, viral-transfected fluorescent protein engineering, immuno-labeling techniques, and transgenic animal engineering have been helpful in elucidating the detailed structure and dynamics of dendritic spines seen in different brain diseases (Sala and Segal, 2014) (Fig. 4).

4.2. Advanced microscopic tools

Using optical microscope and electron microscope (especially single sections), researchers classically defined the clear distinction between stubby, thin, and mushroom shaped spines (Peters and Kaiserman-Abramof, 1970). Many advanced microscopic techniques such as confocal laser scanning microscopy and two-photon microscopy/multi-photon laser scanning microscopy overcome the diffraction barrier of light to provide spatial resolution from the microscale to the nanoscale (Maiti et al., 2015). Digital recording of spine images, including semi-automated software-guided tracing systems (example NeuroZoom, Neurolucida), were later developed to characterize the fine 3-D structure of dendritic spines (Glaser and Glaser, 1990; Sala and Segal, 2014).

4.2.1. Two-photon laser scanning microscopy (Fig. 5)

- Widely used as the long wavelength-excitation light helps to penetrate the intact nervous tissue to a depth of several hundred microns (Denk et al., 1990).
- Neurons of interest are typically labelled with fluorescent proteins such as GFP or YFP either in transgenic mouse lines or after labelling through viral transduction in in vitro models, and in in vivo studies up to depths of approximately 800 μm can be studied (Mittmann et al., 2011).
- Within a single spine, two-photon microscopy activates proteins tagged with photoactivatable GFP enabling the study of the dynamics of dendritic spines during activation-dependent plasticity (like LTP) (Gray et al., 2006; Steiner et al., 2008).
- Direct structure-function relationships in dendritic spines during synaptic activation are studied using two-photon uncaging of a caged glutamate compound (Branco et al., 2010; Branco and Häusser, 2011; Govindarajan et al., 2011). The disadvantage of this methodology is that the quality of the picture through a thinned skull, without the incorporation of other methods like microendoscopy, declines at distances of more than 50 μm from the brain surface (Isshiki and Okabe, 2014).

4.2.2. Super-resolution dendritic spine imaging techniques

Recent developments in imaging technologies enable researchers to produce very vibrant images of the dendritic spines of living neurons and show extraordinary details in spine structure and dynamics. These include

- Saturated stimulated emission depletion microscopy which enables us to view the morphology of each spine in detail. The thickness of the spine neck or subtle changes in the head shape and size (from thin to mushroom shaped spines) at a resolution less than 70 nm (Hell, 2007) is shown. It provides images of dendritic spines at a nanoscale resolution (Nägerl et al., 2008) and also in the living brain (Berning et al., 2012; Heilemann, 2010).
- Photoactivation localization microscopy (Betzig et al., 2006) and stochastic optical reconstruction microscopy (Rust et al., 2006) rely on the sequential, statistical excitation of a fraction of fluorophores spaced at distances larger than the diffraction limit (Giannone et al., 2010; Huang et al., 2010). Both approaches give a spatial resolution of around 20 nm and are commonly suitable in fixed cell cultures.
- Digital holographic quantitative phase microscopy (Marquet et al., 2013) and fiber-optic endo-microscopes (Barretto and Schnitzer, 2012; Gu et al., 2014; Murari et al., 2011) are also used to study the distributions and dynamics of receptors and signaling molecules in dendritic spines.

4.3. Viral-mediated neuronal tracing

In recent decades, viral strains are genetically engineered by recombinant technology and used as tools to map and trace the motor, visual, and auditory neural circuits in in vivo set-up. Advancements in viral vector technology led to the development of new tracing tools using viruses which help the researchers to distinctly label the neural pathways embedded in complex brain circuits underlying particular brain functions. Viral-mediated tracing technology uses natural viruses that infect, persist, and migrate within neurons. These viral tracers can also spread across the synaptic connections either in retrograde or anterograde directions (Branco and Häusser, 2011). These tracers provide an excellent imaging toolbox to precisely map the input and output connectivity of specific neuronal population or a particular cell type (Callaway and Luo, 2015; Junyent and Kremer, 2015; Oyibo et al., 2014; Defalco et al., 2001; Gradinaru et al., 2010b; Schwarz et al., 2015; Ugolini, 2010). Viruses which replicate and spread across the

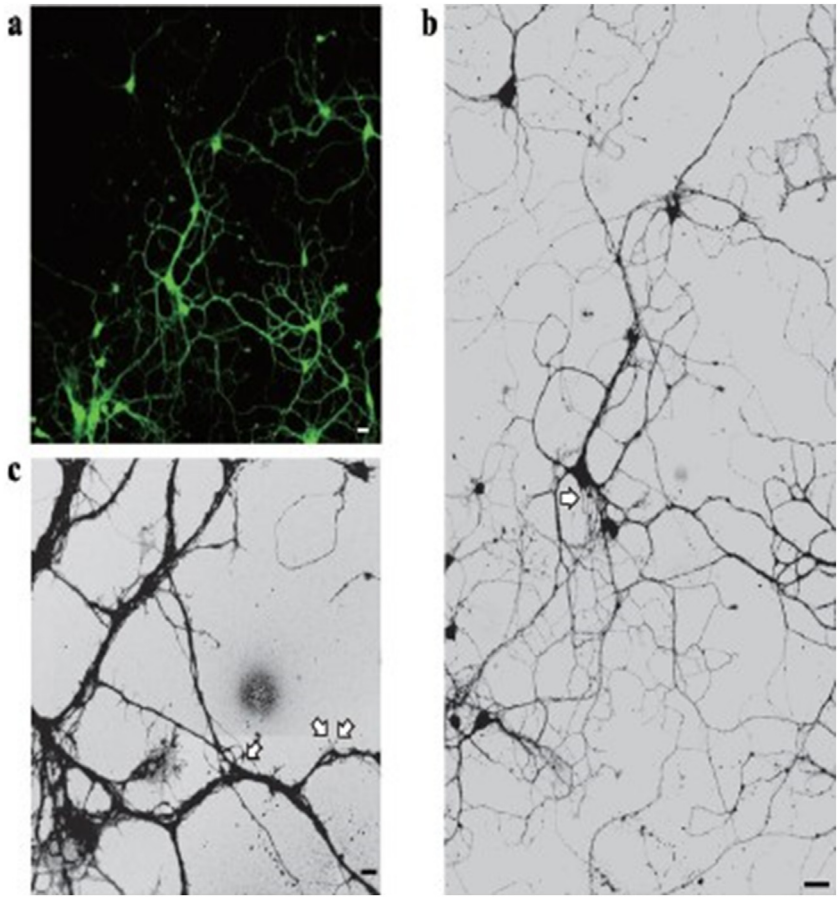

Fig. 4. Single neuronal cell with axon, dendritic tree and spines visualized using fluorescent Golgi method. (a) RGM colour image (low magnification) and (b, c) gray scale images (high magnification). Arrows indicate (b) axon or (c) spines (reproduced with permission from Yassine Amrani, Editor OA Anatomy)

presynaptic connections are known as retrograde trans-synaptic viral tracers (Oztas, 2003), and those viruses that replicate and spread across the downstream post-synaptic connections are known as analogous anterograde trans-synaptic tracers (Oztas, 2003, Wickersham et al., 2007) (Fig. 6)

Most common retrograde trans-synaptic viral tracers include Rabies Virus (RABV) and the Bartha strain of pseudorabies virus (Dietzschold et al., 2008). These retrograde trans-synaptic viral tracers replicate and spread in a synapse-specific manner and are used traditionally for mapping presynaptic inputs to transduced neurons (Wichmann and Delong, 2007; Wall et al., 2010; Defalco et al., 2001; Ekstrand et al., 2008, Callaway, 2008, Luo et al., 2008, Ugolini, 2010 and Ugolini, 2011). Remarkably, RABV is the most promising retrograde tracer tool to map the synaptically connected neuronal populations (Kelly and Strick, 2000; Wickersham et al., 2007a; Ugolini, 2011). However, the native RABV spreads across multiple serial synapses non-specifically, providing ambiguous results on the interpretation of the synaptic steps crossed at any given time. Thus, it was difficult to map the input and output connections precisely between rabies labeled neurons. To prevent the polysynaptic expansion of RABV, glycoprotein (GP) gene deleted-RABV, a variant of RABV has been developed recently, using trans-complementation approach, which enables the scientists to label only a neuronal connection via a single synaptic step. Monosynaptic neural circuit tracing using GP-deleted RABV (RVdG) has been a generally used tool to study the anatomy and function of neural circuitry (Callaway and Luo, 2015; Wickersham et al., 2007b). Using trans-complementation strategy, a recombinant RABV with its GP gene replaced with the coding sequence for enhanced GFP (EGFP) was developed (RVdG-EGFP). Even though RVdG-EGFP cannot spread beyond initially infected neurons, it can replicate within the viral core, and produce marked levels of EGFP to brightly label the fine dendritic and axonal structures (Wickersham et al., 2007a). By pseudotyping GP-deleted RABV with EnvA (envelope protein of avian sarcoma and leukosis virus), it became much easier to target RABV infection to specific transduced cell types or even single neurons, and to trans-synaptically map only their direct presynaptic inputs in the mammalian central nervous system (CNS) (Wickersham et al., 2007b). This new methodology enabled the tracing of monosynaptic connections of defined neurons (Wickersham et al., 2007b; Callaway, 2008; Marshel et al., 2010). By combining this methodology with the expression of a variety of genes, optical or electrophysiology methods, and behavioral assays, the researches have access to perform integrative studies about the neural circuits and their physiological functions (Callaway, 2008; Arenkiel and Ehlers, 2009; Osakada et al., 2011; Wickersham and Feinberg, 2012).

Despite the successful development of retrograde trans-synaptic viruses, analogous anterograde trans-synaptic tools for tagging post-synaptical neural pathways labeling downstream of targeted neurons remains an active area of investigation. Analogous anterograde trans-synaptic viral tracers use viruses like Herpes Simplex Virus (HSV, Norgren Jr. and Lehman, 1998, McGovern et al., 2012), Vesicular stomatitis virus (Beier and Saunders, 2011), Sindbis virus (Beier and Saunders, 2011) and Adeno-associated virus (AAV, Chamberlin et al., 1998). Even though HSV and vesicular stomatitis virus migrate through neurons only where it can replicate, they spread across several synaptic connections labeling a large neuron population (Ugolini et al., 1989). But, the neurotoxicity of these viruses and their uncontrollable spread across multiple serial synapses limits their applications in precisely mapping the neural circuits (Lo and Anderson, 2011; Beier and Saunders, 2011). In brain regions, AAV tracers spread across multiple

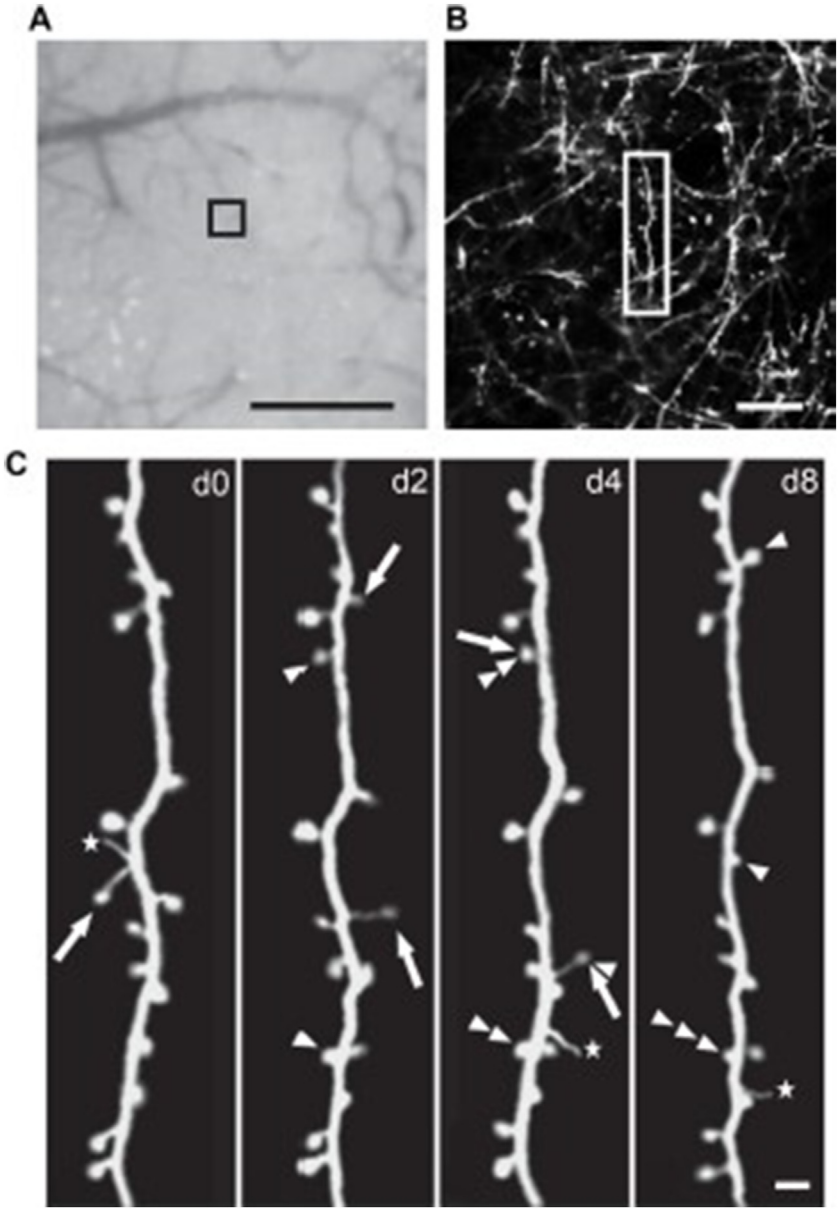

Fig. 5. Two photon microscopy imaging illustrating changes in a dendritic spine. (A) A charge coupled device image with the black box showing the areas of the photon where two photon images were taken (Scale bars: 500 μm). (B) A low-magnification image of a dendritic spine in the motor cortex of mouse (Scale bar 20 μm). (C) Repetitive pictures of dendrite under higher-magnification showing newly formed dendritic spines with arrows denoting eliminated spines and stars showing filopodia (Scale bar 2 μm) (Xinzhu et al., 2014, reproduced with permission from Benjamin Werth, Editor JOVE)

synaptic connections and transduce wide variety of neuronal populations. Though, AAV vectors expressing various fluorescence reporter genes have been widely used for anterograde circuit mapping, mostly it provides mixed results (Salegio et al., 2013; Hutson et al., 2015; Harris et al., 2012; Oh et al., 2014). Recently, studies using AAV1 as tracing tool reveal anterograde trans-synaptic tagging down the axon (Castle et al., 2013; Castro et al., 2014). Combination of AAV with a conditional expression strategy (such as two-step viral injection approach) enabled the researchers to map the output synapses of distinct subpopulations of superior colliculus neurons that receive different corticocollicular inputs and demonstrate their unique functional roles in driving different types of defense behavior (flight and freezing). A recent study (Brian et al., 2017) shows that AAV1 and AAV9 viruses are effective anterograde trans-synaptic tracers for mapping input-defined functional neural pathways, and pseudotyping AAV1 with GFP -tagged CAG failed to show any GFP + cell bodies in regions postsynaptic to the primary visual cortex. AAV provides an adaptable platform that can be combined and customized easily with up-to-date tools, promoters and recombinase-dependent expression control systems (Cai et al., 2013). Application of two-step viral injection method provides a direct means for examining the potential role of downstream structures in mediating a function or behavior observed from activation of a given upstream structure (Brian et al., 2017). Altogether, these results suggest that AAV-based anterograde trans-synaptic tagging approach is the most successful model to screen the functional circuits across multiple synaptic steps due to its ability to express high levels of protein with lower levels of toxicity and restricted spread to first-order downstream neurons.

