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Review

Molecular regulation of dendritic spine dynamics and their potential impact on synaptic plasticity and neurological diseases

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ABSTRACT

The structure and dynamics of dendritic spines reflect the strength of synapses, which are severely affected in different brain diseases. Therefore, understanding the ultra-structure, molecular signaling mechanism(s) regulating dendritic spine dynamics is crucial. Although, since last century, dynamics of spine have been explored by several investigators in different neurological diseases, but despite countless efforts, a comprehensive understanding of the fundamental etiology and molecular signaling pathways involved in spine pathology is lacking. The purpose of this review is to provide a contextual framework of our current understanding of the molecular mechanisms of dendritic spine signaling, as well as their potential impact on different neurodegenerative and psychiatric diseases, as a format for highlighting some commonalities in function, as well as providing a format for new insights and perspectives into this critical area of research. Additionally, the potential strategies to restore spine structure–function in different diseases are also pointed out. Overall, these informations should help researchers to design new drugs to restore the structure–function of dendritic spine, a "hot site" of synaptic plasticity.

Abbreviation: ADHD, attention deficit hypersensitive disorders; FXS, Fragile X-syndrome; CNS, central nervous system; GABA, gamma amino butyric acid; DiI, 1,1′-Dioctadecyl-3,3,3′,3′-Tetramethylindocarbocyanine Perchlorate; STED, stimulated emission depletion; STORM, stochastic optical reconstruction microscopy; PALM, particle tracking photo activated localization microscopy; FPALM, fluorescence photo activation localization microscopy; PAINT, point accumulation imaging in nanoscale topography; PSD, post synaptic density protein; SAP, synapse-associated proteins; NMDA, *N*-methyl D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; SER, smooth endoplasmic reticulum; ATP, adenosine triphosphate; cDNA, Complementary deoxyribonucleic acid; GTP, guanosine triphosphate; miRNA, microRNA; CaMKII, calcium/calmodulin-dependent protein kinase II; GEF, guanine exchange factor; GAP, GTP-ase activating proteins; InsP3R, inositol triphosphate receptor; GKAP, guanylate kinase associated proteins; mGluRs, metabotropic glutamate receptors; LTP, long term potentiation; LTD, long term depression; AD, Alzheimer's disease; PD, Parkinson's diseases; HD, Huntington's disease; NFT, neurofibrillary tangle; Aβ, amyloid beta protein; APP, amyloid precursor protein; ADDLs, amyloid beta derived diffusible ligands; CaN, Calcineurin; PI3K, phosphatidylinositide 3-kinases; mTOR, mammalian target of rapamycin; ROCK-II, Rho-associated protein kinase-III; LIMK1, LIM kinases-1; PAK, p21 activated kinases; PC12, pheochromocytoma; N2a, Neuro-2a; DA, dopamine; 6-OHDA, 6-hydroxydopamine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MEF2, myocyte enhancer factor-2; MSN, medium spiny neurons; YAC, Yeast artificial chromosome; NGFIB, nerve growth factor IB; LrrK2, Leucine-rich repeat kinase 2; HTT, huntingtin protein; HAP1, huntingtin-associated protein-1; KIF5, kinesin family motor protein 5; BDNF, Brain derived neurotropic factor; TrkB, tyrosine kinase receptor B; PrP, prion proteins; PrP^{c}, prion protein cellular form; DRMs, detergent-resistant cholesterol-sphingomyelin-enriched membrane domains; Cdc42, cell division cycle 42; Rac1, Ras-related C3 botulinum toxin substrate 1; ASD, autism spectrum disorders; NRXN, neurexin; NLGN, neuroligin; FXS, Fragile X-syndrome; FMRP, fragile X mental retardation protein; KO, knock out; MECP2, methyl CpG binding protein 2; TBI, traumatic brain injury; ALS, amyotrophic lateral sclerosis; SPAR, spine-associated Rap guanosine triphosphatase activating protein; Snk, serum-induced kinase; PTSD, post-traumatic stress disorders; MAPK, mitogen activated protein kinases; REMS, rapid eye movement sleep; CREB, cyclic cAMP Responsive Element Binding protein; PKA, protein kinase A; IEG, immediate early gene; ROS, reactive oxygen species; NO, nitric oxide; NOS, nitric oxide synthase; RNS, reactive nitrogen species; DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acid; NGF, nerve growth factor; GDNF, glial derived neurotropic factor; CNTF, Ciliary neurotropic factor.

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Contents

1. Introduction

The brains of most vertebrates communicate and store information by changing their nervous system through a fundamental process known as synaptic plasticity (Nicoll and Schmitz, 2005; Voglis and Tavernarakis, 2006; Zucker and Regehr, 2002). This involves several mechanisms, including alteration of existing synapses, or substitution of aged synapses to new ones (Nicoll and Schmitz, 2005; Voglis and Tavernarakis, 2006; Zucker and Regehr, 2002). These alterations, or plasticity, involve numerous tiny, specialized, semi-autonomous, postsynaptic compartments that protrude from main dendritic shaft, known as dendritic spine (Hering and Sheng, 2001). These spines are knob-like structures with various shapes and sizes which ultimately are responsible for excitatory postsynaptic input (Hering and Sheng, 2001). They also have rapid rearrangement capabilities, depending on stimulus, cellular environment and location. The spines undergoes constant turnover throughout life and play a fundamental role in information processing in the mammalian nervous system, especially for excitatory synaptic transmission (Fiala et al., 2002; Hering and Sheng, 2001; Sala and Segal, 2014). They are highly plastic in nature and their morphological variations determine the strength of a synapse (Voglis and Tavernarakis, 2006). That is why dendritic spines are considered as the "hot spot" of synaptic plasticity (Bourne and Harris, 2008; Eccles, 1979; Engert and Bonhoeffer, 1999; Maiti et al., 2015). Since their first demonstration as a genuine structure of the synapse by Santiago Ramón y Cajal, it is now widely accepted that they are specialized and distinct compartments, containing several neurotransmitter receptors, actin filaments, polyribosomes, and several cellular organelles, including the spine apparatus and coated vesicles (Sala and Segal, 2014). The morphology of spines not only determine the strength, stability and synaptic transmission, but they also control the calcium dynamics, receptor content, and the ability to change their shape and size over time (Bloodgood and Sabatini, 2007; Hering and Sheng, 2001; Sabatini and Svoboda, 2000; Sala and Segal, 2014). Most interestingly, the majority of spines are stable in mature neurons, but under certain conditions, such as in sensory input, social interactions, stress, environmental enrichment, learning and other behavioral paradigm, this steady state is impaired and they are remodeled to appropriately sub serve specific functions (Fiala et al., 2002; Hering and Sheng, 2001). Further, rearrangement of the structures and functions of most spines can influence synaptic connectivity and neuronal plasticity, which could control our learning, memory, behavior, and motor coordination (Fiala et al., 2002). In contrast, aberrant spines are highly associated with several psychiatric disorders, including autism spectrum disorders, schizophrenia, mental retardation, attention deficit hypersensitive disorders (ADHD), Fragile X-syndrome, Down syndrome, drug addiction, hypoxic/ischemic stress, and epilepsy (Fiala et al., 2002; Hering and Sheng, 2001; Sala and Segal, 2014). Similarly, in several neurodegenerative diseases, particularly those exhibiting cognitive impairments such as

Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), autism and Rett's syndrome, the dendritic spines are altered in numbers and shape before eventual neuronal death is observed (Fiala et al., 2002; Penzes et al., 2011). However, despite extensive research on dendritic spine dynamics, structure–function regulation, and underlying, detailed mechanisms of their frequent remodeling, their role in different brain diseases remain unclear. The paucity of information surroundings theses mechanism is particularly acute for addressing the following questions: (i) which class of spines is lost in different brain diseases, transient or persistent spines; (ii) does spine loss always correlate with symptoms in different neurological diseases; (iii) how do spine sense a stressful cellular environment; (iv) how do spine cope with the stressful conditions; (v) what are the extreme conditions under which spine lose their appearance; and (vi) would rescue of neuronal loss be able to restore spines structure–function. In this review, we highlight the essential background concerning the structure, function, morphogenesis and the plasticity of dendritic spines. We also address recent insights and uncover details of the molecular mechanisms underlying the regulation of spine pathology in different neurological conditions and psychiatric diseases, and explore potential ways to restore dendritic spine integrity under these conditions.

2. Importance of the study of dendritic spine

Postsynaptic activity is intimately linked with the dynamics of dendritic spines. As such dendritic spines are vital for our higher brain functions, including learning and memory. Scientists believe that the dendritic spine is the smallest neuronal compartment capable of performing a complete neurotransmission in a single synapse (Shepherd, 1996). Such spines are considered as the anatomical substrate for synaptic transmission, and are involved in formation of local synapse-specific compartments (Shepherd, 1996), including formation of a number of possible synapses (Bloodgood and Sabatini, 2007; Hering and Sheng, 2001; Nimchinsky et al., 2002; Sabatini et al., 2001; Sala and Segal, 2014). Dendritic spines are highly dynamic in nature and, hence, are considered as a "hot site" of synaptic plasticity (Fiala et al., 2002; Sala and Segal, 2014). Spines play three essential roles in nervous system: maintain long-term potentiation, regulation of calcium dynamics, and amplification of synaptic signals (Fiala et al., 2002; Hering and Sheng, 2001; Sala and Segal, 2014). As a semi-autonomous micro-compartment, they are involved in calcium signaling and protect the dendrites and neurons from Ca^{2+} excitotoxicity (Fiala et al., 2002; Harris and Kater, 1994; Segal, 1995). In addition, understanding the plasticity of spines in extreme stress or pathological conditions will help to elucidate the maximum capacity or strength of a synapse during neurodevelopment, and during the process of learning and memory in mature brain (Alvarez and Sabatini, 2007; Bloodgood and Sabatini, 2007; Holthoff et al., 2002). The study of dendritic spine dynamics attracts the attention of basic scientist for several reasons, including the fact that in several neurodegenerative and psychiatric illness the morphology of spines including their densities, shapes, and sizes are significantly altered (Fiala et al., 2002; Hering and Sheng, 2001). Their anomalies, including loss or decrease, immature structure, and reduction of size, distortion of spine shape, increase number of varicosities, enhanced ectopic spine formation are associated with cognitive impairment in several neurological diseases (Fiala et al., 2002; Hering and Sheng, 2001; Penzes et al., 2011). Further, the ratio of mature to immature spines is a vital indicator of synaptic transmission. Besides gross morphological alterations, certain ultra-structural changes within a single spine have been observed by electron microscopy in different neurological conditions, such as mental retardation, malnutrition, toxic exposure, and epilepsy (Fiala et al., 2002; Nimchinsky et al., 2002). The alteration and hypertrophy of spine organelles, increases in total spine volume, cytoplasmic densification, and formation of aberrant synapse-like connections are among other abnormalities observed in dendritic spines (Fiala et al., 2002; Nimchinsky et al., 2002). However, there are certain conditions, such as during brain development, phenylketonuria, fragile-X syndrome and exposure to enriched environment, in which the spine numbers may increase (Berman et al., 1996; Globus et al., 1973; Huttenlocher and Dabholkar, 1997; Irwin et al., 2001; Lacey, 1985), although these increases in spine numbers are often less than the amount of decline. However, due to such importance after their discovery as a genuine structure of neuron and their involvement in synaptic communication, the structures, functions, and regulation of spine plasticity have been elucidated by several investigators over hundred years.

Table 1
Upper: estimated number of neurons and synapses in the nervous system of various animal species; Below: estimated numbers of neurons in the cerebral cortex of various mammals.

Animal species	Neurons in the brain/whole nervous system	Total synapse	References
C. elegans	300	5×10^3	White et al. (1986)
Jellyfish	800	?	Herculano-Houzel and Lent (2005)
Zebrafish	1×10^7	?	Hinsch and Zupanc (2007)
Snail	1.1×10^4	?	Roth and Dicke (2005)
Fruit fly	1×10^5	$\approx 10^7$	Herculano-Houzel et al. (2006)
Honey bee	9.6×10^5	$\approx 10^9$	Menzel and Giurfa (2001)
Mouse	7.1×10^7	$\approx 10^{11}$	Herculano-Houzel et al. (2006)
Frog	1.6×10^8	?	Herculano-Houzel et al. (2006)
Rat	2×10^8	4.48×10^{11}	Herculano-Houzel et al. (2006)
Octopus	2.67×10^8	?	Roth and Dicke (2005)
Elephant	2.67×10^{11}	?	Herculano-Houzel et al. (2014)
Human	8.5×10^{10}	10^{14}–10^{15}	Herculano-Houzel (2012)

Mammalian species	Neurons in cerebral cortex	References
Mouse	4×10^6	Roth and Dicke (2005)
Rat	1.4×10^7	Herculano-Houzel et al. (2006)
Dog	1.6×10^8	Roth and Dicke (2005)
Cat	3×10^8	Roth and Dicke (2005)
Squirrel monkey	4.3×10^8	Hofman and Falk (2012)
Rhesus monkey	4.8×10^8	Fasolo (2011)
Gorilla	4.3×10^9	Hofman and Falk (2012)
Dolphin	5.8×10^9	Hofman and Falk (2012)
Chimpanzee	$5.5–6.2 \times 10^9$	Roth and Dicke (2005)
killer whale	1.05×10^{10}	Hofman and Falk (2012)
African elephant	1.1×10^{10}	Hofman and Falk (2012)
Human	$1.9–2.3 \times 10^9$	Herculano-Houzel (2009)

3. Number and distribution of dendritic spines

In the vertebrate brain, particularly in mammalian, most excitatory neurons consist of dendritic spines (Harris and Kater, 1994; Hering and Sheng, 2001). They are found mostly in pyramidal neurons of neocortex, medium spiny neurons in the striatum and the Purkinje cells in the cerebellum (Hering and Sheng, 2001; Table 1).

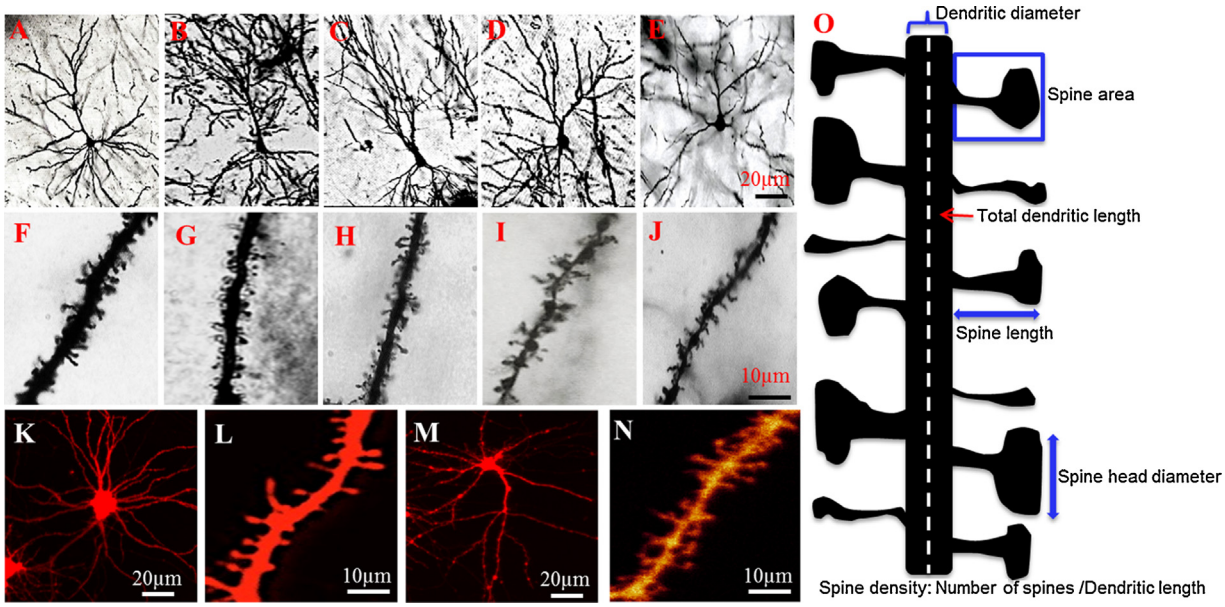


Fig. 1. Morphology of different spiny neurons from rat brain. Pyramidal neurons from layer-II/III of cerebral cortex (A); CA1 (B), CA3 (C) regions of hippocampus, layer-II/III of entorhinal cortex (D); medium spiny neuron from the striatum (E), and the morphology of dendritic spines from theses respective regions (F–J) as revealed by Golgi–Cox stain. (K)–(N) Images of hippocampal and cortical neurons and their dendritic spines stained by DiI after 21 days in culture. (O) schematic diagram of a typical dendritic branch with spines (*Note:* Different parameters, including total dendritic length, dendritic diameter, spine area, spine length and spine head and neck diameter are measured to study spine pathology).

Interestingly, the majority of these synapses are located in the cerebral cortex (Table 1). Scientists assume that the numbers of neurons in an adult human brain is close to the number of stars in the Milkyway galaxy. The estimated number in the human brain is about 100 billion (10^{11}) neurons, and each neuron makes approximately 1000 contacts with other neurons. Therefore, our super-complex brain contains an estimated 100 trillion (10^{14}) synapses. However, not all neurons in mammalian brain are spiny neurons. The spiny neurons in central nervous system (CNS) are mostly glutamatergic (pyramidal neurons of the neocortex) or GABA-nergic (Purkinje neurons in cerebellum except GABA-nergic interneurons; Hering and Sheng, 2001). In contrast, dendritic spines are absent in lower organisms (Hering and Sheng, 2001), indicating that this specialized structure is necessary for making interconnections to process complex information as required in higher organisms, like humans. However, the spine density varies from neuron to neuron; making accurate quantification a challenging task. For example, the pyramidal neurons from CA1 may have three spines per μm of dendrite (Harris et al., 1992), whereas, the cerebellar Purkinje neurons often contain a minimum of 10 spines per μm of dendrite and a maximum of up to 15 spines per μm of dendrite (Harris and Stevens, 1988). Indeed, the density of spines depends on the degree of connectivity among the neurons and the axons that pass through their dendritic arbors. The spine number also varies in different brain areas, or even within a single neuron (Fig. 1).

For example, number of spines in basal dendrite of pyramidal neurons in layer-III of cortex is three times greater than the number in the primary visual cortex, and two times more dense than parietal visual cortex of macaque monkey (Elston, 2003). Similarly, the number which is observed in the basal dendrites are more in cortical neurons from layer-III when compared to those in the prefrontal and orbitofrontal cortex of adult human brain (Elston, 2003; Nimchinsky et al., 2002; Oga et al., 2013). The morphology and density of dendritic spine can also vary in response to many factors, including environmental enrichment, pharmacological manipulation, hormonal status, learning and synaptic activity (Fiala et al., 2002; Yuste and Bonhoeffer, 2001).

