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REVIEW

Structural plasticity of dendritic spines

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Abstract Dendritic spines are the major targets of excitatory synaptic input. They exist in a wide variety of shapes and sizes, from thin to mushroom-shaped to stubby. One of the striking characteristics of dendritic spines is their motile nature. Spines can undergo various structural modifications such as changes in density, shape, size, and motility. During development, spines are highly dynamic and many spines are formed and eliminated. As animals mature, most spines become stable and the vast majority of them can last throughout life. However, spine morphology can still undergo progressive changes. Structural dynamics of dendritic spines is thought to play important roles in synapse plasticity and information processing. Abnormal spine structures are often associated with malfunction of the nervous system.

1 Introduction

Dendritic spines are small protrusions from neuronal dendritic surface. These thorn-like structures were first described by the Spanish neuroscientist Santiago Ramon y Cajal in 1888 (Ramon y Cajal, 1888). The spine was introduced initially as an anatomical structure and the importance of spine structure was not well appreciated until late 1950s when electron microscopy (EM) revealed that spines are critical components of interneuronal synaptic contacts. We now know that spines are present in all vertebrate and even some of the invertebrate central nervous system. Spines are the primary postsynaptic sites of excitatory synapses. In the cortex, approximately 90% of all excitatory synapses and more than 30% of all inhibitory synapses occur on dendritic spines (Gray, 1959a; Sala, 2002; Shepherd, 2004). In the adult human brain, there are more than 10^{13} spines. However, the number of spines can change during life. Spinogenesis starts shortly after birth and spine density reaches the peak during early developmental stages. But spine density reduces subsequently until it reaches mature density several months later (Rakic et al., 1986; Nimchinsky et al., 2002; Zuo et al., 2005a). Although spines are relatively stable in an adult animal, spine turnover (spine formation and elimination) still occurs throughout the lifetime of the animal (Grutzendler et al., 2002; Trachtenberg et al., 2002; Holtmaat et al., 2005; Zuo et al., 2005a; Holtmaat et al., 2006; Majewska et al., 2006). In addition to the change in spine number, spines can also undergo other types of morphological modifications such as changes in size, shape, and even motility (Dailey and Smith, 1996; Ziv and Smith, 1996; Fischer et al., 1998; Dunaevsky et al., 1999; Lendvai et al., 2000; Bonhoeffer and Yuste, 2002; Zhang and Murphy, 2004; Zuo et al., 2005a). Therefore, spines are essentially dynamic structures that can undergo various structural rearrangements. Although spines have been discovered for more than a century, the functional significance of spine dynamics, and its roles in the modulation of higher order brain function such as learning and memory remain largely unclear. Recent studies, especially those with *in vivo* time-lapse imaging techniques, have provided valuable information about how the structural modifications of dendritic spines are associated with changes in synaptic function. Here we review recent advances in the study of spine structural plasticity, and discuss the potential function of spine dynamics.

2 Structure of dendritic spines

Dendritic spines are tiny membranous structures. They have a typical length ranging from 0.1 to 2 μm (can up to 6 μm in hippocampal CA3 region) (Chicurel and Harris, 1992; Harris and Kater, 1994; Shepherd, 1996; Hering and Sheng, 2001) and a volume less than 1 μm×1 μm×1 μm (Peters and Kaiserman-Abramof, 1970; Harris and Stevens, 1989; Harris and Kater, 1994; Harris, 1999). A typical spine has a bulbous head and a thin spine neck

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which connects the spine head to the main shaft of the dendrite. However, spines can have a variety of appearances. Based on their shape and the relative size of the spine head and neck, spines are commnonly divided into three major categories: mushroom spines, thin spines and stubby spines (Fig. 1) (Peters and Kaiserman-Abramof, 1970; Nimchinsky et al., 2002; Lippman and Dunaevsky, 2005). Mushroom spines have a mushroom-shaped appearance with typical bulbous spine heads and short spine necks. Thin spines have smaller spine heads but narrower and relatively longer necks. Stubby spines are short protrusions lacking a clearly distinguishable head and neck (McKinney, 2005; Calabrese et al., 2006). This morphological classification of different spine types is largely qualitative. Because spines can vary in size, shape, and length, a continuous spectrum of intermediate morphology may exist. Currently, there are no consensus criteria for differentiation of different spine types. In addition, spines may have various appearances. For examples, some spines have small protrusions called spinules emerging from their heads (Tarrant and Routtenberg, 1977; Harris, 1999). This structure may play a role in adjusting membrane surface area and therefore may be important for regulating structural plasticity of spines (Harris, 1999; Nimchinsky et al., 2002). Some neurons have specialized spines. For example, the proximal dendrites of CA3 pyramidal neurons possess large and branched spines called thorny excrescences. These thorny excrescences are specialized postsynaptic structures. Each excrescence has a single spine neck but may have two or more spine heads (Chicurel and Harris, 1992; Lauer and Senitz, 2006; Bourne and Harris, 2008). They form synapses with mossy fiber terminals of granule cells.