A perfect comprehensive model for neuronal tracing and network mapping requires antero- and retrograde labeling, synaptic restriction, and controlled monosynaptic and polysynaptic spreading across the targeted neuronal species. These viral-mediated tracing methods are less neurotoxic and provide accurate mapping of neuronal connections when compared with other neuroscience methods such as

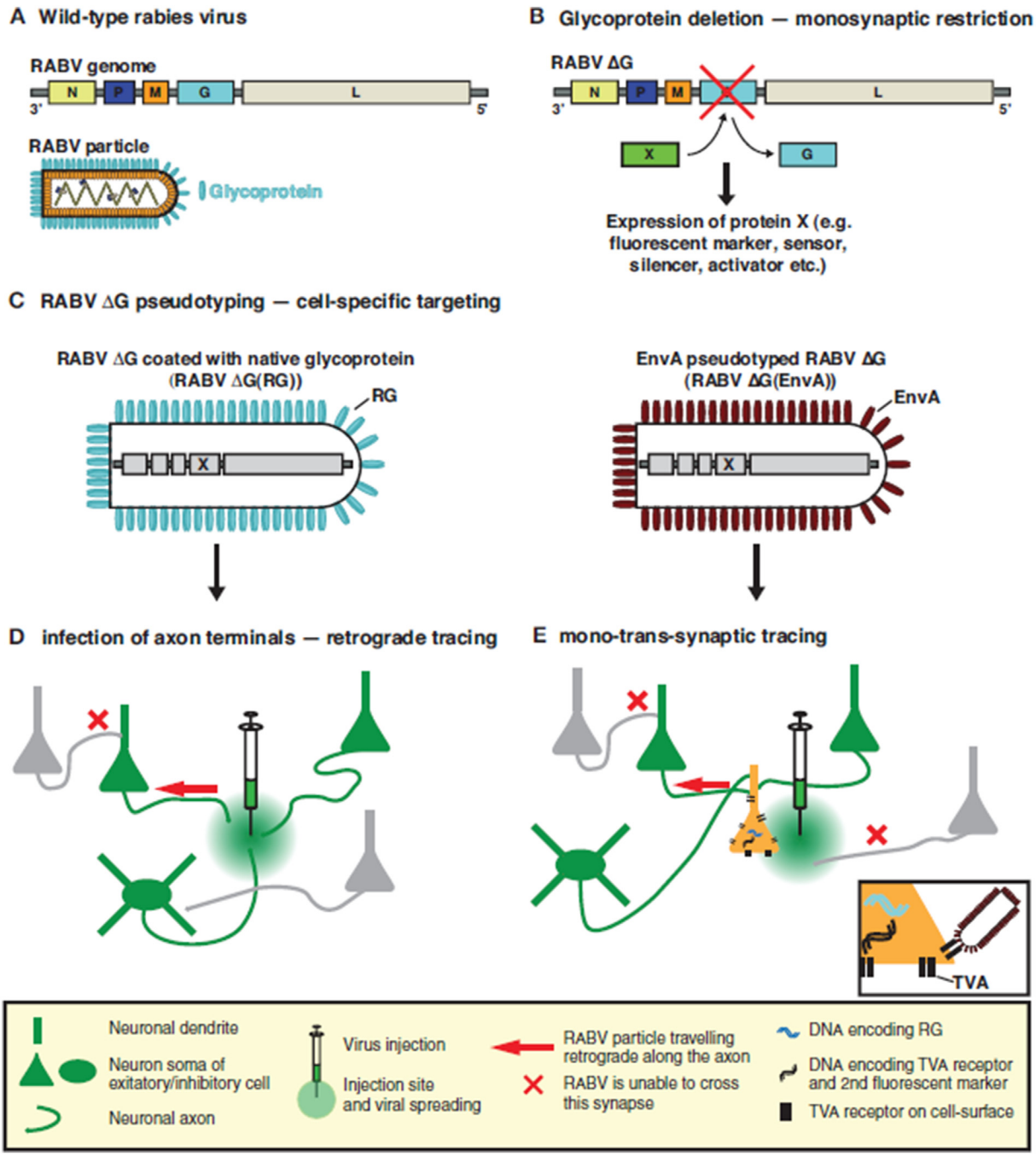

Fig. 6. Viral-mediated neuronal tracing (Example: RABV). (A) Wild-type RABV genome consists of five proteins including GP. (B) deletion of GP prevents trans-synaptic spreading and restricts the spread in a single-step vector. The gene of interest usually tagged with a fluorescent protein like GFP or YFP, and inserted in the space of deleted (GP). These viral transfected neurons can be visualized using fluorescent screening. This technique also permits the expression of various genetically encoded tools to visualize neuronal circuits, e.g., biosensors, synapse markers, activators/repressors of neuronal activities. (C) GP-deleted RABV is pseudotyped either with its native GP (that provides normal infection capabilities) or an engineered surface protein (like EnvA that provides cell-specific infection).(D) GP-deleted RABV tagged with its native GP is carried by axon terminals and used to trace neurons retrogradely. (E) EnvA pseudotyped GP-deleted RABV only infects the neurons expressing cognate (TVA) receptors. Trans-complementation strategy allows EnvA pseudotyped GP-deleted RABV to cross one synaptic step and infect the pre-synaptic neurons specifically, as it cannot infect other presynaptic cells due to the lack of envelope GP. This limiting strategy makes this tracing tool as a valuable one to decipher a mono-synaptic event in the selective neuronal population.

electrophysiological recordings or conventional fluorescent tracers. Trans-synaptic spread of viral tracers can be controlled genetically and thus neural circuitry of specific neuronal population can be studied in detail (Nassi et al., 2015). In contrast to classical polysynaptic viral tracers, improved neuronal tracing can be achieved by optogenetically controlled transgenes, pseudotyping technology and other genetic targeting approaches (Ginger et al., 2013), which may reveal not only the anatomy of neuronal connections, but also provide for visualizing neuron connections that are functionally relevant, i.e. activity-dependent neuronal tracing.

4.4. Optogenetics

The term “optogenetics” was coined first by Deisseroth et al. (2006)

to describe genetically targeted photoreceptor expression in neurons for their selective activation or inhibition with light. Optogenetic experiments provide a platform to study the physiology of specific neuronal types and projections in normal and disease-related models. Optogenetics comprise a combination of optical and genetic techniques to map the synaptic activation of specific neurons within intact or living neural circuits (Gobbo et al., 2016a). The precision of optogenetics has provided major experimental leverage (Lin et al., 2011) and has provided insights into neural circuit function and dysfunction.

The basis of optogenetic approach is to label the fast light-sensitive membrane channels at synapses by delivering RNA and protein regulatory sequences into specific neurons using viral vectors. These RNA and protein-targeting genes induce the expression of reporter proteins, including optogenetic probes, at activated synapses. This results in selective mapping of previously active synapses and the reactivation of neurons particularly only at these synaptic sites (Mahalaxmi, 2017).

Main components of optogenetic toolbox include

(i). Opsin, the functional unit of optogenetics which are defined as small membrane bound proteins that integrate with minute organic retinal particles and functions as a light receptor. Commonly, opsins are of microbial origin or proteins like bacteriorhodopsins, the halorhodopsins and the channel-rhodopsins (Deisseroth, 2015). Opsin variants provide both unique advantages and individual limitations in controlling cellular activity or neuronal signaling (Zhang et al., 2007, 2008 and Zhang et al., 2011; Nagel et al., 2002 and Nagel et al., 2003; Berndt et al., 2009 and Berndt et al., 2011; Gradinaru et al., 2010a; Chow et al., 2010; Gunaydin et al., 2010; Mattis et al., 2011).

(ii). Light-delivery method such as fiber optics. The numerical aperture, diameter and mode of the fiber have an impact on the spread of light. Optical fibers are most commonly used in light delivery method to deep neural somas or axon terminals. (Yizhar et al., 2011; Aravanis et al., 2007; Atasoy et al., 2008; Kuhlman and Huang, 2005; Tsai et al., 2009).

(iii). Targeting strategies to specific cell somas or axons widely include viral vector to express the specific opsin in target cells (Gradinaru et al., 2010a; Atasoy et al., 2008; Kuhlman and Huang, 2005; Tsai et al., 2009). Viral vectors widely used in optogenetic methods include lentivirus and AAV to induce the expression of opsin into the injection site. Herpes simplex virus or rabies virus are generally avoided due to their high toxicity (Mahalaxmi, 2017). Many kinds of viral transduction can restrict cell-body expression of opsin to the injection site and can be used in wild-type animals or Cre recombinase lines.

Genetically encoded optical sensor proteins permit the researchers to monitor several cellular parameters like ion and metabolite levels, enzyme activities, and membrane voltage. Spatio-temporal precision in neuronal control has been attained using optogenetic actuators and sensors (Packer et al., 2012a). The two types of genetically encoded photosensitive proteins used in optogenetic toolbox (Dugue et al., 2012; Medina, 2010) include

- Actuators or reporters (which control the neuronal activity in a light-dependent manner) such as channel-rhodopsin, halorhodopsin and archaerhodopsin.
- Sensors or indicators (which display the neuronal activity) for calcium (Aequorin, Cameleon, GCaMP), Chloride (Clomeleon) or membrane voltage (mermaid) (Packer et al., 2012b).

Genetically defined, cell-type-specific expression of optogenetic probes has been improved to a level where neuronal circuits can be more meticulously untangled and the activity of dispersed cell populations controlled or monitored in situ (Rost et al., 2017). Optogenetic methods facilitate the selective activation or inhibition of individual spines that affects the presynaptic terminal in the intact, alive animal, thus proving to be an essential tool to record the behavioral changes in both healthy and diseased models (Packer et al., 2012a). Most optogenetic manipulations are localized with limited discrimination throughout the neurons (Rost et al., 2017). Recent developments have begun now to target and/or control specific subcellular compartments using optogenetic actuators. The promising benefits of subcellular compartment-specific optogenetic manipulations include re-localization of organelles van Wyk et al., 2015) and neurotransmitter receptors (Sinnen et al., 2017), control of spine size (Hayashi-Takagi et al., 2015), and light-activated filling of synaptic vesicles (Rost et al., 2015). This approach is widely used tool to identify the mechanisms underlying pathogenetic process in neoplastic and degenerative diseases. Both activity-dependent double-strand DNA breakage in neurons (Suberbielle et al., 2013a) and acceleration of amyloid-β (Aβ) plaques as the disease progresses (Yamamoto et al., 2015) in mouse model of Alzheimer's disease (AD), and altered striatal inhibition in mouse model of Huntington's disease (Cepeda et al., 2013) are identified using defined neuronal populations expressing microbial opsin genes. Stimulation of neurons using optogenetic methods shows regenerative results like optogenetic activation of cones using halorhodopsin restored blindness due to neuronal loss in retinitis pigmentosa (Busskamp et al., 2010) and improved neuropsychiatric sleep disorders (Adamantidis et al., 2007). Optogenetic stimulation of spiral ganglion in deaf mice restored auditory activity (Hernandez et al., 2014).

As dendritic spines are the major anatomical structures of neural plasticity, optogenetics enables the researchers to directly visualize the changes in the spines and synapses during potentiation in an activity dependent manner. Optogenetics when used in combination with protein targeting and RNA-targeting sequences has been shown to enrich the expression of opsins at the synapses, especially in the dendritic spines. To facilitate the targeting of opsins specifically at the postsynaptic sites in dendritic spines, combination of RNA targeting and regulatory sequences with a short amino acid tag are used. These target a specific protein in the spine (Gobbo et al., 2016b). Similar to the endogenous synaptic proteins, these optogenetic reporter proteins also anchor and relocalize within the spines following local translation in an activity-dependent manner. These synaptic membrane proteins are synthesized primarily in the spine apparatus (Steward and Reeves, 1988; Spacek and Harris, 1997). These findings are consistent with observation found with the Arc-regulatory sequence used in synapse potentiation (Steward and Worley, 2001; Minatohara et al., 2015). These reports suggest that the regulation of translation conferred by Arc UTRs is maintained when connected to a different protein coding sequence like a membrane-tagged form of Cherry fluorescent protein. Interestingly, ArcSYP-Ch (fast-spiking ChETA-Cherry22-MS2 engineered with the entire Arc 5'- and 3'UTRs tagged with SYP) and Arc-Ch (ChETA-Cherry-MS2 engineered with Arc 5' and 3'UTR) are specifically found in bigger spines and are expressed locally only at stimulated spines (Gobbo et al., 2016a). Using Arc RNA regulatory sequences, a Channel rhodopsin variant is expressed at synapses undergoing potentiation, thus providing a novel tool to map and reactivate these sites selectively and specifically. Hayashi-Takagi et al. (2015) developed a novel synaptic optoprobe, AS-PaRac1 (activated synapse targeting photoactivatable Rac1), that labels recently potentiated spines specifically in the motor cortex during motor learning task. In vivo imaging revealed that light induces selective shrinkage of AS-PaRac1-containing spines, which severely disrupts the motor learning process. Hence, optogenetics is a versatile and novel tool to tag spines and synapses and to enhance the local expression of an opsin of the Channel rhodospin family (Gobbo et al., 2016b).

Major limitation in optogenetics include potential for toxicity (of viral vectors) at very high expression levels or long-term expression (of opsins) in neurons. Improvement in modes of light delivery is immediate requirement to promote the accuracy and efficiency of optogenetic tool. Induction of heat by light emitted from optogenetic fiber

may be detrimental to cell health, hence this is another limitation in optogenetic toolbox. To verify the exact functioning of optogenetic tools, confirmation using electrophysiology, immunohistochemistry, behavioral assessments or other assays are crucial for data interpretation (Tye and Deisseroth, 2012).

5. Molecular functions of dendritic spines

In addition to transmitting the synaptic signals from synapse to the neuronal cell body recent detailed analyses of the structure, density and function of dendritic spines have reported its cardinal role on the complex regulation of different molecular signaling mechanisms upon neuronal activation and synaptic plasticity. Apart from acting as a single organic unit the dendrites are typically compartmentalized into many individual processing units called “dendritic spines”.

Dendritic spines usually receive synaptic contact from a single presynaptic terminal, including glutamatergic synapses. In 2002, Nimchinsky et al. made a striking discovery that dendritic spines have the remarkable capacity of modulating the original synaptic signals. Molecular understanding of dendritic spines has revealed that they serve as biochemical compartments while the narrow neck provides an isolated compartment where the biochemical signals are localized without disturbing the neighboring synapses along the parent dendrite. This compartmentalization confines the membrane trafficking to a localized region. Phillips et al. (2015), refined the earlier findings and indicated that the spine head serves as a localized biochemical compartment, while the spine neck is thought to function as a diffusional barrier for intracellular organelles, signaling ions and signaling molecules. Using electron microscopy, a good correlation of the spine head size with PSD size and receptor expression levels on synaptic stimulation are confirmed.

Existing evidences suggest that each dendritic spine functions as a partially autonomous compartment with its own membrane-trafficking events which regulates the components in- and out-side of the spine membrane. Typically, delicate molecular organization of the pre- and post-synaptic apparatus requires positional information to manifest the correct placement of pre- and post-synaptic elements. Postsynaptic potentials could be electrically altered via structural variability in passive membrane properties and by active regulation via voltage-gated ion channels within spines (Tsay and Yuste, 2004). The electrical properties and biochemical compartmentalization of spines enables them to modulate the expression of receptors and activation of intracellular signaling pathways and second messengers, such as calcium (Koch and Zador, 1993; Majewska et al., 2000; Matsuzaki et al., 2001; Noguchi et al., 2005; Yuste, 2010).

Once the synapses have been established, the next important steps are to ensure the synaptic specificity and to strengthen or weaken synaptic connections (Zhang and Benson, 2000) depending upon the synaptic stimulation. Hence, in both synaptogenesis and synaptic plasticity basic processes involved in learning and memory depend on the physiology of dendritic spines. One common hypothesis regarding the dendritic spines is that either the formation of new spines or a morphological change in existing spine occur during the learning process. Furthermore, when these changes are strengthened by new or repeated synaptic connections, dendritic spines serve as the anatomical locus of memory storage.

Recently, many studies revealed that dendritic spines are the major site of synaptic plasticity (Bosch and Hayashi, 2012; Bourne and Harris, 2008; Penzes and Rafalovich, 2012; Urbanska et al., 2012). During both structural and synaptic plasticity, actin filaments and myosin in dendritic spines undergo significant changes to aid the alterations depending on the synaptic stimuli and strength. Apart from the modifications noted in dendritic spines morphology, variations in its density are also shown clearly using various cellular models of synaptic plasticity. During brain development an increase in the number of dendritic spines followed by pruning appears to be dependent upon many factors (Urbanska et al., 2012). Furthermore, a recent study confirms that once the synaptic connectivity is established between the neurons, dendritic spines turnover continues (Koleske, 2013). During the process of building new neural networks, both dendritic branches and new dendritic spines continue to develop, while maturation and/or retraction of novel dendritic spines depends specifically upon the stimuli in synaptogenesis. Some studies have report that synaptic plasticity mainly involves the dendritic spines in adolescent brain vs. the dendritic tree in the adult brain.