4. Ultrastructure of dendritic spines

Understanding the ultra-structure of dendritic spines is a crucial step in determining the synaptic strength or efficiency of a synapse (Nimchinsky et al., 2002). Spine ultrastructure was first elucidated when transmission electron microscope (TEM) was introduced, whereas recent introduction of high-resolution, time-lapse, two-photon laser scanning microscope, stimulated emission depletion (STED) microscope, and super-resolved single-fluorophore microscopes (e.g. STORM, PALM, FPALM, PAINT) provided better images for revealing the complex spine dynamics from different brain areas (Maiti et al., 2015; Sala and Segal, 2014). These spines are typically 0.5–2 μm in length (but could be up to 6 μm, as observed in the pyramidal neurons of CA3 region of the hippocampus), depending on age, cell types, position along the dendrite, and the method of measurement (Hering and Sheng, 2001; Sala and Segal, 2014). In general, an ideal and mature spine contains a bulbous head that is connected with main dendrite by a narrow neck (Fig. 2). A typical spine head volume may be ranging from 0.01 μm^3 to 0.8 μm^3 (Table 2). Since the last few decades, several research groups have performed meta-analysis and documented several aspects of dendritic spines in order to categorize spines from the neurons that originated from various animals and human brain regions. Here we summarize their analysis, including total dendritic spines length, head volume, neck diameter, total surface area, volume, post synaptic density (PSD) protein and the ratio of head to PSD area.

Several investigators imaged and studied the detailed morphology of spines over last few decades and, based on the shape (which includes the total length, head and neck diameter), the various dendritic spines can be subdivided into five main categories: filopodium, thin, stubby, mushroom, and cup-shaped (Fiala et al., 2002; Fig. 2A–E). For example, the hippocampal CA1 neurons contain 60% thin and filopodial spines, 10% stubby, 20% mushroom shaped, and rest 10% are cup-shaped spines (Baj et al., 2014; Tatavarty et al., 2009). Interestingly, these spines change their shape and size continuously between these categories, whereas

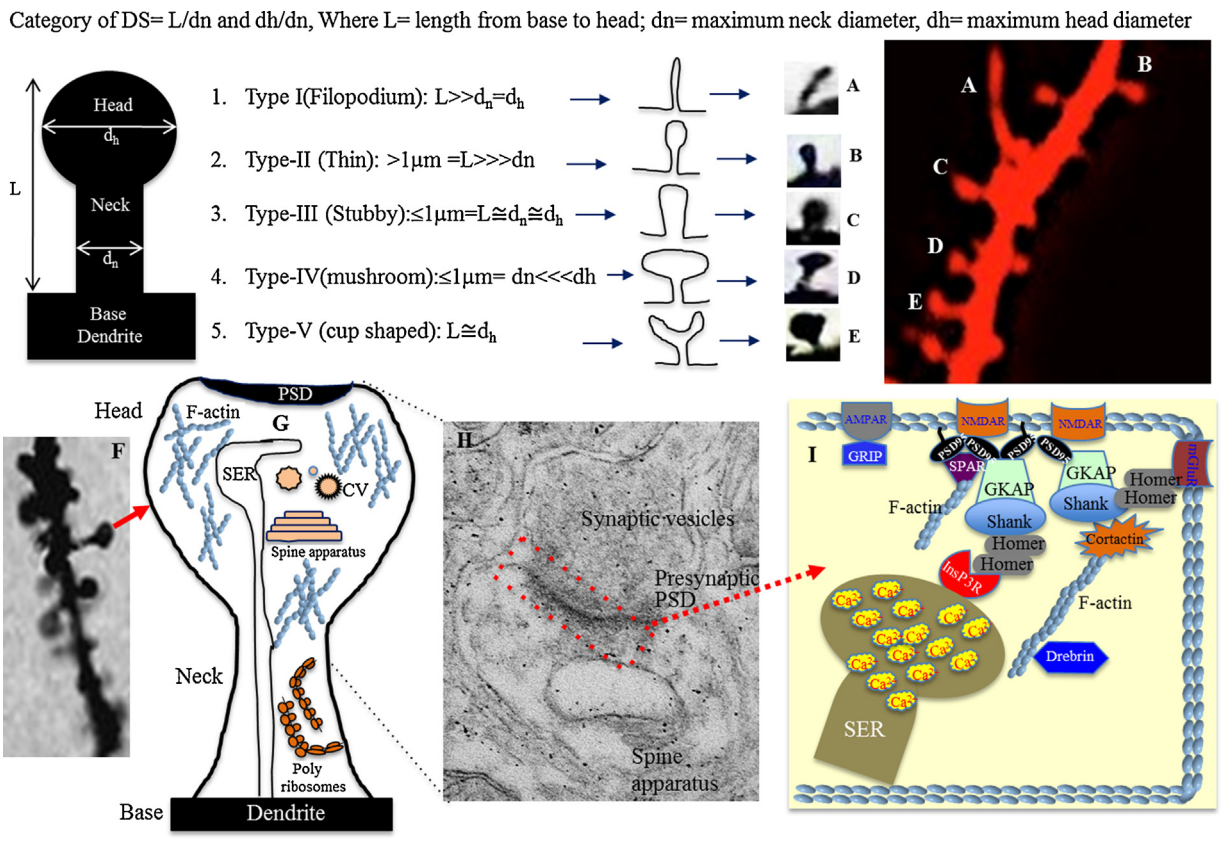


Fig. 2. Different types of spines and ultrastructure of a mature spine. Upper: On the basis of the total length, head and neck diameter, dendritic spines are categorized into 5 subtypes: filopodium (A), thin (B), stubby (C), mushroom (D) and cup-shaped (E). Below: A dendritic branch with dendritic spines (F), a cartoon of a typical spine containing cellular organelles, including smooth endoplasmic reticulum (SER), coated vesicles, polyribosomes, spine apparatus and PSD (G), ultra-structure of a typical spine from rat hippocampal neuron by electron microscopy (H), glutamate receptors (NMDA, AMPA), and numerous signaling molecules (I).

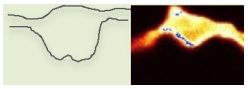
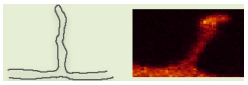
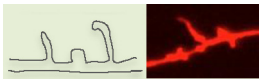
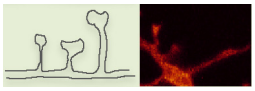
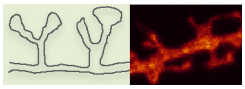
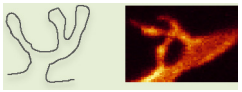
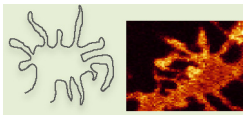
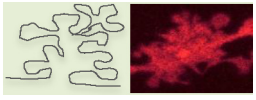
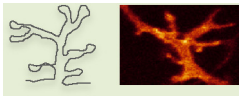
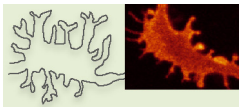
the remodeling of spine shape, size and volume is intimately linked with the strength and maturity of each spine in a particular synapse. The head is the most critical part of spine, due to its abundance of most of the neurotransmitter receptors and signaling molecules that are required for synaptic transmission. The outer surface of spine head is composed of several receptors, adaptor and cytoskeletal proteins, including numerous signaling molecules involved in synaptic plasticity (Nimchinsky et al., 2002). In general, scientists believe that a larger spine head means stronger synaptic contacts. The surface of spine head consists of a complex, electron-dense structure, containing a family of proteins called synapse-associated proteins (SAP). The most abundant SAP in the spine head is the post synaptic density protein-95 (PSD95). The size or surface area of PSD varies from neuron to neuron. Besides PSD, spines also contain several other organelles, including polyribosomes, smooth endoplasmic reticulum (SER) and coated endosomal vesicles (Spacek, 1985; Spacek and Harris, 1997; Fig. 2G). The polyribosomes are generally observed at the base of spines, may increase their level during long-term potentiation (Ostroff et al., 2002), an important neurophysiological process for memory storage. Presence of polyribosomes inside spine indicates that it can act as a semi-autonomous compartment, with local translational capabilities (Steward and Levy, 1982). Whereas SER regulates and optimizes the calcium signaling during synaptic transmission (Nimchinsky et al., 2002), most mushroom shaped spines in some neurons (e.g. CA1 pyramidal neuron of hippocampus) contain numerous, large SER and form a laminated structure called spine apparatus (Spacek and Harris, 1997). The reason for having coated vesicles in spine head is that

Table 2
Showing types of dendritic spines, their density, and other details of spiny neurons of mammalian nervous system. Lower panel: Meta-analysis of dendritic spine from different spiny neurons of mammalian nervous system.

CNS spiny neurons	Glutamatergic (pyramidal neurons in cortex, hippocampus), GABA-nergic (medium spiny neurons in striatum, Purkinje cell in cerebellum)
Types of spines	Filopodium, thin stubby, mushroom, cup shaped
Density	1–10/μm dendrite (average 5/μm)
Head volume	0.01 μm^3–0.8 μm^3
Average total length	0.5–2 μm (up to 6 μm CA3 neurons)
Organelles	Polyribosomes, smooth ER, actin, coated vesicles, spine apparatus

Neurons in different brain areas	Total length (μm)	Neck diameter (μm)	Neck length (μm)	Total volume (μm^3)	Total surface area (μm^2)	PSD area (μm^2)	PSD head area ratio
Purkinje neuron	0.7–3.0	0.1–0.3	0.1–2.0	0.06–0.2	0.7–2.0	0.04–0.4	0.17 ± 0.09
CA1 neuron	0.2–2.0	0.04–0.5	0.1–2.0	.004–0.6	0.1–4.0	0.01–5.0	0.12 ± 0.06
Pyramidal neuron of visual cortex	0.5–3.0	0.07–0.5	–	0.02–0.8	0.5–5.0	0.02–0.7	0.10 ± 0.04
Striatal spiny neuron	–	0.1–0.3	0.6–2.0	0.04–0.3	0.6–0.3	0.02–0.3	0.125
Neurons of DG	0.2–2.0	0.05–0.5	0.03–0.9	.003–0.2	0.13	0.003–0.2	–

Table 3
Variety of dendritic spines in mammalian nervous system other than the five classical subtypes of spines [*Sources:* Harris and Stevens, 1988; Harris and Stevens, 1989; Spacek and Hartmann, 1983; Wilson et al., 1983].

Types of spine	Characteristic features	Localized in CNS	Shapes
Varicosity	An enlargement in a thinner dendrite associated with synaptic contacts	Amacrine cells of retina	
Filopodium	A long, thin protrusion with a dense actin matrix and few internal organelles	Normally only seen during development	
Sessile	Synaptic protrusions without a neck constriction	Pyramidal cells of cortex cerebellar dentate nucleus	
Pedunculated	Bulbous enlargement at tip of the spine	Pyramidal cells of cortex, olfactory bulb granule cell	
Branched	Each branch has a unique presynaptic partner with a simple spine	CA1 neurons, granule cells of dentate nucleus	
Claw ending	Synaptic protrusions at the tip of the dendrite associated with one or more glomeruli	Granule cells of cerebellar cortex & dorsal cochlear nucleus	
Brush ending	Spray of complex dendritic protrusions at the end of dendrite that extends into glomerulus and contains presynaptic cochlear nucleus elements	Unipolar brush cells of r cerebellar cortex and dorsal	
Thorny	Densely lobed dendritic protrusion into excrescence a glomerulus	Proximal dendrites of CA3 and dentate gyrus cells	
Racemose	Twig-like branched dendritic appendage appendages that contain synaptic varicosities and bulbous tips	Inferior olive relay cells of lateral geniculate nucleus	
Coralline Excrescence	Dendritic varicosity extending numerous thin protrusions, filamentous expansions and tendrils	Cerebellar dentate nucleus, lateral vestibular nucleus	

it can help in endocytosis and membrane recycling (Spacek, 1985; Spacek and Harris, 1997).

In addition, the head of a spine contains abundant cytoskeletal proteins, including F-actin, drebrin, kalikrin-7, cortactin, synbindin, Shank and Homer proteins, and other signaling molecules (Fiala et al., 2002; Hering and Sheng, 2001; Sala and Segal, 2014; Fig. 2I). The reason for having coated vesicles in the spine head is because it can help in endocytosis and membrane recycling (Spacek, 1985; Spacek and Harris, 1997). Drebrin, and cortactin (a F-actin-binding protein), are critical for spine actin polymerization, its stabilization, branching, nucleation (Koleske, 2013; Sala and Segal, 2014), and they are the major structural contributor in spine morphogenesis (Sala and Segal, 2014). Abundance of all these cytoskeletal proteins in dendritic spines helps them in remodeling, or rearrangement, of their shape and size during development or cellular stress and injury. In contrast, mitochondria, the powerhouse of cells is rarely found to be localized in dendritic spines, which indicates that the energy (ATP) required for signaling mechanism in dendritic spines might come via a diffusion process from the mitochondria localized in cell body (Fiala et al., 2002; Hering and Sheng, 2001).

5. Structural variability of dendritic spines in different brain regions

One of the striking phenomena observed in spine morphology is its structural variability. Using advanced imaging techniques, scientists have described two major groups of spines in the neocortex: transient spines and persistent spines (Holtmaat et al., 2005). The transient spines may vary from day to day in their appearance and disappearance. Their morphology fluctuates with stimuli and cellular environment, and they are predominant in developing cortex and different brain regions during maturation. The second group of spines is the persistent spines, which have a more stable structure and morphology throughout life (Grutzendler et al., 2002; Holtmaat et al., 2005; Trachtenberg et al., 2002). As this group of spines are more mature and stable in nature, their numbers increase during adulthood (Holtmaat et al., 2005). Most interestingly, the transient spines are also present in the adult brain, and during synaptic remodeling, can be converted to mature structure, but their shapes, and characteristic features vary with different brain regions (Bourne and Harris, 2008; Nimchinsky et al., 2002).

Table 4
Proteins and signaling molecules localized inside dendritic spines. Based on the functions, they are categorized into five different types. As a major cytoskeletal protein actin has several specific functions in dendritic spine signaling mechanism.

Categories of proteins	Specific example of protein in each category
Actin binding and cytoskeletal proteins	Actin, Abi-1, Abi-2, Abi-3/NESH, N-Catenin, Arp2/3, Calponin, Cortactin, Drebrin A, MLC, Myosin IIB, Myosin VI, Neurabin I, Neurabin II, Spinophilin, Profilin I/II, SPIN90, Synaptopodin, VASP,WAVE1, WAVE3, CP, Eps8, EB3, p140Cap/SNIP, MAP1B
Small GTP-ases and associated proteins	GTP-ases: ARF6, Cdc42, Rac1, Rap1, Rap2, Rem2, RhoA, Rif, Rnd; Rho-GEF:ARHGEF6/PIX, ARHGEF7/PIX, Dock180, GEFT, Kalirin-7, Lfc/GEF-H1, Tiam1, Vav; Rho-GAP: α1-Chimerin, oligophrenin1, p190RhoGAP, p250GAP, RhoGAP2, SrGAP2
Cell surface receptors and adhesion molecules:	Receptors: beta2-nAChR, GABAAR, GluA2, GluN1, GluN2B, Npn-2, NgR1, PGC-1, Adhesion proteins: α3-Integrin, α5 Integrin, Arcadlin, DSCAM, IL1RAPL1, N-cadherin, Neuroligin1,2,3,4, SALM2, Syndecan-2, Telencephalin, APP, TSPAN7, Vezatin
Receptor tyrosine kinases and other kinases:	(i) Tyrosine kinase receptors: EphB1/2/3, EphA4/ephrin-A3, ErbB2/B4, ErbB4, p75NTR, TrkB; (ii) Other kinases: PAK,PAK1, PAK3, CaMKII, CaMKII-α, CDKL5, DCLK1, DGKf, LIMK-1, MARK4, NDR1/2, PAR1b, PI3K, PKMz, Plk2, Wnt7a; Dvl1
Postsynaptic scaffolding proteins, adaptor proteins	(i) Scaffold proteins: CASK, CTTNBP2, cypin, DISC1, GIT1, Homer1a, Homer1b intersectin-s, IQGAP1, N-WASP, PICK1, PSD95, Preso, SAP102, Shank1,2,3, TANC1/2, WAVE1, IRSp53, PAR-3, PAR-6, (ii) Adaptor proteins: afadin, IRSp53, Numb
Micro RNA (miRNA), mRNA binding protein, and transcription factors	(i) MicroRNA: miR-29a/b, miR-125a, miR-125b, miR-132, miR-134, miR-138, miR-185, (ii) DNA binding proteins: Satb1, (iii) RNA binding proteins: hnRNPK, Staufen2 (Stau2), TLS, (iv) Transcription factors: Cux1/Cux2, FoxO6
Specific activity	Actin binding protein involved
Polymerization	Shank3, Abi-1/2/3, Rac-1,CaMKII, cortactin, PSD95, SPIN90, VASP
Branching activity	Cdk5, WAVE, Arp2/3
Contractility	GIT1/PAK, Myosin-II, Myosin-VI, AMPAR
Stabilization	GEF-H1, Neurabin-I/II, Myosin, Ras, Drebrin-A, Gelsolin, profilin, calpoin
Capping activity	Actin-CP, Eps8

On the basis of total dendritic length, spine head volume, and neck diameter, most scientists divide dendritic spines into five main categories, as mentioned above, but several other forms of spines can be observed throughout the CNS as the brain matures (Fiala et al., 2002; Table 3). Other types of spines include varicosity, simple spine sessile, pedunculated, branched, claw ending, brush ending, thorny excrescence, racemose appendage and coralline excrescence. Some of them can be seen in the cortex, cerebellum, olfactory bulb, and hippocampal subfields of the developing brain (Fiala et al., 2002). For example, dendritic varicosities represent the cellular equivalent of vacuolar degeneration of the neuropil, and may form in response to transformation of the growth cone into a synaptic terminal after contacting a postsynaptic cell, as well as along axons, even in the absence of a postsynaptic target (Krueger et al., 2003; Morgenthaler et al., 2003; Takao-Rikitsu et al., 2004). The shape of these spines may be due to the loss of isotonicity and acute swelling or due to acute neuronal damage, like acute excitotoxicity, caused by anoxia/ischemia (Akulinin et al., 2004; Park et al., 1996) or epilepsy (Belichenko and Dahlstrom, 1995). However, dendritic spines are very common in a variety of progressive neurodegenerative diseases, including Alzheimer's, Huntington's disease (Sotrel et al., 1993), frontal lobe dementia, and motor neuron disease (Ferrer et al., 1991). Similarly, sessile spines have no neck constriction, similar to "stubby" spine, where the length of the spine is more or less equal to its width.