In addition to the above-mentioned spine protrusions on dendrites, there is another type of dendritic protrusions called filopodia. These structures are generally not classified as spines. However, they are related to spines and are often considered as spine precursors. Filopodia are highly abundant during early development but are scarce in adulthood. A typical filopodium is a long (can up to 10 μm) and thin protrusion lacking a bulbous head, normally with a pointy ending (Sorra and Harris, 2000). In transgenic mice where neurons are labeled with genetically encoded fluorescent proteins, filopodia are easily distinguishable from spines by their hair-like appearance and they are usually dimmer in fluorescence than spines. One of the remarkable features of filopodia is that they are highly dynamic. Their length and shape can change on the time scale of minutes or even seconds. Another feature is that filopodia are transient. They have a lifetime on the order of minutes to hours. Filopodia on cultured neurons can appear and disappear within minutes, with an average lifetime of approximately 10 minutes (Dailey and Smith, 1996; Ziv and Smith, 1996). However, filopodia have a longer lifetime *in vivo*. Zuo et al have shown that filopodia turnover is less than 20% within 1 h in young animals, and is about 6% over 1 h in adult animals (Zuo et al., 2005a). Although most filopodia disappear within hours, a small percentage of filopodia can transform into spine-like protrusions and last over days (Zuo et al., 2005a). Therefore, it is generally believed that filopodia are precursors of spines. Consistent with the idea that filopodia are spine precursors, both *in vivo* and *in vitro* experiments have shown that filopodia can form synaptic contacts with neighboring axons (Ziv and Smith, 1996; Fiala et al., 1998). However, it should be noted that most filopodia are not associated with presynaptic boutons and that most filopodia disappear without forming spine-like structures (Ziv and Smith, 1996; Zuo et al., 2005a). On the other hand, new spines can form without necessarily going through a filopodial stage (Engert and Bonhoeffer, 1999; Marrs et al., 2001). In addition, motile filopodia-like structures have been observed on immature dendrites of smooth neurons which do not have spine structures (Wong and Wong, 2001). Therefore, filopodia might not only act as spine precursors but also may have other important functions during early development. In fact, studies have shown that terminal filopodia on non-spiny neurons and those located at the tips of growing dendrites are involved in dendritic growth, branching and synaptogenesis (Niell et al., 2004; Yuste and Bonhoeffer, 2004).

As the major postsynaptic targets of excitatory synapses,

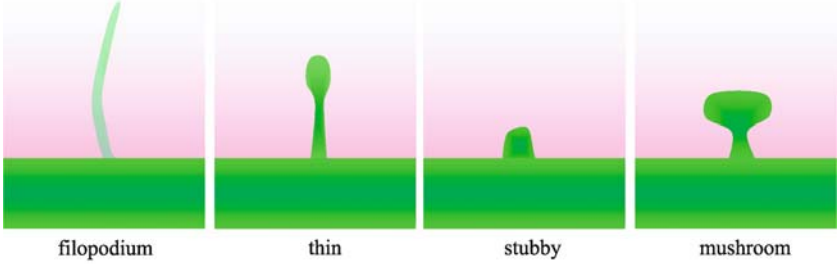

Fig. 1 Schematic representation of different spine morphologies. Filopodia are long and thin protrusion lacking a bulbous head. Thin spines have smaller spine heads but narrower and relatively longer necks. Stubby spines are short protrusions lacking a clearly distinguishable head and neck. Mushroom spines have a mushroom-shaped appearance with typical bulbous spine heads and short spine necks (Peters and Kaiserman-Abramof, 1970; Sorra and Harris, 2000; Yuste and Bonhoeffer, 2004; Ethell and Pasquale, 2005; Lippman and Dunaevsky, 2005)

