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Chapter 8

# Dendritic Spine Modifications in Brain Physiology

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**Abstract**

An essential feature for an organism to survive is to adapt and learn. Studies in the past decades have revealed that synaptic plasticity is a key cellular mechanism underlying learning and memory functions in the adult, and the refinement of neural connections during development. Memory and refinement of connections can last for a long period of time, and hence requires the corresponding structural changes to take place. Alterations in dendritic spine morphology (enlargement or shrinkage) and/or spine density (increase or decrease) have been shown to occur with synaptic modifications, and have been proposed to enable persistent, long-term modifications of synapses. In this chapter, we will review the basics of spine plasticity and its functional contributions to synaptic modification, with focus on modifications of spine morphology (enlargement and shrinkage).

**Keywords:** spine formation, synaptic plasticity, AMPA receptor trafficking, cytoskeleton, long-term potentiation, long-term depression

## 1. Introduction

Dendritic spines are small protruding structures from the dendrites, around 1 μm in diameter. Spines are the primary site of excitatory inputs onto neurons and about 90% of excitatory synapses occur on spines of the excitatory neurons in the adult cortex [1].

Based on the size, spine head size and spine neck length, they can be roughly divided into three distinct types: mushroom, thin and stubby spine. Mushroom type spines have large spine heads and narrow spine necks, thin spines have small spine heads and thin spine necks, while stubby spines bear no distinction between spine heads and necks [2, 3]. In reality, the distribution of spines is not in these distinct sets but in a continuous distribution.

A major component of dendritic spines is cytoskeleton, which is critical to the structure and function of spines. Cytoskeletons consist of actin filaments and microtubules. Actin filaments

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are highly enriched in spine heads, while microtubules are found mostly in the dendritic shafts [4, 5]. Actin filaments inside spines are of two pools, G-actin and F-actin. G-actin is a monomer form of actin and F-actin is the polymer form, while they are found in the tip and base of spines, respectively [6]. Actin filaments bind to the scaffold proteins such as PSD-95 and Shanks, which anchor receptors and signaling molecules at the synapses [7]. Actin filaments are dynamic since actin monomer dissociates from the pointed end while new actin monomers are recruited into the barbed end. Certain actin-binding proteins regulate this dynamic process [8].

Spines are dynamic features in that they are in a constant motion (termed morphing), and their sizes fluctuate around a mean value [9, 10]. Dendritic filopodia are highly motile and flexible, and their lifetime is on the order of minutes to hours [11, 12]. This high motility may allow filopodia to explore the space around them in search for potential presynaptic inputs to form connections [13]. To understand this dynamic nature and to monitor these changes accurately, two-photon imaging has become an invaluable tool. With two-photon imaging, spine morphology and dynamics can be studied in much more details using time-lapse and repetitive imaging. This approach has revealed spine modifications under physiological or pathological conditions or events [14–16] and has greatly advanced our understanding of spine function and allowed in-depth study on the underlying structure–function relationship. During brain development dendritic spines are dynamic in their genesis and elimination, while in adolescence spines show much higher elimination than formation which results in a net spine loss or pruning. In contrast, the rate of spine genesis and elimination in adult is much lower and about equal, and this balance maintains the stability of spine density [17, 18].

Spine is considered as a unique calcium compartment, because the transfer of electrical charge is limited by the spine neck. The length of spine neck controls the degree of interaction between spines and their parent dendrite. In general, short spines and parent dendrites show similar responses to glutamate, while long spines exhibit faster and larger responses [19]. Spine plasticity is evidenced by their rapid (on the order of seconds) and persistent (for months to years) changes in response to physiological or pathological stimuli. Large spines has been suggested to be the site of stable long-term memory storage [1] while filopodia are considered by most to be an immature form of spine. Filopodia may transform into mature spines or are eliminated [20]. Hence, we define spine plasticity in two forms: alterations in their morphology/size and alterations in their density. We note that both forms of plasticity reflect modification of synaptic connections. In neurodegenerative and psychiatric diseases, spine density and spine morphology are altered, and changes in spine density and morphology may at least partially account for altered brain functions in these diseases [1, 21–24]. Therefore, better understanding of spine pathology may provide better therapeutic intervention.

In this chapter, we will discuss signaling mechanisms underlying the formation and maintenance of spines, plasticity of spine morphology and its relationship to modification of synaptic strength.

## 2. Development of dendritic spines during brain development

The relative sequence of synapse and spine genesis during brain development is still in debate. Some evidences suggest that spine genesis lags behind synapse genesis. Fiala et al.

showed that axonal fibers made synaptic contacts with long filopodia, which subsequently were transformed into mature spines [25]. Durand et al. reported during the first postnatal week in rats, synapses on the excitatory neurons are functional and plastic in the absence of dendritic spines [26]. Hence synaptic function and plasticity can take place without spines. After induction of long-term enhancement of synaptic connections in area CA1, new spines appeared on the postsynaptic dendrite [27]. Maletic-Savatic found that with axonal inputs activation, these small filopodia-like protrusions enlarged and became dendritic spines [28]. For those filopodia that do not connect with axonal inputs, they did not turn into mature spines and were absorbed back into dendrites [12]. Interestingly, increase of spine synapse might inhibit the mobility of nearby filopodia on the same dendrite and diminish the formation of synapses [29]. These results indicate that synapse formation or strengthening promotes the formation or maturation of spines, and lend support for the notion that synapse genesis occurs prior to spine genesis.

