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Structural plasticity of dendritic spines

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Dendritic spines are small mushroom-like protrusions arising from neurons where most excitatory synapses reside. Their peculiar shape suggests that spines can serve as an autonomous postsynaptic compartment that isolates chemical and electrical signaling. How neuronal activity modifies the morphology of the spine and how these modifications affect synaptic transmission and plasticity are intriguing issues. Indeed, the induction of long-term potentiation (LTP) or depression (LTD) is associated with the enlargement or shrinkage of the spine, respectively. This structural plasticity is mainly controlled by actin filaments, the principal cytoskeletal component of the spine. Here we review the pioneering microscopic studies examining the structural plasticity of spines and propose how changes in actin treadmilling might regulate spine morphology.

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Morphology of the dendritic spine

In the vertebrate central nervous system, excitatory synapses are usually formed on small, mushroom-like protrusions on dendrites called dendritic spines [1,2]. Typically, one single glutamatergic synapse is formed at the head of a spine, although some spines may receive multiple presynaptic termini or non-excitatory inputs [1,3]. Spines are composed of highly specialized subdomains exerting different functions in synaptic transmission and plasticity. Beneath the synapse, one can find an electron-dense disc-like structure, called the postsynaptic density (PSD). The PSD is composed of multiple proteins that bind with each other through specific domain–domain interactions, forming a mesh-like structure organized in consecutive layers [4–7]. These proteins include neurotransmitter receptors, scaffolding proteins that stabilize those receptors, signal transduction molecules, ion channels, and cytoskeletal components [7]. In addition to the PSD, the spine membrane may contain specialized microdomains for endocytosis or exocytosis [8,9]. The cytoskeleton in spines is mainly formed by actin filaments (F-actin), which serve both as a structural framework and as the principal regulator of protein and vesicular trafficking [10–12]. Mature spines may also contain intracellular membranous structures (e.g. spine apparatus or amorphous vesicular clumps), protein synthesis machinery such as polyribosomes, and mitochondria [13–17]. The spine head is connected to the dendritic shaft via a thin neck (width of $\sim$0.2 μm) that is thought to work as a diffusion barrier for molecules and ions. Moreover, the spine and the presynaptic terminus are surrounded by perisynaptic glial processes, thereby forming a tripartite synapse [18,19]. These morphological characteristics have led researchers to consider that the dendritic spine may function as a microcompartment that confines postsynaptic signaling both chemically and electrically [1,2,20,21].

Spines exhibit a wide range of size and shapes, even within a single neuron. During cortical development, spines are rather thin and elongated and gradually gain a typical mushroom-like structure with a prominent head and a thin neck as the tissue matures [22–24]. There is a positive correlation between the spine head volume, the PSD area, the presynaptic active zone area, the number of AMPA-type glutamate receptors, and the synaptic strength [25–27,28•]. These correlations suggest that spine structure is tightly coupled to synaptic function. Furthermore, time-lapse studies have shown that spines are extremely plastic and motile. In sensory cortex, this motility is regulated by sensory experience and significantly decreases with age [22,29,30]. However, we still do not fully understand the intrinsic relationship between structural and functional plasticities of the spine. Therefore, it is of great interest to know how spine head and neck morphologies are regulated by neuronal activity to ultimately comprehend why spines have such unique shape and how its modifications affect synaptic functions.

Electron microscopic studies on the activity-dependent structural plasticity of dendritic spines

The very first evidence supporting the structural modification of dendritic spines associated with synaptic activity came from a series of electron microscopic (EM) studies by Eva Fifková and co-workers in 1970s to 1980s. They induced long-term potentiation (LTP) at synapses between hippocampal perforant path and dentate granule cells *in vivo*, using the same preparation

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wherein Bliss and Lømo [31] reported the first synaptic plasticity in the mammalian central nervous system. Only two years after the study by Bliss and Lømo, Fifková and co-workers found that dendritic spines on stimulated pathway were larger than those in unstimulated pathway or in control animals [32••]. This enlargement was found as early as 2 min after tetanic stimulation and lasted up to 23 h [33•]. At the same time, they found wider and shorter spine necks after LTP induction [34•]. If we approximate the spine neck to a cylinder, we calculate that these changes reduce the spine electrical resistance by 74% at 4 min and by 54% at 60 min. These changes may lead to more efficient transmission of electrical current generated at the dendritic spine head.