6. Signaling molecules involved in dendritic spine dynamics

Over the last few decades, using cDNA transfection methods several hundreds of signaling proteins molecules, hormones, and growth factors has been identified in dendritic spines. On the basis of their functions, they are divided into six main categories: (i) actin binding and cytoskeletal proteins; (ii) small GTP-ase and associated proteins; (iii) cell surface receptors and adhesion molecules; (iv) receptor tyrosine kinases and other kinases; (v) postsynaptic scaffolding proteins and adaptor proteins; and (vi) microRNA (miRNA), including mRNA binding protein and transcription factors (Sala and Segal, 2014; Table 4). Most interestingly, the majority of these signaling molecules that regulate dendritic spine structure and dynamics has an influential role on actin polymerization and its stabilization (Sala and Segal, 2014). Therefore, spine density can be controlled by modulating actin dynamics through regulation of these signaling molecules. Depending on the function involved, spine actin binding proteins are also categorized into five sub-types, such as the proteins which have branching activity (e.g. cdk5, arp2/3), contractility/stabilization activity (e.g. myosin-II, VI, AMPAR etc.), stabilization activity (e.g. Drebrin-A, gelsolin, profiling, myosin, Ras etc), polymerization activity (e.g. PSD95, Shank3, Rac1, CaMKII, cortactin etc.) and capping activity (e.g. Actin-CP, Eps8; Sala and Segal, 2014; Table 4). Recent experimental data suggest that the spine cytoskeleton depends on the nature of actin polymerization, whereas microtubules actively participate in the shaping of spine morphology (Kaech et al., 1997). Other findings suggest that most actin polymerization is controlled by small GTP-ase proteins of the Rho family.

The Rho families of proteins are regulated by a number of upstream and downstream molecules, and several nucleotide exchange factors (GEFs) and GTP-ase activating proteins (GAPs; Sala and Segal, 2014). Similarly, cell surface receptors, extracellular matrix, and adhesion molecules also play a pivotal role in the formation and development of synapses and involve spine formation by regulating actin polymerization. In addition, receptor tyrosine kinases and other kinases are implicated in regulating the spine structure and dynamics, as well as long-term maintenance of neuronal plasticity and memory. Further, postsynaptic scaffolding proteins and adaptor proteins, harboring several postsynaptic neurotransmitter receptors (e.g. NMDA/AMPA/mGlu etc), are mainly localized in the spine head. The most abundant scaffolding protein is PSD, which is mainly localized adjacent to postsynaptic membrane and directly interacts with subunits of inotropic glutamate receptors (NMDA/AMPA), regulating their functions (Fujita and Kurachi, 2000; Kim and Sheng, 2004). Among them, the four members of the PSD95 family (PSD95/SAP90, PSD-93/chapsyn-110, SAP102, and SAP97), have a common structure formed by three PDZ domains and are very important players in synapses and dendritic spines (Kim and Sheng, 2004; Table 4). The other two postsynaptic scaffolding proteins which regulate spinogenesis, especially spine maturation, are Shank and Homer (Hering and Sheng, 2001). These proteins directly interact with PSD95 and several other membrane proteins including pro-SAP and other signaling molecules. Among all these SAP, Shank1 and Shank3 proteins play pivotal role in the maturation and enlargement of dendritic spines. It can crosslink with Homer and PSD95 complexes and regulate signal transduction of mGluRs and NMDA receptors (Tu et al., 1999). It can also react with other SAP including sharpin, cortactin, InsP3R and guanylate kinase associated proteins (GKAP; Fig. 2; Boeckers et al., 1999; Lim et al., 2001; Naisbitt et al., 1999; Tu et al., 1999). Mouse with Shank1

Table 5
Specific functions of different dendritic spine proteins and signaling molecules.

Spine proteins	Functions
Actin	Regulate spine motility
Actinfilin	An actin binding protein
Adducin	Promotes actin-spectrin interactions and F-actin polymerization
α-actinin	Actin filament binding protein help actin polymerization
β-catenin	Binds actin filaments to cell adhesion proteins through a-catenin
Cortactin	Promote binding of F-actin and thus help polymerization of action
Calponin	Actin, myosin-II and calmodulin binding protein
Caldesmon	Actin binding and myosin modulating protein
CaMKIIb	Calmodulin dependent protein kinase IIb
Cofilin	Depolymerizes actin filaments,
Debrins	Actin binding proteins
EphA/EphrinA	Regulate neuron-glia signaling and induces retraction of spine, synaptic pruning
EphB/EprinB	Regulate spine morphology by recruiting molecule involved in actin polymerization
Shank	As a master organizer of the PSD and recruit and form multimeric complexes with postsynaptic receptors, signaling molecules etc.
Homer	Bind with Shank, glutamate receptor and other protein and regulate [Ca^{++}]
PSD95	Stabilizing nascent spine & anchor receptor, scaffolding proteins at the synapse
N-cadherin	Stabilizes mature synapse and regulates spine morphology and synaptic efficacy
Myosin-IIb	Contractile/motor function, stabilize mushroom spines structure
Myosin VI	Regulate clatherin mediated endocytosis of AMPA receptors
Profilin	Promotes activity–dependent actin polymerization and stabilization.
Synaptopodin	Binds to spine apparatus and help spinogenesis, regulate calcium signaling
Spectrin	Membrane cytoskeletal constituent
miR-134	Negatively regulate spine development by inhibiting transcription factor Lim kinase-1
Rap1/AF-6	Elongates spine and removes AMPA receptors
SynGAP	Maintain filopodia during spine development, negatively regulate Ras signaling pathway which promote spinogenesis
Telencephalin	Maintain filopodia during spine development, down regulate spine development

knockout showed abnormalities in PSD protein scaffold composition, along with smaller dendritic spine and weaker excitatory synaptic transmission (Hung et al., 2008).

The second most important signaling protein in spine is Homer. It interacts with metabotropic glutamate receptors (mGluRs) and inositol tri phosphate receptors (InsP3R) in SER surface and regulates calcium signaling inside spine head (Sala et al., 2001). In addition to scaffolding proteins, other spine regulatory proteins, including at least five micro RNA, mRNA binding protein, and transcription factors (e.g. miR-134, miR-138, miR-132, miR-125b, and miR-29a/b) have been identified recently and all of these possess a functional role in controlling synaptogenesis and spine morphology (Sala and Segal, 2014; Tables 4 and 5). Among them, miR-134 and miR-138 negatively regulate the size of dendritic spines and excitatory synaptic transmission by inhibiting the translation of Limk1, which controls spine development. Whereas miR-125a miR-125b and miR132 control PSD95 expression and promote spine formation, their numbers increase during maturation (Sala and Segal, 2014; Table 5).

7. Development of dendritic spine

Generally, newly formed dendrites are devoid of dendritic spines. The spine having small head or absence of head have less capability for neurotransmission, which indicates they require maturation after formation. However, as these spines start to develop (spinogenesis), they acquire a long thread-like nascent form, called a filopodium (Fiala et al., 2002). However, these kinds of spines are rarely observed in the mature neurons. During embryonic brain development, even up to first week of birth, these spines can be characterized by the abundant of filopodia. However, through the process of several spinogenesis steps, filopodia are replaced by thin, stubby, and relatively mature mushroom and cup-shaped spines (Hering and Sheng, 2001). In response to optimum stimuli, they become relatively stable and increase or decrease their numbers and also their shapes or sizes (Fig. 3). Experimental data suggest that the number of mature spines can increase up to 40% within couple of weeks after birth, indicating that filopodia are the precursors of mature spines (Fiala et al., 1998). Interestingly, in case of hippocampal neurons spine numbers can double within this time frame and sometimes it can increase up to four fold, whereas, with other spiny neurons the numbers are stable (Harris et al., 1992).

In contrast, the mature forms, such as mushroom or cup-shaped spines, are predominant in adulthood. Although, most mature spines are stable for certain periods, increases or decreases in the number of spines are common and morphological rearrangement is a common the normal phenomena during spinogenesis, as well as during the course of learning and memory (Bosch and Hayashi, 2012; Engert and Bonhoeffer, 1999; Maletic-Savatic et al., 1999).

8. Spine formation and stabilization: Role of calcium and glutamate receptors

The head of a dendritic spine contains PSD, which bears several receptors and signaling molecules, including inotropic (NMDA, AMPA) and metabotropic (mGluR) glutamate receptors. Out of all glutamate receptors, AMPA receptors play an important role in basal synaptic transmission, while NMDA receptors open calcium channels during high synaptic activity (e.g. in long term potentiation; LTP), which can induce spine growth (Lacor, 2007; Lynch, 2004). The hypertrophy or atrophy of spines can be observed by manipulating the glutamate receptors *in vitro* and *in vivo*. For example, during long-term depression, activation of NMDA receptors is very low, which can decrease the levels of AMPA receptors, leading to spine loss (Henley and Wilkinson, 2013; Luscher and Malenka, 2012). Administration of glutamate to primary neuronal culture increases spine motility, including increase in the head diameter along with increase in PSD, as well as expression of glutamate receptors (Nimchinsky et al., 2002). Activation of inotropic glutamate receptors increases the influx of extracellular calcium into spine and suppresses actin dynamics, which can block spine motility (Lamprecht and LeDoux, 2004; Sala and Segal, 2014). This leads to morphological stabilization of spine that can last for 12 h, whereas this phenomenon is very transient and disappears when glutamate is washed out from the culture media.

The spine dynamics can also be regulated by increasing expression of glutamate receptors through electrical stimuli. Electrical stimulation in certain brain areas can develop LTP (required for learning and memory), which can increase spine volume (Lamprecht and LeDoux, 2004; Nimchinsky et al., 2002). This increase in spine volume can be sustained for a long time. The establishment of LTP has been shown to increase expression of glutamate receptors. It has been verified that the development of LTP enhances the influx of Ca^{2+}, which induce the growth of new spines or filopodia-like spine precursors (Higley and Sabatini, 2012; Oertner and Matus, 2005). Further, several small and new spines are also generated by the induction of LTP. In contrast, inhibition of synaptic transmission causes atrophy and spine loss in an experimental model with hippocampal slice culture, suggesting

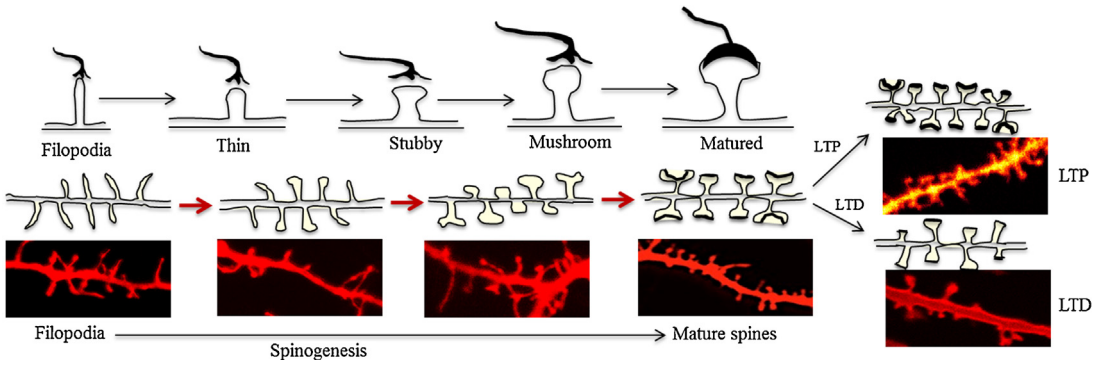


Fig. 3. Schematic diagram of steps of spinogenesis. The spine formation starts with filopodia, which become mature mushroom or cup-shaped through several developmental stages. The number of mature spines may increase (after long term potentiation) or decrease (after long term depression) following exposure to external stimuli. Below: representative pictures of different stages of spine development taken by laser scanning confocal microscope from three week cultured rat primary hippocampal neurons, stained by DiI.

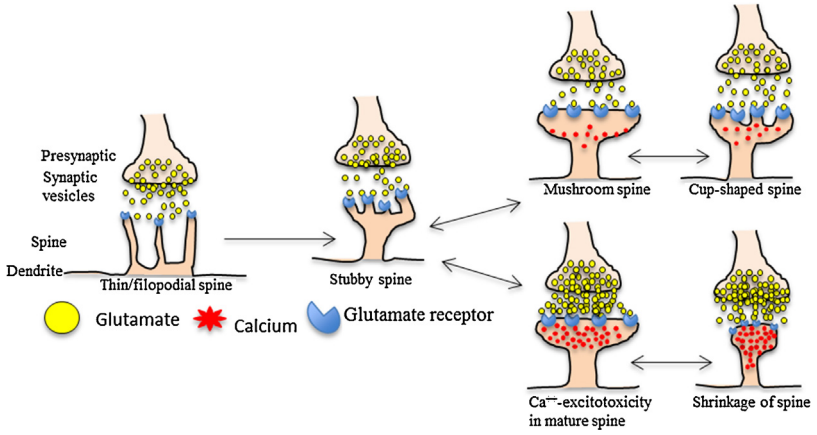


Fig. 4. Hypothetical scheme of the role of glutamate receptors and calcium in dendritic spine development. When glutamate (Yellow) binds to NMDA receptor (blue), it can induce accumulation of actin at nascent spines, which leads to outgrowth of motile filopodia to stubby, mushroom and cup-shaped spines. Excess glutamatergic stimulation can cause calcium excitotoxicity, which leads to spine shrinkage or loss. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

that calcium and glutamate receptors are the positive modulator of spine dynamics (Lamprecht and LeDoux, 2004). Similarly, excess glutamate administration to primary neuronal culture causes glutamate excitotoxicity, which has been shown to produce extensive spine loss with the disappearance of filamentous actin (F-actin) within few minutes (Fig. 4). This is due to influx of extracellular Ca^{2+} through NMDA receptors and can cause Ca^{2+} excitotoxicity and leads to stabilization of filamentous actin, mitochondrial damage, and eventually energy failure and cell death (Kritis et al., 2015). Hence, glutamate receptors have significant roles in spinogenesis, its development, maturation, and, also, its loss or disappearance (Fig. 4).

9. Plasticity of dendritic spine

One of the most striking phenomena of dendritic spine plasticity is their morphological diversity. For the formation or development of new synaptic circuits, spine dynamics including its motility, turnover, changes of shape, size are crucial (Calabrese et al., 2006). Using advanced imaging techniques, several investigators came to the conclusion that spines are very dynamic in nature and are considered as the morphological basis of synaptic plasticity (Maiti et al., 2015). The degree of plasticity highly depends on actin dynamics inside spine, whereas size and volume of spine, including head diameter, also depend on calcium signaling inside the spine as demonstrated using an *in-vitro* experimental paradigm (Sabatini et al., 2001). The timeline for spine plasticity might be short or long depending on the intensity and duration of stimulus (Sala et al., 2001; Fig. 5).

9.1. Short-term plasticity

Recently, using early time-lapse video microscopic imaging techniques, scientists discovered that new spine could be generated within 30 min after induction of LTP, as observed in dissociated neuronal or slice cultures (Segal, 2005). Similarly, excess stimulation or pharmacological manipulation, including administration of glutamate in dissociated hippocampal neurons or in hippocampal slice cultures also produce an increase in the number of filopodia-like spines, which indicate that formation of new synapses (Shi et al., 1999). Although nascent spines containing glutamate receptors (e.g. AMPAR), can be observed within 10 min of LTP induction the development of functionally mature spines requires about a day. Interestingly, new spines can emerge within 2 min after glutamate uncaging near the dendritic shaft of layer 2–3 pyramidal neurons in brain slices of young mice (P8–12) and they behave like mature ones (Sala and Segal, 2014). In contrast, with time-lapse imaging of neocortex, Knott et al. (2006) observed that it takes at least 4 days to become mature spines. In general, it appears that nascent spines takes hours to a single day to become structurally

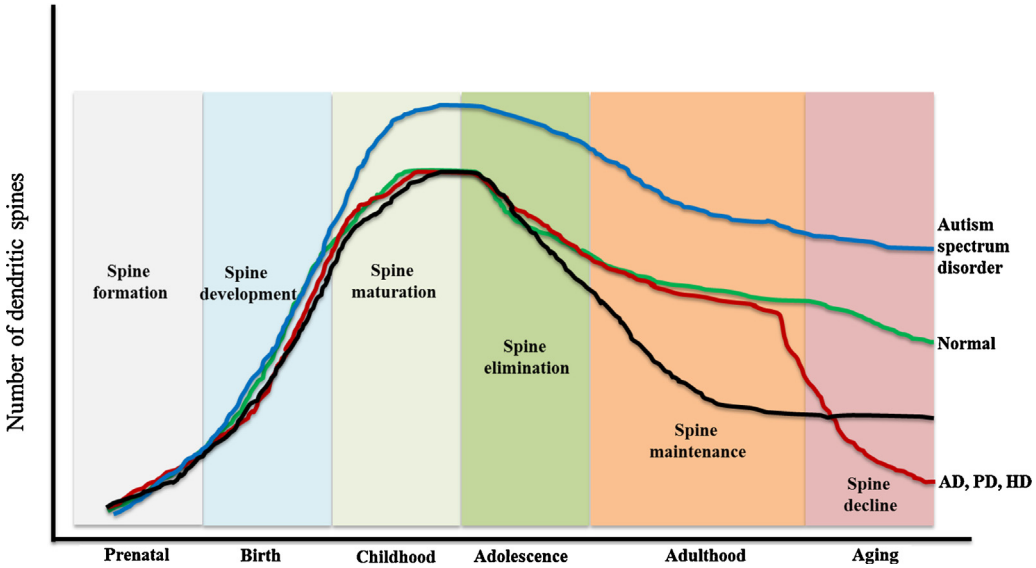


Fig. 5. Schematic diagram show dynamics of spine numbers in a life span and their profile in different neurological conditions. *Note:* In most neurological diseases, spine numbers decline, except in autism spectrum disorders, where the numbers of spines increase.

and functionally mature, but the mechanistic details as to why they take so much time to become mature presently is unclear.