6. Density and dynamics of dendritic spines

In mammalian brain, most of the excitatory neurons consist of dendritic spines (Harris and Kater, 1994; Hering and Sheng, 2001). Generally, the number of dendritic spines depends upon the age, cell type, position along the dendrite and also on the method of measurement applied. Most commonly, the pyramidal neurons of neocortex, medium spiny neurons of the striatum and the Purkinje cells of the cerebellum consist of dendritic spines (Hering and Sheng, 2001). Dendritic spine density shows a heterogenous distribution throughout the dendritic branch, and the spine number also varies among different cortical regions and layers. Commonly, more than 100,000 spines can be found in the dendritic arbor of a single neuron (Yuste, 2010). The numbers of dendritic spines range from 0.2 to 3.5 spines/μm of dendrite in the human postmortem cortex (Benavides-Piccione et al., 2013). In adult hippocampal CA1 pyramidal and granule cells, dendritic spines density ranges 2-4 spines/μm of dendrite (Harris et al., 1992; Sorra et al., 1998) vs. 10-15 spines/μm in Purkinje cells (Harris and Stevens, 1989; Harvey and Napper, 1988), indicating the independent regulation of synaptic system among diverse parts of the dendritic tree. In both humans and macaque monkeys, the neurons of frontal and orbitofrontal cortices show higher dendritic spine density when compared with the neurons of the primary visual and somatosensory cortices (Elston, 2003; Jacobs et al., 2001). Among 8 cortical areas studied in human brain, layer III basal dendritic spine density is found to be higher in the prefrontal and orbitofrontal cortical areas, and about 40% higher in the frontal polar cortex (area 10) than in the primary somatosensory cortex (Jacobs et al., 2001). Further research analysis reveals that basal dendrites of pyramidal neurons in layer-III of the cortex (Brodmann areas 10, 11, and 12) have 3 times more dendritic spines when compared to the neurons of the primary visual cortex (area 17), and 2 times more density than the parietal visual cortex (area 7a) of the macaque monkey (Elston, 2003). Basal dendrites show a higher dendritic spine density in the neurons from the layer-III cortex as compared to the prefrontal and orbitofrontal cortex of the adult human brain (Elston, 2003; Nimchinsky et al., 2002; Oga et al., 2013). These results postulate that higher order cortical regions involved in higher grade of processing require more synaptic connections and hence more dendritic spines.

Turnover of dendritic spine number is a normal physiological process during brain development. Although the majority of the dendritic spines are stable for longer periods of time, a significant proportion of the dendritic spines transiently appear and disappear during synaptic activity driven by experience-dependent remodeling of specific neuronal circuits, and these transient changes of the number of spines are called dendritic spine turnover (Knott and Holtmaat, 2008). Advancements in imaging techniques like chronic two-photon imaging have emerged as a powerful tool to study the spine motility in different cortical areas during various developmental stages (Grutzendler et al., 2002; Trachtenberg et al., 2002). In a neuronal development model, researchers show that a postsynaptic neuron receiving a local synaptic input projects in to thin filopodia and then matures into a dendritic spine upon continuous synaptic inputs. Those filopodia that do not receive inputs may be pruned (Bhatt et al., 2009). Using many animal models, researchers have shown that

- The density of dendritic spines is highly dynamic at early postnatal ages (Lendvai et al., 2000) spine turnover decreases with age and spine density reaches its peak level after significant pruning during adolescent life (Zuo et al., 2005).
- The total number of spines decrease to a relatively stable level over time due to similar rates of spine formation and elimination in adult life (Hofer et al., 2009; Xu et al., 2009; Zhang and Benson, 2000; Zuo et al., 2005).
- Spine turnover and morphological changes in dendritic spines continue to occur in the adult brain after the induction of experience-dependent plasticity.

Spine turnover varies greatly during postnatal development (Xu et al., 2009), affecting approximately 10-15% of spines per 24 h in very young mice. By using a transcranial two-photon imaging technique, Zuo et al. (2005) revealed that dendritic spines in layer 5 pyramidal neurons become progressively more stable over months with less pruning in barrel, primary motor and frontal cortices of adult mice. In young adult mice (1-2 months old), the percentage of stable spines ranges from approximately 55% in the somatosensory cortex (Holtmaat et al., 2005; Trachtenberg et al., 2002) to 75% in the visual cortex (Grutzendler et al., 2002; Majewska and Sur, 2003). In mature adult mice (4–5 months old), more than 70% of the dendritic spines in the somatosensory cortex show increased stability and more than 90% of the dendritic spines in the visual cortex are persistent for more than 30 days (Holtmaat et al., 2005; Trachtenberg et al., 2002; Zuo et al., 2005). More than 70% of the dendritic spines in the adult barrel cortex remain stable for more than 18 months. Another study declared that the majority of adult spines are stable over weeks, while 21.4% of the total spines in adolescent mice have transient and persistent loss in few days (Holtmaat et al., 2005). Experiments using repetitive confocal imaging and multiphoton microscopy over days to months in living mice have confirmed the long-held belief that spines and their synapses can form and retract throughout adulthood (Grutzendler et al., 2002; Trachtenberg et al., 2002). It is also thereby confirmed that the mature brain retains the capacity to form new synapses and remodel its neural circuitry throughout life.

The process and frequency of spine dynamics appears to vary in different brain regions and also exhibits cell-type specificity (Holtmaat et al., 2005). In rat hippocampal slices, spine density reaches its maximum level at the third postnatal week, and then it remains relatively static during the following weeks. However, in the mouse sensory cortex, spine numbers show a steady decline from adolescence till the late adulthood. Dendritic spines in the mouse somatosensory cortex show shorter half-life (hours to days) in adulthood (Trachtenberg et al., 2002); whereas in the mouse primary visual cortex, the number of dendritic spines is reported to be dynamic during adolescent life and then, it becomes remarkably stable in adulthood (Grutzendler et al., 2002). Studies have shown that the spine turnover is affected by sensory activities, i.e. the synaptic networks (Holtmaat et al., 2006). Mice raised in total darkness have shown fewer dendritic spines on the apical dendrites of pyramidal cells which strongly suggests on the importance of afferent inputs (Valverde, 1967). Deafferentation of hippocampal granule cells, following lesions of the entorhinal cortex, results in a decrease in spine number - an effect that is reversed with reinnervation (Parnavelas et al., 1974).

Studies of spine dynamics in higher order cortical brains have shown that during song learning process, the increase in the rate of spine turnover is associated with an enhanced capacity for song imitation in the forebrain nucleus HVC of zebra finches (Barretto and Schnitzer, 2012). In another in vivo study, it is shown that fear conditioning increases the rate of spine elimination, whereas fear extinction increases the rate of dendritic spines formation in the layer 5 pyramidal neurons of the frontal cortex in living mice (Lai et al., 2012). Spine dynamics is inhibited by the activation of glutamatergic receptors in hippocampal cultures, while the addition of antagonists to NMDA receptors has no effect (Fischer et al., 2000), indicating that the motility of dendritic spines is not linked with the expression of AMPA and NMDA receptors or with the influx of calcium ions which would stabilize the actin filaments. Matsuzaki et al. (2004), reported that changes in the size and shape of dendritic spines correlates with the individual synaptic activity during adulthood. It is reasonable to speculate that the turnover of spines and synapses varies with different frequencies in different brain circuits. Altogether, these results show that the overall turnover of dendritic spines accounts for the synaptic plasticity underlying the development of novel neural circuitry in accordance with the new learning process. Turnover of dendritic spines also declines in the absence of significant inputs, thus balance between formation and pruning of dendritic spines is important in stabilizing the crucial synaptic connections in the neural circuitry. Researchers have proven that spine dynamics also varies between the normal and diseased brains. Thus, detailed investigation on the turnover of dendritic spines in synaptic regulation and molecular mechanisms behind their structural changes is crucial to understand the physiology of brain function and dysfunction. These findings may pave the way for the identification of therapeutic targets for various neurological disorders.

7. Plasticity of dendritic spines

During brain development from the embryo till adulthood, plasticity of dendritic spines is the most striking crucial phenomenon in the formation of new neuronal circuits. Many neuroscientists have proven the morphological diversity of spine dynamics like spine motility, changes in their shape and size occur depending upon the strength of the synaptic stimuli using advanced imaging technologies (Calabrese et al., 2006). These imaging results suggest that dendritic spines are highly dynamic structures that characterize the fundamental morphological changes of synaptic plasticity. The plasticity of dendritic spines can be categorized broadly into short-term and long-term plasticity.

- Short term plasticity (phase of formation and development of new spines) mainly includes the emergence of nascent spines which occurs within 30 minutes of LTP induction in dissociated neuronal slice cultures (Segal, 2005). A glutamate uncaging study shows that new spines protrude from the dendritic shaft of layer 2–3 pyramidal neurons in mouse brain slices and within 2 minutes they behave as mature spines (Sala and Segal, 2014). On the contrary, another in vivo study using time-lapse imaging reported that nascent spines in the neocortex require a minimum period of 4 days to become mature (Knott et al., 2006). These nascent spines are often very long and have frequent filopodia-like shapes. Generally, nascent spines may take few hours to a single day to become structurally and functionally mature.
- Long-term plasticity (phase of maturation and stabilization of newly formed spines) mainly includes an increase in dendritic spine density and spine head size along with a decrease in their overall mean length, the number of dendritic filopodia, and spine motility (Dunaevsky et al., 1999; Nimchinsky et al., 2001). The initial expansion of spines mainly depends on the activation of NMDA and glutamate receptors in the spine head, while a long-lasting expansion depends upon the activation of kinases (Yang et al., 2008). Approximately half of the newly-formed spines in the neurons of mouse barrel cortex become stable (Trachtenberg et al., 2002) and mature after their emergence (Fu et al., 2012). Time taken for the maturation of nascent spines ranges from several hours to almost 1 or more days depending on strength of the stimulus and functional requirements (Holtmaat and Svoboda, 2009).

An in vivo study reported that following extensive motor learning, alterations in spine turnover for long term result in a rearrangement of synaptic connectivity in the mouse neocortex (Holtmaat et al., 2005) and these changes may last for many days after the training (Dayan and

Cohen, 2011; Sala and Segal, 2014). The maturation process continues until the dendritic spines make synaptic contact and form synapses that conduct the transmitting signals. However, the generation or elimination of spines depends upon the nature of the stimuli (weak or strong), functional requirements (learning new tasks or fear conditioning) and local environment (stress or enrichment). Both the morphology and density of dendritic spines vary in response to various other factors like the environmental enrichment, pharmacological therapy, hormonal changes, and learning skills (Fiala et al., 2002; Yuste and Bonhoeffer, 2001). In both physiological and pathological conditions, these activity-dependent structural changes of dendritic spines are noted in the primary sensory, motor and frontal cortical areas (Rochefort and Konnerth, 2012).

7.1. Dendritic spines morphological changes in response to LTP and LTD induction

In the neural circuitry, multiple mechanisms like the formation of new synapses, the destabilization of existing synapse, and turnover of dendritic spines underlie the experience-dependent plasticity processes (Bourne and Harris, 2012; Caroni et al., 2012; Hill and Zito, 2013; Holtmaat and Svoboda, 2009; Kasai et al., 2010). Such a synaptic plasticity is believed to be the key fundamental process for learning and memory (Kandel and Schwartz, 1982). In the experimental setup, synaptic plasticity is demonstrated in terms of LTP and LTD induction (using stimuli of different frequency) by electrophysiological means which could be otherwise defined as long-lasting enhancement or the reduction of synaptic transmission, respectively (Bliss and Lomo, 1973; Bliss and Collingridge, 1993; Malenka and Bear, 2004; Malenka and Nicoll, 1999) (Fig. 7).

Excitatory synapses contain AMPA and NMDA receptors localized on dendritic spines with basal synaptic transmission largely mediated via AMPA. Intense synaptic stimulation opens NMDA receptors leading to long-lasting changes in postsynaptic AMPA receptor number and LTP (Bliss and Lomo, 1973), thereby resulting in the growth of dendritic spines. During the downstream signaling cascade of LTP-induced NMDA receptor activation, the binding of CaMKII to NMDA receptor GluN2B subunit is important for the induction and maintenance of LTP (Barria and Malinow, 2005; Lisman et al., 2002; Sanhueza et al., 2011; Zhou et al., 2007) and new spine outgrowth (Hamilton et al., 2012; Hill and Zito, 2013).

In dissociated hippocampal neurons, the activation of NMDA receptors via chemically-induced LTP (Engert and Bonhoeffer, 1999; Maletic-Savatic et al., 1999) increases the connectivity of specific neurons in 4 different ways:

- Rapid enlargement of spine heads (Kopec et al., 2006; Lang et al., 2004; Park et al., 2006) that precedes the increase in AMPA receptor abundance (Kopec et al., 2006).
- Increase in neck width and decrease in length of spines (Fifková and Anderson, 1981).
- Rapid formation of new spines (Lin et al., 2004; Nägerl et al., 2004; Park et al., 2006).
- Stabilization of newly-formed spines (Harvey and Svoboda, 2007; Matsuzaki et al., 2004; Tanaka et al., 2008).

After the induction of LTP, enlargement of spine head size is mainly due to the appearance of more perforated and complex PSD (Popov et al., 2004) followed by the accumulation of more number of multiple presynaptic buttons, more AMPA and NMDA receptors (Kopec et al., 2006) and F-actin levels (Kramár et al., 2006; Lin et al., 2005) along with a significant increase in the number of recycling endosomes, coated vesicles (Harris et al., 1992) and amorphous vesicular clumps (Park et al., 2006), polyribosomes (Ostroff et al., 2002), and mitochondria (Li et al., 2004). These functional changes in spine structure account for enhanced synaptic transmission and remodeling of synaptic connections underlying the development of new learning and memory processes.

In vivo studies conducted to monitor the individual spines over weeks to months found that smaller spines are more labile (Trachtenberg et al., 2002). On the other hand, the larger spines are more functionally active, but show less plasticity and sometimes remain morphologically resilient for the animal's entire adult life (Grutzendler et al., 2002). Many studies have shown that morphological differences contribute to a spine's response to LTP-inducing stimuli via diffusional properties, whereas other groups have found neck diffusion to be greatly influenced by pre- and post-synaptic activity and depolarization (Bloodgood and Sabatini, 2005; Grunditz et al., 2008). Although the relationship between spine morphology and activity-induced plasticity is still under debate, generally, the larger, more stable, mushroom and stubby spines are designated as "memory spines" (Trachtenberg et al., 2002) and thin dynamic spines are defined as "learning spines" due to their enhanced ability to undergo structural changes (Holtmaat et al., 2005; Kasai et al., 2003b; Trachtenberg et al., 2002).

Hebbian LTP and LTD are well-studied forms of synaptic plasticity that form the cellular basis of hippocampal-dependent learning and memory. In synaptic studies, Hebbian plasticity shows direct correlation with the volumetric changes in the corresponding dendritic spines (Govindarajan et al., 2011; Harvey and Svoboda, 2007; Matsuzaki et al., 2004).

The induction of LTP either by tetanic stimulation or by theta-burst stimulation induces a marked increase in spine densities (Muller et al., 2000) and formation of new, mature and probably active synapses (Toni et al., 1999). But, LTD induced by low-frequency stimulation causes a distinct reduction in both spine densities (Bastrikova et al., 2008; Monfils and Teskey, 2004) and spine size within the CA1 area of the hippocampus, which in turn contributes to the activity-dependent elimination of synaptic connections (Zhou et al., 2004). Thus, dendritic spines can undergo bidirectional morphological changes in response to neuronal activity (Nägerl et al., 2004). Two-photon imaging shows that LTP induction using high-frequency stimuli induce both an increase and a decrease in spine densities (Engert and Bonhoeffer, 1999; Nägerl et al., 2004), indicating a strong correlation between the synaptic stimulation and alterations in dendritic spines. Studies have shown that LTP increases the turnover of protrusions and formation of new spines that preferentially grow in close proximity to activated synapses and become functional (Bastrikova et al., 2008). Controversial report has also been reported, as induction of LTP at one spine, reduces the threshold stimuli for neighboring spines, sometimes causing retraction of these spines (Harvey and Svoboda, 2007). Thus, LTP-induced activity can induce long-lasting changes in the hippocampal pyramidal network.

