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Mini Review

Dendritic Spine Modifications in Synaptic Plasticity

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Abstract

Synaptic plasticity is regarded as the cellular mechanism underlying the refinement of neural connections during development and learning/memory functions in adults. Alterations in dendritic spine morphology (elongation or shrinkage) and/or spine density occur with synaptic plasticity. This structural modification has been proposed to enable persistent, long-term change in synapses. Here we review spine modifications associated with synaptic plasticity and discuss their contributions to synaptic plasticity and brain diseases.

Keywords: Synaptic plasticity; Spine morphology; Learning and memory; Brain diseases

Abbreviations

LTP: Long-Term Potentiation; LTD: Long-Term Depression; PSD: Post Synaptic Density; AMPAR: α-Amino-3-hydroxy-5-Methyl-4-isoxazole Propionic Acid Receptor; NMDAR: N-Methyl-D-Aspartate Receptor; PKA: Protein Kinase A; CaMKII: Ca2+/calmodulin-dependent protein Kinase II; PP2A: Protein Phosphatase 2; Rac1: Ras-related C3 botulinum toxin substrate 1

Introduction

Dendritic spines are small postsynaptic structures protruding from dendrites and the primary site of excitatory input. About 90% of excitatory synapses occur on spines on the excitatory neurons in the adult cortex [1]. Spines are usually divided into three types based on the size, spine head shape, and spine neck length. Mushroom spines have large heads and constricted narrow necks, thin spines have small heads and slender necks, while stubby spines have no distinct heads and necks [2,3]. This categorization is to provide an easy classification while the actual distribution of spine shapes is of a continuum.

The recent development of two-photon imaging allows spine morphology and dynamics to be studied in great detail using time-lapse and repetitive imaging, and has enabled the study of spine alterations in response to physiological or pathological events [4,5]. For example, dendritic spines are dynamic in genesis and elimination, especially during brain development. In adolescence, spines show much higher elimination than formation which results in net spine loss or pruning. However in the adult, the rate of spine genesis and elimination is much reduced and roughly equivalent, which maintains the stability of spine density [6,7].

Spines are considered a unique calcium compartment [8]. Spine plasticity is demonstrated by their capacity to undergo both rapid (seconds) and persistent (months to years) alterations in response to either physiological or pathological events. Large spines may be the storage site of stable long-term memory [1], while filopodia are considered as the immature form of spine which can be transformed into mature spines or eliminated. Spine plasticity is exhibited in two forms: changes in spine morphology/size and changes in spine density. Both changes reflect altered synaptic connections and strength. In neurodegenerative and psychiatric diseases, spine density and morphology are altered, and these changes may partially account for alterations in brain functions associated with these diseases. Thus a better understanding of spine pathology may provide better therapeutic intervention.

Spine plasticity

Changes in spine density reflect an altered connection density between presynaptic and postsynaptic neurons, and this type of plasticity is most commonly observed during development (increase and decrease/pruning) and aging/degeneration (decrease). Changes in spine morphology, especially of the spine head have been documented using various methods, and is believed to be associated with changes in the strength of synapses.

Due to the heterogeneity of spine morphology, the most convincing way of demonstrating altered spine morphology is provided by comparing the same set of spines before and after synaptic plasticity-inducing stimuli in brain slices or learning *in vivo*. Many studies have examined how spines are altered with the induction of Long-Term Potentiation (LTP) and Long-Term Depression (LTD). These two forms of synaptic plasticity are generally regarded as the cellular basis of synaptic modifications [9].

Spine modifications associated with LTP

In general, spines can undergo bi-directional changes, just as synaptic alterations. Enlargement of spine heads was seen with LTP and shrinkage of spines with LTD [10-12]. The same spines can undergo enlargement and shrinkage with consecutive induction of LTP and LTD [13], indicating that morphological modifications can occur in a bi-directional manner and that these changes are driven by synaptic modifications. The uncaging of caged glutamate onto a single spine [13,14] and electrical stimulation of a population of synapses/spines [15,16] supported the above conclusion.

There is generally a strong correlation between the strength of a given synapse and the size of spine. For example, Takumi *et al.* found that AMPAR density was linearly related to the diameter of Post-Synaptic Density (PSD) [17,18]. Matsuzaki *et al.* reported a large range of AMPAR numbers in spines; AMPARs were enriched in mushroom spines but were sparsely distributed on thin spines and filopodia, revealing a strong correlation between the number of AMPAR and the volume of spine head [18].