Using a similar approach, Desmond and Levy observed an increase in the proportion of concave-shaped spines with a concomitant decrease in those with simple and ellipsoid shape [35]. Along with it, total PSD surface area associated with concave spines increased significantly [36]. Harris and co-workers examined CA1 pyramidal cells in hippocampal slices, a conventional preparation for studying LTP, with electron microscopy and found that the percentage of spines containing polyribosomes increased 2 h after a tetanic stimulation [15]. Those spines contained significantly wider PSD as well. Other features commonly found after LTP induction is an increase in the number of spines with perforated PSD [23,37,38], the number of bifurcated spines ([39], but also see [40]) and the formation of spinules from the spine head [41,42]. These studies strongly support the view that the structure and contents of a dendritic spine can undergo long-term modifications during synaptic plasticity.

Light microscopic studies on the activity-dependent structural plasticity of dendritic spines

In these EM studies, because of an obvious lack of capability of time-lapse imaging, it was not possible to demonstrate whether existing spines became enlarged or whether spines with larger size were generated *de novo* by LTP induction. It was even not possible to know whether a given synapse under observation was actually potentiated or not. Those results relied on statistical differences between different populations of spines and, therefore, had a certain limitation in interpretation as to whether they were truly observing phenomena directly associated with LTP or processes occurring in parallel and not directly involved in the induction or maintenance of LTP itself.

Hosokawa *et al.* were the first to attempt time-lapse imaging of the same set of dendritic spines in hippocampal slices before and after LTP induction [43]. They used a confocal microscope to observe DiI-labeled neurons and found an increase in length in a subpopulation of small spines 3 h after the induction of chemical LTP. Maletic-Savatic *et al.* employed two-photon microscopy in GFP-transfected neurons and induced LTP by local stimulation with a glass electrode [44•]. They observed the generation of new filopodia-like protrusions and, at the same time, the loss of existing spines. Engert and Bonhoeffer [45•] also carried out a similar experiment by locally perfusing a dendritic segment with Ca^{2+}-containing extracellular fluid while suppressing synaptic transmission in the rest of the dendrite by Cd^{2+}-containing solution. Electrical stimulation resulted in the generation of new spines only in the segment where Ca^{2+} was available. However, the generation of new spines did not synchronously occur with the increase in the synaptic transmission. While the increase in excitatory postsynaptic current (EPSC) amplitude was observed within a few minutes after LTP induction, the generation of new spines occurred much later.

Therefore, it still remained an unanswered question whether the enlarged spines indeed underwent LTP or not. To elucidate this issue, Matsuzaki *et al.* [28•,46••] employed a two-photon-induced glutamate uncaging technique, which allows the controlled release of glutamate in a very small volume compared with other approaches (such as local glutamate application through pipette or conventional UV-mediated uncaging method). Combined with electrophysiological recordings, they showed that repeated uncaging of glutamate in Mg^{2+}-free solution induced both an expansion of the dendritic spine as well as an increase in the synaptic electrical response. Okamoto *et al.* [47•] found a similar expansion of the dendritic spine that synchronized with the local electrical stimulation of presynaptic fibers (Figure 1a). The same result was observed when glutamate uncaging was paired with channelrhodopsin-induced depolarization of the postsynaptic neuron [48]. In addition to these studies demonstrating structural changes of existing spines, a recent study demonstrated a *de novo* formation of new spines after local glutamate uncaging in the dendrite [49]. Whether the diameter and length of the spine neck change or not has not been confirmed using live imaging techniques available so far. The recent development of superresolution imaging methods will be key to answering this question [50•,51•,52•,53•,54•].

Conversely, the induction of long-term depression (LTD) by either electrical or chemical stimulation induces shrinkage [47•,55•,56,57] or loss of dendritic spines [47•,58•]. Spine shrinkage is persistent but reversible, as it can be reverted by a potentiation stimulus [55•]. These studies on LTD and other recent studies on LTP [59,60] show that structural plasticity can be dissociated from functional plasticity. Although they share the same initial triggering mechanisms, they seem to be regulated by parallel but distinct downstream intracellular signaling pathways. Thus, the role of morphological changes of spines in synaptic transmission and plasticity still remains an open question.