LTP consists of 2 distinct phases:

- Early LTP phase is described as the "short-lasting phase" (about 1 hour) which includes the activation or rapid insertion of post synaptic (AMPA-glutamate receptors) into existing synapses and post-translational modification of synaptic proteins. This phase is also known as LTP induction phase (Malenka, 2003; Malenka and Nicoll, 1999; Malinow and Malenka, 2002; Malinow and Tsien, 1990; Stevens and Wang, 1994).
- Late LTP phase is described as the "long-lasting phase" of LTP which includes translational and transcriptional changes involved in protein synthesis; and structural changes (C H Bailey and Kandel, 1993; Yuste and Bonhoeffer, 2001), including synaptogenesis (Bourne and Harris, 2012). This phase is also known as the LTP maintenance phase (Bolshakov et al., 1997; Bolshakov and Siegelbaum, 1995; Reymann and Frey, 2007; Toni et al., 1999; Trommald, 1990; Voronin et al., 1995).

When LTP is inhibited by post-synaptic inhibition via exocytosis, protein synthesis or protein kinase A (important signaling factors

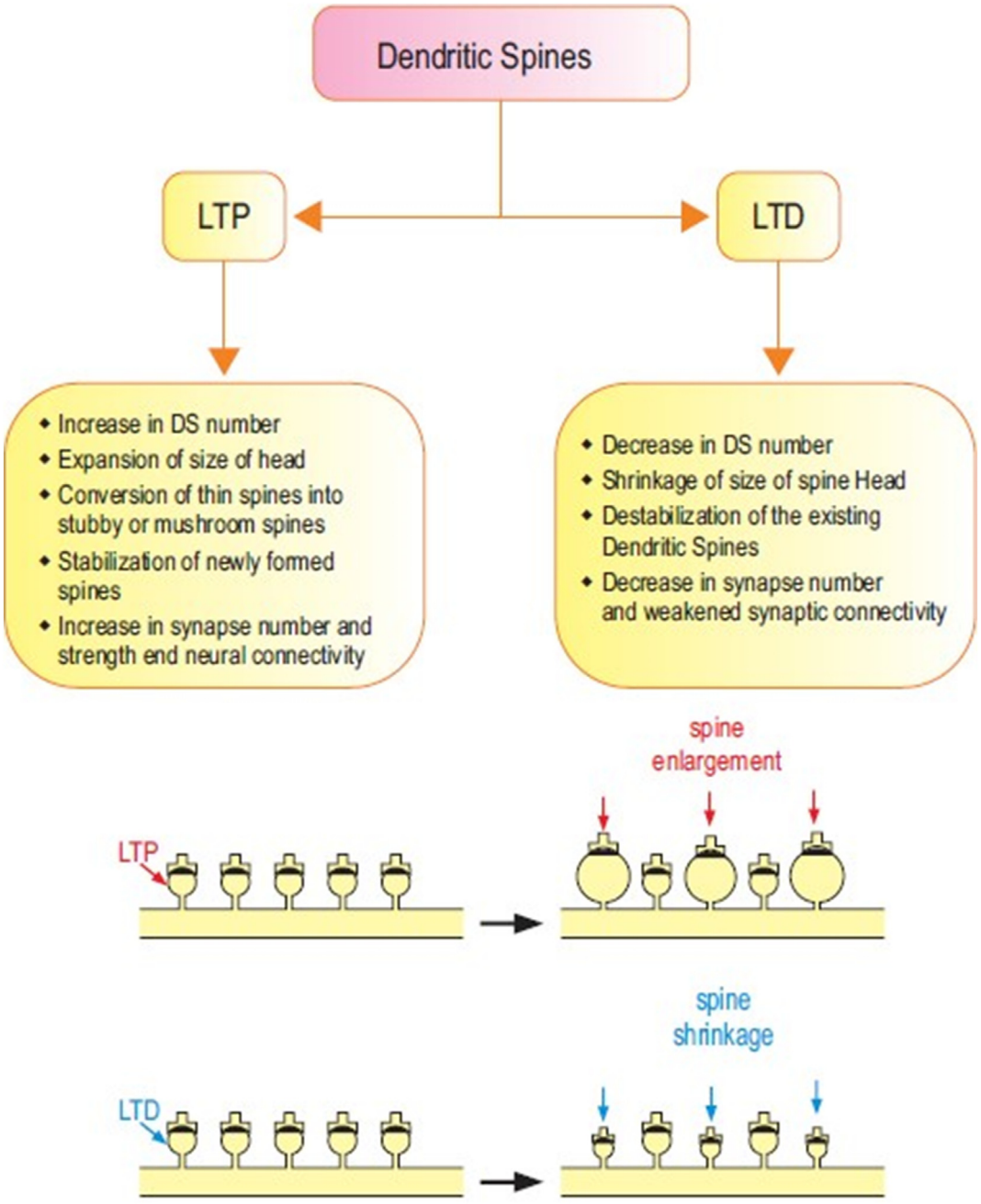

Fig. 7. Structural changes in a dendritic spine (a) repetitive LTP induction (via activation of AMPA and NMDA receptors) causes enlargement of spine head. (b) repetitive LTD induction causes spine head shrinkage (due to actin depolarization)

involved in LTP induction phase), an increase in dendritic spine volume can still occur; however, the process become unstable and they collapse immediately (Yang et al., 2008). Finally, with regard to the spine expansion, LTP induction phase requires different signaling pathways, while maintenance phase may require similar molecular pathways. Common signaling pathways involved in the induction and maintenance phase of LTP associated with the increase in dendritic spines are still unclear.

On the other hand, low frequency stimulation of the synapse activates NMDA receptors to produce LTD (Lynch et al., 1977) which causes the removal of postsynaptic AMPA receptors and loss of dendritic spines (Lee et al., 2002; Lüscher et al., 1999; Man et al., 2000; Nägerl et al., 2004; Snyder et al., 2001; Xiao et al., 2001; Zhou et al., 2004).

The main changes observed after LTD induction are

- Steady reduction in the size of dendritic spines (Nägerl et al., 2004; Okamoto et al., 2004)
- Accelerated shrinkage of spine head (Zhou et al., 2004).
- Few spines and/or filopodia retracted (Zhou et al., 2004).

In glutamate uncaging model, live imaging of dendritic spines following LTD induction (Oh et al., 2013) shows spine shrinkage mainly on the stimulated spine, but not neighboring spines. During LTD induction, size reduction is noted in both large and small spines, but the mechanisms by which they occur are different. The retraction of small spines depends on NMDA receptor, while that of large spines requires both NMDA and metabotropic glutamate receptors. Both LTD and spine shrinkage require the activation of NMDA receptors and calcineurin (Zhou et al., 2004), while the electrophysiological changes are mediated through PP1/2A signaling; and spine remodeling is mediated by

the activation of cofilin (a family of actin binding proteins), indicating the involvement of various downstream signaling pathways in dendritic spine shrinkage and LTD. These results provide clear evidence for the stable alteration of dendritic spines in neural circuits during experience-dependent plasticity (Hill and Zito, 2013). Several studies have shown that NMDA receptor hypofunction leads to reduction in spine numbers (Brigman et al., 2010; Ramsey et al., 2011; Roberts et al., 2009; Ultanir et al., 2007).

7.1.1. Homeostatic plasticity

Homeostatic synaptic plasticity (HSP) is generally defined as a negative feedback mechanism through which the density of dendritic spines and population of synapses are maintained within optimum range globally in brain and help stabilize its neuronal activity (Turrigiano et al., 1998). In contrast to Hebbian plasticity which exerts input specificity (Barrionuevo and Brown, 1983) and fundamentally promotes the number of dendritic spines and increases the synaptic strength, HSP is expressed over a wide range of synapses and induces a non-specific decrease in global activity that proportionally scales all synapses of a given neuron (up or down). Altogether, HSP maintains the relative strengths of all synaptic inputs into the neuron, and makes the neuronal network function optimally (Turrigiano and Nelson, 2000 and Turrigiano and Nelson, 2004; Turrigiano, 2011). Both in vivo and in vitro studies have shown the presence of HSP, supporting its crucial role in stabilizing the neural network activity and optimizing its functions (Desai et al., 2002). During HSP, modulations in AMPA receptor trafficking to and from the post-synaptic density, and coherent presynaptic changes that result in altered neurotransmitter release leads to appropriate modulations in synaptic strength (Murthy et al., 2001; O'Brien et al., 1998). In the dendritic spines of mouse hippocampal neurons, induction of HSP via activity blockade shows a generalized increase in the size of dendritic spines and it prolongs LTP induction in dendritic spines with a concomitant increase in growth rate and a reduction in plasticity threshold. Computational studies have postulated that HSP can influence previous Hebbian events at a synapse (Rabinowitch and Segev, 2008). HSP enhances the magnitude of synaptic potentiation by promoting the growth of unstimulated neighboring small spines and also by enhancing the structural plasticity at clustered inputs following Hebbian plasticity (activation of one input) within the dendrite, at single synapses. HSP enhances the synaptic activity in nearby group of synapses in an activity-dependent manner within a distance of 5 μm of the stimulated synapse, over which plasticity related proteins can spread across the co-active synapses (Harvey et al., 2008). These results suggest that induction of Hebbian plasticity on a background of HSP results in compromised input specificity, as neighboring small spines grow and thus, modulate the neuron's response to activity by promoting the sensitivity of spines to smaller stimulus. In addition, several studies indicate that HSP also induces local homeostatic changes within dendrites (Branco et al., 2008; Ju et al., 2004; Liu, 2004; Sutton et al., 2006). Many electrophysiological studies show that synaptic threshold modulation after HSP is found in small spines than large spines, and in a reversible manner, suggest that synaptic scaling mechanisms are separable from plasticity mechanisms. Thus, HSP drives the local expression of Hebbian plasticity and reduces input specificity. Few reports (Toyoizumi et al., 2014; Keck et al., 2017) show that stability of neuronal responses depends on the operation of slow HSP and fast Hebbian plasticity at different sites. Together, these results highlight the important role of HSP in modulating synaptic efficacy and promote learning without compromising previous memory (Stryker, 2017).

7.2. Spine remodeling during process of learning and memory

Alterations in the structure and/or number of synapses in neural circuitry are important substrates of memory formation following learning. Rapid remodeling of spines is the main focus in learning-related synaptic plasticity in the matured brain. Generalized hypothesis regarding the role of dendritic spines in learning and memory have shown a periodic change from the previous notion that density of dendritic spines has a correlation with learning to the idea that morphological alterations within dendritic spines show a stronger and direct association with new learning and memory formation than spine turnover (van der Zee, 2015). A two-photon microscopy study shows that motor learning tasks rapidly induce the formation of new spines in the pyramidal neurons of motor cortex in mice. Most of the newly formed spines persist for weeks and months following training. Interestingly, the motor task performance positively correlates to the amount of new spines formed (Xu et al., 2009). Similarly, mice trained for novel forelimb skills show the development of new dendritic spines in clusters in layer V of pyramidal neurons in the motor cortex, during the acquisition phase of learning. The clustered new spines possess a bigger head size and persist even after the training had stopped when compared to the non-clustered new spines (Fu et al., 2012).

Using enhanced YFP-expressing mice, a spine dynamic study on the primary motor cortex following a motor learning (accelerated rotarod running) task or in the barrel cortex following sensory experiences (environmental enrichment) reports experience-induced de novo spine formation within two days of training (Yang et al., 2009). Some of these newly formed spines persist for months by subsequent exposure to novel experiences. The degree of dendritic spine formation shows linear correlation with the degree of learning acquisition (Xu et al., 2009) along with the prolonged maintenance of the acquired skill (Yang et al., 2009). The results of the above mentioned studies suggest that repetitive tasks induce formation of new *de novo* dendritic spines during learning, thereby providing a morphological basis for spatial coding of motor memory storage by creating new synaptic connections in neural circuitry of the mammalian brain (Stepanyants and Chklovskii, 2005). Moreover, rapid spinogenesis during the initial learning is followed by significant pruning of dendritic spines, making the total spine number return to the basal levels after prolonged training (Yu and Zuo, 2011). Pruning occurs selectively for dendritic spines that have existed before training, while new learning-induced dendritic spines are stabilized during subsequent training and endure long enough even after the training has ended (Xu et al., 2009).

Few researchers postulate that dendritic spines with small diameters and/or lengths are unstable, easily eliminated, and involved in memory acquisition, while dendritic spines with bigger head diameters are more stable and involved in consolidation processes and long-term memory formation (Kasai et al., 2010; Kasai et al., 2003b). Recent research analysis reveals that the formation of new memories in a conditioning paradigm shows a significant increase in dendritic spine density in CA1 pyramidal neurons in both adult male (Jedlicka et al., 2008; Leuner et al., 2003) and female (Beltrán-Campos et al., 2011) rats. Rats exposed to a spatially challenging environment, like Morris water maze, show an increased spine density on CA1 pyramidal neurons, and also display faster and precise learning ability (Moser et al., 1994). In novel object recognition and object placement tasks, trained rats astoundingly discriminate newer objects, and show higher spine density in the CA1 region of hippocampus and layer II/III of medial prefrontal cortex (Eilam-Stock et al., 2012). Altogether, these results suggest that an increase in spine density enhances the number of synapses per neuron resulting in a strong neural connectivity, which can be attributed to the mechanisms underlying memory consolidation and retrieval process.

An electron microscopy study (O'Malley et al., 1998) confirms an increase in the number of dendritic spines in the rat dentate gyrus after the training of passive avoidance learning task. Another confocal microscopy study (Moser et al., 1994; Moser and Moser, 1998) reports similar findings like an increase in the total dendritic spine number per unit length in the basal dendrites of CA1 pyramidal cells, following the spatial training of rats in a complex environment. In the dentate middle molecular layer of rats trained in the passive avoidance task, a significant and transient increase in dendritic spine density is observed after 6 hours of training session, but dendritic spine density is reported

to return to basal levels after 72 hours of training (O'Malley et al., 1998). Similarly, a significant time-dependent increase in the number of spines is noted in the dentate gyrus of the adult rat, following water maze training (O'Malley et al., 2000). Transient changes in spine density are suggested to increase the synapse turnover rate, which concurrently induce changes in the connectivity pattern of the neuronal network in the long-term memory consolidation process.

During synaptic stimulation, thin spines that are mostly responsive to the stimuli (either low or high in strength) are labeled as 'learning spines', while mushroom spines that are stable for longer periods are labeled as 'memory spines' (Sala et al., 2008). Many researchers show that thick spines remain stable for a month, while thin spines are transient (Geinisman, 2000; Holtmaat et al., 2005). In response to LTP and environmental enrichment, branched and mushroom spines show greater changes vs. modest alterations seen in thin and stubby spines (Desmond and Levy, 1986; Geinisman et al., 1989; Johansson and Belichenko, 2002; Trommald et al., 1996). These results indicate that thick, mushroom and branched spines may be responsible for the development and maintenance of long-term memory.

In both pathological studies and live time-lapse imaging of dendrites in animal models, the induction of LTP causes a rapid increase in dendritic spine number or expansion of spine size (Desmond and Levy, 1988; Engert and Bonhoeffer, 1999; Lang et al., 2004; Maletic-Savatic et al., 1999; Matsuzaki et al., 2004; Trommald et al., 1996). Additionally, abnormalities in dendritic spines and synapses have been frequently found in different syndromic and non-syndromic forms of mental retardation in people, suggesting again on the role of spines in cognitive function and learning (Armstrong et al., 1995; Hinton et al., 1991; Huttenlocher, 1974; Kaufmann and Moser, 2000; Marin-Padilla, 1976; Purpura, 1974; Takashima et al., 1981).