Do spines form from filopodia, or from existing synapses on the dendritic shafts? In mature cultures, some stable spines could emerge without going through the dynamic filopodia stage [12]. The series sample analysis in young hippocampal area CA1 also revealed that most of synapses are on dendritic shafts, with rare synapses on stubby and mushroom spines [3]. Despite all this, the transformation from dendritic shaft synapses to spines has not been supported by direct observations [30]. On the other hand, several *in vitro* studies revealed that during the initial 1–2 weeks in culture, the long and headless filopodia bear no synaptic contacts associated with the presynaptic axons. Over the subsequent 4 weeks, these dynamic filopodia turned into stable, mushroom-like spines [29, 31, 32]. Fiala et al. also found that in the hippocampal CA1, synapses were present on both filopodia and dendrites. From PN1 to PN12, the number of shaft synapses and filopodia synapses was decreased, while the number of stubby and spine synapses was significantly increased [25]. Thus, it is likely that during early development, shaft synapses are the dominant form of synaptic contact. With development, and likely the need for increasing contact area, spine synapse replace shaft synapses to become the major form of synapses, at least in the adult cortex. Recently, shaft synapses are shown to define the locations where dendritic spines are formed [30] (**Figure 1**), providing more evidence for the transition from shaft synapse to spine synapse as a major process in synapse formation and maturation.

The initial surge of spine genesis leads the generation of more spines than what eventually is retained in the adult brain, and pruning of excessive spines after spine genesis allows a better adaptation to the environment [33]. This pruning process could be evoked by low-frequency glutamatergic stimulation and requires activation of NMDA receptors [34–36].

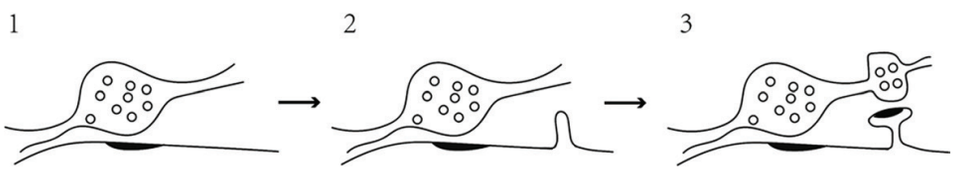


**Figure 1.** Dendritic spines are derived from filopodia with the assistance of shaft synapses. (1) presynaptic axon forms synapses with dendritic shaft. (2) a dendritic protrusion occurs adjacent to the dendritic shaft synapse. (3) the dendritic protrusion contacts with the presynaptic axon and eventually a mushroom dendritic spine is generated. Modified from [30].

In young adolescent mice (1-month old), within a 2 week period of time, 13–20% of total spines were eliminated with 5–8% formed in the barrel, motor and frontal cortices, and this imbalance led to a significant spine loss in many brain regions. However, in the adult mice (4–6 months old), 3–5% of spines were eliminated and formed in 2 weeks [18]. Most evidences support that dendritic spines are stable in the adulthood [37, 38]. Grutzendler et al. reported that spines in the primary visual cortex of young adolescence have a turnover rate of 27% per month but this rate dropped to only 4% in the adult [15]. In contrast, Trachtenberg et al. found that adult spines are highly dynamic with about 20% turnover per day in the mouse barrel cortex [16]. This discrepancy is likely due to differences in the methodology in that the use of cranial window in the latter study triggered inflammatory responses in the brain which resulted in elevated turnover rates. It should be pointed out that spine turnover rate differs in various brain regions. For example, Holtmaat et al. reported that spines turn over more slowly (both generation and elimination) in the visual cortex than in the somatosensory cortex, with the fraction of transient spines (lifetime ≤ 4 days) also lower in visual cortex [17].

## 3. Signaling events during spine formation and maintenance

Motility of dendritic spines is regulated by the dynamic balance between G-actin and F-actin [39]. F-actin consists of two pools, a large dynamic pool in the tip of the spine head and a small stable pool in the base of spine [6] [40]. With LTP induction, the stable F-actin is severed into short segments and reorganized to expand the spine [41]. Thus, the dynamics of actin cytoskeleton controls dendritic spine morphological remodeling and plenty of signaling molecules participate in this process [42–44].

Spine morphology is regulated by actin binding and cytoskeleton proteins. Drebrin was the first identified to modify dendritic spines since overexpression of drebrin in cultured neurons increased the length of spines [45]. Spines in the drebrin knockout mice exhibited normal morphology but altered plasticity [46]. Takahashi et al. reported that drebrin entered filopodia and formed an actin filament cluster to recruit postsynaptic components (including scaffolding protein PSD95), and this process enables the transition from filopodia to mature spines. Based on this observation, filopodia are classified into two types, an immature diffuse-type and a mature cluster-type. A filopodium with a drebrin cluster, whose maximum intensity was higher than twice the average intensity of the filopodium, was classified as a cluster-type filopodium. Otherwise, it was classified as a diffuse-type filopodium. The cluster-type filopodia were likely to be converted to mature spines [47]. In addition, overexpression of drebrin in neurons caused F-actin to accumulate in the growth cone, whereas knockdown of drebrin reduced F-actin level [48]. Drebrin binds to F-actin to generate thick bundles of F-actin [49], and drebrin also competes with other actin binding proteins such as ADF/cofilin which depolymerizes F-actin [50, 51].