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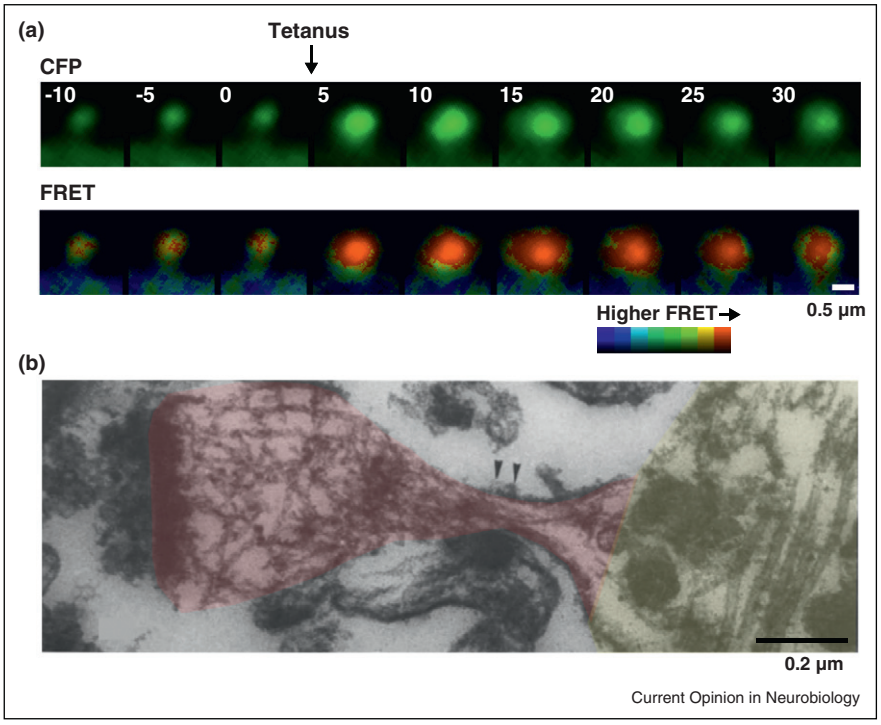
Figure 1



Actin filaments in the dendritic spine. **(a)** Expansion of the dendritic spine and rapid polymerization of actin by local tetanic stimulation. Actin polymerization was visualized by FRET-based imaging method, which detects the proximity of actin molecules. Obtained from [47•]. **(b)** An electron micrographic image of a dendritic spine showing S1-fragment labeled F-actin. Contrast was adjusted from the original, and coloring (red, spine head; yellow, dendritic shaft) was added by the authors of this review. Arrowheads point to the spine neck. Obtained from [12].

F-actin regulation as a mechanism underlying structural plasticity

What molecular mechanisms are responsible for the structural plasticity of dendritic spines? By decorating F-actin with myosin subfragment 1 (S-1 fragment), Fifková *et al.* demonstrated that actin filaments are associated with the plasma membrane and the PSD at their barbed ends and form a lattice structure within the spine head matrix [12] (Figure 1b). By contrast, the actin filaments are organized in long strands in the spine neck and dendritic shaft. This finding was also confirmed by a recent EM study [61]. The authors predicted that, given the dynamic properties of actin, actin filaments play a crucial role in synaptic plasticity, by changing the shape of the presynaptic and postsynaptic side and, in neuronal circuits, by mediating the retraction and sprouting of synapses [12].

Consistent with the important role of F-actin regulation in synaptic plasticity, the pharmacological manipulation of actin polymerization and depolymerization effectively blocks LTP [62,63] and, at the same time, suppresses the structural enlargement of dendritic spines [46••]. The rapid polymerization of actin in spines during LTP was demonstrated by a FRET-based method that detected actin-actin interactions in real time [47•] (Figure 1a). Using the same system, it was also demonstrated that LTD is accompanied by depolymerization of F-actin [47•].

Actin undergoes a rapid turnover in the spine, replacing almost the entire molecular population every 2–3 min [64,65•]. Recent studies have revealed the fine details of actin dynamics within dendritic spine subdomains by using photoactivatable and photoswitchable fluorescent protein-tagged actin [65•,66••]. They found that actin undergoes a constant inward flow from the periphery to the center of the spine on the order of minutes. Because the speed of diffusion of monomeric actin (globular or G-actin) is expected to be much faster (on the order of seconds), the observed fluorescence movement reflects the treadmilling of F-actin, i.e., the movement of the monomer within the filament while it polymerizes at one side (the barbed end, mainly located at the periphery) and depolymerizes at the other one (the pointed end, located at the spine core; Figure 2a). This is consistent with the polarity of actin filaments revealed by electron microscopic observation [12].