7.3. Spine remodeling under conditions of excitotoxicity

Recently, many researchers have reported that dendritic spines undergo changes during excitotoxic conditions induced by either high intracellular glutamate or calcium levels. In cultured hippocampal neurons, application of glutamate shows a dual effect (elongation to shrinkage) on the same group of dendritic spines by activating different cascades of postsynaptic second messengers, depending on the magnitude and/or duration of the intracellular calcium$^{2+}_{i}$[Ca^{2+}] influx produced by it. Mostly, glutamate-induced $_{i}$[Ca^{2+}] increase in dendritic spines occurs via activation of NMDA receptors (Korkotian and Segal, 1999). During excitotoxicity, a rapid and marked loss of dendritic spines followed by loss of actin filaments is reported (Segal et al., 2000). Prolonged application of glutamate to the hippocampal neurons (over 2 hours) induces an NMDA receptor-dependent decrease in dendritic spine length by about 30% (Segal, 1995), while short applications induce a slow onset increase in spine length (Korkotian and Segal, 1999).

In cultured pyramidal neurons, flash photolysis of caged glutamate shows that larger spines are affected more by glutamate application than small spines, suggesting that large spines are the basic substrates of functional synaptic connections, while small thin ones are only on their way to mature and become functional (Kasai et al., 2003b). Cultured hippocampal neurons exposed to DL-2-amino-7-phosphonovalerate, a NMDA receptor antagonist, show an increase in AMPA receptor-mediated excitatory postsynaptic currents and higher synchronization among neuronal cells. An enhancement in synchronicity is followed by the formation of novel dendritic spines which will become functional when they are innervated by active presynaptic terminals and by pruning of existing spines (Goldin et al., 2001).

Hippocampus of neonatal rats exposed to monosodium glutamate shows both neuronal loss and morphological changes in the surviving pyramidal CA1 cells. The number of dentate granule cells and CA1 pyramidal neurons in glutamate-treated rats are 11.5% less than those counted in sodium chloride-treated control rats. Moreover, after a glutamate treatment, the dentate granule cells show more dendrites and branched spines, along with a greater number of thin and mushroom spines. These results strongly suggest that the neuronal loss and cytoarchitectural modifications in the surviving neurons can lead to functional alterations in the hippocampal integrative activity due to an early excitotoxicity (González-Burgos et al., 2009).

7.4. Dendritic spines remodeling under conditions of enriched environment

The environment plays a major role in synaptic plasticity, and density of dendritic spines is believed to be a sensitive measure of environmental influence, more than dendritic branching (Bryan and Riesen, 1989). Animals exposed to an enriched environment (reared in larger cages with toys, tunnels, and obstacles, and in groups to allow for ample opportunities for problem-solving and complex social interactions) show greater number of dendritic spines in hippocampus (Kozorovitskiy et al., 2005) and improved performance of several learning tasks (Bruel-Jungerman et al., 2005). In addition to aerobic exercise and healthy diet, enriched environments can have a promising effect on the recovery of damaged dendritic spines and/or dendritic spine loss in diseased brains. Experimental rats reared in enriched environments show increased formation of new neurons along with increased synaptic and neuronal plasticity. This is reflected in stimulation of new dendritic branching and synapse formation, along with increase in the genetic expression of neurotrophic factors (BDNF, NGF, GDNF, and other growth factors). Altogether, these changes in neural circuitry lead to enhanced learning and memory. These results suggest that exposure to enriched environments can be one of the potential ways to optimize the synaptic plasticity, and can delay progression of several neurological disorders (Fratiglioni et al., 2004; Mora et al., 2012; Pham et al., 2002). In a behavioral study, rats housed in enriched environments show increased expression of brain-derived neurotrophic factor gene in comparison to rats housed in isolation (Falkenberg et al., 1992). Using 3-D confocal laser scanning microscopy, intact rats exposed to an enriched environment reveal a marked increase in the number of dendritic spines in the layers II/III and V/VI pyramidal neurons of the somatosensory cortex vs. rats housed in standard environment. On the contrary, spontaneously hypertensive rats with an infarct brain (induced by occlusion of middle cerebral artery distal to the striatal branches) housed in an enriched environment for 3 weeks show a significantly high number of dendritic spines in layers II/III pyramidal neurons (in the contralateral hemisphere) when compared to the rats in infarct group housed under standard environment (Johansson and Belichenko, 2002). Major morphological changes observed in dendritic spines after an exposure to environmental enrichment include an increase in dendritic branching of cortical and hippocampal pyramidal neurons, spine density, number of synapses, polyribosomes, the number of perforated PSD and the mean PSD length (Altschuler, 1979; Diamond et al., 1975; Globus et al., 1973; Greenough, 1975; Greenough et al., 1985; Kozorovitskiy et al., 2005, 2005; Leggio et al., 2005; Rampon et al., 2000; Schapiro and Vukovich, 1970; Volkmar and Greenough, 1972). A recent primate study confirms that environmental enrichment enhances dendritic branching and spine density in the pyramidal neurons of the CA1 region of the hippocampus and prefrontal cortex (Kozorovitskiy et al., 2005). Many studies have proven that environmental enrichment prevents the age-related loss of dendritic spines in rats (Saito et al., 1994) and fasten the recovery on both morphological and behavioral basis in mouse models of fragile X syndrome (FXS) (Restivo et al., 2005). Additionally, environmental enrichment reduces the Aβ-plaque deposition in an animal model of AD by increasing the Aβ degrading endopeptidase activity (Lazarov et al., 2005). Animals reared in rich environment after trimming the whiskers show higher functional plasticity in the barrel cortex (Rema et al., 2006). Altogether, these studies suggest that enriched environment plays an important role in enhancing the optimal synaptic connections of neural circuits, which in turn promotes higher cognitive skills, learning and memory in

healthy individuals. Also, enriched environment positively regulates the neural circuity to combat the spine or neuronal loss in diseased brains and delays the progression of neurodegenerative diseases.

7.5. Spine changes associated with aging

Even though aging is a normal physiological process, several changes are observed in neural circuitry, dendritic spines and synapses during aging. In some individuals, aberrant alterations in the dendritic spine number, morphology and synapses results in impaired cognition, working memory and behavior. Although neurons, dendrites and dendritic spines undergo significant attrition during aging, changes in dendritic spine pathologies vary in different brain regions (Dickstein et al., 2013). In cerebellar Purkinje cells, about a 17% decrease in dendritic spine density is reported in 26-month vs. 6-month old rats (Rogers et al., 1984). In rat amygdala, an age-related increase of dendrite length and unchanged spine densities are discovered (Braidy et al., 2011; Marcuzzo et al., 2007; Rubinow et al., 2009). In 1980, Cupp and Uemura et al., revealed marked reduction in the dendritic branch order, number of branches, total dendritic length, and spine density in the apical and basal dendritic spines of layers III and IV of pyramidal cells in the prefrontal cortex of rhesus monkeys (aged 27–28 years). Aged primates (27–32 years of age) showed a loss of apical dendritic tufts of pyramidal cells in layer I of area 46 when compared with young monkeys (6–9 years of age) (Peters et al., 1998). An age-related, significant and consistent decline in the total number of dendritic spines and spine density are observed on both the apical and basal dendrites of layer 3 pyramidal neurons of prefrontal area 46 in old vs. young macaque monkeys. Only the second branch order of the apical dendrites shows specific age-related reduction in dendritic length and segment numbers (Duan et al., 2003). A recent study confirms that the pyramidal neurons of aged Rhesus monkeys show 33% of dendritic spine loss and almost 50% of thin spines loss in the prefrontal cortex region along with impaired performance on the Delayed Non-matching to Sample task (Dumitriu et al., 2010). Neurologically intact aged subjects (above 50 years) show decrease in total dendritic length (9-11%) and decrease in the numbers of spines (approximately 50%) in layer III of pyramidal cells in prefrontal and occipital areas when compared with young aged subjects (below or equal to 50 years) (Jacobs et al., 1997). In the substantia nigra of human, severe spine loss is observed in aged (70–91 years) compared to middle-aged subjects (Cruz-Sánchez et al., 1995). These data strongly support aging-related loss of dendritic spine density and turnover results in reduced synaptic connectivity, which in turn causes significant decline in higher cognitive functions like learning and memory.

8. Dendritic spines status in acute and chronic neurological disorders

Both post-mortem studies of patients and transgenic animal models have shown a strong link between the aberrant dendritic spine structure and number, altered synaptic plasticity in critical regions of the brain in neuropsychiatric, and neurodegenerative disorders (Table 1). Dysmorphogenesis of dendritic spines can lead to defective or excessive synapse function and connectivity, which in turn disrupts the neural circuitry. Many researchers have successfully proven the direct correlation of dendritic spine anomalies and/or dendritic spine loss with the impaired synaptic connectivity and plasticity that results in altered mental status and impaired cognitive, motor and learning skills (Kasai et al., 2010; Penzes et al., 2011). In addition, the post-mortem reports also confirm the presence of malformation or loss of dendritic spines in patients with epilepsy, stroke, schizophrenia, dementia, major depression and chronic substance abuse (Fiala et al., 2002; Glantz and Lewis, 2001; Nimchinsky et al., 2002; Swann et al., 2000).

8.1. Alzheimer's disease

AD is an age-related neurodegenerative disease and the common leading cause of dementia and death in the elderly (Braidy et al., 2011; Jack et al., 2011). Main symptomatic features of AD are memory deficits, dementia, and a decline of cognitive and intellectual performances (Kelley and Petersen, 2007). Cardinal neuropathology of AD includes accumulation of Aβ protein, which is called senile plaque extracellularly and phosphorylated tau, which is called neurofibrillary tangles intracellularly (Holtzman et al., 2011; Selkoe and Schenk, 2003). Several studies suggest that synaptic loss and dendritic spine dysfunctions can be significant preceding and contributing factors to neuronal loss and degenerative pathology in AD (Masliah et al., 1991; Scheff et al., 2006; Terry et al., 1991). Early postmortem brain samples of many AD patients persistently show marked synapse and dendritic spine loss (DeKosky and Scheff, 1990; Knobloch and Mansuy, 2008; Walsh and Selkoe, 2004) and other dendritic changes (DeKosky and Scheff, 1990; Selkoe, 2002) in the hippocampus and throughout the cortex, when compared with age-matched control brains. The loss of dendritic spines and synapse in the hippocampus and throughout the cortex, the principal areas that are commonly affected by AD-related pathology (DeKosky and Scheff, 1990; Walsh and Selkoe, 2004), give a morphological evidence for the lower mental status (DeKosky and Scheff, 1990; Selkoe, 1989).

A recent study reports approximately 45% dendritic spine loss in both the neocortex and hippocampus of AD patients vs. cognitively normal controls (Serrano-Pozo et al., 2011). Another in vivo study reports about a 50% dendritic spine loss near the amyloid plaques region in the living animal model of AD using multiphoton microscopy (Spires et al., 2005). Primary hippocampal neurons challenged with Aβ oligomers show dendritic spine loss along with an increase in premature dendritic spines and varicosities formation (Attar et al., 2012; Maiti et al., 2011; Maiti et al., 2010). Tg2576 mice (a widely used AD mouse model that expresses mutant human amyloid precursor protein (APP)) show lower spine density in both CA1 and dentate gyrus (Jacobsen et al., 2006; Lanz et al., 2003). Notable cognitive decline is found in these mutant Tg2576 mice when the dendritic spines are depleted. An over-expressed human APP animal model of AD shows significant spine loss and neurite dystrophy around amyloid plaques, which alters the neuronal circuits and results in cognitive decline (Garcia-Alloza et al., 2006; Spires et al., 2005; Spires-Jones et al., 2007; Tsai et al., 2004).

In AD, excessive accumulation of soluble Aβ leads to synaptic depression and removal of AMPA receptors, which results in synapse and spine loss (Selkoe, 2008; Yu and Lu, 2012). Molecular mechanisms involved in Aβ toxicity in dendritic spines and synapses are believed to include signaling cascades from Aβ to tau and PSD-95, involving tau kinases like PAR-1/MARK and its activating kinase LKB1 (Yu and Lu, 2012). Toxicity studies on Aβ suggest that Aβ can also affect LTP and LTD by modulating glutamate receptor-dependent signaling pathways (Hsieh et al., 2006; Li et al., 2009; Shankar et al., 2007), triggering aberrant patterns of the neural network (Palop et al., 2007), inducing mitochondrial dysfunction (Lin and Beal, 2006) and lysosomal failure (Nixon and Cataldo, 2006). Cultured neuronal cells from Tg2576 mutant APP transgenic mice (mimicking Aβ-induced synaptic dysfunction) show synaptic changes like fewer smaller postsynaptic compartments and fewer enlarged active presynaptic compartments. A reduction in PSD-95 is observed to be the prime change in the synaptic components of mutant mice (Kim and Sheng, 2004). In the hippocampus of AD patients and in animal models of AD, the activation of p21-activated kinase (PAK, actin regulator and downstream effector molecule of Rac) is markedly reduced and delocalized (Penzes et al., 2003; Zhao et al., 2006). Brain tissues from AD patients and transgenic animal models of AD show severe decrease in drebrin, a postsynaptic protein involved in actin stability in dendritic spines. Dendritic spine and synaptic loss in AD by abnormal signaling pathways results in aberrant neural circuitry, which underlies basic causative factor for all the cognitive deficits and

Table 1
Abnormalities in dendritic spines in various neurological disorders

S. No	Neurological/neurodegenerative condition	Dendritic spine pathology	References
1.	Alzheimer's disease	Marked spine loss, increase in premature dendritic spines and varicosities formation	14, 272, 247, 245, 203
2.	Parkinson's disease	Decrease in dendritic length, dendritic spine loss and varicosities formation	342, 459
3.	Huntington's disease	In mild cases, significant increase in dendritic branching, spine density and spine size are seen. In advanced cases, decrease in dendritic arborization, focal swellings on dendrites and decrease in spine density are reported.	115, 144
4.	Intellectual disability or mental retardation	Both changes in dendritic spine density and/or spine shape	117, 318, 452, 296
5.	Autism spectrum disorder	Higher dendritic spine density	188, 345
6.	Fragile X syndrome	Increase in dendritic spine density and many dendritic spines show immature morphology like long, thin, torturous nature	193, 82
7.	Rett syndrome	Size of neurons gets reduced along with increase in neuronal cell density; lower dendritic spine density especially mushroom-type spines; and impaired dendritic arborization	12, 29, 70, 125, 319
8.	Down's syndrome	Dendritic spines show larger spine heads along with distinct reduction in DS number and altered spine morphology	27, 28
9.	Schizophrenia	Marked reduction in spine number	134, 235
10.	Depression	Spine dysfunction, impaired signal transmission across synapse and dendritic spine loss	256, 471
11.	Epilepsy	Frequent loss of dendritic spines, varicose swelling of dendrites and dendritic abnormalities such as changes in dendritic length, shape and branching patterns	432, 472, 314, 39, 65, 29, 195
12.	Stroke	Spine loss and reduction in spine number	112, 500
13.	Prion disease	Significant decrease in spine density and dendritic spine loss	56, 246
14.	Sleep disorders	Harmful effects on signaling molecules, polymerization of F-actin and dynamics of dendritic spines	89, 486

dementia.