Besides drebrin, other actin-binding proteins including myosin II, Abi-1 and spinophilin regulate actin polymerization in the dendritic spines. Myosin II belongs to the family of molecular motors which is highly expressed in dendritic spines, and regulates dendritic spine morphology and

synaptic plasticity [52]. Blockade of myosin II with shRNA suppressed the formation of mushroom-like spines and increased the presence of filopodia [53]. Abi-1 is a member of the c-Abl tyrosine interactor (Abi) protein family, which interacts with scaffolding proteins and F-actin in the spines [54]. Knocking down of Abi-1 by RNAi shifted spines to an immature form [55]. Spinophilin has an actin-binding domain at its N terminus and can bundle F-actin filaments [56]. Knockout of spinophilin in mice increased the presence of filopodia [57].

Actin polymerization is regulated by actin binding proteins, whose active and inactive states are regulated by small GTPases. Of the Rho family of small GTPases, three are most actively involved in spine morphogenesis, RhoA, Rac1 and Cdc42. These three GTPases are distinguished by two opposite activities: RhoA inhibits whereas Rac1 and Cdc42 promote spine growth. Tashiro et al. reported that in hippocampal neurons, Rac1 increased spine density but reduced spine length, while RhoA decreased both spine density and spine length [58]. Interestingly, RhoA and Cdc42 play opposite roles in stress fiber formation by controlling the phosphorylation of myosin light chain. RhoA inhibits myosin phosphatase via the Rho kinase while Rac1 and Cdc42 activate it via the serine/threonine kinase PAK [59, 60]. Thus, Rac1 and RhoA might have opposite effects on the same target proteins and hence opposite effects in regulating spine density. Similarly, Nakayama et al. found that Rac1 is essential for the maintenance of dendritic spines while enhanced RhoA activity led to significant simplification of dendrites [61].

Receptor tyrosine kinases also regulate spine morphology. Among them, the erythropoietin-producing hepatocellular carcinoma (Eph) receptors have unique activity on synapse. They consist of type A and type B receptor subclasses based on their binding capability to Ephrin A and Ephrin B ligands. Moeller et al. reported that activation of EphB2 in the cultured hippocampal neurons led to shortening of filopodia [62]. Furthermore, activation of EphB likely phosphorylates guanine exchange factors (GEFs) such as kalirin7, which further stimulates Rho family GTPases Rac1 and Cdc42 [63]. Opposite to EphB2, activation of EphA4 by its ligand, ephrin-A3, located in the perisynaptic processes of astrocytes, decreased spine length and density. Loss of EphA4 led to spine elongation and disorganization [64]. Similarly, in the hippocampus of ephrin-A3-null mice, EphA4 phosphorylation was decreased and abnormal spine elongation was observed [65]. Thus, either loss of EphA4 or ephrin-A3 induces identical dendritic spine deficits.

In summary, we have reviewed three types of important and representative signaling molecules in spine function. The first signaling pathway is mediated by actin binding proteins, the second is the family of small GTPases (including Rac1, RhoA and Cdc42, which determine the activity states of actin binding proteins), and the third is receptor tyrosine kinases. The absence or malfunctioning of the above three signaling pathways leads to altered spine morphogenesis and function.

## 4. Spine plasticity

Spine plasticity may be exhibited in two forms—changes in spine density and spine dimension. Change in spine density reflects modification of connection density between the presynaptic and postsynaptic neurons, which happens most commonly during brain development (increase, decrease/pruning) and aging/degeneration (decrease). Changes in spine

morphology/dimension, especially the size of spine head, have been widely reported, and are believed to be associated with changes in the strength of synapses that reside on these altered spines. In this chapter, we will focus on alterations of spine dimension.

### 4.1. Changes in spine morphology

Due to the heterogeneity of spine size/morphology, the most convincing way to demonstrate that spine morphology is altered is to compare the same set of spines before and after a manipulation, such as synaptic plasticity-inducing stimuli in brain slices or learning *in vivo*. By using time-lapse two-photon imaging on the same set of spines, Yang et al. found new spines were formed after *in vivo* experience in the form of sensory or motor, and a fraction of these newly appeared spines persisted for months after the experience. More importantly, of the appearance of these new spines is specifically related to the *in vivo* experience or training [66]. In addition, Hayashi-Takagi et al. showed that motor learning on rotarod led to an enhanced *Arc* signaling, together with an expansion of a subset of spines in the motor cortex. By expressing a photoactivatable GTPase Rac1 in spines, they further showed that prolonged photo-activation of Rac1 resulted in reversal of spine expansion and loss of motor memory. This is a striking demonstration that potentiated synapses and enlarged spines are likely the underlying biological substrates of stored memory and formed memory can be erased by reversing these changes [67].