9.2. Long-term dendritic plasticity

The maturation of newly formed spines varies from several hours to almost a day or even more, depending on stimulus and functional requirements (Holtmaat and Svoboda, 2009). It has been observed that almost 50% of nascent spines from the neurons of mouse barrel cortex become stable and mature after their formation (Fu and Zuo, 2011). The transformation of immature to mature spines continues until they make contact and form synapses that transmit the signals. However, as mentioned above, the generation or elimination of spines depend on local the environment, the cellular requirements, and or nature of stimulus. For example, long-term spine dynamics can take place in the mouse neocortex following extensive motor learning and these changes may last for many days after the training (Dayan and Cohen, 2011; Sala and Segal, 2014). In contrast, fear conditioning is actually associated with a reduction in spine density. Time lapse microscopy of layer 5 pyramidal neurons of the frontal cortex in living mice have shown that fear conditioning was associated with elimination of dendritic spines, whereas fear extinction involved reappearance of spines (Lai et al., 2012). In general, the density or size of dendritic spines is increased during the development of long-term memory. It is also known that thick spines may persist for a months, while thin spines are very transient, which indicate that perhaps thick spines are more responsible for development and maintenance of long-term memory (Geinisman, 2000). Several researchers have suggested that induction of LTP-enhanced synaptic activity increases spine size and density, whereas long term depression (LTD) has opposite effects (De Roo et al., 2008; Yang et al., 2008). This indicates that spine plasticity depends on neuronal activity, and the disappearance or reappearance of spines depends on synaptic activity. For example, a marked reduction of spine number has been observed in hibernating animal brain, but these spines reappear when the animal comes out of hibernation (Fiala et al., 2002; Segal, 2005). Similarly, pharmacological manipulation such as blocking AMPA receptors significantly reduce spine numbers, while spine density reappears with increased in efficiency of synaptic transmission (Hanley, 2008; Henley and Wilkinson, 2013).

9.3. Plasticity of dendritic spine in adulthood

During development, dendritic spines take several steps to become mature. Spine development and plasticity are not restricted to the embryonic stage, but rather it exists throughout life. Normally, in adulthood, most spines become mature and stabilized, so the degree of spine development becomes significantly reduced (Koleske, 2013). However, diverse morphological changes of spines, including their shapes, size, and numbers, can occur during adulthood (Fig. 6A), depending on cellular environment and external stimuli. For example, exposure of animal to an enriched environment has been found to generate a greater number of spines in hippocampus (Kozorovitskiy et al., 2005), along with improvements in the performance of several learning tasks (Bruel-Jungerman et al., 2005). Similarly, electrical stimulation, such as development of LTP, can increase number of spines, including enlargement of spine size. This in turn can enhance synaptic transmission and, thus, strengthen development of learning and memory, whereas development of LTD shows the opposite effects (Bliss and Lomo, 1973; Bliss and Collingridge, 1993; Malenka and Nicoll, 1999).

At several time points during LTP induction, electron microscopic images of spine have revealed that the normal spine contains simple and continuous PSDs, whereas after induction of LTP, the segmented or perforated PSDs increase, followed by enhancement of the number of multiple buttons, along with a decrease in numbers of simple PSD95 (Hering and Sheng, 2001; Fig. 6B). The significance of an increase in the number of perforated PSDs and a relatively larger spine head is that it provides more PSD area and more glutamate receptors, as well as a higher number of coated vesicles in the spine. Further, rearrangement or remodeling of synaptic connections, as well as alterations in spine structure–function have been observed in the adult brain after brain injury (Gao et al., 2011). All these phenomena provide additional evidence that spine plasticity commonly takes place during adulthood.

10. Anomalies of dendritic spines

The loss or gain of spines is a common feature of spine dynamics during development or while under stimulation or inhibition

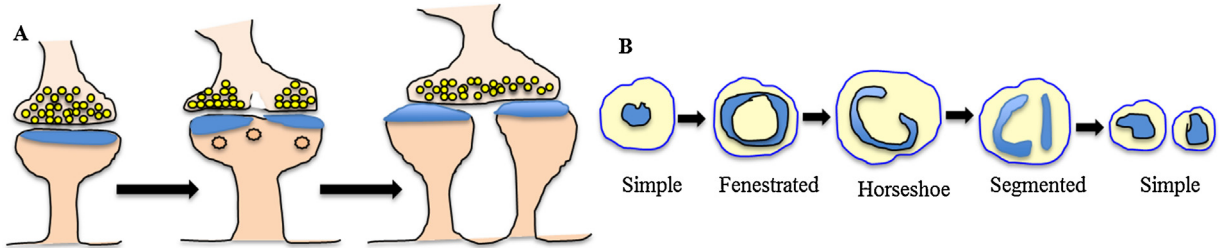


Fig. 6. (A) Schematic depiction of changes of dendritic spine morphology associated with long-term potentiation (LTP). (B) Model of changes in spine and PSD morphology after LTP (Hering and Sheng, 2001).

(Calabrese et al., 2006; Calabrese et al., 2014). In general, shape, size, and volume of dendritic spines are maintained at an optimal level of synaptic activity, whereas abnormal spine structure and their loss represent a common hallmark of several neurological diseases (Table 6). Scientists report that several of the impairment of cognitive functions observed in different brain diseases are due to spine abnormalities or decrease in number of spines and their level of maturity (Fiala et al., 2002; Penzes et al., 2011; Smith and Villalba, 2013). Using several imaging and electrophysiological techniques, it has been revealed that the ratio of mature to immature spines are important in synaptic transmission, because immature spines have impaired synaptic signaling (Fiala et al., 2002; Nimchinsky et al., 2002). The important changes observed in spine morphology in different brain diseases include decreases in their size and density, distortion of spine shape, and/or increases in the number of varicosity or enhanced ectopic spine formation (Fiala et al., 2002; Giachello et al., 2012; Table 6). According to Fiala et al. (2002) dendritic spine abnormalities can be classified into two main categories: (a) pathologies of distribution and (b) pathology of structure. Pathology of distribution includes dramatic increases and decreases in spine density, and widespread changes in morphology including overall alteration of spine shape and size, increases or decreases in their number, and sprouting of spines in abnormal locations. On the other hand, pathology of structure comprise ultra-structural changes within a single spine, including cytoplasmic densification, hypertrophy of organelles or spine volume, alteration of spine organelles, and the formation of aberrant synapse-like connections (Fiala et al., 2002). Total neuronal loss causes axonal loss or deafferentation, which is the principal reason for permanent spine loss observed in several neurological diseases, including in mental retardation, malnutrition and toxin exposure, epilepsy, and different neurodegenerative diseases (Fiala et al., 2002). Of course, in some progressive neurological diseases such as AD, PD, and HD, spine loss may begin with axon degeneration before neuronal loss is detected (Brown et al., 2001; Guidetti et al., 2001).

In contrast, increase in spine density is less common and the detailed mechanism is also unclear. There are certain situations, such as during normal brain development, cases of phenylketonuria and fragile-X syndrome, and exposure to enriched environments, in which spine numbers and synapse density may increase on pyramidal cells in occipital cortex and in hippocampal area CA1 (Fiala et al., 2002). However, the large, perforated spines or decreased spine volume have been observed in different abnormal cases. For example, reduction of spine size, as well as loss of entire dendrites, have been reported in the striatum of schizophrenics, and in motor cortex of infants having Down's syndrome (Kaufmann and Moser, 2000). Similarly, distorted spines including those lacking head or those with one enlarged head, or those with long and tortuous filopodia, with multiple fusiform swellings have been associated with mental retardation (Fiala et al., 2002). Formation of varicosities is common in different brain injuries, which might be due to abnormal organization of microtubules or actin polymerization, and abnormal intracellular inclusions (Fiala et al., 2002; Giachello et al., 2012). Loss of isotonicity is also associated with abnormal actin dynamics and the swelling of dendritic trunks, producing varicosities as observed in progressive neurodegenerative diseases such as AD, PD, HD, Pick's diseases, frontal lobe dementia and motor neuron disease (Fiala et al., 2002). The appearance of a dendritic spine in the wrong location is known as an ectopic spine. These are common during early development, olivopontocerebellar atrophy, fetal alcoholic syndrome, Menkes disease, hypothyroidism, and transmissible spongiform encephalopathy, epilepsy, metabolic storage disorders, gangliosidosis and sphingomyelin lipidosis (Fiala et al., 2002). Degenerated neurons, including necrosis, can cause dendritic hydration which causes a densification of cytoplasm, followed by a loss of organelle integrity. Dark electron-dense spines can be observed by transmission electron microscopy in traumatic injury, AD, and in convulsion-induced degeneration (Eid et al., 1999). Apart from phenotypic changes, aberrant spines may be due to alteration of spine organelles, such as postsynaptic density, polyribosomes, endosomes, and the spine cytoskeleton, due to excitotoxic injury from excessive presynaptic glutamate release (Fiala et al., 2002). For example, the postsynaptic density is thickened by anoxia/ischemia. In addition, higher density of polyribosomes has also been observed in spines after deafferentation. Further, changes in spine endosomes and javascript:void(0); cytoskeleton, elaborated or atrophied spine apparatus, hydropic swelling and vacuolization of the ER of dendrites and spines have also been observed (Fiala et al., 2002). A reduction in spine apparatus has also been reported in anesthetized animals (Devon and Jones, 1981), along with a complete absence of smooth ER in spines of Purkinje cells (Dekker-Ohno et al., 1996) in ataxic mutant rat. Among other spine abnormalities, are formations of giant spines and axon-less

Table 6
Dendritic spine variability in different disease conditions (Fiala et al., 2002).

Spine pathology	Occurrences
Decrease spine density	Deafferentation, agenesis, mental retardation, malnutrition, poisoning, alcohol abuse, epilepsy, spongiform encephalitis, Alzheimer's disease and others
Increase spine density	Some types of deafferentation, environmental enrichment, fragile-X-syndrome, sudden infant death syndrome, stimulatory drug use
Reduction in spine size	Sensory deprivation, schizophrenia, down syndrome
Distortion of spine shape	Deafferentation, agenesis, mental retardation, malnutrition, poisoning, alcohol abuse, epilepsy, spongiform encephalitis
Varicosity formation	Acute excitotoxicity, traumatic injury and edema, epilepsy, hypoxia/ischemia
Ectopic spines	Olivopontocerebellar atrophy, Menkes disease, metabolic storage diseases

spines (they are axon-free PSDs like structure at synapse-like junctions with glia or other dendrites) due to deafferentation. Although, most of the dendritic spine anomalies have been observed in animal models of diseases, in humans, aberrant spine densities or shapes have been reported and are usually associated with brain diseases, including mental retardation, Down's syndrome, Fragile X-syndrome, epilepsy, and several neurodegenerative diseases (Fiala et al., 2002; Penzes et al., 2011).

11. Mechanistic details of dendritic spine pathology in different brain diseases

11.1. Alzheimer's disease

Alzheimer's disease is the most common age-related neurodegenerative disease and is the leading cause of death in the elderly (Jack et al., 2011). Early memory deficits, followed by gradual decline of cognitive and intellectual functions or dementia, is one of the cardinal features of this disease (Kelley and Petersen, 2007). The principal neuropathological features are the aggregation of amyloid beta protein known as senile plaque which are mainly deposited in extracellular spaces (Glenner and Wong, 1984; Haass, 2004; Haass and Selkoe, 2007; Lichtenthaler et al., 2011; Masters et al., 1985), and phosphorylated tau known as neurofibrillary tangles (NFTs), which are found intracellularly (Dickson, 2004; Kosik et al., 1986; Nukina and Ihara, 1986; Spires-Jones et al., 2008; Wakasaya et al., 2011). The etiology and mechanism of memory deficits in this disease is unclear. Experimental evidence indicates that loss of synapses or neuronal death in numerous brain regions, including hippocampus, cerebral cortex, and other subcortical areas, are involved in AD. Numerous reports suggested that the amyloid plaques contain Aβ polypeptide derived from proteolytic cleavage of amyloid precursor protein (APP). An abundance of research suggests that synaptic loss can be better correlated with cognitive impairment in AD progression than the amyloid plaques burden (Masliah et al., 1991; Scheff et al., 2006; Terry et al., 1991). It has been reported that spine pathology starts before neuronal death, which is indicated by abnormal spines, one of the early pathological signs of AD (Garcia-Alloza et al., 2006; Spires et al., 2005; Tsai et al., 2004). A significant decrease in dendritic spine number and changes in morphology have been reported in over-expressed human APP animal model of AD. Recent experimental data shows that about 45% of dendritic spines disappear in the neocortex and hippocampus of AD patients, in comparison to cognitively normal control (Serrano-Pozo et al., 2011). Further, in the living animal model of AD, almost 50% of the dendritic spines that are near the vicinity of amyloid plaques disappear as observed by multiphoton microscopy (Spires et al., 2005). Similarly, 30% spine loss was observed in pyramidal neurons of a tau transgenic mouse model, including significant decrease in dendritic arborization (Boekhoorn et al., 2006; Dickstein et al., 2010; Eckermann et al., 2007; Rocher et al., 2010; Thies and Mandelkow, 2007). Our laboratory has extensively worked on structure–function relationship of Aβ and their effects on synaptic toxicity, especially on morphological changes of dendritic spines. After challenging primary hippocampal neurons with Aβ oligomers, we have observed severe abnormalities in dendritic spine morphology, including spine loss, increase premature spines and large number of varicosities (Attar et al., 2012; Maiti et al., 2010; Maiti et al., 2011). However, the molecular mechanism of spine abnormality in AD is not clear yet. Recently, scientists have proposed several possible mechanisms involved in spine loss, synaptic failure, as well as memory loss in AD. One promising hypothesis is that Aβ oligomers or amyloid beta-derived diffusible ligands (ADDLs) directly bind to the glutamate (NMDA) receptors that are present in the PSD area of dendritic spines. Binding of these toxic species causes influx of extracellular Ca^{2+}, which can disrupt calcium homeostasis causing oxidative stress, which leads to synaptic failure (De Felice et al., 2007; Shankar et al., 2007; Tu et al., 2014; Fig. 3A). Excess Ca^{2+} can activate calcineurin (CaN), which can induce actin depolymerization through different pathways, including activation of cofilin (Kang et al., 2011; Zhang et al., 2012). The calcium excitotoxicity and spine loss is also supported by recent work reported by Ohnishi et al. (2015). They have demonstrated that the amylospheroids (ASPD), the spherical Aβ oligomers (size 10–15 nm) derived from AD patient, cause selective degeneration of mature neurons through targeting neuron specific Na+/K+-ATPase α3 subunit (NAKα3). According to them, ASPD can bind to NAKα3, and impaired NAKα3-specific activity, which can open N-type voltage-gated calcium channels, and caused mitochondrial calcium overload, tau abnormalities, and neurodegeneration (Ohnishi et al., 2015).

Other groups believe that the shrinkage or loss of dendritic spines may occur through the cofilin-mediated depolymerization of actin filaments (Kang et al., 2011; Zhang et al., 2012). Cofilin is a ubiquitous actin-binding factor which inhibits the reorganization of actin filaments (Kang et al., 2011). However, after binding of Aβ oligomers/ADDLS to glutamate receptor, Rho-GTPases, such as RhoA, Rac and Cdc42, are phosphorylated and become active. These activated GTP-ases then act on Rho kinase, such as ROCKII. When ROCK-II becomes activated, it can phosphorylate LIM kinases-1 (LIMK1), which directly activates cofilin, an important mediator for actin depolymerization. Therefore, actin depolymerization loses its dynamics and leads to spine collapse (Fig. 7) (Newey et al., 2005; Wennerberg et al., 2003; Zhou et al., 2004). The third hypothesis is that Aβ may work through PI3K/Akt/mTOR pathway to control actin dynamics (Kumar et al., 2005). According to this concept, PI3K/Akt co-ordinates with the mammalian target of rapamycin (mTOR), a serine threonine kinase (Bekinschtein et al., 2007; Kumar et al., 2005). It has been established that, together, mTOR and Rho-GTP-ases (RhoA & Rac1) play pivotal role in actin reorganization (Liu et al., 2010). When Aβ binds to glutamate receptors, it can inhibit PI3K, which subsequently inhibits Akt/mTOR pathway leading to inactivation of p21 protein activated kinase (PAK). Direct attenuation of PAK activity activates LIM-kinases, which can activate cofilin, severely affecting actin dynamics which leads to dendritic spines collapse (Fig. 7). Pei et al. (2003) suggests that PI3K/Akt/mTOR pathways are impaired or down-regulated in AD. These observations were supported by studies which show that activation of the PI3K/Akt pathway could protect against Aβ induced neurotoxicity in PC12 cells (Martin et al., 2001), in cultured cortical and hippocampal neurons (Abbott et al., 2008), in N2a cell line (Lafay-Chebassier et al., 2005) and also in mouse models of AD (Stein and Johnson, 2002).

11.2. Parkinson's disease

Parkinson's disease (PD) is characterized by gradual and selective degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), with a subsequent decline in dopamine (DA) in the nigro-striatal pathway (Alexander, 2004; Dauer and Przedborski, 2003). Most PD cases are sporadic, but in rare cases, the disease may be inherited. The common symptomatic features of PD are bradykinesia, tremor, rigidity, abnormalities in gait and posture. The hallmark pathology of PD is accumulation of α-synuclein, the main component of Lewy bodies in midbrain dopaminergic neurons (Dauer and Przedborski, 2003). Striatal spine loss is a cardinal pathological feature of PD. About 95% of all striatal neurons that are highly affected by PD are represented by medium spiny neurons (Chang and Kitai, 1982; Kemp and Powell, 1971). These neurons loose almost 30–40% of dendritic spines as observed in animal

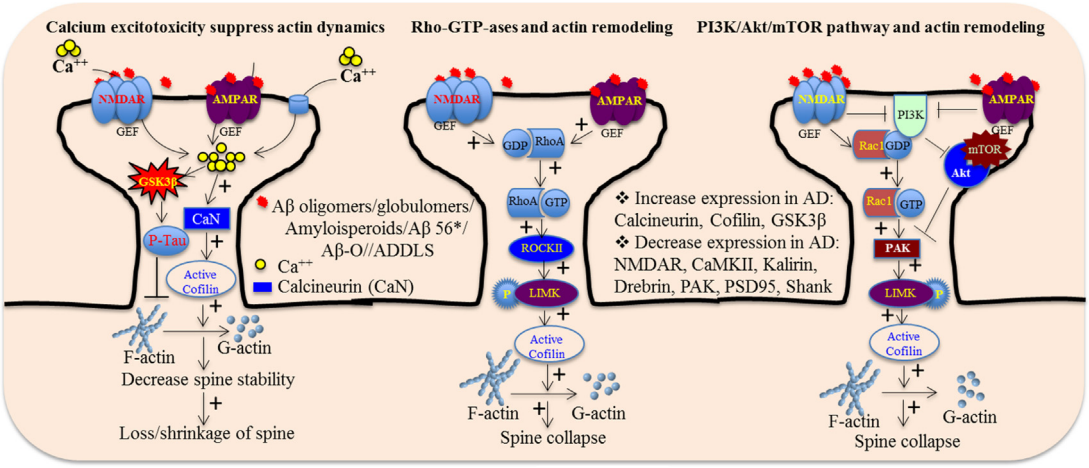


Fig. 7. Schematic diagram showing the pathways involved in loss/shrinkage of dendritic spines in AD. (A) Aβ-induced calcium excitotoxicity involved in spine loss; (B) Aβ-induced Rho-GTP-ase activity in spine remodeling; (C) Aβ-induced involvement of PI3K/Akt/mTOR pathway in spine remodeling. In all these signaling pathways are involved in activation of cofilin, which disrupt actin cytoskeleton, thus dendritic spines become collapsed.

models of PD (Villalba et al., 2009). Research evidence suggested that unilateral administration of 6-hydroxydopamine (6-OHDA) cause neurodegeneration of the nigrostriatal dopaminergic system leading to a 20% loss of dendritic spine in the caudate-putamen in rats. Similarly, monkeys given with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) show significant loss of dendritic spine along with inhibition of spinogenesis in medium spiny neurons of the striatum (Stephenson et al., 2005; Smith and Villalba, 2008; Villalba et al., 2009; Zaja-Milatovic et al., 2005). The degree of dopaminergic neurodegeneration highly correlate with spine loss in both monkey and human subjects (Smith and Villalba, 2008; Villalba et al., 2009; Zaja-Milatovic et al., 2005). Recent evidence suggests that MPTP-lesioned monkeys lose approximately 50% of their dendritic spines in medium spiny neurons of the striatum, along with significant depletion of striatal dopamine, whereas only 25% losses of dendritic spine are observed in nucleus accumbens (Villalba et al., 2009). Besides spine loss, different dendritic varicosities are also very common in PD. Glausier and Lewis (2013) found four major varicosities (bulging of neuronal branching) in an animal model of PD and designated them as types A to D. Type A varicosities are large (40 pm or more in length), fusiform, multiple, irregularly contoured, with frequent connection of adjacent varicosities without any spines. Type B varicosities are medium-sized (25–35 pm in length), fusiform, smoothly contoured, sometimes bore, and elongated spines (Glausier and Lewis, 2013). High loads of Lewy bodies cause type C varicosities, characterized by round, small (20-25 pm), smoothly configured, and of variable sizes, which are devoid of spines. Type D varicosities are the smallest among the major types (10–25 pm in length), and are indistinguishable from each other (Alexander, 2004; Glausier and Lewis, 2013).