8.2. Parkinson's disease

Parkinson's disease (PD) is characterized by a dramatic and selective loss of dopaminergic neurons in the substantia nigra pars compacta along with a gradual and significant decrease in dopamine levels (Alexander, 2004; Dauer and Przedborski, 2003; Sathiya et al., 2013). Major symptomatic features of PD are tremor, bradykinesia, rigidity, impaired gait and abnormal posture. Main neuropathology of PD is the aggregation of alpha-synuclein in the midbrain dopaminergic neurons (Dauer and Przedborski, 2003). Using Golgi-Braitenberg method, neuropathological changes such as a decrease in dendritic length, dendritic spine loss and the formation of different dendritic varicosities are found in the substantia nigra pars compacta neurons of PD patients (Patt et al., 1991). Striatal medium spiny neurons show a greater loss of dendritic spines in PD patients and in animal models of PD (Villalba and Smith, 2013). In animal models of PD, rats with unilateral degeneration of the nigrostriatal dopaminergic system induced by 6-hydroxydopamine show distinct striatal spine loss (about 20%) in the caudate-putamen complex (Ingham et al., 1989). Further investigations reveal that the spine loss is accompanied by a reduction of the total number of asymmetric glutamatergic synapses in the striatum (Ingham et al., 1998). Several post-mortem striatal tissue samples from PD patients show spine loss (Stephens et al., 2005; Zaja-Milatovic et al., 2005). Monkeys with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD also show marked spine loss along with the inhibition of spinogenesis in the medium spiny neurons of the striatum (Stephens et al., 2005; Villalba et al., 2009; Villalba and Smith, 2010). The degree of spine loss is in accordance with the pattern of dopamine denervation (Smith and Villalba, 2008; Villalba et al., 2009; Zaja-Milatovic et al., 2005). A recent research study shows that MPTP-lesioned monkeys have about a 50% striatal dendritic spine loss and a significant reduction in striatal dopamine levels, while about a 25% dendritic spine loss is noted in the nucleus accumbens (Villalba et al., 2009). The 3D ultrastructural analysis reveals an increase in the spine head size along with an increase in length, complexity and the extent of perforations of PSD of corticostriatal and thalamostriatal glutamatergic synapses in the striatum of Parkinsonian monkeys (Villalba and Smith, 2011a) and a massive growth of the spine apparatus (Villalba and Smith, 2011b, 2010). The PSD length and number of perforated synapses are significantly higher in dendritic spines of caudate nucleus neurons in 3 PD patients vs. 3 matched controls (Anglade et al., 1996). The most common pathway for dendritic spine loss in PD is the activation of cortical glutamatergic system that results in glutamate excitotoxicity in striatal neurons (Calabresi et al., 1996; Mallet et al., 2006; Wichmann and Delong, 2007). Both spine loss and inhibition of development of novel spines in the striatal regions accounts for the progression of PD.

8.3. Huntington's disease

Huntington's disease (HD) is an autosomal dominant, progressive neurodegenerative disorder, which usually causes movement, cognitive and psychiatric disorders with a broad variety of signs and symptoms. Common symptomatic features are involuntary movements of the face and body; abnormalities in gait, posture and balance; obsessive-compulsive behavior, and dementia (Bertram and Tanzi, 2005). The main neuropathological feature is the abnormal accumulation of the huntingtin protein intracellularly due to the repetition of glutamine (Evans-Galea et al., 2013). Brain samples obtained from both human HD patients and various transgenic and knock-in animal models of HD show a progressive loss of dendritic spines in the cortical and the striatal neurons (Ferrante et al., 1991; Guidetti et al., 2001). Post-mortem brain tissues from patients with HD show severe dendritic degeneration. Patients with mild HD show an abnormal bending of distal dendrites along with a marked increase in dendritic branching, spine density and spine size in the striatal area (Ferrante et al., 1991; Graveland et al., 1985). However, during the advanced stages of HD, degenerative changes like dendritic arbor truncation, focal swellings on dendrites and decrease in spine density are noted. Brain samples from HD patients show a remarkable increase in the number of primary dendritic segments along with an increase in total dendritic length, total surface area, dendritic branching and the number of dendritic branching points in layer-3 and -5 of pyramidal neurons when compared to the control participants. The total number and density of dendritic swellings are markedly increased in layers-3 and -5 of the pyramidal neurons of HD brains. Although the degeneration of prefrontal, cortical, and pyramidal neurons are noted at a smaller scale in HD patients, the plasticity of the remaining pyramidal neurons occurs temporarily as a compensatory response (Sotrel et al., 1993). Transgenic R6/1 and R6/2 mice expressing a larger CAG trinucleotide expansion (closely related animal model of human HD) show progressive cognitive, psychiatric and motor symptoms (Mangiarini et al., 1996; Miller and Bezprozvanny, 2010; Nithianantharajah et al., 2008; Spires et al., 2004). In YAC128 mouse

model of HD, reduced striatal dendritic spine density and other spinal morphological anomalies along with distinct decline in cognitive and motor skills are noted at 16 weeks of age (Slow et al., 2003; Xie et al., 2010). These results demonstrate a significant positive correlation between the loss of dendritic spines and dendritic anomalies and the progression of motor and cognitive deficits in HD.

8.4. Intellectual disability or mental retardation

Intellectual disability is a generalized neurodevelopmental disorder and its prevalence ranges from children below 3 years of age to adults. The main characteristic features include impairment in intelligence quotient and adaptive functioning along with a wide spectrum of emotional and behavior disorders. Classical sign intellectual disability is a nonverbal intelligence quotient below 70. Several functional studies show that numerous genes coding for synaptic proteins and involved in synapse and dendritic spine formation are mutated in intellectual disability patients (Verpelli and Sala, 2012). A common neuropathological feature is decreased dendritic spine number with normal morphology in intellectual disability patients (Fiala et al., 2002). Several genes linked to intellectual disability and autism code for proteins implicated in the Rac1/Cdc42/PAK and Rho pathways, like the upstream regulators of Rac/Cdc42 such as PIX/ARHGEF6 and srGAP3/MEGAP (Slit Robo Rho GTPase-activating protein 3), or downstream effectors such as PAK3 and LIMK and the RhoGAP protein oligophrenin-1. Dysregulated protein synthesis or deficits in the regulation of dendritic cytoskeleton, synaptic anomaly, alterations in dendritic spine density, and/or distortions in spine shape are reported in several forms of mental retardation (Fiala et al., 2002; Maul et al., 2008; Newey et al., 2005; Vanderklish and Edelman, 2005). Maul et al., (2008) show a direct correlation of abnormal hippocampal dendritic spine morphology and length with impaired spatial memory in the angiotensin type II receptor knockout mice. Both these pathological features of dendritic spines are also detected in some cases of mental retardation. Other forms of mental retardation e.g. Tuberous sclerosis type I, fetal alcohol syndrome, non-syndromic mental retardation or Trisomy 21 are also shown to have abnormalities in dendritic spines (Armstrong, 2005; Kaufmann and Moser, 2000; Nimchinsky et al., 2002). Hence, genetic mutation-mediated decrease in spine density and morphological abnormalities results in aberrant neural circuitry throughout the brain which impairs the intelligence and higher cognitive functions of the individuals significantly.

8.5. Autism spectrum disorder

Autism spectrum disorders (ASD, which includes autism, Asperger's syndrome) are defined as severe neurodevelopmental disorders characterized by low intelligence quotient, impaired social communication and adaptation, disordered language, and repetitive and stereotypic behavior (Matsuzaki et al., 2004). Autism symptoms generally appear in early childhood (Courchesne et al., 2007) and are associated variably with mental retardation, seizures, sleep disorders, intellectual disability and gastrointestinal problems. In comparison to age-matched control subjects, the mean dendritic spine densities are higher in the cortical pyramidal neurons of ASD subjects (Hutsler and Zhang, 2010). In the analyses of golgi-impregnated ASD brain slices restricted to the apical dendrites of pyramidal cells, greater spine densities are found commonly within layer II of the frontal, temporal and parietal lobes and within layer V of the temporal lobe in ASD subjects. High spine densities are associated with lower levels of cognitive functioning and decreased brain weights in ASD subjects (Penzes et al., 2011). Brain samples of ASD patients show a higher dendritic spine density with reduced dendritic spine elimination in layer V pyramidal neurons in the temporal lobe (Tang et al., 2014). In a genetic research study on ASD patients, major mutations in cell adhesion molecules like neurexins (Nrxn1) and neuroligins (Nlgn1, Nlgn3, and Nlgn4) genes are found to have a stronger correlation with ASD (Dalva et al., 2007; Dean and Dresbach, 2006; Ruddy et al., 2015; Südhof, 2008). Abnormal expression of Shank-3, Homer or cortactin is found in ASD patients (Südhof, 2008). In both the mouse models of intellectual disability and autism, when functional and behavioral phenotypes are successfully restored by pharmacological and genetic managements, a parallel recovery in spine alterations is observed, indicating the cardinal role of dendritic spines in the pathogenesis of neurodevelopment diseases (Landi et al., 2011; Pop et al., 2014; Restivo et al., 2005; Tropea et al., 2009).

8.6. Fragile X syndrome

Fragile X syndrome (FXS) is the most common congenital intellectual disorder. FXS is more common in males than in females. Characteristic features include mental retardation (like reduced intellectual ability), impaired visuospatial processing, and developmental delay (Walter et al., 2009). The concurrent prevalence of ASD ranges 15-60% in patients with FXS, while 2–5% of autistic children have FXS (Hagerman et al., 2009). The absence of FMR protein, caused by the excessive expansion of CGG sequence (more than 200 repeats) in the fmr1 gene, results in the development of FXS (Willemsen et al., 2011). FMR protein is a RNA-binding protein that regulates the transport and translation of a subset of neuronal mRNAs (PSD95, elongation factor 1a, SAPAP3/4, AMPA receptor subunit GluR1/2, NMDA receptors, CaMKII, and other cytoskeletal proteins) to synapses (Bassell and Warren, 2008) and the activation of metabotropic glutamate receptors (Antar et al., 2006; Antar et al., 2004; Bagni and Greenough, 2005; Bassell and Warren, 2008; De Rubeis and Bagni, 2010; Restivo et al., 2005; Wang, 2015).

Patients with FXS show an increased number of long dendritic spine and a reduced number of shorter dendritic spines in both the temporal and visual cortical areas when compared to the control subjects. In both the cortical areas of FXS patients, the distal segments of apical and basilar dendrites show a greater dendritic spine density than the controls. FXS patients also show significantly more dendritic spines with immature morphology and fewer dendritic spines with a more mature morphology (Irwin et al., 2001). Golgi-impregnated cerebral cortex of Fragile X knockout mice (transgenic mice that lack Fmr1 gene expression) show long, thin and tortuous dendritic spines and increased spine density on the apical dendrites of layer V of the pyramidal cells when compared to the dendritic spines noted in the wild-type mice. Such morphological and density variations result in an impaired developmental organizational of synapse stabilization and turnover processes (Comery et al., 1997). In an in vivo study (Cruz-Martín et al., 2010), during the first two postnatal weeks, Fragile X knockout mice exhibit an abnormally high spine turnover and over-abundance of immature protrusion subtypes (filopodia) in layer 2/3 neurons of the somatosensory cortex. On the contrary, the wild-type mice show a rapid decrease in dendritic spine dynamics; immature small filopodia and protospines are replaced by mushroom spines. Generally, FMR protein controls the balance of the mGluR5 and AMPA trafficking, but the overexpression of metabotropic glutamate receptors causes synaptic damage and spine abnormalities leading to the behavioral deficits seen in FXS (Cook et al., 2014). The absence of synaptic proteins results in aberrant spine development, like an increased number of long, thin, and immature filopodia-like spines in cortical neurons of FXS patients (Sutton and Schuman, 2005; Weiler et al., 2004). Put together, these results show that the development of immature dendritic spines and impaired spine turnover results in the cortical areas of FXS patients with the development of intellectual disability.

8.7. Rett syndrome

Rett syndrome is a rare neurological disorder commonly found in childhood, especially in girls. Its characteristic features include wide range of motor to intellectual deficits. Main clinical features are

hypotonia, difficulties in breathing, speaking, chewing, feeding, crawling, and walking, teeth grinding, impaired posture, delay in milestone achievements, wringing movements, seizures, walking on the toes, and a gradual decline in cognitive development and intellectual abilities (Collins et al., 2004; Samaco et al., 2012). Rett syndrome is caused by sporadic X-linked mutation in the methyl-CpG-binding protein-2 (MECP2) gene, which encodes methyl cytosine binding protein-2, a protein that regulates gene transcription by binding to methylated DNA, which is an essential protein in normal brain development (Gonzales and LaSalle, 2010). The MECP2 protein plays a vital role in the regulation of synaptic development, synaptic plasticity and dendritic spine structure (Chapleau et al., 2009; Jiang et al., 2013). Another gene found to be mutated in Rett syndrome is CDKL5. CDKL5 is found to be involved in the positive regulation of dendritic spine morphology and synapse activity by phosphorylating NGL-1 and alleviating its correlation with PSD95 in synapse (Ricciardi et al., 2012). Brain samples of Rett syndrome patients show a decrease in neuronal size and an increase in neuronal cell density (Bauman et al., 1995) along with a marked decrease in dendritic arborization (Armstrong et al., 1995) and spine dysgenesis (P. V. Belichenko et al., 1994b; Chapleau et al., 2009; Kaufmann et al., 1995). Brain slices of Rett syndrome patients show a lower spine density and a decreased number of mushroom-type spines in the cortex and hippocampus (Armstrong et al., 1995; P. V. Belichenko et al., 1994a; Chapleau et al., 2009). In animal models, MECP2-deficient mice show impaired dendritic complexity (Fukuda et al., 2005; Nguyen et al., 2012), lower dendritic spine density (Castro et al., 2014; Chapleau et al., 2012; Landi et al., 2011; Tropea et al., 2009) and a lack of mushroom spines in cortical and hippocampal neurons (Baj et al., 2014; Chao et al., 2007). These results suggest that both spine dysgenesis and decreased dendritic arborization in many cortical areas is the key mechanism for the development of motor and cognitive deficits in Rett syndrome. Therefore, selective restoration of spine density and morphological abnormalities of dendritic spines using therapeutics may delay the disease progression in Rett's patients.

8.8. Down's syndrome

Down's syndrome is a highly prevalent neurodevelopment genetic disorder. It is caused by the presence of a third copy of human chromosome 21 which regulates the transcription of almost 300 genes (Haas et al., 2013) and thus, it is also known as trisomy 21. The pathological hallmark features in Down Syndrome patients are abnormal physical growth and spine dysgenesis resulting in a cognitive deficits including learning and memory (Haas et al., 2013; Takashima et al., 1981; W. Moser, 1995). Other symptoms include poor immune function (Hammer and McPhee, 2014), stunted growth, flattened nose and head, decreased muscle tone, protruding tongue, strabismus, slanted eyes, short neck and abnormal teeth. Down's Syndrome patients show a higher risk of leukemia, thyroid diseases, congenital heart defects, epilepsy, and mental disorders (Hickey et al., 2012). The dendritic spine number is generally normal in Down's syndrome patients, but decreases quickly around 20 years of age (Takashima et al., 1994).

Using the mouse models of Downs Syndrome (Ts1Rhr and Tc mice), it was shown that, markedly fewer thin spines are found in Ts1Rhr mice (aged 3 weeks) and significantly fewer mushroom spines with a concomitant increase in the number of stubby spines are reported in Tc1 mice (aged 3 months). Mouse models of Down's syndrome show significantly bigger spine heads in the dendritic spines of the motor cortex along with a decreased dendritic spine number in the hippocampal dentate gyrus (Belichenko et al., 2009; Belichenko et al., 2007). Rapid Golgi method reveal a marked reduction in dendritic spine number in the apical (middle, distal and oblique segments) and basilar (thick and thin segments) dendritic arbors of CA1 and CA2-3 segments of the hippocampal neurons in Down's syndrome patients with no evidence of AD. A significant decrease of dendritic spines in every segment is noted in Down's syndrome patients associated with AD when compared to age-matched controls and Down's syndrome patients without AD. In Down's syndrome (either associated or not to AD), thin basilar dendrites are severely affected; while in AD patients, CA1 pyramids are more severely affected than the pyramidal neurons of CA2-3 areas (Ferrer and Gullotta, 1990). The developmental morphology of the visual cortical neurons in newborns and older infants with Down's syndrome shows shorter basilar dendrites and decreased numbers of spines with altered morphology and defective cortical layering (Takashima et al., 1981). Altogether, these results suggest that dendritic spine abnormalities are an important cause for cognitive decline in Down syndrome patients in comparison to the neuronal structural defects (Haas et al., 2013).