Many studies have examined spine modifications with the induction of long-term potentiation (LTP) and long-term depression (LTD), since this procedure allows the examination of the same set spines associated with fast, large and long-lasting changes in synaptic strength. These two forms of synaptic plasticity refer to the increase and decrease in synaptic strength respectively, and are generally regarded as the cellular basis of synaptic modifications underlying developmental remodeling of neuronal connections, and learning and memory function in the adult brain [68]. When studied in brain slices (acute or organotypic culture), LTP or LTD is induced by stimulation of the presynaptic inputs with distinct patterns. In some studies, changes in the synaptic strength were also monitored, and thus changes in synaptic function and spine morphology can be related to each other in the same set of spines/synapse, or even a single synapse/spine [34, 69–71]. In general, spines exhibit the capacity of bi-directional changes in that spine enlargement is observed with LTP while spine shrinkage with LTD [72–74] (**Figure 2**). Either uncaging of caged glutamate onto a single spine [75] or electrical stimulation of a population of synapses [70, 71] had confirmed the above observations. Uncaging of glutamate directly enhances postsynaptic AMPAR function, and since it bypasses presynaptic release, and thus has provided the unambiguous evidence that postsynaptic changes can underlie the expression of LTP [69, 75]. These observations further indicate that morphological and functional changes are likely driven by the same stimuli or process (see below).

In general, there is a good correlation between the strength of a given synapse (measured by electrophysiological responses) and the size of spine. Electrophysiological responses are further determined by the number/density of AMPA receptors at a given synapse. Takumi et al. found a linear relationship between AMPAR density and the diameter of PSD [76]. Matsuzaki et al.

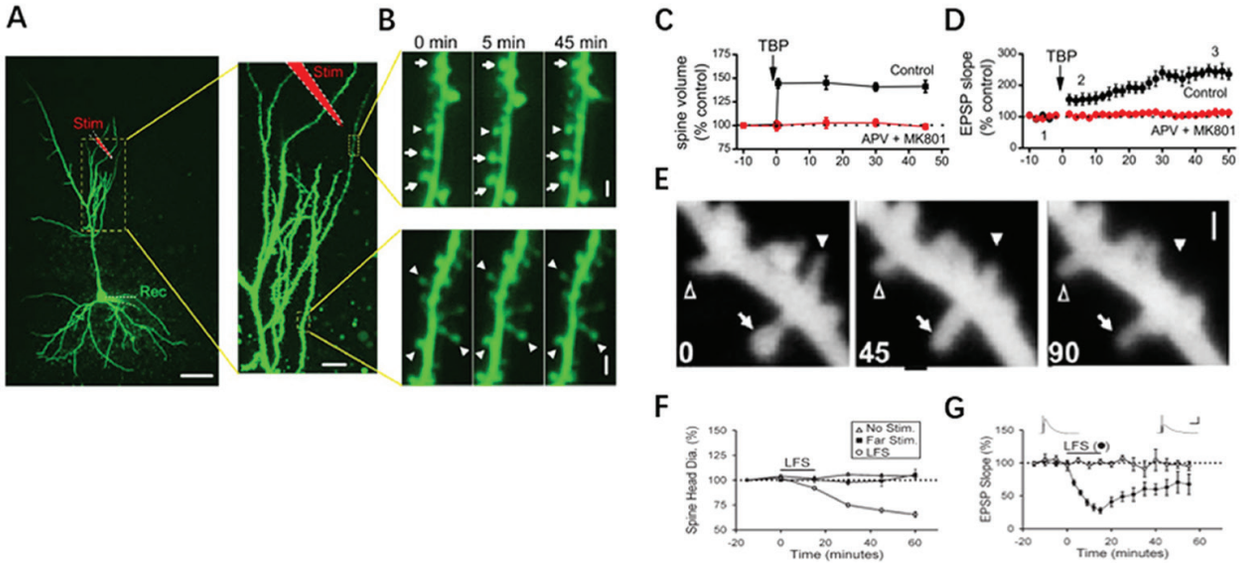


**Figure 2.** Bi-directional modification of spine size by synaptic plasticity. (A) Recording, synaptic stimulation and fluorescence imaging of the same set of synapses and spines in acute hippocampal slices. (B) Spine enlargement associated with LTP induction by theta burst stimulation, this enlargement is persistent and long-lasting. In addition, enlargement was restricted to spines close (upper) but not far away from the stimulation site (lower). (C) Change in spine volume before and after LTP induction and its requirement of activation of NMDARs since it was prevented by bath application of NMDAR antagonists APV and MK-801. (D) Increase in synaptic strength (EPSPs) as a result of LTP induction. LTP occurred in two phases, an initial rapid increase (indicated by 2 on the plot) and a slower gradual increase (indicated by 3). LTP was also sensitive to NMDAR blockade. (E) Spine shrinkage associated with LTD, it is persistent and long-lasting. (F) Shrinkage of spines occurred to those spines close to, but not to those far away from the stimulating electrode, or those had not received any stimulation. Compared to the almost instantaneous enlargement of spine heads after LTP, spine shrinkage develops slowly and takes much longer to reach a plateau. (G) Low frequency stimulation led to depression of EPSPs. Taken from [34, 71].

reported that the number of AMPAR in spines is of a large range. In addition, mushroom spines are enriched with AMPARs, compared to the low distribution of them in the thin spines and filopodia. These observations support a strong relationship between number of AMPAR and volume of spines [77]. In addition, it provides direct evidence that mushroom spines are functionally mature while thin spines and filopodia are not.

