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Review

Structural plasticity of dendritic spines: The underlying mechanisms and its dysregulation in brain disorders

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ABSTRACT

Dendritic spines are specialized structures on neuronal processes where the majority of excitatory synapses are localized. Spines are highly dynamic, and their stabilization and morphology are influenced by synaptic activity. This extrinsic regulation of spine morphogenesis underlies experience-dependent brain development and information storage within the brain's circuitry. In this review, we summarize recent findings that demonstrate the phenomenon of activity-dependent structural plasticity and the molecular mechanisms by which synaptic activity sculpt neuronal connections. Impaired structural plasticity is associated with perturbed brain function in neurodevelopmental disorders such as autism. Information from the mechanistic studies therefore provides important insights into the design of therapeutic strategies for these brain disorders.

1. Introduction

Dendritic spines, which were first described by Ramón y Cajal more than one hundred years ago, are the specialized subcellular compartments that characterize dendritic arbors and are where excitatory synapses are located. In the adult mouse neocortex, the majority (96%) of dendritic spines encapsulate large electron-dense structures known as the postsynaptic densities that mark synaptic contacts [1]. On the other hand, very few excitatory synapses are found on the dendritic shaft. Consequently, the density of dendritic spines directly indicates the number of excitatory synaptic inputs onto a particular neuron. Dendritic spines are largely heterogeneous in both size and shape, even within a single dendritic segment of a given neuron. The morphology of dendritic spines can be generally classified into three classes: the stubby spine, which lacks an apparent neck; the thin spine, which contains a small bulbous head and a thin, long neck; and the mushroom spine, which contains a large mushroom-shaped head [2]. In addition, there are elongated dendritic protrusions called filopodia, which are longer than 4 μm (as opposed to spines which typically are <2 μm in length) and do not possess distinctive heads. Filopodia are more prominent in the developing brain at early postnatal stages and diminish with adulthood [3]. One prevailing view is that filopodia represent the spine precursors during synapse formation [4]. The long necks of filopodia would render them highly motile and hence facilitate the search for presynaptic partners during synaptogenesis. However, it has also been reported that during the first postnatal week, many synaptic contacts occurred directly on dendritic shafts rather than on the tips of filopodia [5], suggesting that the pre-requisite of filopodia for synaptogenesis might not apply to all synapses [6].

As recently indicated by Yuste [7,8], in order to understand how the neural circuit functions it is important to ask: Why do excitatory axons choose to form synapses on dendritic spines rather than the dendritic shafts of the postsynaptic neuron? Dendritic spines likely offer distinct advantages for excitatory neurotransmission and function of the brain circuits. One distinct advantage is that the presence of spine necks allows the formation of isolated biochemical and electrical compartments, which enable each synapse on a single spine to function and be regulated independently. It is widely believed that the functional property of dendritic spines is highly correlated with their morphology. Parameters such as the dimension of spine head and spine neck determine different aspects of dendritic spine function, including the abundance of neurotransmitter receptors, the diffusion of small molecules between spine and shaft, as well as the motility and stability of the spine [6]. The narrow spine neck might also compartmentalize calcium [7], thus allowing the strength of individual synapses to be modulated differently during synaptic plasticity such as long-term potentiation (LTP) and long-term depression (LTD). Altered spine morphology has been observed in neurological disorders such as fragile-X syndrome [9], underscoring the importance of the tight regulation of spine morphology in proper brain function.

Dendritic spines are highly dynamic during development as well as in the mature nervous system. Spine formation, turnover and morphology continue to be modulated in the adult brain by input from the environment in the form of synaptic activity, which is central to memory formation and other adaptive changes of the brain. Notably, activity-

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dependent spine morphogenesis is impaired in many neurological disorders. Investigating the molecular mechanisms that underlie structural plasticity of synapses will therefore be crucial in understanding how the brain functions, and should provide important insights on identifying therapeutic targets for various neurological disorders. In this review, we focus on recent progress in (1) demonstrating activity-dependent spine remodeling during synaptic plasticity and learning/memory, (2) elucidating molecular mechanisms that underlie activity-dependent structural plasticity, and (3) delineating the relationship between impaired spine morphogenesis and neurological disorders.

2. Activity-dependent spine morphogenesis: the phenomenon

2.1. Spine maintenance and maturation

Whereas most recent studies on activity-dependent structural plasticity focus on the rapid spine remodeling in learning-related synaptic plasticity of the mature brain, it is important to realize that synaptic transmission and neuronal activity also play key roles in sculpting neural circuits across development by regulating the maturation and maintenance of dendritic spines [10]. In dissociated hippocampal neurons, blocking neuronal activity by tetrodotoxin (TTX) reduces spine number or leads to the appearance of long immature dendritic protrusions that lack clear spine heads [11–13]. Excitatory neurotransmission involving ionotropic glutamate receptors appears particularly important to structural plasticity. Pharmacological blockade of AMPA receptor by NBQX in dissociated hippocampal neurons or organotypic slice cultures also causes spine loss [14,15]. Interestingly, inhibition of NMDA receptors by APV results in appearance of filipodia-like processes without reducing density of the total dendritic protrusions, indicating differential roles for the two types of receptors in spine maintenance and maturation [14]. Moreover, unlike the situation in dissociated neurons, blocking neuronal activity by TTX affects neither spine density nor spine maturation in hippocampal slice culture. This leads to the interesting hypothesis that miniature glutamate release serves to maintain dendritic spines, which potentially explains why synapses that might be inactive most of the time can be retained in the adult brain without elimination [14]. One should emphasize, however, that contrasting studies have demonstrated an increase in spine density upon blockade of synaptic transmission (for example, [16–18]), which can potentially be explained by homeostatic regulation of structural plasticity.