spines contain all the essential organelles and signaling molecules involved in synaptic transmission. Most spines have a thick electron dense region called postsynaptic density (PSD) on the inner surface of the postsynaptic membrane. In excitatory synapses, PSD covers about 10% of the spine surface and are thicker than the presynaptic active zones, therefore, forming a characteristic asymmetric appearance in glutamatergic synapses (Gray, 1959b; Garner and Kindler, 1996; Harris, 1999). The PSD contains structural proteins, receptors, ion channels, signaling proteins and many other molecules associated with synaptic plasticity. Therefore, PSD may be the most complex organelle in dendritic spines. Some spines also have smooth endoplasmic reticulum (SER) (Spacek and Harris, 1997). In large spines such as mushroom spines, multiple disks of SER can be organized together and form a specialized structure called the spine apparatus (Gray and Guillery, 1963; Nimchinsky et al., 2002). Spine apparatus is a characteristic organelle in many mature spines; whereas developing spines normally lack a well-developed spine apparatus (Westrum et al., 1980; Harris et al., 1992). Spine apparatus has been suggested to be a major intracellular Ca^{2+} store. In addition, they may be involved in postsynaptic protein trafficking (such as receptors and ion channels) (Ethell and Pasquale, 2005). Thus, spine apparatus may play a role in synaptic plasticity. Free ribosomes are rarely found in spines, but polyribosomes can be found in some spines (Sorra and Harris, 2000; Steward and Schuman, 2001). Therefore, local protein synthesis can take place within spines. Although mitochondria and microtubules are abundant in dendrites, they often do not extend into spines (exceptions are the thorny excrescences, which contain mitochondria, free ribosomes, and microtubules) (Adams and Jones, 1982; Chicurel and Harris, 1992; Koch and Zador, 1993). In some cases, mitochondria can redistribute into spines after synaptic stimulation (Li et al., 2004), suggesting they might also be involved in synapse development and plasticity.

In addition to the aforementioned organelles, spines contain a complex network of signaling molecules that controls spine structural plasticity, including receptors, channels, cell adhesion molecules, scaffolding proteins, and many cytoplasmic signaling molecules. Several good reviews have described these molecular signals in detail (Ethell and Pasquale, 2005; Lippman and Dunaevsky, 2005; Tada and Sheng, 2006). Among many of these signaling molecules, Ca^{2+} is special in that they can coordinate intracellular events and regulate spine structural plasticity through multiple mechanisms. In neurons, Ca^{2+} elevation can be induced by multiple stimuli such as neurotransmitter release, binding of extracellular matrix molecules to their receptors, or back-propagating action potentials (Gomez et al., 2001; Nimchinsky et al., 2002). The sources of Ca^{2+} are also diverse. Ca^{2+} influx can come from Ca^{2+}-permeable transmitter receptors (such as N-methyl-D-aspartate (NMDA) receptors and Ca^{2+} permeable *a*-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors), voltage-gated Ca^{2+} channels, reversal of Na^{+}-Ca^{2+} exchange, or intracellular Ca^{2+} stores (Hoyt et al., 1998; Svoboda and Mainen, 1999; Catsicas et al., 2001; Lohmann and Wong, 2005). Calcium signaling in dendritic spines and the effects of Ca^{2+} signaling on spine plasticity have been discussed in detail in other reviews, and interested readers can refer to (Segal et al., 2000; Nimchinsky et al., 2002; Oertner and Matus, 2005; Higley and Sabatini, 2008). Actin is another essential molecule that has been thought to play a fundamental role in activity-dependent modifications of spine structure and function (Rao and Craig, 2000). Actin is highly enriched in spines and turnovers rapidly in spine head. A study using fluorescence recovery after photobleaching suggests that 85% of actin in the dendritic is dynamic with a turnover time of less than one minute (Star et al., 2002). Studies have suggested that the dynamic behavior of actin may underlie spine structural plasticity. For example, actin polymerization inhibitors, such as latrunculin (by sequestering monomeric actin) and cytochalasin D (by capping and stabilizing the fast growing end of actin filaments) can reduce spine motility (Fischer et al., 1998; Dunaevsky et al., 1999). A study using fluorescence resonance energy transfer (FRET) imaging technique has revealed that spine shape change is correlated with the shifting of actin equilibrium following synaptic activity (Okamoto et al., 2004). By using rhodamine-phalloidin to label polymerized actin, a recent study has found that long-term potentiation (LTP) stimulation selectively induced actin polymerization concurrently with an increase in spine head size and spine density (Lin et al., 2005). These observations suggest that actin turnover may be the major driving force for spine structural changes. Controlling the dynamics of actin may be a converging mechanism for regulating spine structural plasticity. The roles of actin dynamics in spine structural plasticity have been well discussed in some recent reviews (Matus, 2000; Matus et al., 2000; Ethell and Pasquale, 2005; Tada and Sheng, 2006; Cingolani and Goda, 2008).