### 4.2. Synaptic plasticity

Synapses can change their strength by the activity patterns that they receive, and this modification allows synaptic strength to be adjusted to better suit the need for adaptation. Originally put forwarded by Donald Hebb and later adopted as "fire together, wire together" model, the current model of synaptic modification states that neurons sharing spike activity have increased connections between these two partners [78]. After the discovery of LTP in 1973, this activity-driven increase in synaptic strength has been extensively studied, both in acute brain slices and *in vivo* [68]; and has been used widely as a tool to induce synaptic modification in order to study the associated processes. Various molecules have been identified to be required for the induction and expression of LTP [68]. In general, Ca2+ entry or elevated intracellular Ca2+ concentration is required to convert electrical activity into intracellular signaling that determines the direction of synaptic changes. Usually a large but transient elevation in

Ca2+ concentration induces LTP while a small but much longer elevation in Ca2+ concentration results in LTD [79]. This Ca2+ entry can be through opening NMDA receptors, voltage-gated Ca2+ channels or metabotropic glutamate receptors [68]. Increase in postsynaptic kinase activity is usually required for LTP while phosphatase activity required for LTD. After a long debate, it is now generally agreed that synaptic modifications are expressed in the postsynaptic neurons, except in a few specific cases (such as mossy fiber LTP in the hippocampal CA3 region) [80, 81]. Postsynaptic changes involve the translocation of AMPARs and their phosphorylation state, in that LTP is associated with translocation of AMPARs to synapse and/or increased phosphorylation of AMPARs while LTD with endocytosis of AMPARs and/or dephosphorylation of AMPARs [82–85].

### 4.3. Relationship between spine and synapse plasticity

Since both increase in the synaptic strength and enlargement of dendritic spine occur with LTP, an obvious question is whether changes in synaptic physiology/function are casually related to changes in spine morphology/structure. More specifically, are these two processes driven by the same initial process? Does the occurrence or persistence of one process require the occurrence/presence of the other? It is now well established that influx of Ca2+ through synaptic NMDARs during LTP induction drives AMPAR phosphorylation and/or insertion [68], and polymerization of action filaments inside spines which drives enlargement of spine heads [74] (**Figure 3**). Thus, the initial changes in function and structure are driven by the same signaling process. This initial increase in synaptic response and spine volume occurs very rapidly (less than 1 min) [71].

Dendritic spine heads accumulate F-actin during the rapid expansion phase of synaptic modification. Potentiation of single synapse/spine with uncaging of glutamate led to a significant expansion of the spine head and a shortening and widening of the spine neck [86, 87]. Spine expansion takes place rapidly after LTP, as fast as it can be measured (~ 20 sec after LTP induction) [71]. F-actin concentration inside the spine head rises, together with the entry of actin-severing, actin-depolymerizing/−polymerizing, actin-capping proteins, while actin-stabilizing proteins leave the spines [6, 39, 86, 88–90]. Actin-depolymerizing agent, cofilin, is highly elevated in spines during this initial process [89]. Interestingly, unlike the expression of LTP, this initial spine expansion did not require postsynaptic exocytosis or PKA signaling [71], suggesting the involvement of different signaling pathways in spine enlargement than that supports LTP. After this initial rapid expansion, the next phase of events lasts up to 1 h, with spine head volume decreased from the initial increase, but still larger than the pre-LTP baseline. In addition, the total actin concentration in the spine may drop to the baseline level [89].

LTD is associated with the shrinkage of spines and removal of synaptic AMPARs via internalization [34, 36, 39]. During the induction of LTD with low frequency synaptic stimulation, Ca2+ influx through the activated NMDARs is required for both LTD and spine shrinkage [34, 70]. Ca2+ entry through synaptic NMDARs leads to the activation of calcineurin which is also required for both LTD and spine shrinkage, while activation of protein phosphatase 2A is required for LTD expression but not spine shrinkage, while elevated cofilin activity is required for spine shrinkage but not LTD [34, 39, 70, 91]. Consistent with the above conclusion, Sdrulla