More insight into activity-dependent spine maintenance has been gained from *in vivo* studies using two-photon microscopy. It has long been suggested that dendritic spines are over-produced during early postnatal stages, after which extensive spine pruning occurs to refine the circuit [19]. Spine turnover of the neocortical pyramidal neurons has been monitored at different postnatal stages, which indicates that spine elimination indeed exceeds spine formation in adolescent animals. Spines become more stable in the adult brain, when spine pruning is significantly reduced [20,21]. Furthermore, mushroom spines are more persistent than thin spines, suggesting a correlation between spine morphology and stability. Time-lapse two-photon imaging also demonstrates that whisker trimming in mice modulates spine elimination of layer V pyramidal neurons in the barrel cortex [22,23]. Likewise, monocular deprivation accelerates spine pruning on the apical dendrites of layer II/III pyramidal neurons of the visual cortex [24]. These studies therefore provide compelling evidence that sensory experience can modify spine stability of neurons in the relevant cortical region.

2.2. Spine remodeling after induction of synaptic plasticity and learning

Hebbian LTP and LTD are well-studied forms of synaptic plasticity that form the cellular basis of hippocampal-dependent learning and memory. It is believed that the persistent changes of synaptic strength during late-phase LTP and LTD involve structural changes of the synapse, which include the formation and elimination of synaptic connections and changes in spine morphology. An increase in synaptic strength by LTP in hippocampal slices is associated with the rapid formation of new spines that depend on NMDA receptor [25,26]. This is confirmed in dissociated hippocampal neurons upon the induction of chemically-induced LTP (cLTP) [27,28]. LTP induction also triggers rapid enlargement of the spine heads [28–30]. Spine enlargement precedes the increase in AMPA receptor abundance [30] and larger spines are associated with larger PSD and greater glutamate-induced current and calcium influx [31,32], suggesting that spine enlargement is essential for the increased postsynaptic response in LTP. More recent studies employ two-photon glutamate uncaging to demonstrate NMDA receptor-dependent enlargement of individual spines, which reconciles with the input-specific property of LTP [33,34]. Interestingly, although structural remodeling is specific to the stimulated spine, there is cross-talk to neighboring spines such that the threshold of inducing subsequent spine enlargement for them is reduced [35,36]. Recently, LTP-inducing glutamate uncaging has also been shown to stabilize newly-formed spines: upon stimulation, about half of the new spines can survive beyond 20 h after their initial growth, as opposed to ~25% for unstimulated spines of the same neurons [37]. Taken together, these studies suggest that during LTP, activation of NMDA receptor increases connectivity of specific neurons through modulation of dendritic spines in three different ways: the enlargement of pre-existing spines, the stabilization of newly-formed spines, and the formation of new spines.

Contrary to the growth of dendritic spines in response to LTP, a reduction of synaptic strength during LTD is correlated with spine shrinkage and retraction [38–40]. Live imaging of dendritic spines after stimulation by low-frequency uncaging glutamate further demonstrates that LTD-inducing stimulus leads to spine shrinkage specifically on the stimulated spine but not neighboring spines. Therefore, like LTP-induced spine enlargement, spine shrinkage induced by LTD is also synapse-specific [41]. Although size reduction is observed for both large and small spines, their mechanism is different, such that the retraction of small spines depends on NMDA receptor, while that of large spines requires both NMDA receptor and metabotropic glutamate receptor [41]. This latter observation is consistent with studies showing the involvement of mGluR in experience-dependent structural plasticity [13,42].

Can the structural plasticity induced by LTP be observed during natural learning (as opposed to experimental manipulation of sensory experience such as whisker trimming)? This important question has been addressed recently by different laboratories using two-photon microscopy. By monitoring spines of pyramidal neurons in the motor cortex, it has been demonstrated that training mice with a motor learning task rapidly induces the formation of new spines. Importantly, many of these new spines can persist for weeks and months after training, and the mice performance of the motor task positively correlates with the extent of new spine formation [43,44]. Repetitive motor learning leads to the formation of new spines in clusters, which also show increased head size and stability compared to non-clustered new spines. The formation of clustered spines upon repeated training is particularly interesting, since neighboring spines are proposed to function within the same neural circuit and transmit similar information to the postsynaptic neuron, therefore encode related memory [45].

3. Activity-dependent spine morphogenesis: the mechanisms

Dendritic spines are enriched in actin, and activity-dependent spine growth and remodeling depend on signal transduction that modulates actin dynamics [46,47]. Here, we summarize recent advances in our understanding of the molecular mechanisms by which activity-dependent spine morphogenesis is regulated, focusing in particular on the role and regulation of small GTPases (Fig. 1).

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