8.9. Schizophrenia

Schizophrenia is a complex neuropsychiatric disorder affecting the cognitive and socio-psychological skills, with an incidence rate of 0.5–1% of the population (Awad and Voruganti, 2008; Wu et al., 2005). Mostly, schizophrenia appears in late adolescence or early adulthood (Lewis and Lieberman, 2000) and is more commonly seen in males (Aleman et al., 2003; Grossman et al., 2008; McGrath et al., 2004). The main symptoms are social isolation, agitation, aggression, compulsive behavior, disorganized behavior, excitability, hostility, delusions, hallucinations, paranoia, disturbing thoughts, amnesia, memory loss, mental confusion, slowness in activity, altered emotional expression or lack of emotional response, circumstantial speech, incoherent speech, and repetitive movements (Yoon et al., 2013) along with cognition impairment, executive dysfunction, hallucination, and problems with working memory (Elvevåg and Goldberg, 2000; Lesh et al., 2011). Main pathology of schizophrenia is due to the interference inconnectivity and deficit in association among various brain regions. Of the 100 genetic variants involved in schizophrenia, DISC1, ERBB4, and NRG1 are found to show constant association with schizophrenia in relation of synapse and spine function (Lipska et al., 2006; Mei and Xiong, 2008; Schumacher et al., 2009; Shamir et al., 2012; St Clair et al., 1990; Walsh et al., 2008). Most important neuropathological feature of the schizophrenic brain is the loss of grey matter, like the shrinkage or loss of neurons in the dorsolateral prefrontal cortex, superior temporal gyrus, subicular complex, and CA3 area of hippocampus (Glausier and Lewis, 2013).

In layer 3 of the prefrontal and temporal cortical areas, spine density is approximately 60% lower in schizophrenia subjects (Garey et al., 1998). Post-mortem brain samples of schizophrenic subjects show approximately 20% lower spine density on the basilar dendrites of pyramidal neurons located in layer deep 3 of the dorsolateral prefrontal cortex area 46 and in layer 3 of the primary visual cortical area 17 compared with the normal healthy controls and psychiatric subjects (Glantz and Lewis, 2001; Kolluri et al., 2005). In deep layer 3 of the primary and association auditory cortices areas 41 and 42, the dendritic spine density is significantly decreased in 15 schizophrenic subjects vs. normal comparison subjects (Sweet et al., 2009). In schizophrenic brains, both the pyramidal neurons (in frontal and temporal cortices) and medium spiny neurons (of the striatum) show reduced dendritic spine number. Postmortem brain slices of schizophrenic patients show smaller pyramidal somas and reduced neuropil. These results altogether suggest that the neurobehavioral alterations in schizophrenic patients are mainly due to deficits in dendritic spines, which in turn results in altered neuronal circuitry (Glausier and Lewis, 2013).

8.10. Depression

In today's urbanized life style, the increased levels of struggles and competition affect the mental health leading to anxiety, stress and depression. Depression is a severe psychiatric disorder affecting approximately 20% of the American population (Kendler et al., 2006; Patel

et al., 2001) and is more common in females than in males (Bangasser and Valentino, 2014; Kessler et al., 2005; Levinstein and Samuels, 2014; Thompson et al., 2015). The most common symptoms are anxiety, apathy, fatigue, mood swings, grieving, excess of sleepiness or insomnia, excessive hunger, loss of appetite, irritability, agitation, lack of concentration, slowness in activity, and suicidal thoughts. Depression is closely associated with alterations in dendritic spine morphology and spine density.

Short-term or moderate stressful conditions make individuals more adaptive and augment the neuronal function in most cases, but severe or chronic stressors are harmful and eventually disrupt the ability to handle normal stress resulting in fear, anxiety and depression in later stages of life (de Kloet et al., 2015; Lupien and McEwen, 1997; McEwen, 2005; Radley and Morrison, 2005). Compared to healthy individuals, depressive patients show a smaller hippocampus due to a marked reduction in dendritic arborization and dendritic spine density in hippocampal neurons (Bremner et al., 2000; Caetano et al., 2004; Drevets et al., 2008; Lorenzetti et al., 2009; Sawyer et al., 2012; Videbech and Ravnkilde, 2004). Patients with major depressive disorders also show reductions in dendritic spines of hippocampal regions (Law et al., 2004).

Under chronic stress, the neurons of the brain regions like amygdala, hippocampus, and prefrontal cortex show remodeling of the synaptic connectivity, neuronal degeneration, impairment of neuroplasticity and dendritic spine loss (Christoffel et al., 2011; Radley and Morrison, 2005). Meanwhile, the neurons of the amygdala and nucleus accumbens exhibit an increase in spine density. These alterations induced by chronic stress are often accompanied by depression-like behaviors like cognitive disturbances, poor concentration and negative thoughts (Gualtieri and Morgan, 2008). Chronic stress induces the release of stress hormones (glucorcorticoid and epinephrine) that can activate many kinases and phosphatases resulting in the activation of the cortactin pathway. Phosphorylated (activated) cortactin promotes the polymerization and branching of actin in dendritic spines resulting in spine dysfunction and an altered signal transmission across the synapse (Leuner and Shors, 2013). Under chronic stress, increased secretin of corticosterone is found to be the major cause for the induction of depression-like behaviors, synaptic dysfunction and dendritic spine loss in the hippocampus of male mice and rats (Wang et al., 2013).

Treatment with antidepressants significantly increase the spine density in hippocampal CA1 and BDNF mRNA in a rat brain (Altar, 1999). Since BDNF and its specific receptor trkB are found to play an important role in the regulation of hippocampal spine densities and spine shape (Chapleau et al., 2008), significant reductions in density of dendritic spines are noted in trkB-deficient mice (von Bohlen und Halbach et al., 2008; von Bohlen Halbach et al., 2006). Dysregulation of fibroblast growth factor 2 seen in individuals with major depression is found to correlate with the altered mean length of hippocampal dendritic spines (Zechel et al., 2009). Based on these data, it is clear that aberrant alterations in spine density and morphology of hippocampal neurons are important mechanisms underlying the development of depressive neural circuitry. Hence, therapeutic targets aimed at restoring the spine loss and dysfunction in cortical regions like amygdala, hippocampus and prefrontal cortex may help the depressive patients significantly.

8.11. Epilepsy

Epilepsy is a chronic neurological disease characterized by recurrent epileptic seizures (Wong and Guo, 2013). The incidence rate of epilepsy is approximately 1% of the world population and it is associated with high risk of morbidity and mortality (Dodrill, 2002; Elger et al., 2004). Epilepsy can be defined as a multifactorial disease as several neurobiological, cognitive, psychological, environmental and social factors contribute to this condition (Todorova et al., 2006). Several factors like tumors, strokes, head trauma, previous infections of the central nervous system, genetic abnormalities, exposure to environmental toxins (pesticides, herbicides, insecticides, xenobiotic etc.), neurodegenerative diseases and a variety of metabolic disorders can be possible causes for epileptic seizures (Todorova et al., 2006). Epileptic seizures can be classified as focal and generalized seizures. Symptoms commonly found in focal seizures are muscle contractions followed by relaxation, contractions on just one side of your body, abnormal head or eye movements, numbness, tingling, abdominal pain, tachycardia, repetitive movements, sweating, nausea, pupillary dilation, vision changes, hallucinations, mood changes and blackouts. The symptoms found in generalized tonic-clonic seizures are fatigue, temporary confusion, depression, anxiety, fear, uncontrollable jerking movements of the arms and legs, loss of consciousness, tingling, dizziness, muscle stiffening, urinary incontinence, atonia, and tongue biting.

Histological sections of rat brain with acute seizures or chronic epilepsy induced by convulsant drugs (pilocarpine, monosodium glutamate or kainate) or electrical kindling show a frequent loss of dendritic spines and varicose swelling of dendrites (Ampuero et al., 2007; González-Burgos et al., 2009; Isokawa, 1998; Jiang et al., 1998; Nishizuka et al., 1991; Willmore et al., 1980). On the contrary, an increase in dendrites or dendritic spines is also reported rarely (Bundman et al., 1994; Spigelman et al., 1998; Suzuki et al., 1997). In vitro seizure models including epileptiform bursting in brain slice-cultures have provided the evidence for marked spine loss and other dendritic changes (Drakew et al., 1996; Müller et al., 1993; Nishimura et al., 2008; Zhao et al., 2006). In vivo time-lapse studies of acute seizure models show marked emergence of dendritic injury following seizures, which is characterized by the temporary beading of dendrites that resolved within a couple hours after a seizure and then followed by constant loss of dendritic spines (Mizrahi et al., 2004; Rensing et al., 2005; Zeng et al., 2007). In rats with pilocarpine-induced acute status epilepticus, the dendrites of dentate granule cells show a generalized spine loss immediately after the seizures. However, these spine losses are transient, recovery and dynamic changes in the shape and density of dendritic spines are noted during the chronic phase of seizures.

Pathological studies of cortical and hippocampal samples of patients with intractable epilepsy show a number of dendritic abnormalities, which mainly included a significant loss of dendritic spines (Swann et al., 2000; Wong, 2005). Hippocampal pyramidal neurons and dentate granule cells of patients with temporal lobe epilepsy show dendritic spine loss either alone or concomitantly with varicose swelling of dendritic branches (Belichenko et al., 1994b; Isokawa and Levesque, 1991; Scheibel et al., 1974; Schewe et al., 1998; von Campe et al., 1997). Similarly, spine loss and dendritic swellings are noted in the pyramidal neurons of the neocortex, including sites distant from the primary epileptogenic focus (Multani et al., 1994). In humans with temporal lobe epilepsy, the proximal dendrites of dentate granule cells reveal greater spine density (Isokawa, 2000). Other less commonly found dendritic abnormalities are changes in dendritic length, shape and branching patterns, along with a focal increase in dendritic spines in patients with neocortical and hippocampal epilepsy (Belichenko et al., 1994a; Isokawa, 1997; Multani et al., 1994; Schewe et al., 1998; von Campe et al., 1997). Hippocampal neurons of temporal-lobe epileptic patients show dendritic swelling, varicosities formation, bigger spine heads and electron-dense spines on deteriorating dendrites (Fiala et al., 2002). Morphological abnormalities in dendrites (spine loss and dendritic beading) are often found in human pathological studies and animal models of epilepsy, which contribute mainly for the neurological dysfunction along with other neurological/cognitive deficits (Wong, 2008). Epileptic seizure induced spine loss is mediated mostly by the cofilin pathway, which is involved in the positive regulation of actin polymerization and spine dynamics (Kang et al., 2011). The activation of PAK/LIMK or calcineurin pathway by epileptic seizures-induced glutamate excitotoxicity are the other common pathways involved in disrupting of spine cytoskeleton in turn to spine collapse (Wong and Guo, 2013). These studies reveal the distinct correction of

spine beading, spine loss and dendritic swelling with abnormal neural circuitry which causes outburst of seizure activity.

8.12. Stroke

As the brain consumes about 20% of the total energy generated in the body, adequate blood flow is crucial to meet the high demand of oxygenation for the generation of energy. As neurons hold a higher metabolic rate, the demand of oxygen supply is generally high, and neurons are vulnerable to hypoxic stress (Baburamani et al., 2012). The clinical condition of interrupted or reduced blood flow to the brain results in stroke. The impairment of cerebral circulation due to a blocked artery (like thrombus formation) is defined as ischemic stroke (incident rate approximately 87%) or due to leaking/rupture of blood vessel (like aneurysms) is defined as a hemorrhagic stroke (incident rate about 13%; Naranjo et al., 2013). Ischemia is generally defined as a reduced blood flow to a particular region of brain which causes the deprivation of adequate oxygenation, leading to tissue hypoxia (reduced oxygen) or anoxia (absence of oxygen). Common symptoms include fatigue, vertigo, gait disturbances, loss of balance and coordination, blurred or double vision, temporary vision loss, difficulty in speaking and swallowing, slurred speech, speech loss, numbness or weakness in limbs and facial muscles, headache and muscle paralysis.

After 20 minutes of hypoxia, increases in dendritic varicosities and spine loss are observed (Hasbani et al., 2001). Early symptoms of neuronal injury due to ischemia include synaptic failure or the failure of neurotransmission due to alterations in dendritic spine shape like varicosite formation or constriction (Hori and Carpenter, 1994). The main sign of ischemia/hypoxia is energy failure due to the impairment of mitochondrial oxidative phosphorylation (Solaini et al., 2010). Additionally, excessive $Ca2+$ influx through glutamate receptors causes calcium excitotoxicity which impairs actin dynamics by activating actin depolymerization via the cofilin pathway (Kang et al., 2011) and causing mitochondrial damage leading to high levels of reactive oxygen species (Solaini et al., 2010). Therefore, neuronal death and dendritic spine loss are the main consequences of ischemia/hypoxia (Akulinin et al., 1997; Kolb and Gibb, 1993).

The experimental models of cerebral ischemia used in various in vitro and in vivo studies report spine loss within minutes to hours following the insult (Babu and Ramanathan, 2011; Corbett et al., 2006; Hasbani et al., 2001; Jourdain et al., 2003). Focal ischemia induced by photo-thrombosis causes spine loss in layer 1 apical dendritic tufts of the ischemic YFP-labelled layer 5 neurons (Enright et al., 2007; Kalaivani et al., 2014; Zhang et al., 2005). Golgi-Cox labelling technique traces the rapid reduction of neurons in sensorimotor cortex layer 2/3 and 5 of mice with photo-thrombotically induced stroke. Substantial loss in spine density (approximately 38%) is recorded during the first 24 h following insult and the reduction continues during the delayed phase (approximately 25% at 6 hours) in the penumbra area of cortex. These effects are restricted mainly to the peri-infarct regions (less than 200 m from the core area / infarct border (Brown et al., 2008).

In mouse models of transient global ischemia, rapid distortion of dendrites along with fewer number of loss of spines are noted following ischemia in the somatosensory cortices. Majority of the disrupted synaptic structures are rapidly reinstated following reperfusion, suggesting that the restored dendrites can survive the initial ischemia challenge. Spines on the restored dendrites undergo rapid and sustained structural reorganization following the transient ischemia. Such results suggest that the increase in spine/synapse number may represent an adaptive response of post-ischemic neurons to the compromised cortical (Babu and Ramanathan, 2011; Zhu et al., 2017) functions.

8.13. Prion disease

Prion diseases belong to a rare variety of fatal neurodegenerative disorders of animals and humans called transmissible spongiform encephalopathies. They may occur in sporadic (Jakob-Creutzfeldt disease), genetic (genetic Jakob-Creutzfeldt disease, Gerstmann-Straussler-Scheinker syndrome, and fatal familial insomnia), and acquired (kuru, variant Jakob-Creutzfeldt disease, and iatrogenic Jakob-Creutzfeldt disease) forms (Geschwind, 2015). They are caused by the conversion of the normal (cellular) prion protein (PrP) with a primarily α-helical structure into an abnormal disease-associated form of the protein called the prion with a primarily β-pleated sheet structure (Prusiner, 1998) inside the brain. As prion proteins are not broken down by proteases, they can accumulate extracellularly within the CNS to form plaques, called as prion plaques, which disrupt neuronal morphology (Brundin et al., 2010; Prusiner, 1998). Eventually, progressive neuron destruction causes brain tissue to become filled with holes in a sponge-like or spongiform pattern (Brundin et al., 2010). Cognitive deficits (memory loss, aphasia, dysphasia, mental confusion, decreased alertness, apraxia) are the most commonly noted symptom, followed by cerebellar (difficulty in walking, altered gait and posture, limb ataxia), constitutional (dizziness, vertigo, lethargy, fatigue, sleep disturbance, headache, urinary incontinence, weight loss, palpitations), and behavioral (agitation, irritability, depression, anger/aggression, apathy, mania, social isolation, panic attack) symptoms. In both animal models of prion diseases (Belichenko et al., 2000; Sisková et al., 2009) and in the brain samples of patients with prion disease, called Creutzfeldt-Jakob disease (Landis et al., 1981), reductions in dendritic spine number and emergence of varicosities are reported. Mice infected with scrapie prions show an accelerated reduction in synaptic density along with degeneration of the presynaptic compartment and dendritic spine loss in neurons of hippocampus and cerebral cortex which are followed by nerve cell loss (Brown et al., 2001). In vivo two-photon imaging in YFP-H mice inoculated with Rocky Mountain Laboratory prion strain over several months show a steady decline in density of dendritic spines in layer-5 cortical neurons. Another study on prions disease shows that cellular prion protein is a mediator of Aβ-induced synaptic dysfunction and spine loss as both treatment with anti-PrP antibodies or PrP knockout reverses oligomeric Aβ-induced impairment of synaptic plasticity and spatial memory deficits in mice (Laurén et al., 2009).