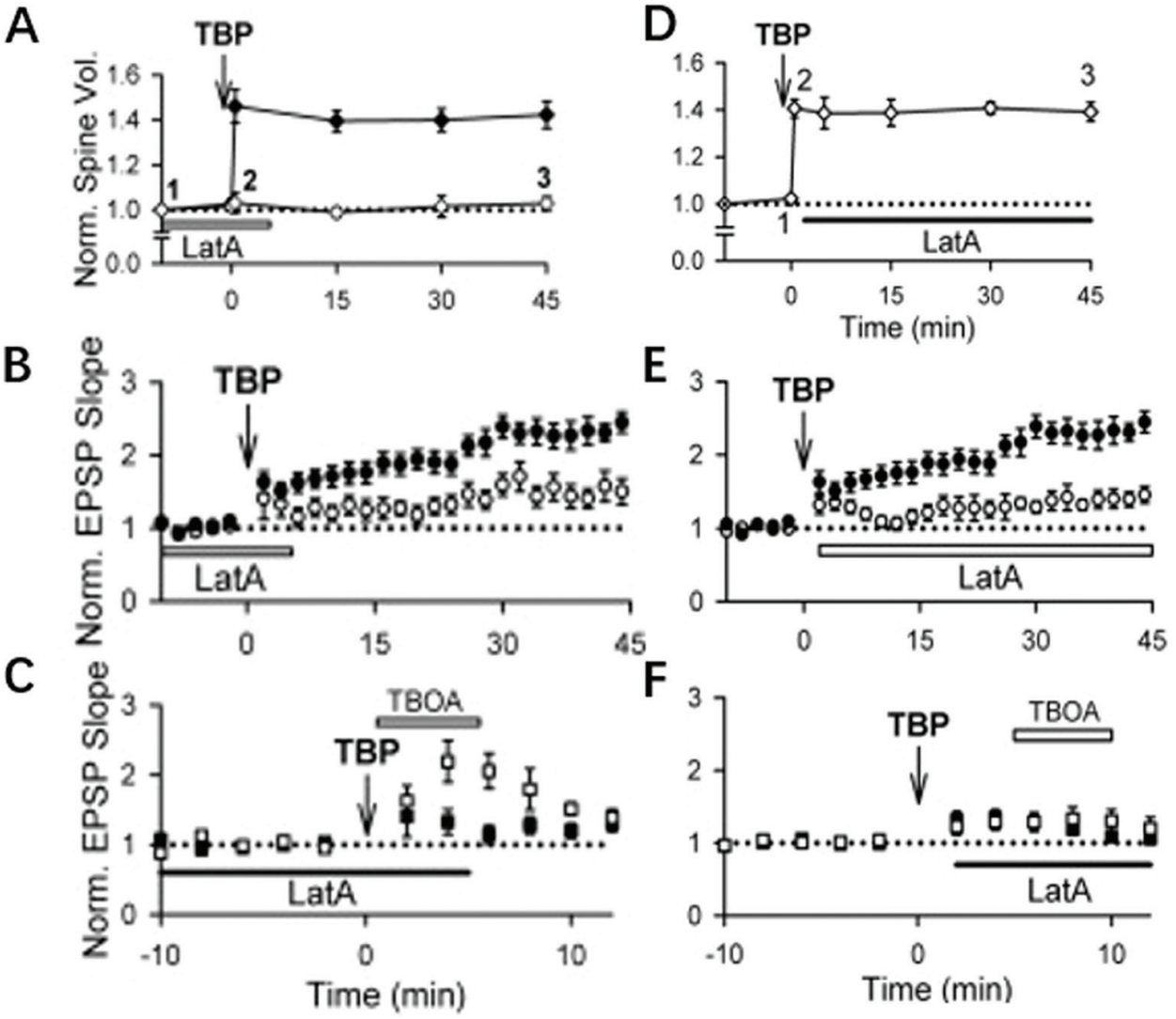


**Figure 3.** Time-dependent reversal of synaptic and spine modification. (A) Spine shrinkage induced by low frequency stimulation (LFS) can be readily reversed by subsequent high frequency stimulation (HFS). (B) Spine enlargement induced by HFS is also readily reversed by subsequent LFS. (C) Spine enlargement induced by TBP can be reversed by LFS only if LFS is given within a time window of about 15 min after TBP. (D) this critical reversal window also holds for reversing TBP-induced LTP. (E) LFS given outside this reversal window does not affect spine size. (F) LFS given outside the reversal window does not reverse LTP either. Taken from [34, 71].

and Linden demonstrated that LTD expression and spine changes in cerebellar Purkinje cells could be induced independently of each other, and induction of one did not affect the other [92]. Wang et al. reported that trafficking of AMPARs to and away from PSDs was activity-independent and not associated with alterations in spine size. The significance of this finding requires further investigation [70].

One interesting and important feature of synaptic modification is its reversibility. This reversibility is defined by reversal of synaptic modification after its induction [34, 93]. There are a few aspects to this reversal: (1) reversal applies to both LTP and LTD, and spine enlargement and spine shrinkage [34, 71] (**Figure 4**). More specifically, low frequency stimulation reverses LTP and spine enlargement, while high frequency stimulation reverses LTD

and spine shrinkage. (2) There is a critical time window only during which reversal can occur [34, 71, 93, 94] (**Figure 4**). In hippocampal slices, the window for LTP reversal is about 15–30 min [71]. (3) The typical stimuli that can induce reversal are not capable altering basal synaptic strength or spine dimension [71, 93, 95, 96].

Although it is generally believed that expression of LTP requires the addition of synaptic AMPARs, some evidences suggest that these newly added AMPARs are not delivered directly into the PSDs inside spines, but rather they are either delivered to regions outside synapses (i.e., the perisynaptic regions; [82] or onto dendritic shaft [83]. These AMPARs