Experimental findings suggest that some common molecular signaling pathways are involved in spine loss in PD. The most common pathway involved in spine loss is the activation of cortical glutamatergic system, which causes glutamate excitotoxicity in medium spiny neurons (MSNs) of striatum (Calabresi et al., 1996; Mallet et al., 2006; Wichmann and Delong, 2007). It is postulated that excess glutamate can open L-type of calcium channels in MSNs, which can activate calcium dependent protein, calceneurin (CaN; Fig. 8). Activated CaN can cause spine loss by different means: (i) it can activate myocyte enhancer factor-2 (MEF2), which can decrease postsynaptic function through activation of nerve growth factor IB (NGFIB) or Nurr7 and Arc gene, which are ultimately linked to spine shrinkage or collapse; (ii) it can also activate some kinases which stimulate Leucine-rich repeat kinase 2 (LrrK2, also called dardarin)

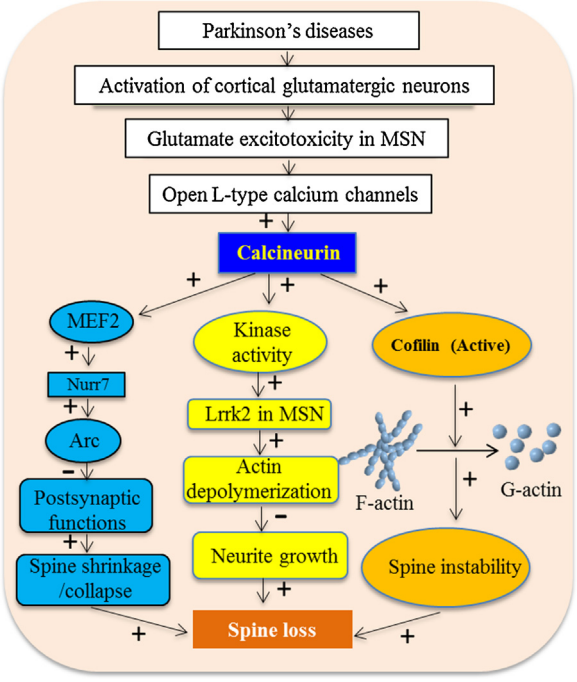


Fig. 8. Schematic diagram showing the signaling pathway of spine abnormalities in Parkinson's diseases. Excess activation of cortical glutamatergic neurons can cause activation of Calcineurin, which can either activate MEF2, or the cofilin pathway, or increases kinase activities, thus ultimately leads to spine loss.

gene in MSNs, which directly impairs spine actin polymerization, (iii) it can dephosphorylate cofilin, which ultimately leads to stimulation of actin depolymerization and, thus, increase spine instability and loss of dendritic spines (Kang et al., 2011; Fig. 8).

11.3. *Huntington's disease*

Huntington's disease (HD), a poly-glutamine disease, is an autosomal dominant, progressive neurodegenerative disorder, causing involuntary movements of the face and body, as well as psychological problems, and dementia (Bertram and Tanzi, 2005). It is characterized by abnormal accumulation of huntingtin protein (HTT) in the intracellular spaces, due to the repetition of glutamine (also called poly-Q; Evans-Galea et al., 2013). Misfolded HTT

aggregation causes selective neuronal loss, primarily in the cortex and MSNs of the striatum, which can lead to the cognitive, psychiatric and motor impairments common to this disorder (Miller and Bezprozvanny, 2010). However, the repetition of glutamine residue in HTT is critical for its toxicity (CAG: gene code for glutamine). It means an increase the number of CAG repeats will have greater HTT deposition, which could lead to an increase in neurotoxicity (Arrasate et al., 2004). One characteristic neuropathological feature of HD is progressive loss of dendritic spines in cortical, and the striatal neurons (Ferrante et al., 1991; Guidetti et al., 2001). This neuropathological feature has been observed both in human HD brain at post mortem, as well as various transgenic and knock-in animal models of HD. At post-mortem the brains of patients with mild cases of HD show an increase in dendritic branching, including spine density and size (Ferrante et al., 1991; Graveland et al., 1985), whereas at advanced stages degenerative changes, such as truncated dendritic arbors, focal swellings on dendrites and decrease in spine density are observed (Ferrante et al., 1991; Graveland et al., 1985). Similarly, the density of dendritic spines in layer V neurons of cortex in HD patients is significantly decreased (Sotrel et al., 1993). Further, R6/1 and R6/2 transgenic mice expressing a larger CAG trinucleotide expansion are closely related to human HD, which progressively develop cognitive, psychiatric and motor symptoms (Mangiarini et al., 1996; Miller and Bezprozvanny, 2010; Nithianantharajah et al., 2008; Spires et al., 2004a). However, R6/1 mice exhibit a decrease in number and length of spines within the dorsal striatal spiny neurons of the anterior cingulate cortex, when they are eight months old (Spires et al., 2004b). In addition, a group of mice expressing full-length htt cDNA showed a significant reduction of spine density in striatal and cortical neurons (Guidetti et al., 2001). Similarly, Slow et al. (2003) and later Xie et al. (2010) developed the YAC128 mouse model of HD, which also has decreased striatal spine density and other abnormalities at 16 weeks of age, along with significant cognitive and motor impairments.

Aggregation of htt can disrupt the interactions between huntingtin-associated protein 1 (HAP1) and the kinesin family motor protein 5 (KIF5), which are essential for transport of GABA receptors (Twelvetrees et al., 2010). This leads to imbalance between excitatory and inhibitory neurotransmitter systems in striatum and impairs neuronal connectivity between cortical and subcortical areas with striatum (Fig. 9). Similarly, mutant htt can decrease serum and forebrain levels of brain derived neurotropic factor (BDNF) and its receptor TrkB. BDNF promotes activity-dependent actin polymerization in dendritic spines (Yoshii and Constantine-Paton, 2010). Impairment of actin polymerization, due to deficiency of neuronal trophic factors, affects dendritic spine formation, which leads to spine abnormalities. Further, accumulation of htt can also activate cortical glutamatergic neurons to secrete more glutamate, which ultimately leads to glutamate excitotoxicity as described above, which damages medium spiny neurons in striatum, and thereby causing decreases in the spine numbers (Fernandes and Raymond, 2009; Fig. 9).

11.4. Prion disease

Prion diseases are rare, fatal, transmissible, progressive neurodegenerative diseases, which can affect both humans and animals (Prusiner, 1998). The “prions” are transmitted to tissue and induce abnormal folding of specific proteins and transform them into pathogenic agents, called prion proteins (PrP; Prusiner, 1998). Prions can aggregate extracellularly within the CNS to form plaques, known as prion plaques, which disrupt neuronal morphology. As a consequence, several “holes” are observed in the tissue, with a resultant spongy architecture, due to the vacuole formation in the neurons (Brundin et al., 2010). The central feature of prion diseases are the aggregation of pathologic prion proteins, such as PrP^{c}, an abnormal isoform of the cellular prion protein. Interestingly, these α-helix rich PrP^{C} can convert to a β-structure-rich insoluble conformer (PrP^{Sc}) in brain tissues, which is thought to be infectious (Brundin et al., 2010; Prusiner, 1998). Due to aggregation of misfolded PrP^{Sc} deposition, spongiform degeneration with extensive neuronal, synaptic, and dendritic loss, as well as astrogliosis in cerebral cortex have been observed in this disease (Prusiner, 1998). Like other neurodegenerative diseases, major dendritic abnormalities, including decreased spine density, appearance of neuritic swellings, called varicosities, have been found in animal models of prion diseases (Belichenko et al., 2000; Siskova et al., 2009) as well as in the brains of humans who had a prion disease, called Creutzfeldt-Jakob disease (Landis et al., 1981). Although, molecular mechanism of varicosities and spine loss in prion disease are not well documented, it is suspected that perhaps detergent-resistant, cholesterol-sphingomyelin-enriched membrane domains (DRMs) have a pivotal role in conversation of PrPc to PrP^{Sc}. This hypothesis suggests that the interaction of DRMs with prion proteins is considered to be the principal cause of the emergence of varicosities, and subsequent spine loss in prion disease due to the accumulation of PrP^{Sc} (Fuhrmann et al., 2007; Galvan et al., 2005; Russelakis-Carneiro et al., 2004; Sandberg and Low, 2005). Similarly, Laurén et al. reported that cellular prion protein mediates impairment of synaptic plasticity, and spine loss by Aβ Oligomers. The soluble Aβ-oligomers can bind with nanomolar affinity to PrP^{C}, but the interaction does not require the infectious PrP^{Sc} conformation, whereas PrP knockout or treatment with anti-PrP antibodies can rescue oligomeric Aβ-induced synaptic dysfunction and spatial memory deficits in mice. These findings suggest that prion protein is a mediator of Aβ-oligomers induced synaptic dysfunction and spine loss (Lauren et al., 2009).

11.5. Schizophrenia

Schizophrenia is a complex neuropsychiatric disorder which severely affects higher brain functions. Most common symptoms are hallucinations, delusions, and thought disorder, altered emotional expression, poverty of speech, inability to initiate and persist in goal-directed activities (Yoon et al., 2013). It also includes impairment of cognition, executive dysfunction, perception of reality and motivation, attention and problems with working memory (Elvevag and Goldberg, 2000; Lesh et al., 2011). The incidence of schizophrenia is of 0.5–1% of the population (Awad and Voruganti, 2008; Wu et al., 2005) and is more common in males (Aleman et al., 2003; Grossman et al., 2008; McGrath et al., 2004). It mainly appears in late adolescence or in early adulthood (Lewis and Lieberman, 2000). The main indication of schizophrenia is interference of connectivity and deficit correlation among different brain regions. The most conspicuous neuropathological feature of the schizophrenic brain is the loss of grey matter, including shrinkage or loss of neurons in dorsolateral prefrontal cortex, superior temporal gyrus, subicular complex, and CA3 area of hippocampus (Glausier and Lewis, 2013). Since schizophrenia is highly associated with impairment of working memory, attention, sensory-motor processing, and sociability, it is not surprising that it has strong links with spine pathology (Brennaman et al., 2011; Hains et al., 2009; Liston et al., 2006). The pyramidal neurons in frontal and temporal cortex and MSNs of the striatum in the schizophrenic brain show decreased numbers of dendritic spines (Glausier and Lewis, 2013). Further, the postmortem brains of patients with schizophrenia show smaller pyramidal cell bodies and decreased neuropil, as well as smaller cortical gray matter volumes in the dorsolateral prefrontal cortex and auditory cortices. It is assumed that neurobehavioral impairments of schizophrenia is due to alterations in neuronal circuitry in different brain areas caused by deficits in dendritic spines (Glausier and Lewis, 2013).

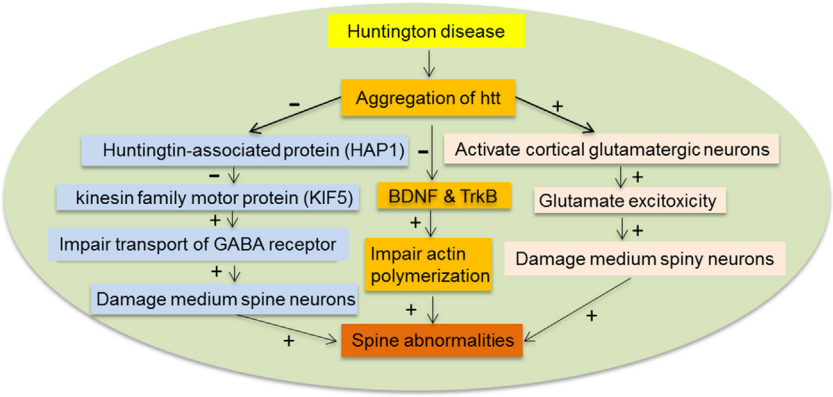


Fig. 9. Possible molecular signaling pathway (s) involved in spine loss in medium spiny neurons in the striatum of Huntington's disease.

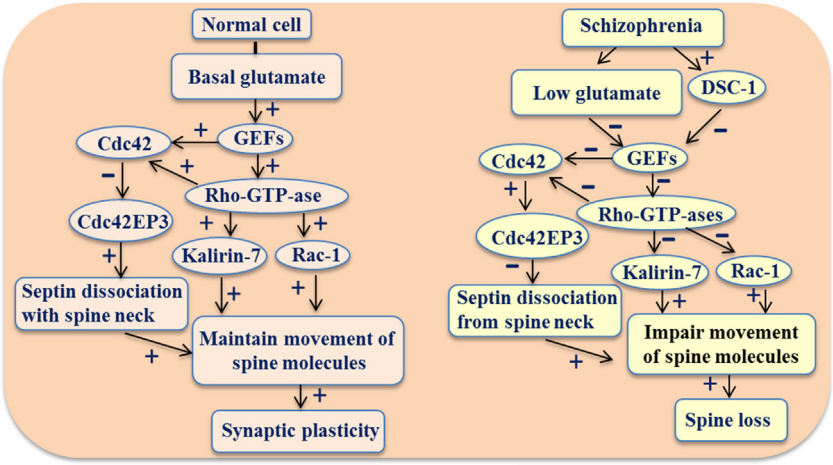


Fig. 10. Schematic diagram of proposed roles of Cdc42-Cdc42EP3-septin interactions in dendritic spine dysfunction in schizophrenia.

Abnormal spine morphology including alteration of their shapes, size and structure has been reported in the striatum and hippocampus of schizophrenic patients. Several research groups have documented that the lower density of dendritic spines exist in multiple neocortical areas, including pyramidal neurons located in layer 3 in schizophrenia (Kritzer and Goldman-Rakic, 1995; Melchitzky et al., 1999). According to Rosoklija et al. (2000) almost 70% apical spine losses have been observed in cortical neurons in schizophrenic patients, relative to the healthy comparison group (Rosoklija et al., 2000). Some studies have revealed significantly higher levels of total synaptic density in the putamen, while other studies show an increase in asymmetric axospinous in the caudate of schizophrenic patients. Several molecular markers, which are essential for spine formation, maturation and maintenance, are significantly changed in schizophrenic patients, such as Rho GTP-ases, an important signaling protein for intracellular signaling and actin remodeling inside dendritic spine (Calabrese et al., 2006; Negishi and Katoh, 2005). In normal cell, guanine nucleotide exchange factors (GEFs) can regulate Rho GTP-ases activity, which can stimulate Cdc42 (cell division cycle 42), Rac1 (Ras-related C3 botulinum toxin substrate 1) and Kalirin-7. These are very essential for spine plasticity (Bongmba et al., 2011; Cerri et al., 2011; Irie and Yamaguchi, 2002; Kreis et al., 2007; Nakayama et al., 2000; Scott et al., 2003). Normally, basal glutamate level can activate GEFs, which activates Rho GTP-ases. Activated Rho GTP-ases further activate Cdc42 which strongly inhibit Cdc42EP3 activity. Inactive Cdc42EP3 helps to dissociate the complex of septin filaments (a vital cytoskeleton anchoring protein observed in spine necks), in spine necks, and allows the movement of dendritic signaling molecules, which are essential for maintenance of synaptic potentiation (Ide and Lewis, 2010). However, in case of schizophrenia, improper activation of GEFs can cuase down-regulation of Cdc42 level which can cause increased activation of Cdc42 effector protein 3 (Cdc42EP3). Activation of Cdc42EP3 dissociates septin filaments from spine neck region, which in turn impairs the movements of the second messengers, spine signaling molecules, leading to spine collapse or shrinkage (Arion et al., 2007; Hill et al., 2006; Ide and Lewis, 2010; Fig. 10).

