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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