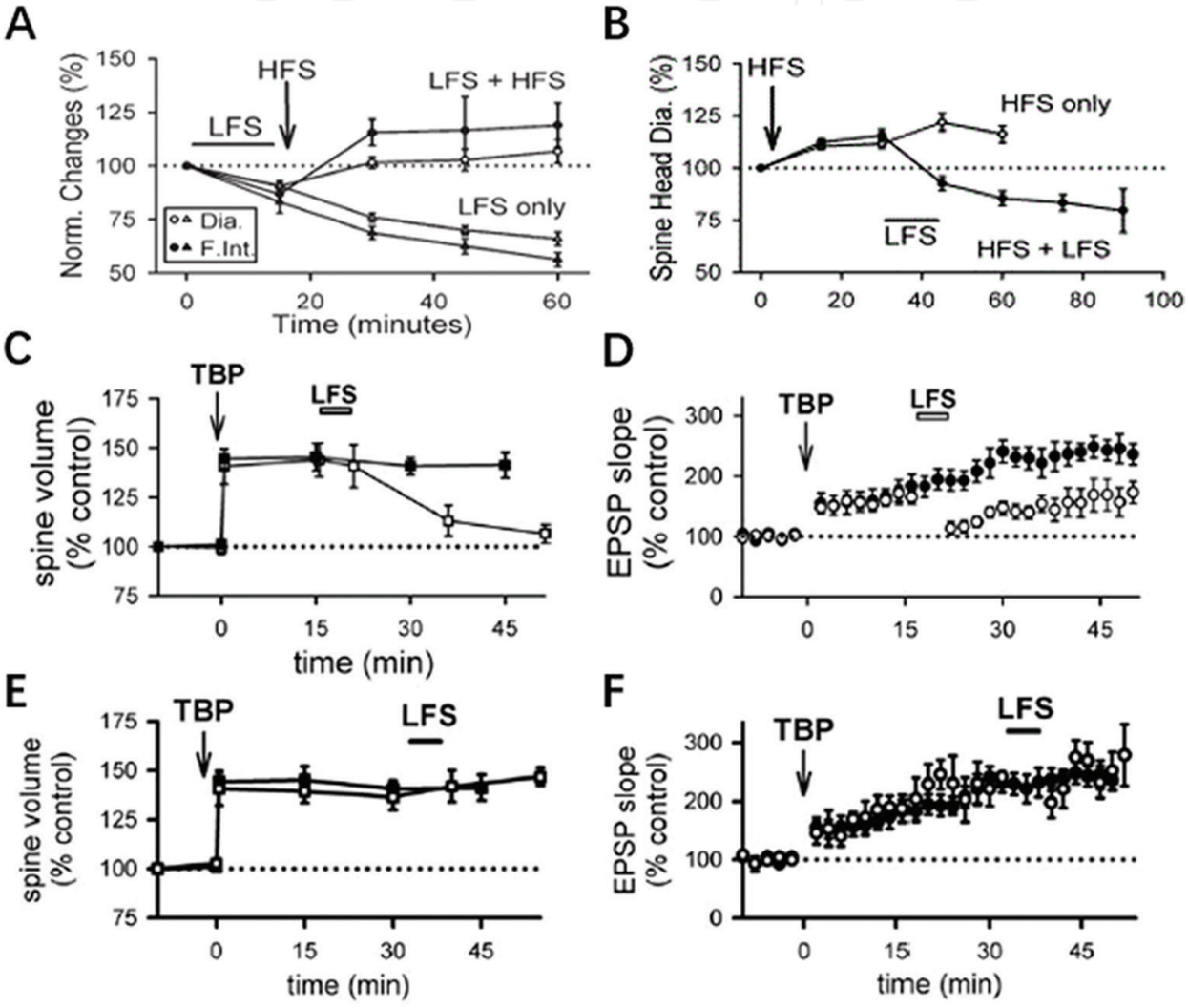


**Figure 4.** Actin polymerization is required for spine expansion and maintenance of perisynaptic AMPA receptors. (A) Actin depolymerizing agent Latrunculin A (LatA) added before and during TBP abolished spine expansion. (B) Bath perfusion of LatA before and during TBP impaired enhancement of synaptic response (EPSPs). (C) Bath perfusion of LatA 2 min after TBP did not disrupt the delivery of AMPARs to perisynaptic site, as revealed by the increased in responses to application of glutamate transporter blocker TBOA (open symbols). (D) Bath perfusion of LatA 2 min after TBP did not affect spine enlargement, indicating that persistent spine enlargement does not require persistent actin polymerization. (E) Bath perfusion of LatA 2 min after TBP prevented the occurrence of gradual increase in EPSP enhancement which requires the synaptic addition of new AMPARs. (F) Addition of LatA 2 min after TBP removed the newly delivered perisynaptic AMPARs as revealed by the absence of increase in response to TBOA. Taken from [83].

then move laterally into spines/PSDs. Thus, with LTP induction, two rapid processes (within 30 sec) occurs independent of each other: spine expansion which requires actin polymerization and activation of NMDARs but not postsynaptic PKA activation, and delivery of AMPARs to the perisynaptic regions which requires activation of NMDARs and postsynaptic PKA signaling but not actin polymerization. The next 15 min or so (reversal time window) determines whether LTP and spine expansion can be stabilized into a long-term change. During this period, translocation of the newly delivered perisynaptic AMPARs stabilized spine expansion, while removal of these receptors led to collapse of enlarged spines [71]. On the other hand, reversal of spine enlargement also removed these perisynaptic AMPARs. Hence, there is a mutual interaction between perisynaptic AMPARs and spine enlargement in that the presence of one is required to sustain the other (**Figure 3**). Yang et al. found that postsynaptic PKC activity is required for the translocation of perisynaptic AMPARs to synapse, and in the absence of PKC activity, these AMPARs remain perisynaptic. Importantly, as long as the perisynaptic AMPARs are present, both LTP and spine expansion exist in a labile state in that they can either be reverted to the baseline state (no plasticity), or they can enter a stabilized state of persistent increase in synaptic strength and spine size (persistent plasticity). Low frequency synaptic stimulation given within a 15 min "grace period" post-LTP induction reversed spine expansion and removed AMPARs from the perisynaptic regions and hence blocked the conversion of short-term plasticity to a long-term one (**Figure 5**) [71, 82].