11.6. Autism spectrum disorders

Autism spectrum disorder (ASD) is loosely used as a penumbra for several developmental disorders, including autism, Asperger's syndrome, characterized by deficits in social interaction and communication, absence or delay in language, and stereotypy (Miles et al., 1993). Most ASD symptoms arise in early developmental periods, typically first 2–4 years of early childhood life, especially the time of synapse formation and maturation (Courchesne et al., 2007). The affected individuals will have problems in sensory responses, sleep disorders, intellectual disability, seizures, and gastrointestinal problems. Although the exact cause of ASD is unclear, research suggests that both genes and environment play important roles. Scientists report that almost 80% of ASDs are genetic or inherited. Increased dendritic spines density, with reduced developmental spine pruning in layer V pyramidal neurons, has been observed in temporal lobe of postmortem ASD patients (Tang et al., 2014). In general, the average dendritic spine densities are higher in ASD in cortical pyramidal neurons, than in those of age-matched controls, both for animal and postmortem human

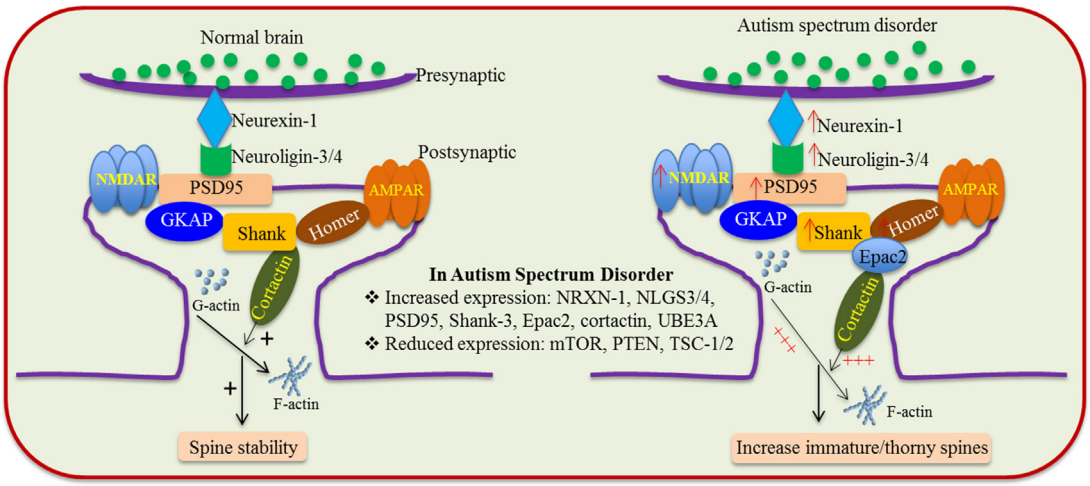


Fig. 11. Role of synaptic adhesion molecules and spine scaffolding proteins in ASD. In case of ASD, the neurexins (NRXN) and neuroligins (NLGN) levels are increased, which promote further interaction with postsynaptic protein and augment signaling process in dendritic spine, leading to increase spine numbers.

ASD brain (Hutsler and Zhang, 2010). Several signaling molecules are involved in the increase of spine densities in ASD. Some are upregulated and alter spine signaling pathway significantly. Major proteins affected in ASD include synaptic cell adhesion molecules, such a neurexins (NRXN) and neuroligins (NLGN; Chen et al., 2014). NRXN is a presynaptic protein which strongly binds with NLGN, located in post synaptic membrane. NLGNs are thought to form a trans-synaptic complex with major dendritic spine scaffolding proteins, the PSD95 (Chen et al., 2014). Thus, by interacting with PSD95, the NRXNs and NLGNs are indirectly connected to other spine signaling molecules, such as GKAP, Shank, Homer, and cortactin.

Therefore, interaction between NRXN and NLGN can promote signal transmission in normal spine (Fig. 11). Mutation or lack of NRXNs or NLGNs can affect signaling pathways involved in synaptic communication, as well as spine maturation as observed in ASD (Sudhof, 2008; van Spronsen and Hoogenraad, 2010), whereas, overexpression can also have severe effect. For example, in case of ASD, excessive activation or mutation of these genes can cause over-expression of those synaptic adhesion molecules, which can multiply the spine signaling pathways several times leading to the over-production of immature or thin, filopodia-like spines (van Spronsen and Hoogenraad, 2010). It can also cause an increase in thorny and immature spines and impair normal signal transmission. In addition to these two genes, abnormal expression of several other genes, such as Shank-3, Homer or cortactin has been observed in patients with ASDs (Sudhof, 2008). All these effects, ultimately, cause over excitation of the postsynaptic terminals, which ultimately leads to synaptic dysfunction, which is a common phenomenon observed in ASDs.

11.7. Fragile X-syndrome (FXS)

FXS is the most common inherited neurological disorder that affects both males and females. It is mainly characterized by mental retardation, including reduced intellectual ability, impaired visuo-spatial processing, and developmental delay (Walter et al., 2009). The FXS patients may also suffer from hyperactivity, hypersensitivity to sensory stimuli, and anxiety. FXS has a strong link with autism, given that almost 30% of FXS patients are also diagnosed with autism and 2–5% autistic children have FXS (Hagerman et al., 2009). The protein involved in this disease is called fragile X mental retardation protein (FMRP; Wang, 2015). This protein can control several essential neurophysiological functions, including local synaptic transcription, translation and transport of proteins to their proper locations. FMRP has an important role in activation of metabotropic glutamate receptors (mGluRs). However, the normal function of this protein become impaired when a trinucleotide (CGG) repeat expansion (>200 repeats) binds to the FMR1 gene. Binding of CGG repeats inactivates transcription of this gene, and in absence or low amount of FMRP, ultimately results in development of FXS (Willemsen et al., 2011). Indeed, FMRP can interact and co-localize with several mRNAs of local synaptic proteins, including PSD95, elongation factor 1a, SAPAP3/4, AMPA receptor subunit GluR1/2, NMDAR, CaMKIIα, and other cytoskeletal proteins (Bassell and Warren, 2008). Therefore, inhibition of FMRP in FXS severely affects synaptic transmission by alteration of synaptic structures (Bassell and Warren, 2008). Impairment of essential synaptic functions of FMRP, including synaptic plasticity, has been well documented in Fmr1 KO mice. Since FRMP can regulate synthesis of local synaptic protein, it has pivotal role in controlling dendritic spine proteins and their dynamics (Sutton and Schuman, 2005).

There is ample of data suggesting that FXS can cause dendritic anomalies, as evidenced by patients and animal models of FXS. Actually, the abundance of long, thin, and immature filopodia-like spines have been found in cortical neurons of FXS, suggesting absence of lower levels of synaptic proteins which ultimately leads to aberrant spine development (Sutton and Schuman, 2005; Weiler et al., 2004). Although the causative factor for abnormal spines in FXS is still not clear, dysregulation of PSD95 mRNA and AMPA receptors trafficking may play important roles in this regard. Ionotropic glutamate receptors (NMDA, AMPA) play important roles in synaptic transmission, whereas AMPA receptor internalization take place in FXS, due to the up-regulation of mGluR5, as observed in FMRP knockout mice (Nakamoto et al., 2007). Down-regulation of AMPA receptors can cause synaptic impairment and develop LTD-like conditions, leading to immature filopodia-like spines in FXS (Nakamoto et al., 2007). The potential link between the FXS and LTD is still unclear. Therefore, FMRP is important for maintaining balance of the mGluR5 and AMPA trafficking, but in absence of FMRP, mGluR expression is increased, which could cause synaptic damage, and spine abnormalities leading to the behavioral deficits observed in FXS (Cook et al., 2014; Fig. 12).

11.8. Rett's syndrome

Rett syndrome is a rare neurodevelopmental disorder, characterized by a deterioration of cognitive and motor development. It

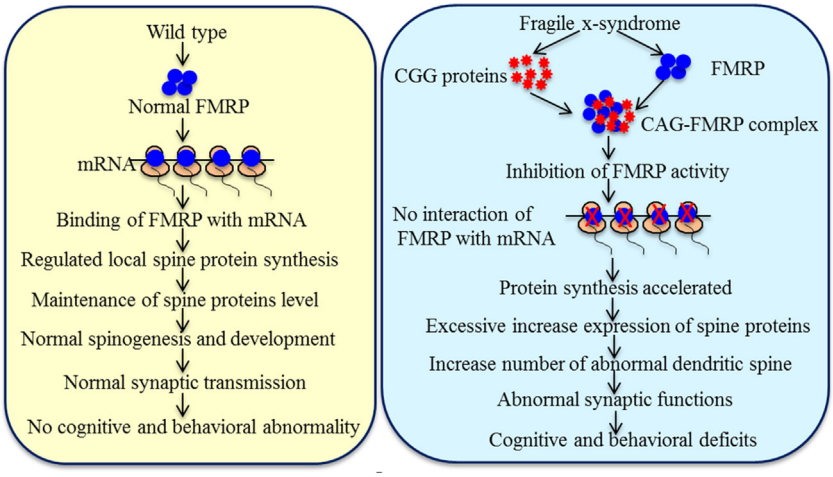


Fig. 12. Role of fragile X mental retardation protein (FMRP) in controlling functions of dendritic spines and development of mental retardation in FXS. Normally, FMRP can regulate translational and maintenance of spine protein synthesis. In the absence or impairment of FMRP function by CGG repeat expansion in FXS, the translations of many synaptic proteins are accelerated several times over. This can cause abnormal and overly active spinogenesis, leads to synaptic dysfunction, which can contributes to cognitive and behavioral impairment in FXS.

mainly affects girls during their early childhood, due to improper brain growth (Lotan et al., 2010). Girls affected by this disease start their early life with normal growth and development. In some cases subtle or negligible abnormalities may develop in early infancy, but a progressive slowdown of their brain and head development occurs with the advancement of childhood (Ramocki et al., 2010). The common symptoms include distinctive wringing movements, hypotonia, loss of purposeful use of the hands, difficulties in feeding, speaking, crawling, walking, seizures, and gradual deterioration of intellectual abilities (Collins et al., 2004). Many other symptoms may arise, including walking on the toes, impairment of gait and posture, sleep loss, teeth grinding and difficulty in chewing, slowed growth, and breathing difficulties, apnea and air swallowing (Samaco et al., 2012). The severity of symptoms may vary with age and from child to child. Rett syndrome is caused by sporadic X-linked mutation in the methyl CpG binding protein 2, (MECP2) gene, which is responsible for production of methyl cytosine binding protein 2, an essential protein for normal brain development (Gonzales and LaSalle, 2010).

The MECP2 protein is involved in regulation of synaptic development and plasticity, including the structure of dendritic spines (Chapleau et al., 2009; Jiang et al., 2013). However, abnormal dendritic spines, including decreased spine density, have been observed in the postmortem brain tissues from patients with Rett syndrome and also in animal models incorporating mutations of MECP2 (Fig. 13) (Belichenko and Dahlstrom, 1994; Chapleau et al., 2009). The mental retardation observed in this disease might be due to spine pathology, which might hamper normal neurotransmission.

11.9. Epilepsy

Epilepsy is one of the most common and chronic neurological disorders, affecting about 1% of population worldwide (Wong and Guo, 2013). The hallmark feature of epilepsy is recurrent seizures, which can cause neuronal hyper-excitability, and is linked to a high risk of morbidity and mortality (Dodrill, 2002; Elger et al., 2004). Long-term epileptic seizures result in cognitive and neuropsychiatric disorders, similar to autism spectrum disorders (Dodrill, 2002; Elger et al., 2004). Epilepsy is considered to be a multifactorial disease, involving several biological, environmental, and psychosocial factors (Todorova et al., 2006). Several factors including brain injury (e.g. tumors, cortical malformations, and stroke), exposure to environmental toxins (pesticides, herbicides, insecticides, xenobiotic etc.), and infections of central nervous system, neurodegenerative diseases and a variety of metabolic and genetic disorders are all considered to be possible causes for development of epileptic seizures (Todorova et al., 2006). However, chronic epileptic seizures can cause further brain injury and contribute to several neurological disorders, including AD, PD, HD and other brain diseases. Accumulated research evidence suggests that prolonged seizures (lasting 30 min) can cause severe brain injury, involving significant neuronal death (Meldrum et al., 1973; Tsuchida et al., 2007; Turski et al., 1983). It is assumed that there is an imbalance between excitatory and inhibitory transmission during seizures. Spine abnormalities, including dendritic swelling, varicosities, large complex heads and electron-dense spines on degenerating dendrites, have been found in hippocampal neurons of temporal-lobe epileptic patients (Fiala et al., 2002).

However, epileptic seizures produce increased electrical signals, which cause neuronal hyper-excitability that severely interferes with synaptic transmission. The impairment of synaptic transmission has tremendous deleterious effects on dendritic spine structures and dynamics (Wong and Guo, 2013). Hyper-excitability deteriorates inhibitory brain circuits to increased excitability, which can destroy normal function of dendritic spines, leading to synaptic collapse. The spine pathology has been documented in animal models of epilepsy, as well as postmortem tissue from the brains of human with epilepsy, but degree of spine abnormalities solely depends on the type and etiology of the epilepsy (Wong and Guo, 2013). The main pathway involved in dendritic spine loss is through cofilin pathway, which has direct impact on actin polymerization and spine dynamics (Kang et al., 2011). Epileptic seizures can cause excess glutamate secretion, which can activate cofilin activation through PAK/LIMK pathway or through the activation of the calcineurin pathway, which ultimately disrupts actin polymerization (Fig. 14), disrupting of spine cytoskeleton which leads to spine collapse (Wong and Guo, 2013).

11.10. Traumatic brain injury

Brain injury may occur through several mechanisms including trauma. Recently, occurrence of traumatic brain injury (TBI) episodes has increased tremendously, and is now the leading cause of death and disability in industrialized countries. Recent research indicates that more than 1.7 million people are affected

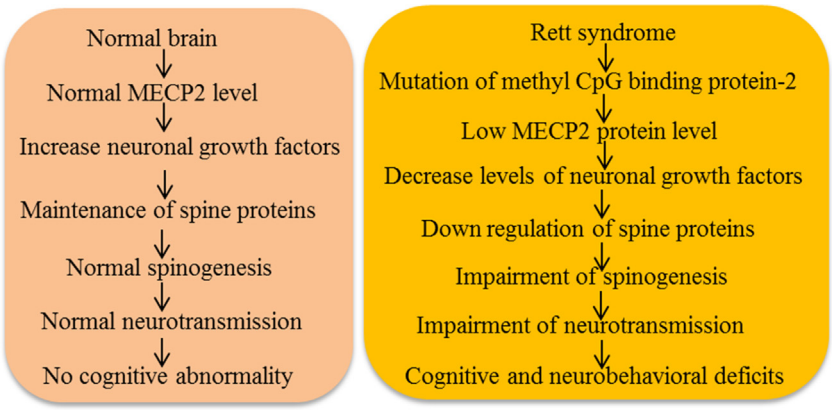


Fig. 13. Schematic diagram showing the possible mechanism of dendritic spines loss and cognitive deficit in Rett syndrome. Mutation of MECP2 gene causes it's under expression leading to down regulation of several dendritic spines signaling proteins and impair spine development and maturation.

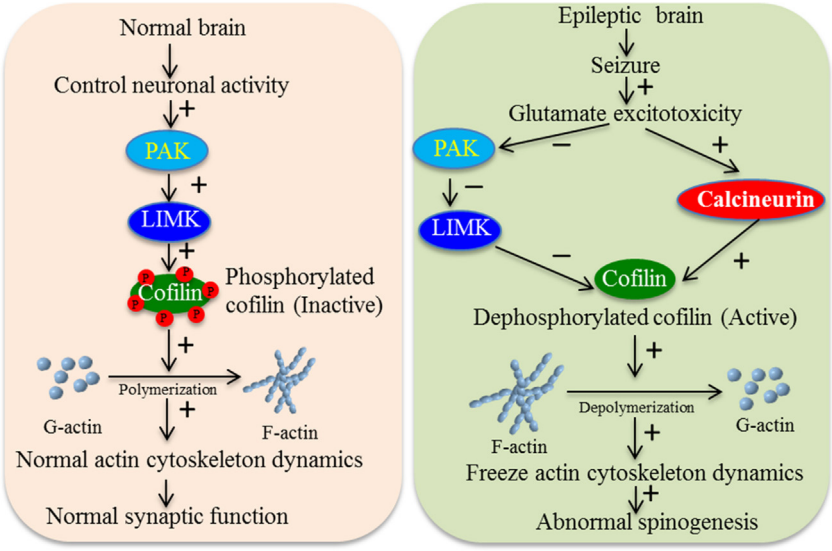


Fig. 14. Possible molecular mechanisms and signaling pathways involved in spine loss in epilepsy. Epileptic seizure may lead to activation of calcium-dependent phosphatase, calcineurin, which, in turn, causes cofilin dephosphorylation. Cofilin activity can also be regulated by phosphorylation via the PAK-LIM-kinase pathway. Thus, higher calcineurin and/or lower PAK/LIM kinase activities in epilepsy leads to less phosphorylation of cofilin, which would potentially increase cofilin binding to F-actin, and this could cause depolymerization of F-actin. Overall, this could lead to the breakdown of the actin cytoskeleton, and disrupt dendritic spine dynamics and cause spine shrinkage/loss.

by TBIs each year in the U.S. and that about 5.3 million Americans are living with long-term or life-long disabilities due to a TBI (Maas et al., 2008; Pearson et al., 2012). Several reasons contribute to the increase of TBI in civilian populations, including car accidents, violence (gun and knife wounds), and falls (particularly in the elderly population) (Maas et al., 2008; Pearson et al., 2012). Among athletes or sportsman, TBI is very common, but most significant is the incidences of TBI amongst military populations. Recently, blast-induced TBI has become one of the leading causes of acute brain injury and disability (Maas et al., 2008; Xiong et al., 2013). In general, TBI can cause subdural hemorrhage, diffuse axonal injury, which has long-term adverse effects. Due to TBI, higher brain functions, including cognition, learning and memory, are severely affected, along with significant increase in other disabilities. Many civilian and military personnel, alike suffer from short-term memory and attention deficits from mild TBI, accounting for 75–85% of all TBIs (Maas et al., 2008). Repetitive, mild TBI can cause much more significant long-term emotional and cognitive disabilities (Levin and Robertson, 2013). Moderate to severe TBIs can result in more long-term, persistent cognitive deficits (Dikmen et al., 2009). However, a recent MRI study showed that TBI-induced long-term cognitive impairment is due to damage of medial temporal regions, dorsolateral prefrontal cortex, as well as sub-cortical white matter tracts and hippocampus (Bigler et al., 1997; McAllister, 2011). However, TBI may be acute or chronic insults, depending on duration and degree of severity. Scientists report that TBI may contribute to chronic neurodegeneration, leading to development of several neurodegenerative diseases including AD, PD, and ALS (Walker and Tesco, 2013). Chronic TBI results in neuronal loss, axonal injury, dendritic spine loss, and synaptic dysfunction, often leading to impairment of higher executive functions. Secondary injury often results in activation of a cellular cascade mechanism, including excitotoxicity, which might take hours or days following the initial insult. However, loss/shrinkage/collapsing of dendritic spines, including increase in varicosities, electron-dense spines, along with dilated or hypertrophic or fragmented spine apparatus and SER, have been documented in principal spiny neurons in the TBI brain. This might be due to anterograde axonal degeneration or retrograde degeneration of the neurons (Al-Abdulla et al., 1998; Buffo et al., 1998; Tseng and Hu, 1996).