8.14. Sleep disorders

Sleep is a fundamental neurophysiological mechanism which plays a crucial role in synaptic development, maintenance and plasticity, as extensive synaptogenesis is known to occur in early post-natal life when sleeping hours are longest. Apart from playing a major role in memory consolidation (Grønli et al., 2014), sleep helps in the elimination of toxins from brain and alleviates the abnormal dendritic spines in various neurodegenerative and neuropsychiatric diseases (Picchioni et al., 2014). Sleep disorders have proven to worsen several neuropsychiatric and neurodegenerative disorders (Dorris et al., 2008; Halbower et al., 2006; O'Brien and Gozal, 2004). Many researchers postulate a strong link between spine dysfunction and degeneration in sleep-deprived animal models and in patients with sleep disorders. Sleep loss or sleep deprivation has been shown to have detrimental effects on dendritic spines signaling, actin polymerization, and dynamic changes in dendritic spines. Experimentally, sleep loss can decrease synaptic signaling molecules (PSD95, Shank, Homer, Kalirin, cortactin), synaptic cell adhesion molecules (neurexins and neuroligins), neurotropic factors (BDNF and TrkB) and basal glutamate levels (Davis et al., 2004; Yang et al., 2014). In mice, sleep deprivation for 5 hours increases the expression of phosphodiesterase-4 which in turn reduces PKA activation and expression of several immediate early genes (Vecsey et al., 2009). All of these molecular changes interfere with signaling pathways involved in F-actin stabilization or perturb synaptic protein expressions inside DS resulting in spine instability. Using transcranial two-photon microscopy and EEG/EMG recordings, the turnover of dendritic protrusions (dendritic spines and filopodia) is found to be higher over 2

hours in both the awake and sleep states in the developing mouse somatosensory cortex. The formation of dendritic spines is similar between the wakeful and sleep states, but the elimination of dendritic spines is lower in wakefulness state than sleep state. Similar results are reported on dynamics of dendritic spines and filopodia over 12-hour light/dark cycle (Yang and Gan, 2012). Sleep after motor learning task enhances the formation of dendritic spines in layer V pyramidal neurons in mouse primary motor cortex (Yang et al., 2014). All these data suggest the crucial role of sleep for healthy dendritic spines and direct link between sleep disorders and dendritic spine abnormalities.

9. Effects of therapeutic regimens and new chemical leads on dendritic spines

9.1. Anti-psychotics

Several research studies prove that dopamine plays a major stimulatory role in dendritic spine growth in primary dissociated hippocampal neurons (Critchlow et al., 2006). It was also observed that haloperidol, a dopaminergic D2 receptor blocker, reduces spinophilin (Ouimet et al., 2004). Treatment with chlorpromazine and risperidone (D2 dopamine receptor blockers) or with olanzapine (an atypical neurolepticum and D4-receptor antagonist) increases the expression of microtubule-associated protein 2 in the dentate gyrus of rats (Law et al., 2004). In rats, the depletion of dopamine levels causes a marked reduction in spine length and spine density in the nucleus accumbens (Meredith et al., 1995). D-amphetamine and methylphenidate are common psychostimulants, widely used to treat narcolepsy and attention-deficit/hyperactivity disorder (Morton and Stockton, 2000, David J Heal et al., 2013). Interestingly, treatment with drugs that elevate dopamine levels such as methylphenidate, cocaine and D-amphetamine increases the pre-synaptic proteins GAP-43 and synaptophysin (Stroemer et al., 1998) that stimulate the dendritic growth (Levitt et al., 1997) and increase the dendritic spine density (Lee et al., 2006; Zehle et al., 2007).

9.2. CNS stimulants

In rats, repeated intraperitoneal treatment with D-amphetamine sulphate (3 mg/kg) or cocaine HCl (15 mg/kg) for 5 consecutive days for 4 weeks significantly increases the dendritic arborization and the density of dendritic spines on medium spiny neurons in the shell of the nucleus accumbens and pyramidal cells in the medial prefrontal cortex. The brain samples of cocaine-treated rats show increased branching of dendrites and spine density on the basilar dendrites of pyramidal cells (Robinson and Kolb, 1999). In an earlier context drug-associated study on learning, David and colleagues reported that rats treated with amphetamine (1 ml/kg, i.p.) and immediately paired with a specific chamber spend significantly more time in the amphetamine-paired (AMPH CPP) than the unpaired chamber during the conditioned place preference test (Rademacher et al., 2010). Another important finding was that neurons from the basolateral nucleus of the amygdala of amphetamine-paired group show an increase in the total number of asymmetric (Gray Type I, excitatory) synapses contacting spines and dendrites (Figge et al., 2013; Rademacher et al., 2010) and symmetric (Gray Type II, inhibitory or modulatory) synapses contacting the dendrites of neurons in the basolateral nucleus of the amygdala (Figge et al., 2013) than the saline-treated controls. In a recent stereological analysis (Rademacher et al., 2015), the above mentioned findings were further augmented by proving an increase in asymmetric (excitatory) and symmetric (inhibitory or modulatory) inputs contacting the gamma-aminobutyric acid (GABA)-ergic interneurons. Specifically, increases in excitatory synapses onto dendrites of GABAergic interneurons and inhibitory or modulatory synapses onto dendrites were observed in AMPH CPP group, but not in the delayed pairing group. The results suggest that the changes were mainly due to the formation of context-drug associations rather than repeated exposures to amphetamine.

9.3. MK-801, a NMDA antagonist

In mouse striatal neurons, acute exposure to MK-801 (0.2 mg/kg, i.p.) markedly reduces spine density after 24 hours; but has no distinct effects on the spine density of cortical pyramidal neurons. Administration of MK-801 for 7 days substantially reduces spine density in the striatum of wild type mice (Ramsey et al., 2011). Similarly, subchronic administration of MK-801 (0.2 mg/kg/day for 7 days) causes a transient decrease in dendritic spine density in medium spiny neurons in striatum, but induces a marked reduction in spine density in the cortex (Ruddy et al., 2015).

9.4. Ketamine, a NMDA antagonist

Acute treatment with a low dose of ketamine (10 mg/kg, i.p.) increases spine density in rat brain after 24 hrs post-injection (Li et al., 2010). A single low dose of ketamine (10 mg/kg, i.p.) injection produces an increase in spine density in layer V of the pyramidal neurons of the cortex, while mice treated with a higher dose of ketamine (20 mg/kg) do not show such effects. However, there were no changes in the striatal spine density following the administration of ketamine (Ruddy et al., 2015).

Similarly, administration of ketamine (20 mg/kg once daily for 7 days) markedly decreases spine density in layer V of the pyramidal neurons in the cortex, but not in the striatum. Ketamine (5 and 10 mg/kg, i.p.) activates the mammalian target of rapamycin (mTOR) signaling proteins (eukaryotic initiation factor 4E binding protein 1, p70S6 kinase and mTOR), both transiently and dose-dependently, in the synapto-neurosomes of prefrontal cortex, which also returns to basal levels 2 h after administration. Ketamine also producesa rapid and transient enhancement in the phosphorylated and activated forms of extracellular signal-regulated kinases (ERK, including ERK1 and ERK2) and protein kinase B (Li et al., 2010). Pre-treatment with NBQX (10 mg/kg, i.p.) blocked ketamine (10 mg/kg, i.p.) induced activation of phospho-mTOR, phosphor-4E binding protein 1, and phosphor-p70S6K, as well as the other upstream signaling of kinases like phospho-ERK and phospho-Akt (Li et al., 2010).

9.5. Agomelatine, a melatonergic antidepressant

Agomelatine is known to be a safe antidepressant with relatively no significant withdrawal symptoms (Hickie and Rogers, 2011; de Bodinat et al., 2010). Exposure to agomelatine completely normalizes the stress-affected cell survival by completely reversing the reduced c-Fos and double cortin expressions, but only partially reverses the synapsin-1 expression in rat hippocampal dentate gyrus (Dagyte et al., 2010; Dagytė et al., 2011). Chronic oral administration of agomelatine (40 mg/kg for 20 weeks) enhances the spatial memory in rats in the Morris water maze task. It causes significant volumetric and numerical enhancements in granular and pyramidal neurons in the dentate gyrus and CA1-3 subregions; and a marked increase in the number of the mushroom and stubby types of dendritic spines, without affecting the number of thin-shaped spines. The above mentioned reports suggest that agomelatine produces nootropic effects through spine structural changes (Demir Özkay et al., 2015).

9.6. 9-Methyl-beta-carboline, a heterocyclic amine of beta-carboline family

A neuro-morphological study reports that 9-methyl-beta-carboline administration stimulates the growth of granule cells in the dentate gyrus of rats. Rats treated with 9-methyl-beta-carboline (0.2 umol/100 g, i.p., for 10 days) show improvements in spatial learning in the radial arm maze along with increased hippocampal dopamine levels and an

increase in the spine length, number of dendritic spines and the dendritic complexity in several concentric rings of granule cells in dentate gyrus (Gruss et al., 2012). Also, other in vitro studies (Hamann et al., 2008; Polanski et al., 2010) show that treatment with 9-methyl-beta-carboline (10-150 uM for 48 hours) increases the number of dopaminergic neurons in a dose-dependent manner. Newly formed dopaminergic neurons show an increase in the number and ramification of neurites.

9.7. Vinpocetine, a synthetic derivative of the Vinca Alkaloid extracted from the periwinkle plant

Vinpocetine, a phosphodiesterase inhibitor, known for great potential in cognitive enhancement (DeNoble, 1987; Deshmukh et al., 2009; Filgueiras et al., 2010; Ishihara et al., 1989) and effective anti-inflammatory action (Alexandre E. Medina, 2010). Two-photon laser scanning microscopy revealed that perfusion with vinpocetine significantly increases the dendritic spine motility in the neocortical layer 2/3 pyramidal neurons of rats (Lendvai et al., 2003). Rapid increases in the length of existing spines often appears as growths from the heads of mushroom spines. The formation of new spines is more frequent than the complete retraction of spines during vinpocetine administration. Veratridine, a steroid-derived neurotoxin alkaloid, enhances sodium influx, but fails to induce any change in spine motility. The results indicate that rapid changes in spine shape and size occur when calcium and sodium influx is altered by vinpocetine. Spine motility induced by vinpocetine might be associated with microtubule alterations.

10. Modification of life style for maintenance of healthy dendritic spines

Many researchers have shown that life style plays a main role in neuronal vulnerability, synaptic plasticity and cognitive development. Factors such as reduction of chronic stress, healthy food and nutritional diets along with physical (aerobic and cardiac) and cognitive exercises enhances the molecular mechanisms of dendritic signaling and plasticity (Mora, 2013). Chronic stress negatively regulates dendritic spine morphology, dynamicity and function along with synaptic plasticity and secretion of stress hormones (corticosterone). This affects neuronal energetics leading to spine or neuronal loss mainly during advanced age (Mora, 2013; Mora et al., 2012). Avoiding chronic stress is essential for the maintenance of significantly better neural and synaptic functioning.

A diet rich in antioxidants can nurture our brain and provides better protection from oxidative damage during advanced age (Colman et al., 2009; Johnson et al., 2007). Docosahexaenoic acid from fish oil has been shown to improve cognitive processes by increasing neurogenesis and the secretion of neurotropic factors (brain-derived growth factor, nerve growth factor, glial derived neurotropic factor and ciliary neurotropic factor) in humans (Gómez-Pinilla, 2008) and positively regulates the genes important for maintaining synaptic function and plasticity in rodents (Wu et al., 2007). A caloric restriction diet is found to reduce dendritic spine loss along with concomitant increases in neurogenesis which in turn enhances the cognitive functions of an individual (Johnson et al., 2007). In transgenic mouse model of AD, a long-term and regular intake of pomegranate, dates and figs is shown to reduce the neuroinflammatory effects (Essa et al., 2015). A study suggests that dietary phytochemicals, particularly flavonoids, have neuroprotective effects by protecting neurons from stress-induced injury, by suppressing neuroinflammation and by promoting LTP and synaptic plasticity. These beneficial properties are mediated by their ability to interact with signaling pathways (lipid kinase) and a number of synaptic proteins are known to play a crucial role in LTP, acquisition, consolidation and storage of memory in humans (Spencer, 2008). Regular aerobic exercise is proven to enhance neurogenesis, synaptic signaling and dendritic spine number in elderly people. Daily exercise protects neuronal and synaptic loss, and delays the onset or progression of age-related neurodegenerative diseases (Cotman et al., 2007; Gitler, 2011; Hillman et al., 2008).

11. Summary

Dendritic spines are believed to be an important anatomical focus of neural connectivity and plasticity for many decades. Ultra-structural components of dendritic spines include actins, myosins, endosomes, GTPase, PSD95, spine apparatus, NMDA and AMPA receptors. Many investigations provide evidence on the prominent role of dendritic spines in the formation of new neural circuitry as well as synaptic plasticity. Numerous in vivo and in vitro studies have proven that dendritic spines undergo change in size, shape and number throughout life. The density of spines varies with age, peaking at adolescence and then the number slowly declines near adulthood. As the brain matures, the turnover and the density of dendritic spines gets stabilized, while the rate of elimination slows down. Even in the adult brain, morphological and volumetric changes in dendritic spines mark the stimuli-induced synaptic plasticity and novel synaptogenesis. The development of advanced imaging techniques like two-photon laser scanning microscopy combined with glutamate caging and super-resolution spine imaging, crystal-clear neuroanatomical details of dendritic spines unfolded the mysteries behind the synaptic connectivity and plasticity. With recent technologies such as viral-mediated neuronal tracing and optogenetics, in vivo imaging studies have taken a great leap forward. These viral-mediated genetic and fluorescent techniques enable the researchers to target and decipher the specific neuronal population or neural networks involved in a specific behavior and motor activities. Novel synaptogenesis and alterations in synaptic connections can be visualised directly using these latest technologies.

Depending upon the synaptic stimulation, dendritic spines undergo speciific morphological and volumetric changes. Generally, LTP induction causes the enlargement of spine head and increases spine density, while LTD induction causes a decrease in spine size and density. During LTP induction, emergence and stabilization of the novel spines, and maturation of thin spines to mushroom or stubby spines results in strengthening of the neural network, while LTD induces significant pruning of the existing spines and prevents the maturation of filopodia to mature spines. Multiple evidences reveal that the morphology of spines and their synaptic complexes depletes under the conditions of excitotoxicity.

Many imaging studies have proven that both, changes in the morphology of individual dendritic spines and spine density are related to neuronal plasticity, learning and memory. During the learning process, both dendritic spine density and maturation of spines enhance significantly. During memory formation, the neural circuitry gets stablilized as the synaptic connectiivity gets strengthened along with a prominent increase in the density of mushroom spines. However, till date the molecular mechanisms underlying the correlation between the morphological and volumetric changes in dendritic spines with learning and memory processes are not clearly understood.

Several investigations on spines have shown that the signaling pathways that control spine morphogenesis have to be tightly regulated at multiple levels. Dysregulation of these signaling pathways, either by hyperactivation or hypoactivation leads to damaging effects on cognitive function, learning and memory.

The dynamic nature of spines mediated by various signaling cascades that characterize the synaptic plasticity of the brain either by strengthening or pruning the synaptic connections depends upon the induction (LTP or LTP), environment (stress or enrichment), and trauma (injury or disorders). The two common types of synaptic plasticity studied extensively are Hebbian plasticity and HSP. Hebbian plasticity is input specific and significantly increases the dendritic spine density and synaptic strength. HSP operates in a wide range of synapses and stabilizes the neural network activities and optimizes their functions by maintaining the spine density at an optimal level.

Experimental studies have shown strong and clear links between reduction in the spine density and progressive decline in cognitive and motor skills. However, detailed investigations on the morphological, physiological, biochemical and molecular levels of dendritic spines are required. Therapeutics targeted at spine recovery promote the motor skills and quality of life and also delay the progression as well as the onset of degenerative symtoms. Understanding the cellular mechanisms and signaling pathways of spine morphogenesis and their role in structural plasticity of neural networks under both normal physiological and diseased conditions are cardinal for understanding spine function, morphology and their role in cogitive function and behaviour. Specific neuronal stimulation processes using latest imaging techniques will help decode the molecular processess underlying basic homeostasis to higher-order cognitive functions. Detailed investigations on stabilizing the abnormalities of dendritic spines will lay the foundation for powerful therapeutic tools for various neurodegenerative and psychiatric diseases.

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