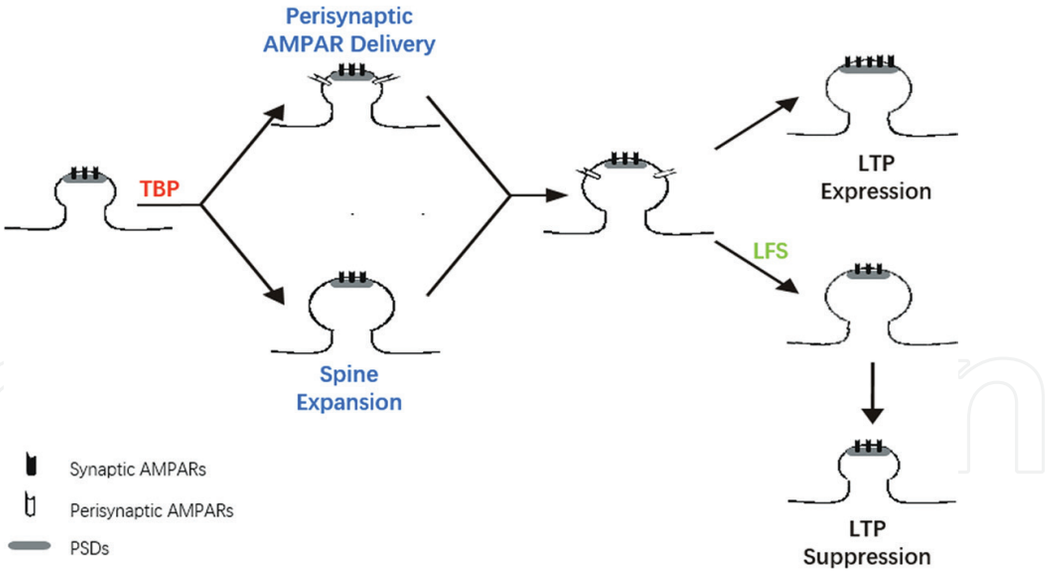


**Figure 5.** Two-step model for coordinated expression of synaptic potentiation and spine enlargement. TBP triggers two initial processes, spine enlargement and perisynaptic delivery of AMPARs. These two processes occur simultaneously and mostly independent of each other. In the absence of any disturbance, perisynaptic AMPARs translocate into synapse, which stabilizes both AMPARs and spine enlargement, and this leads to persistent potentiation of synaptic responses and spine enlargement. On the other hand, when low frequency synaptic stimulation (LFS) is given within this "grace period" when both processes are in a liable state, it readily removes perisynaptic AMPARs. As a result, synaptic potentiation is aborted and spine enlargement collapses, and no LTP and spine enlargement. This model shows the interaction between functional and structural aspects of synapse modification is critical to the persistency and long-lasting occurrence of synaptic modification.

The above results are consist with a model (**Figure 5**) in which (1) the expression of functional plasticity (LTP) and structural plasticity (spine enlargement) are initially two independent processes only share the activation of NMDARs; (2) these two processes then enter an interactive state that the continuous presence of one is required for the persistence of the other; (3) the above state is liable in that interference (such as low frequency stimulation) can revert both changes back to the baseline; (4) once both processes are stabilized, synapse modification has entered a state resistant to reversal. We like to note that during the "grace period" coordinated changes in synaptic plasticity (function and structure) are cross-checked to ensure that they do occur together, and in the situation only one such process occurs (perhaps can be viewed as a mistake), the other process will be aborted albeit in process. This double-proof mechanism is essential to ensure that only appropriate changes are allowed to be sustained, and may thus be especially important in face of the highly dynamic nature of synaptic modifications, such as those occurring during early neural development [94].

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 hence it is difficult to study. Even if monitoring changes in the same set of synapses/spines, it is usually more difficult to exclude the possibility that the reduced synaptic function and spine number is caused by deterioration of the health of the preparation, or by some other unknown or uncontrolled processes that occur randomly during the long period (>hours) between LTD induction and spine loss. Nonetheless, a few studies have examined this process. By using organotypical slices and monitoring both presynaptic boutons and spines, Becker et al. showed that LTD induction increased the turnover rate of presynaptic boutons and resulted in decreased synaptic contacts between the pre- and post-synaptic sites. Although presynaptic boutons and postsynaptic spines disappear at much greater rate after LTD, there is no particular pattern to follow, since disappearance of either presynaptic boutons or spines could occur prior to the other [97]. Therefore, the above observations suggest that the mismatch between presynaptic and postsynaptic sites is more likely a key factor in the elimination of synapse, while the exact sequence might not play much role.

## 5. Conclusions

Dendritic spines are small protrusions on the dendritic shaft as major excitatory inputs site on the excitatory neurons in the adult cortex. Spines play critical roles in the excitatory synaptic transmission and plasticity. Genesis of spines occurs during brain development, and is subjected to activity-dependent modulation to determine their fates, either to transit to mature spines or be eliminated. Spines are the site where physiological/functional and morphological/structural modifications meet and integrate, during both physiological (such as memory formation) and pathological (such as neurodegeneration) processes. Interestingly, early changes in functional and structural aspects of synapse modification occur independently, but they subsequently interact with each other to sustain changes in both. This highly interactive nature ensures that the end result is a coherent modification of synapse function

and structure. Extensive progress has been made on our understanding of the structure and function of spine which vastly has advanced our understanding of neuronal and synaptic communication and plasticity. In addition, changes in spine density and dimension may serve as a marker of pathological processes and hence have potential therapeutic/diagnostic values.

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## Competing interests

The authors declare that they have no competing interests.

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