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Since both an increase of synaptic strength which is mediated by increased phosphorylation and/or insertion of AMPARs into the potentiated synapses and enlargement of spine occur with LTP, a question arises as to whether functional changes are casually related to changes in morphology/structure. Are these two processes driven by the same upstream processes? Does the occurrence or persistence of one process require the other? It is well established that both processes require a Ca2+ influx through the synaptic NMDARs during LTP induction, and elevated intracellular Ca2+ concentration drives AMPAR phosphorylation and/or insertion [9] and polymerization of action filaments inside spines [12]. The initial increase in synaptic response and spine volume occurs very rapidly (< 1 min) [13,16]. Dendritic spine heads accumulate F-actin during this rapid expansion phase, and can persist for weeks together with an increase in synaptic function [19]. Potentiation of single synapse/spine with glutamate uncaging led to a significant expansion of the spine head and a shortening and widening of the spine neck [20,21]. F-actin concentration inside the spine head rises, together with the entrance of actin-severing, actin-depolymerizing/–polymerizing, actin-capping proteins while actin-stabilizing proteins leave the spines [20,22-26]. Cofilin, an actin-depolymerizing agent, is highly elevated in spines during this initial process [25]. Interestingly, unlike LTP this initial spine expansion did not require postsynaptic exocytosis or PKA signaling [16], suggesting the involvement of different signaling pathways than those supporting LTP. After initial rapid expansion, the next phase of events lasts up to 1 hour, with spine head volume declining from the initial increase, yet remaining larger than the pre-LTP baseline [25].

There is some evidence that AMPARs are not delivered directly into the PSDs inside spines, but are instead delivered to regions outside synapses (i.e., the perisynaptic regions) [28] or onto dendritic shaft [27,29]. These newly inserted AMPARs then move laterally into spines or PSDs. Yang *et al.* found that the stability of the perisynaptic AMPARs depends on the persistence of spine enlargement, that reversal of spine expansion led to the removal of perisynaptic AMPARs and absence of LTP. It is unclear as whether spine enlargement is required for the movement of these new AMPARs to PSD, or for retaining them at the PSD. Yang *et al.* also demonstrated that the converse is true that moving of the newly inserted AMPARs to the synapse is required for persistent spine enlargement [28]. Thus, an insurance mechanism is in place for coordinated modifications in synaptic function and spine morphology, i.e., matched changes in physiology and structure. Furthermore, if one process does not occur, the other process will be aborted even in progress. This double-proof mechanism is essential to ensure that only appropriate changes (i.e., coordinated changes) are allowed to become persistent. This mechanism may be especially important in face of the highly dynamic nature of synaptic modifications, such as those occurring during early brain development [29]. About 1 hour after LTP induction, PSD scaffolds are recruited to spines to stabilize the newly added synaptic AMPARs [25]. This process requires protein synthesis [30].

Another mechanism to alter connections between neurons is to change synapse density. In that context, it has been shown that new spines emerged with the induction of LTP, and some of the new spines contribute to the increase in synaptic connection [31,32]. These new spines first appear in an immature form resembling filopodia, they later become mature (mushroom like spines), or are eliminated. A good indication that the new spines will be maintained is if they process synapses [32,33]. Stabilization of these newly generated spines requires the activation of NMDARs and CaMK II signaling [33]. In addition to the de novo genesis of new spines, splitting of potentiated spines also occur with LTP [12,34]. Note that LTP also induces alterations in axonal morphology and actin cytoskeleton leading to genesis of new axonal varicosities and new puncta [35,36].

Spine modifications associated with LTD

LTD is associated with spine shrinkage, opposing spine enlargement [22,37]. In the initial stage, a Ca2+ influx through the activated NMDARs is required for both LTD and spine shrinkage [15,37]. Similar to LTP/spine enlargement, some signaling events (NMDAR activation, elevation of calcineurin activity and postsynaptic depolymerization) are shared by both processes, while others are differentially required for either LTD expression (elevated PP-2A activity) or spine shrinkage (elevated cofilin activity) [15,22,37,38]. In support of this conclusion, Sdrulla and Linden demonstrated a double dissociation between LTD expression and spine changes in cerebellar Purkinje cells [39]. Interestingly, Wang *et al.* revealed that activity-independent constitute trafficking of AMPARs to and away from PSDs was not associated with changes in spine size, but the significance of this observation remains unclear [15].