Recently, several research groups proposed a mechanism of spine collapse in spiny neurons after TBI. The prominent pathways that have been identified for spine loss/collapse in TBI are cofilin pathway and spine-associated Rap guanosine triphosphatase

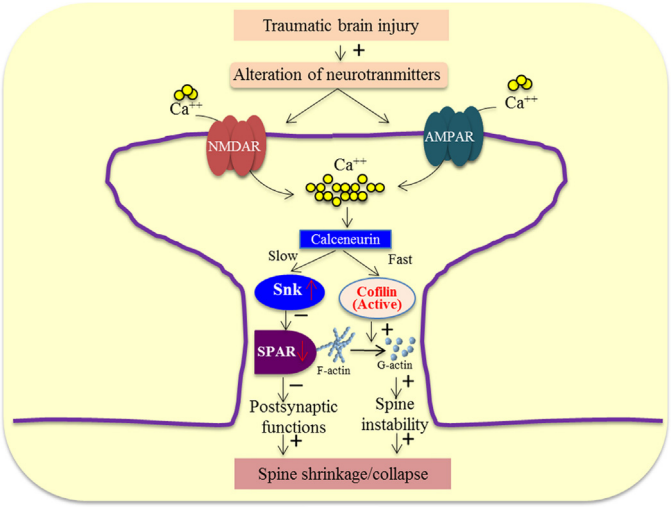


Fig. 15. Possible signaling mechanisms of dendritic spine collapse after brain injury. The calcium-sensitive phosphatase called calcineurin (CaN) becomes activated after brain injury. Activated CaN may lead to a rapid de-phosphorylation/activation of the actin-depolymerizing of the protein, cofilin. Excessive cofilin activity could disrupt the spine's actin-rich cytoskeleton, resulting in spine shrinkage or de-stabilization. Additionally, increase CaN activity can lead to a transcriptional up-regulation of serum-induced kinase (Snk), which results in targeted proteolysis of a spine-stabilizing protein, spine-associated Rap guanosine triphosphatase activating protein (SPAR). SPAR loss is associated with degeneration of post-synaptic function and structure, including spine loss. Overall, cofilin activation and SPAR proteolysis leads to spine loss in traumatic brain injury.

activating protein (SPAR) pathway. Both pathways are involved in activation of calcium regulated phosphatase calcineurin (CaN; Campbell et al., 2012). In general, TBI-induced calcium influx into spine, which causes calcium excitotoxcity, can activate CaN. Activated CaN can dephosphorylate cofilin, which results in activation of actin depolymerization, leading to spine collapse (Fig. 15). On the other side, activated CaN also activates transcriptional upregulation of serum-induced kinase (Snk). Activated Snk increases proteolysis of a spine-stabilizing protein, spine-associated Rap guanosine triphosphatase activating protein (SPAR; Pak and Sheng, 2003). SPAR loss is associated with a decrease or impairment of postsynaptic function, which ultimately leads to spine loss (Pak et al., 2001; Pak and Sheng, 2003).

11.11. Anxiety, stress and depression

Due to volatile and adverse socioeconomic conditions, our modern life is full of struggles, hassles, and competition, which can lead to increased anxiety, stress, and depression for many people. As all these issues, directly or indirectly, affect our mental health and levels of anxiety, stress and depression are now becoming a serious issue in our urbanized life. Recent reports by neuropsychological counsels have revealed that frequent exposure of stress can aggravate anxiety disorders-including symptoms such as excessive fear, typically in response to specific objects or situations, which may or may not actually be endanger to the individual (Shin and Liberzon, 2010). However, prolonged, stressful lifestyles can also promote fear, anxiety and depression in later stage of life, which can induce several forms of mental illness, including post-traumatic stress disorders (PTSD; Helzer et al., 1987; Wimalawansa, 2014). Although stressful lifestyles sometimes make individuals more adaptive and help them cope with these types of situations in their future life, chronic stressful situations often cause cognitive disturbances, poor concentration, and negative thoughts (Gualtieri and Morgan, 2008). Excessive anxiety is also associated with the development of depression and several other mental health problems (Hoffman

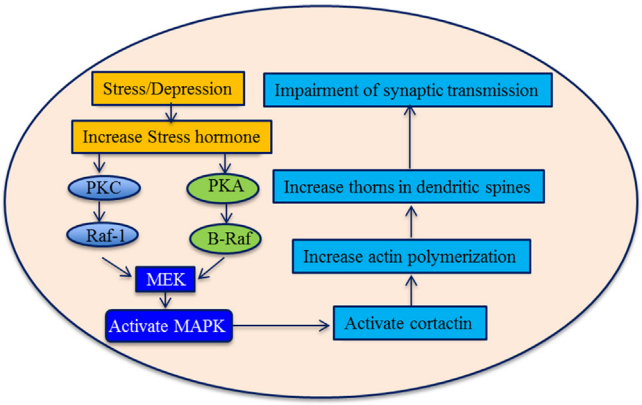


Fig. 16. Effects of stress and depression on dendritic spine pathology. Stress or depression can promote secretion of stress hormones, which can activate several kinases, phosphatases, and signaling molecules. These cascades activate cortactin and promote actin polymerization, which leads to increase thorny spines and impairs normal synaptic transmission.

and Mathew, 2008). Indeed, these situations have deleterious effects on our cognition and emotional behavior, as well as affect functions in our daily life. The brain regions involved in stress management include the amygdala, hippocampus, and prefrontal cortex. Several investigators opine that the hippocampal, prefrontal cortex, and amygdala neurons are highly sensitive and vulnerable to stressful environments (Christoffel et al., 2011; Radley and Morrison, 2005), which can cause synaptic remodeling, atrophy, and neuroplastic changes, as well as dendritic spine loss.

Researchers have found strong reciprocal relationships between dendritic spine structure and function and anxiety, stress and depression (Leuner and Shors, 2013). The effects of stress on dendritic spine dynamics depends on numerous factors, including types and duration of stressful stimuli (Adamec et al., 2012; McLaughlin et al., 2009; Romeo and McEwen, 2006; Weinstock, 2011). The relationship may also vary with the types of stress conditions, such as acute stress, which has severe effects on spine dynamics. Whereas chronic stress can lead to gradual progressive morphological alteration of neurons in the above-mentioned brain regions, including impairment of synaptic plasticity, neuronal loss, and neurobehavioral alterations, chronic stress activates stress hormones like glucorcorticoid and epinephrine, which can activate several kinases and phosphatases (Fig. 16). Activated signaling molecules ultimately phosphorylate cortactin, which becomes activated and promotes polymerization and branching of actin in dendritic spine. This can cause an increase of thorns in the spines, leading to spine dysfunction and impairment of synaptic transmission (Leuner and Shors, 2013).

11.12. Sleep disorders and dendritic spine abnormalities

Sleep is a fundamental neurophysiological mechanism in the vertebrate nervous system. It plays a pivotal role in memory consolidation, long-term neuronal synaptic plasticity, which is essential for memory consolidation (Gronli et al., 2013). Recent experimental research reveals that sleep plays an active role in the elimination of toxins from the brain and has important roles in correcting abnormal dendritic spines found in different neurodegenerative and neuropsychiatric diseases (Picchioni et al., 2014). In contrast, sleep disorders can promote several neuropsychiatric disorders, including autism spectrum disorders and attention deficit hyperactivity disorders (Dorris et al., 2008; Halbower et al., 2006; O'Brien and Gozal, 2004) and also several neurodegenerative disorders, like AD, PD, and HD, where spine anomalies are very prominent. Experiments conducted on animals, suggest that the expressions

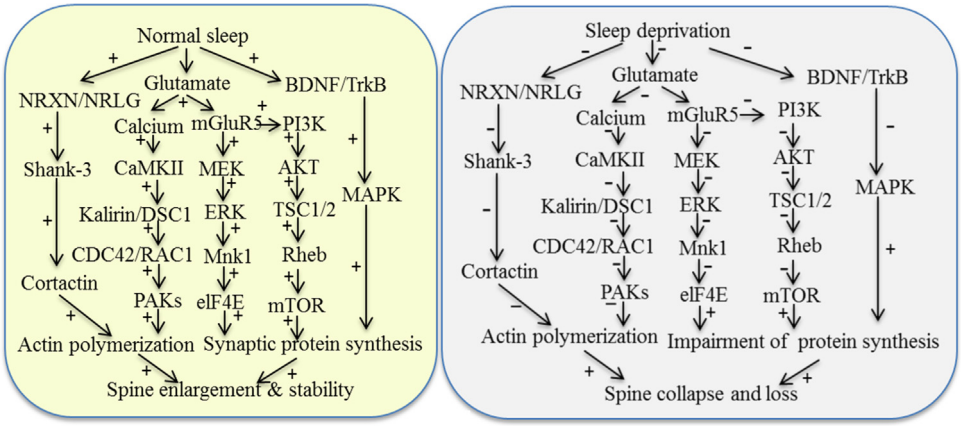


Fig. 17. Schematic diagram showing mechanistic details of spine loss due to sleep impairment. Sleep loss can cause decrease synaptic adhesion molecules and neurotropic factors, and decrease basal glutamate level, which can impair actin polymerization process and inhibit synaptic protein synthesis leading to spine abnormalities.

of several signaling proteins in dendritic spines are increased during the early hours of sleep. Recently, Yang et al. (2014) reported that sleep after motor learning promotes the formation of dendritic spines in layer V pyramidal neurons in primary motor cortex in mice (Yang et al., 2014). Adequate sleep is also associated with up-regulation of numerous transcription initiation factors (eIF4b, eIF5, eIF3 subunits 3, 8 and 12), and eEF2 (Cirelli and Tononi, 2004; Mackiewicz et al., 2007; Mackiewicz et al., 2008) in the rodent brain, which are essential for synaptic signaling mechanism. Therefore, loss of sleep, or deprivation of sleep, has significant effects on neurotransmitter release, dendritic spine signaling, and dynamic changes in dendritic spines. Although the exact mechanism of spine loss after sleep deprivation is not clear, experimental evidence suggests that sleep loss could decrease some synaptic signaling molecules, such as PSD95, Shank, Homer, Kalirin, cortactin, synaptic cell adhesion molecules (NRXN, NLGs), neurotropic factors, such as BDNF, and TrkB as well as their receptors, in addition to several early expression genes (Davis et al., 2006; Yang et al., 2014). Most of these changes interfere with actin polymerization inside dendritic spine, thus causing spine instability.

During normal sleep, adequate expression of synaptic cell adhesion molecules (NRXNs, NGLs) can activate expression of Shank3, which activates cortactin and help actin polymerization (Yang et al., 2014; Fig. 17). Similarly, basal glutamate also increases intracellular calcium, which activates calcium-dependent protein calmodulin kinases-I (CaMKII), a protein involved in dendritic spine remodeling and calcium signaling, through ERK-dependent pathway (Wayman et al., 2008; Fig. 17). In addition, maintenance of basal glutamate during sleep can also activate ERK and mTOR signaling pathways by binding to mGluR5, which helps to express certain essential synaptic proteins for spine growth and development (Kritis et al., 2015; Nakamoto et al., 2007; Tu et al., 1999). Furthermore, adequate sleep can also enhance secretion of neurotropic factors (BDNF), which can increase early expression of synaptic protein through activation of MAPK pathway (Luo et al., 2013). In contrast, total sleep deprivation has deleterious effects on those pathways, as it reduces the phosphorylation of MAP kinases, ERK-1 and ERK-2, attenuates cortactin expression and phosphorylation by decreasing synaptic adhesion molecules and neurotropic factors (Luo et al., 2013). Further, deprivation of rapid eye movement (REM) sleep reduces ERK and cAMP-PKA signaling pathways (Guan et al., 2004; Vecsey et al., 2009), which regulate expression of cyclic cAMP responsive element binding (CREB) protein, a responsive transcription factor for long term memory formation. Similarly, BDNF, BDNF-TrkB signaling, and the expression of synapsin I, CREB, CaMKII are also severely affected in rodent hippocampus after 8–48 h of sleep deprivation (Guzman-Marin et al., 2006). According to Vecsey et al. (2009), mice deprived of sleep for 5h, have increased expression of phosphodiesterase-4, which degrades cAMP levels several times, thus reducing PKA activation and expression of several immediate early genes (IEGs; Fig. 17). All these effects either impair F-actin stabilization or perturb synaptic protein expressions, and ultimately impair spine dynamics (Vecsey et al., 2009).

11.13. Stroke, ischemia/hypoxia/reperfusion injury

The human brain is about 2% of the total body mass, but consumes about 20% of the energy generated in the body (Clark et al., 1999). High demand of energy requires adequate oxygen supply, which can be achieved by adequate blood flow to the brain. Therefore, optimum cerebral blood flow is very crucial for maintenance of brain oxygen, as well as delivery of nutrients and energy. When blood flow is interrupted, the condition developed is called hypoxia/ischemia. Indeed, ischemia is the insufficient blood flow to a particular region which causes deprivation of adequate oxygenation, leading to tissue hypoxia (reduced oxygen) or anoxia (absence of oxygen). The major causes of ischemia/hypoxia are cardiac arrest, which leads to impairment of cerebral circulation, and cerebral hemorrhage or thrombus formation in brain blood vessel (Naranjo et al., 2013). Reduced blood flow decreases availability of oxygen and leads to hypoxic condition resulting in reduction in mitochondrial respiration and oxidative metabolism, and ultimately, energy failure and cell death. Due to their high metabolic activity, neurons require high oxygen demand and are very vulnerable to hypoxic stress (Baburamani et al., 2012). Experimental evidence suggests that severe energy failure, imbalance of ion homeostasis, increased depolarization have been observed after only 2 min of ischemia (Sanderson et al., 2013). Interestingly, increases in dendritic varicosities, along with the loss of spines, have been observed after 20 min of hypoxia (Hasbani et al., 2001). Hence, neuronal death and loss of dendritic spines are important consequences of ischemia/hypoxia (Kolb and Gibb, 1993; Akulinin et al., 1997). Additionally, early symptoms of ischemic/hypoxic brain damage are the structural changes in dendrites shape, including formation of focal varicosities and constrictions, which lead to failure of neurotransmission (Hori and Carpenter, 1994). After several days of hypoxic or ischemic insults, dendritic spines loss has been documented in pyramidal neurons of the hippocampus, motor and sensory cortex, as well as striatal and Purkinje neurons (Baron et al., 2014; Maiti et al., 2008b). However,

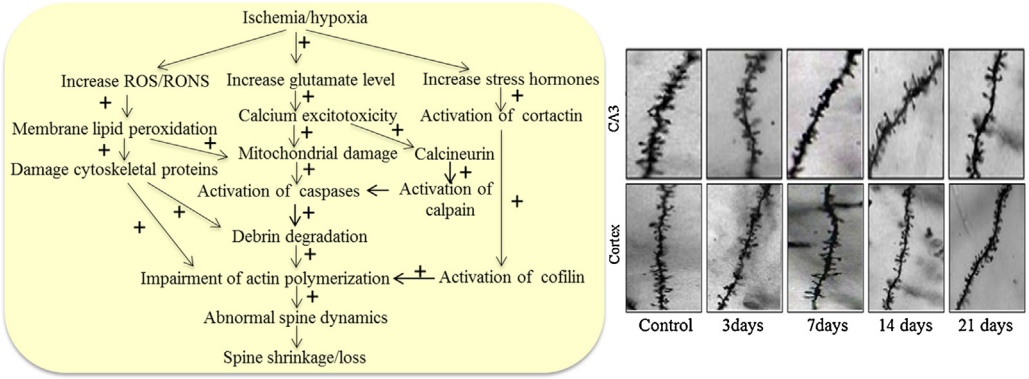


Fig. 18. Left: Schematic diagram showing the possible signaling mechanism(s) of ischemia/hypoxia/reperfusion injury which induces remodeling of actin dynamics and dendritic spine loss. Right: changes of dendritic spine in cortex and CA3 region of hippocampus of rats after exposure to simulated high altitude environment (hypobaric hypoxia) resemblance to 6000 m for different duration. Maximum spine has been observed after 7 days of exposure in cortex and some recovery after 21 days, whereas, damage was continued in case of hippocampus (Maiti et al., 2008a).

researchers have reported activation of several signaling pathways for neuronal death, as well as spine loss after ischemia/hypoxia insult. The most critical sign of ischemia/hypoxia is energy failure due to impairment of mitochondrial oxidative phosphorylation (Solaini et al., 2010). This energy failure can cause disruption of Na^+/K^+ pumps leading to depolarization of neuronal membrane, which can make the neuron more vulnerable to glutamate excitotoxicity. The excessive Ca^{2+} influx through ionotropic glutamate receptors causes mitochondrial damage and activates proteases, such as caspases and calpain. Both calpain and caspases degrade drebrin, an important protein for actin polymerization (Chimura et al., 2015). In addition, Ca^{2+} excitotoxicty can also activate cofilin, which promotes actin depolymerization, thus impairs actin dynamics, as well as causing dendritic spine loss (Kang et al., 2011). Similarly, Ca^{2+} excitotoxicity causes mitochondrial damage, which leads to production of reactive oxygen species (ROS), due to failure of oxidative phosphorylation (Solaini et al., 2010).

Further, Ca^{2+} also activates nitric oxide synthase (NOS) and promotes nitric oxide (NO) production. NO can interact with ROS and form peroxynitrite (ONOO—) causing membrane lipid peroxidation, which damage the cytoskeleton structure and impairs actin polymerization, as well as spine dynamics (Kang et al., 2011). In addition, ischemia/hypoxia also activates stress hormones such as cortisol and epinephrine (Conrad, 2008). These stress hormones can activate cortactin and other dendritic spines signaling molecules, which ultimately activate cofilin and impair actin polymerization, thus altering dendritic spines structure and function (Conrad, 2008). Since the last two decade, our laboratory has worked with hypobaric hypoxia, an adverse environmental condition encountered at high altitude. Similar to ischemic/hypoxic damage, we have also observed that hypobaric hypoxia increases oxidative stress, including reactive oxygen (ROS) and reactive nitrogen species (RNS; Maiti et al., 2006), glutamate excitotoxicity (Hota et al., 2008a,b), increases in stress hormones especially glucocorticoids (Baitharu et al., 2013), which cause neuronal death and dendritic spine loss in cortical and hippocampal neurons leading to impaired learning and memory in rats (Maiti et al., 2008a). We have also been studying the effects of different altitudes (3000–8000 m) and duration of exposure to the degree of neuronal vulnerability, as well as synaptic damage, and we have observed that the degree of spine loss depends on the severity of altitude and duration of stay in that environment (Fig. 18; Maiti et al., 2008a). Further, synaptic plasticity, including recovery of dendritic spines, has been observed in different brain regions of rats subjected to hypobaric hypoxia at 6000 m for 2–3 weeks (Maiti et al., 2008b), which may be due to an acclimatization mechanism (Fig. 18).