Importantly, stimulation of synaptic glutamate receptor slows down F-actin turnover/treadmilling [64,65•]. Furthermore, Honkura *et al.* found that LTP induction

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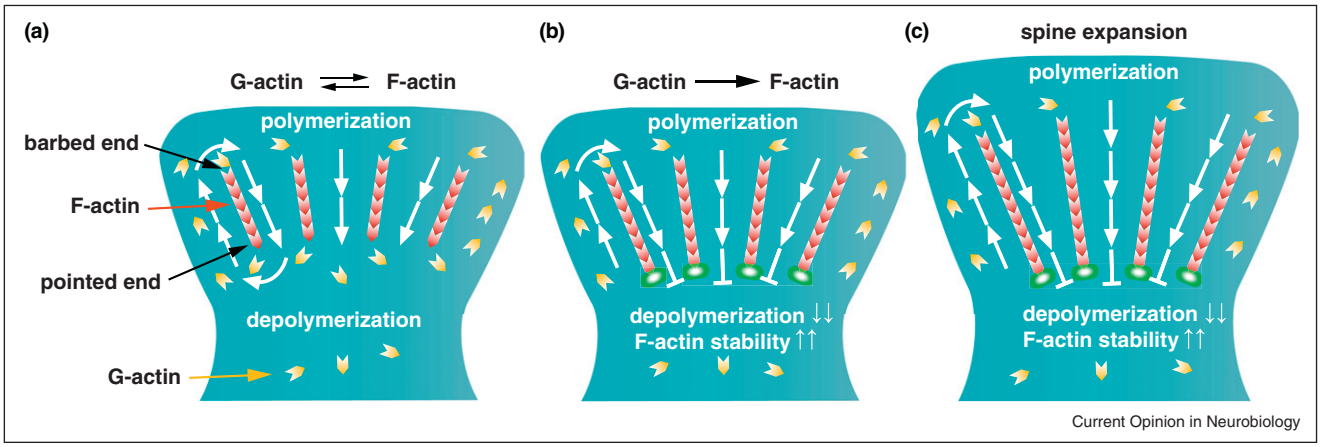
Figure 2



Proposed mechanisms for spine expansion. **(a)** In a naive spine, there is a constant treadmilling of actin from the periphery to the center of the dendritic spine, maintained by an equilibrated rate of F-actin polymerization/depolymerization. **(b)** LTP induction stabilizes the actin filaments and slows down the depolymerization at the pointed end of F-actin located at the core of dendritic spine. **(c)** Polymerization continues in the periphery of dendritic spine, thereby generating the driving force that expands the spine head.

leads to a formation of a new stable population of actin at the core of the spine head [65•]. This could be explained by a reduced depolymerization rate from the pointed end of the actin filament at the core of the spine. Polymerization would continue at the barbed end in the spine periphery, thereby generating the force that enlarges the dendritic spine. This effect would also be responsible for the overall shift in G-actin/F-actin equilibrium towards polymerization. We propose that this is the mechanism of expansion of the dendritic spine during LTP (Figure 2b and c).

It is therefore crucial to elucidate the signaling pathways that regulate F-actin treadmilling during LTP to understand synaptic plasticity [67,68]. The blockade of NMDA-type glutamate receptor (NMDAR) completely inhibits structural LTP [46••,47•]. Inhibition of Ca^{2+}/calmodulin-dependent protein kinases (CaMK) partially blocks the spine enlargement [46••,69]. One of the major members of the CaMK family present in the PSD, CaMKIIβ, bundles F-actin filaments independently of its kinase activity. Interestingly, the activation of CaMKIIβ by Ca^{2+}/CaM inhibits this F-actin bundling capacity [70]. Such ability may determine the time window wherein F-actin can be reorganized [71•]. A recent imaging study detected a persistent activation of the Rho family of small G-proteins in the dendritic spine after LTP induction [72•]. The pharmacological blockade of downstream signaling pathway of these proteins, including p21-activated kinase (PAK) and Rho-associated, coiled-coil containing protein kinase (ROCK), effectively blocked spine enlargement [72•]. These pathways regulate the activity of several actin-binding proteins [68], such as profilin and cofilin, which might ultimately be responsible for altering the rate of actin polymerization/depolymerization and treadmilling and, thus, for controlling spine morphology.

Concluding remarks

The development of new imaging and optical manipulation techniques allows us to visualize the behavior of single dendritic spines during synaptic plasticity in great temporal and spatial detail. This technology revealed a novel aspect of hippocampal LTP, namely the structural modification of the dendritic spine. There is a tight correlation between the physiology of synaptic transmission and the shape of the dendritic spine, although both phenomena could play distinct and complementary functions in neuronal plasticity. The current development of more sophisticated imaging modalities combined with molecular and electrophysiological methods will further elucidate the fundamental role that the morphology of the dendritic spine may play in the processes of learning and memory.

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