Sustained reduction in synaptic strength may eventually lead to the loss of synaptic connections, and this loss is manifested as a reduction in spine density. Spine loss appears to be a protracted process and thus is difficult to study. Nonetheless, a few studies have attempted to examine this process. By using organotypical slices and monitoring both presynaptic boutons and spines, Becker *et al.* showed that LTD induction enhanced the turnover rate of presynaptic boutons and led to reduced contacts between the pre- and post-synaptic sites. Although the disappearance rate of presynaptic boutons and postsynaptic spines were greatly elevated after LTD induction, the sequence of events did not appear to follow a particular pattern, as disappearance of either presynaptic boutons or spines was observed to occur prior to the other [40]. These observations suggest that the exact sequence of events may not matter much, as long as there is a mismatch between the two sites.

Learning and memory *in vivo*

The ultimate proof that spine modifications have significant contributions to physiological process must come from *in vivo* studies, by comparing the same set of spines before and after the occurrence of a physiological process (such as learning or memory). By using time-lapse two-photon imaging on the same set of spines, Yang *et al.* discovered that new spines were formed after *in vivo* experience (sensory or motor), and a fraction of these new spines persisted for months [41]. More importantly, the genesis of new spines is specific to the experience or training, rather than other non-specific factors. Hayashi-Takagi *et al.* showed that motor learning (rotarod) resulted in enhanced Arc signaling and spine expansion in a subset of spines in the motor cortex [42]. By expressing a photo activatable GTPase Rac1 in spines, they showed that prolonged photo-activation led to spine shrinkage (reversed expansion) and loss of recently-acquired motor memory. This is a striking demonstration that enlarged spines are underlying the stored memory and reversing these changes "erased" memory.

Alterations of dendritic spines in brain disorders

It has been convincingly demonstrated that spine alterations occur in various brain diseases, including neurodegenerative diseases and psychiatric disorders. Here we will review briefly evidence of their occurrence and potential contribution to pathology in Alzheimer's disease and schizophrenia.

Alzheimer's disease

Individuals with early-onset Alzheimer's disease had significantly fewer synapses in the inferior temporal gyrus, CA1, dentate gyrus, and posterior cingulate gyrus [43-45]. Spine genesis is likely impaired in AD mice. For example, enriched environment was shown to elevate spine density in wt mice, but failed to do in AD mice [46] and immunohistochemical analysis showed loss of the presynaptic marker synaptophysin [47]. Major contributing factor in spine loss in AD is the presence of amyloid plaque. Numerous studies on both human post-mortem samples and AD transgenic mice have shown that spine loss preferentially occurs in regions near the amyloid plaques [48-50].

In addition, substantial axonal damage is present at the fibrillar plaques [51], which may cause spine loss. It has been shown that the level of oligomer form of Aβ is correlated with the degree of synapse loss [52], suggesting that Aβ oligomers may be a direct culprit in spine loss. Supporting this hypothesis, immunotherapy directed against oligomeric Aβ abolished synapse loss in Tg2576 mice [53]. In addition, many of the identified targets of Aβ are associated with synapses [54-57].

Psychiatric disorders Schizophrenia

Spine loss in neurodegeneration and aging is easy to comprehend. Significant spine loss also occurs in other brain diseases, such as psychiatric disorders, most of which have developmental origins.

Reduced spine density in multiple areas within the frontal and temporal neocortex has been reported in schizophrenia patients [58,59]. Dendritic arborization is also decreased with reduction of dendrite length, field size and dendrite number [60,61]. During adolescence, spine genesis dominates over spine elimination. But there is a net spine reduction/elimination in schizophrenia which is likely caused by the instability of the newly formed spines [62]. In addition, the molecular machinery regulating actin skeleton function was also altered in schizophrenia patients, such as Kalirin-7, Cdc42 [63] and MAP2 [64-66].

Conclusion

Dendritic spines play critical roles in excitatory synaptic transmission and plasticity. They are the site where physiological and morphological modifications meet and integrate. Changes in spine density and dimension contribute significantly in both physiological and pathological processes and also can serve as a marker of such processes. During the LTP, the insertion of new AMPA receptors and spine enlargement are closely related, and appear to be dependent on each other to certain extent. *In vivo* studies demonstrated that learning and memory contributes to spine genesis and morphological changes, and more importantly these changes are required to sustain memory. In neurodegenerative diseases and psychiatric disorders, the density and size of spines are altered which may contribute to pathogenesis. Based on the above evidences, signaling molecules which regulate spine density and morphology may be potential drug targets.

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