11.14. Hormonal imbalance and spine abnormalities

Several hormones, such as those produced from the thyroid, gonadal and adrenal glands actively participate in modulating synaptic plasticity. For example, thyroxin deficiency (hypothyroidism) during brain development can cause decrease in spine density in adulthood (Ahmed et al., 2008; Fiala et al., 2002). Similarly, spine loss can also be observed in cortical pyramidal neurons in adulthood after removal of thyroid gland. Furthermore, it has been observed that iodine deficiency causes severe impairment of synthesis of thyroid hormones leading to mental retardation and cerebral palsy (Eastman and Zimmermann, 2000; Fiala et al., 2002). If there is hypothyroidism during brain development, subsequent loss of neurons and dendritic spines have been observed in particular brain areas, such as in cerebellar granular cells, which lead to underdeveloped spines in Purkinje neurons and cortical pyramidal neurons, as well as hippocampal pyramidal cells in adult animals http://www.sciencedirect.com/science/article/pii/S0165017302001583-BIB106 (Fiala et al., 2002). Further, estrogen is an important female reproductive hormone that also plays a critical role in spinogenesis. Experimental evidence suggests that estrogen receptors are very abundant in hippocampal pyramidal neurons. During puberty there is a huge fluctuation (almost 30%) in the number of dendritic spines in hippocampal neurons. In contrast, the numbers of spines are significantly decreased in the CA1 neurons of hippocampus after removal of the ovaries during reproductive cycles (Woolley and McEwen, 1993) and this decrease in dendritic spines can be countered by estradiol replacement therapy. In contrast to estrogen, removal of testes in male rats causes a decline in testosterone, resulting in increased spine density in hypothalamus (Garelick and Swann, 2014), though the molecular mechanism of such phenomena is unclear. In addition, some stress hormones, such as cortisol or epinephrine, play important roles in synaptic plasticity. The CA3 neurons of hippocampus are highly vulnerable to stress hormones resulting in spine atrophy (Conrad, 2008). Deficiency or abnormalities of adrenal hormones result in spine loss in CA3 and the dentate gyrus neurons of the hippocampus. Similar effects are also observed after adrenalectomy (Joels et al., 2012). Administration of estradiol to animals increases spine density by two folds in hippocampal pyramidal neurons, suggesting estradiol has an important role in spinogenesis and maturation (Spencer et al., 2008). Chronic stress paradigms, or

Table 7
Nutrients involved in brain development and cause and consequences of their deficiency (Gomez-Pinilla, 2008; Mora, 2013).

Nutrients	Requirement for brain	Brain areas affected	Effects on dendritic spine	Effects on cognition
Protein-energy	Cell proliferation, differentiation, synthesis of growth factors, synaptogenesis	Whole brain	Reductions in dendritic arborization and spine numbers	Mental retardation, low cognitive efficiency
Iron	Myelin, white matter, monoamine synthesis, neuronal & glial energy metabolism	Cortex, hippocampus, striatum	Abnormal spine development	It normalizes cognitive function in young women
Calcium, zinc, selenium	DNA synthesis, neurotransmitter release	Autonomic nervous system, hippocampus, cerebellum	Truncated dendritic arbors	Excess calcium is linked to cognitive decline in the elderly; zinc deficiency reduce cognitive efficiency in the elderly; low selenium can cause lower cognitive function
Copper (Cu)	Neurotransmitter synthesis, neuronal and glial energy metabolism, antioxidant activity	Cerebellum	Reduce dendritic spine genesis	Cognitive decline due to Cu deficiency as observed in Alzheimer's disease
Omega-3 fatty acid	Synaptogenesis, myelination, increase neuronal growth factors	Eye, cortex	Impair neurite outgrowth, pre- and postsynaptic proteins level	Amelioration of cognitive decline in the elderly
Choline	Neurotransmitter synthesis, DNA methylation, myelin synthesis	Whole brain, hippocampus, white matter	Decrease postsynaptic signaling protein	Reduction of seizure-induced memory impairment in rodents; decreases release of neurotransmitter and reduce cognition.
Vitamins	Metabolic homeostasis, neuronal plasticity	Whole brain areas	Impair spine formation	Antioxidant vitamin intake delays cognitive decline in the elderly
Flavonoids	Maintain redox status of brain	Whole brain areas	May impair spine development and maturation	Improvement of cognitive function in the elderly by decreasing oxidative stress
Turmeric (Curcumin)	Neuronal growth, increase neurotropic factors	Cortex, hippocampus, cerebellum	Increase dendritic spine signaling proteins	Amelioration of cognitive decay in mouse model of Alzheimer's disease

prolonged and repeated exposure of glucocorticoid, causes atrophy of dendritic branches and loss or reduced spine density on the apical dendrites of hippocampal CA3 and medial prefrontal pyramidal cells (Magarinos et al., 1996). Chronic glucocorticoid exposure causes increase in extracellular glutamate, calcium currents and expression of adhesion molecules and NMDA and GABA receptors. Thus, chronic stress can regulate the rho-kinase/LIM kinase/cofilin signaling pathways (Liston and Gan, 2011; Fig. 18).

11.15. Malnutrition and spine abnormalities

Dendritic spine formation and maturation also depends on nutritional status of an individual. Some essential nutrients, like protein, certain fats, iron, zinc, copper, iodine, selenium, vitamin A, choline, and folate, are essential for proper brain growth and spinogenesis (Benitez-Bribiesca et al., 1999; Georgieff, 2007; Table 7). Undernourishment, malnutrition, or deficiency of certain nutrients, has severe consequences on spinogenesis, especially during the first two years of postnatal life (Georgieff, 2007). Several clinical reports suggest that malnourished and mothers give birth to babies with underdeveloped brains, hydrocephalus, mental retardation, with improper dendritic spine structure (Ramakrishna, 1999). The neurons of these babies are vulnerable to necrosis and become increasingly dysfunctional in their advanced life with ensuing cognitive impairment (Ramakrishna, 1999). Under-nourished children or infants with malnutrition during early postnatal life can have short apical dendrites, fewer spines, and dendritic spine abnormalities in different brain areas, which can cause mental retardation (Georgieff, 2007). Experimental animals suffering from malnutrition during the time of their critical brain development have neuronal deformities in different brain areas, as well as abnormalities in brain growth, leading to impairment of neurotransmission (Georgieff, 2007). For example, animal studies with protein-energy malnutrition in their early development showed diminished neuronal DNA and RNA content and altered the fatty acid profile, which ultimately leads to reduced neuronal population, decline in protein synthesis, and hypomyelination (Winick and Noble, 1966; Winick and Rosso, 1969). The most vulnerable brain areas in protein energy malnutrition are the cortex and hippocampus (Georgieff, 2007).

Malnutrition can cause hormonal imbalance, energy deficiency, and can make the neurons susceptible to death, which can ultimately lead to mental retardation (Morgane et al., 1993). Underdeveloped dendritic spines and brains can result from protein calorie mal-nutrition. For example, protein calorie mal-nutrition can cause severe impairment of neuronal growth and proliferation, which leads to mental retardation (Georgieff, 2007). The consequences of protein malnutrition results in increased thorny excrescences, and decreases in the total number of spines in hippocampal pyramidal neurons, dentate granular neurons (Garcia-Ruiz et al., 1993; Cintra et al., 1990), cerebellar granule cells (Hillman and Chen, 1981), including the giant spines in Purkinje cells (Chen and Hillman, 1980). Similar to protein or calorie deficiency, prolonged vitamin deficiency can cause vulnerability to neuronal death. For example, thiamin deficiency leads to neurodegeneration (Todd and Butterworth, 1999). In contrast, docosahexaenoic acid (DHA), an omega 3 polyunsaturated fatty acid (PUFA) from fish oil, has pleiotropic effects on brain development, including increases in neurogenesis, production of neurotropic factors, such as increased levels of BDNF, nerve growth factor (NGF), glial derived neurotropic factor (GDNF), ciliary neurotropic factor (CNTF), which are essential for maintaining synaptic function and plasticity (Gomez-Pinilla, 2008). Experimental reports suggest that oral supplementation of DHA can increase the number of dendritic spines in the hippocampus of the adult gerbil (Ma et al., 2009; Sakamoto et al., 2007). Importantly, dietary deficiency of omega-3 fatty acids in humans is

linked to attention-deficit disorder, dyslexia, dementia, depression, bipolar disorder and schizophrenia (Freeman et al., 2006). Similarly, other micronutrients, including dietary choline, vitamins, flavonoids, turmeric (curcumin) have been reported to have significant effects on neurotransmitter levels, maintaining redox status, synaptic signaling, and promoting neuronal plasticity, as well as boosting learning, memory, and other cognitive functions in different animal models of neurodegenerative diseases (Cole and Frautschy, 2010a,b; Cole et al., 2010; Hu et al., 2015).

12. Strategies to preserve or recover dendritic spines in different pathological conditions

12.1. Preservation of spines by preventing neuronal loss

Due to nature of neuroplasticity events, dendritic spines may reappear in their original locations after a certain time, if given the appropriate cellular environment. They might emerge in new location as filopodia or reappear in previous locations, due to dendritic recovery (Maletic-Savatic et al., 1999; Ziv and Smith, 1996). Although formation of filopodia-like spines in new locations is uncommon in adult brain, and is not due to recovery of dendritic branches, most spines are recovered at their original sites, due to regeneration processes (Maletic-Savatic et al., 1999). For example, severe ischemia can cause rapid damage of spines and dendrites within 10–30 min of stroke, whereas dendritic and spine structures are mostly restored within 20–60 min of stroke recovery (Brown et al., 2007; Brown and Murphy, 2008). These phenomena are so fast that, within minutes after onset of hypoxia-ischemia, the spine structures are disrupted, but as soon as reperfusion process is started, the dendritic structures are restored and spines quickly re-emerge at their original location (Tseng and Firestein, 2011). These phenomena indicate that spines are highly dynamic and have the capability of remodeling and restoring their original structure and function as needed. In contrast, due to progressive neuronal loss in several age-related brain diseases, a permanent dendritic spine loss is often observed (Fiala et al., 2002; Nimchinsky et al., 2002). Therefore, one possible way to preserved spines would be by preventing or delaying neuronal death or loss. At least by preserving existing neurons, basic neuronal transmission can be maintained. Several drugs/small molecules have been used to prevent or delay neuronal loss in different neurodegenerative diseases and it has been observed that spine loss has been mitigated in these pharmacological manipulations by preventing or slowing neuronal loss. Since most neurological diseases are age-related and progress slowly, it is extremely difficult to know the exact time when the brain starts to loose neurons. For example, in AD, spine pathology may start with the onset of amyloid beta protein accumulation, well before the emergence of symptoms. Therefore, finding reliable biomarkers for loss of neurons and synapses would be helpful to prevent the disease onset or delay the diseases progression. It is understandable that it would be difficult to recover damaged neurons and their spines, but to focusing on preserving functionally active spines on the surviving neurons would help reduce the severity of the disease.

12.2. Prevent varicosity formation

Spine recovery is a dynamic process which includes several steps, including countering their protrusions then reestablishing their connections and restoring their morphology. Scientists agree that most dendritic spines were lost at sites on swollen dendritic membranes where varicosities starts to form, a very common feature of dendritic injury along the length of a dendritic arbor (Ikonomidou et al., 1989). Importantly, the formation of varicosities are rapid and reversible, being triggered by activation of NMDA receptors, involving influx of Ca^{2+} and Na^{+} (Ikegaya et al., 2001). Several cellular pathways are involved in the formation of varicosities, such as volume regulatory pathways, calcium homeostasis, and cytoskeletal rearrangement (Hasbani et al., 1998; Korkotian and Segal, 1999a,b; Segal and Andersen, 2000). According to Ikegaya et al. (2001), the influx of Na^{+} through the NMDA receptor channel mediates the dendrite focal swelling or varicosity formation (Ikegaya et al., 2001). In neurological diseases, glutamate excitotoxicity activates NMDA receptors which stimulate Ca^{2+} or Na^{+} dependent enzymes, including kinases and proteases that eventually cause focal dendritic swellings and neuronal death. Therefore, pharmacological manipulations especially those that inhibit proteases can be used to decrease NMDA-induced excitotoxicity, aiding the ability of the spines to recover from formation of varicosities (Ikegaya et al., 2001).

12.3. Elucidation of common causes of spine loss

Spine pathology is common in the broad spectrum of neurological diseases, and in most of these cases, there are some shared causes for spine damage or loss. Because of their dynamic nature, dendritic spines might reappear in their original site, if the pathological factor is known and eliminated. Therefore, it is vital to understand the changes and common molecular mechanisms or pathways involved in producing spine abnormalities if loss or damage to dendritic spines is to be used. Several investigators have found that one common pathway for spine abnormalities is the impairment of spine cytoskeleton dynamics (Kang et al., 2011). Major dendritic spine signaling pathways can either oppose actin polymerization or induce their depolymerization process (Calabrese et al., 2014; Fifkova and Delay, 1982; Sala and Segal, 2014). Somehow, if actin dynamics are maintained, then spine dynamics can be preserved. Several experimental studies have suggested that actin is the major cytoskeletal element in dendritic spines (Fifkova and Delay, 1982) and plays critical roles for spine motility (Fischer et al., 1998), including postsynaptic receptor localization (Allison et al., 1998; Sattler et al., 2000). Another common cause of spine loss is dysregulation of actin polymerization. Therefore, it is speculated that a major criteria for spine recovery following from their damage is to the maintenance of actin polymerization inside the spine.

12.4. Maintenance of spine signaling proteins

There are several pre- and post-synaptic signaling proteins involved in preserving the dendritic spine structure which can be altered in different pathological conditions. Preserving those signaling proteins would be helpful in maintaining spine structure and function, even when the spine membrane and spine cytosol are engulfed by the parent dendrite. For example, glutamate excitotoxicty can cause loss of PSD95, as well as NMDA receptor subunit NR1, but does not necessarily alter actin and the actin-associated proteins, such as drebrin. This indicates that some of the signaling proteins may remain unaltered following pathologically induced changes in spine structure (Allison et al., 1998; Sattler et al., 2000). Similarly, due to exposure of Aβ oligomers in primary hippocampal neurons, NMDA receptors can be down-regulated, leading to alterations in spine morphology and reductions in spine density (Calabrese et al., 2007; Lacor et al., 2007; Shankar et al., 2007), but pathological changes to the dendritic spines can be prevented by manipulation of NMDA receptors by antagonists, which can facilitate the effects of spine signaling molecules, such as PSD95, Homer and Shank proteins (Calabrese et al., 2007; Shankar et al., 2007). Furthermore, in AD patients the phosphorylation of

the cAMP response element binding protein (CREB) are decreased (Yamamoto-Sasaki et al., 1999) and treatment with the phosphodiesterase type 4 inhibitor (PDE4), Rolipram, can rescue the Ab-induced synaptic dysfunction in vitro (Vitolo et al., 2002), including recovery of spine morphology and density. These findings suggest that restoring spine signaling pathways and their protein markers, such as the cAMP/PKA/CREB pathway, could be important for the recovery of dendritic spines in AD. Another strategy to rescue dendritic spines may be by the way of the vaccination process; where by anti-amyloid specific antibodies can be used to reduce amyloid deposition. This process is very effective in rescuing of the pre- and post-synaptic protein markers (Buttini et al., 2005), and may also improve behavioral deficits in mice (Janus et al., 2000). The treatment with anti-amyloid antibodies can significantly protect spine loss in primary culture neurons (Shankar et al., 2007), and it has also been shown that dendritic spines can be recovered after Aβ removal from the culture medium (Calabrese et al., 2007).

12.5. Modification of life style

An ample of evidence suggest that life style play a fundamental role in the neuronal vulnerability; impairment of synaptic plasticity and risk of cognitive impairment. These factors, including reduction of chronic stress, healthy foods and diets, aerobic exercise, as well as cognitive exercise can influence molecular mechanism of dendritic signaling and plasticity (Mora, 2013). For example, chronic stress negatively regulates synaptic structure and function, as well as dendritic plasticity, which has significant effects on cognitive function, especially during advanced age. Chronic stress enhances stress hormones, such glucocorticoids, which affects neuronal energetics, and make them vulnerable to death. Therefore, avoiding chronic stressful lifestyle would be helpful for synaptic recovery in different brain diseases (Mora et al., 2012; Mora, 2013). Similar to stress, daily healthy diets and nutritious foods of an individual can protect the brain from neuronal injury, especially during aging. Unrestricted, intake of food, or excess intake of calorie, can cuase several metabolic syndromes (e.g. type-II diabetes), which can aggravate neurological diseases. Caloric restriction can decrease dendritic spines loss, and increases neurogenesis, which can obviously improve the cognitive abilities of an individual. Diet containing excess antioxidants, can nurture our brain better, and protects from oxidative damage during advanced age (Colman et al., 2009; Johnson et al., 2007). In addition, healthy diets, daily aerobic physical exercise, can increase brain wiring by increasing secretions of neurotrophic factors, including BDNF, NGF, GDNF, and other growth factors. Most significant effect of aerobic exercise is that it can promotes adult neurogenesis, and enhance synaptic signaling, including increase in the numbers of mature dendritic spines. Therefore, sufficient aerobic exercise, could make aged brain more smatter, and protects further neuronal and synaptic loss, leads to delay onset or progression of age related neurodegenerative diseases (Cotman et al., 2007; Gitler, 2011; Hillman et al., 2008). Furthermore, along with exercise, enriched environments could be another beneficial effect, on recovery of dendritic spines loss in diseased brain. For example, the experimental rats, subjected to enriched environments, showed increased adult neurogenesis, and neuronal plasticity, including promoting dendritic branching, new synapse formation, increases the expression of genes for neurotrophic factors, leads to improving in learning and memory. Therefore, individual experiencing with enriched environments could be a way to maintain synaptic plasticity, and delay progression of several brain diseases (Fratiglioni et al., 2004; Mora et al., 2012; Pham et al., 2002).

13. Conclusion

Dendritic spines play a fundamental role in synaptic transmission as well as information processing in mammalian nervous system. They are tiny, specialized, semi-autonomous compartments originated from the main dendritic shaft. The structure and function of dendritic spines are dynamically regulated by local cellular environment and the nature of stimuli they experience. Their shapes, sizes and numbers significantly influence synaptic transmission and these are usually altered in different neurological diseases. Detailed understanding of ultra-structure and molecular signaling pathways are vital to understand the special role of dendritic spines play in synaptic plasticity and neurological diseases. Numerous signaling protein molecules are intimately involved in spinogenesis, development and maturation of dendritic spines, which are down- or up-regulated in several brain diseases. Therefore, controlling the level of spine proteins could be an important means of rescuing the function of spines and, thus, could be a potential way of preserving normal synaptic transmission. Here we have provided a current overview of importance of dendritic spine dynamics in brain diseases and have outlined recent advances of molecular signaling mechanism involved in the alterations of the structure and function of dendritic spines in various neurological and neuropsychiatric diseases. This information should facilitate and contribute to the basic understanding of the importance of dendritic spines and the possible ways to recover their structure–functions that are compromised in several neurological diseases and disorders.

Conflict of interest statement

Authors declare no conflict of interest to publish this review article.

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