3 Functional significance of spine structural plasticity

When Cajal described the spines, he suggested that spine structures could increase the membrane surface area and therefore contributed to establishing more contacts with axon terminals (Ramon y Cajal, 1899a, b). Spines can extend several microns away from the dendritic shaft. This greatly increases the network flexibility and complexity. However, a spine is not simply a wiring component. Spines are essentially dynamic structures and can exhibit various structural modifications including changes in number, size, shape and motility.What is the functional significance of spine structural plasticity? It has been suggested that

morphological modifications of spine structure might play a role in short-term plasticity (Lendvai et al., 2000; Zuo et al., 2005a). In addition, the fact that a majority of spines are stable in adult animals indicates that spines may act as a physical substrate for long-term information storage (Holtmaat et al., 2005; Zuo et al., 2005a). Thus, any change in spine structure might cause alteraction in synaptic transmission and circuit plasticity. Previous studies have shown that there is a strong correlation between synaptic structure and function. The volume of the spine is correlated with the synaptic strength, the size of the PSD and the number of neurotransmitter receptors (Harris and Stevens, 1989; Takumi et al., 1999; Matsuzaki et al., 2001; Passafaro et al., 2003; McKinney, 2005). Therefore, structural plasticity of dendritic spines may mirror a change in synaptic function.

On the other hand, changes in spine structure may be associated with local signal processing. Variations in the size of spine head or neck may affect signal integration or molecular compartmentalization (Koch and Zador, 1993; Shepherd, 1996; Calabrese et al., 2006). The small spine head has an amplification effect. Because of the small volume, a small increase in the number of signaling molecules inside the spine head can cause a large increase in concentration. Accordingly, smaller spines appear to have a larger amplification effect. Consistent with this, studies have shown that small spines have greater increases in Ca^{2+} signal (Nimchinsky et al., 2004; Noguchi et al., 2005). Spine necks can also facilitate signal amplication and cause molecular compartmentalization. The narrow spine neck can restrict the diffusion of signaling molecules and confine local events such as protein synthesis and membrane trafficking. Experiments using fluorescence recovery after photobleaching (FRAP) technique have shown that the recovery of AMPA receptors is slower in dendritic spines than neighboring denritic area, suggesting the spread of AMPA receptors is limited at the spine neck (Ashby et al., 2006). Thus, alterations in spine structures such as head or neck changes could all play a role in the modulation of synaptic function and therefore, higher order brain function.

4 Dynamic changes in spine number

A fundamental feature of the nervous system is that the synaptic connections between neurons are dynamic and can undergo different modes of modification throughout life. One of the major ways that the neural circuit reorganizes its connections is through spine formation and elimination. In many species, spine formation starts after birth and generally coincides with synaptogenesis (Yuste and Bonhoeffer, 2004). Ever since the first spine is formed, spine turnover has started. However, in the early stages of development, spine formation rate is higher than spine elimination rate. Therefore, there is a net increase in spine number during early postnatal life. The number of spines reaches its peak in the first few weeks. Subsequently, there is a net loss of spines as a result of higher rate of spine elimination (Rakic et al., 1986; Nimchinsky et al., 2002; Zuo et al., 2005a). As animals mature, spine formation rate is comparable to elimination rate and most spines become relatively stable, but spine formation, pruning and remodeling can still occur (Holtmaat et al., 2005; Zuo et al., 2005a).

One of the basic questions related to spine turnover is how a new spine is formed. Some studies suggest that filopodia are the intermediate structure for spine formation. Thus, filopodia are considered as precursors of spines. This concept is supporterd by the observation that a drop in filopodia number coincides with an increase in the number of spines that are formed during development (Dailey and Smith, 1996; Ziv and Smith, 1996). Consistent with this observation, *in vivo* two photon imaging has shown that some filopodia can indeed transform into stable spine-like structures (Zuo et al., 2005a). However, this may not be the only way for spinogenesis, as new spines can emerge without experiencing a filopodial stage (Engert and Bonhoeffer, 1999; Marrs et al., 2001). Multiple mechanisms may be applied during spinogenesis. Nevertheless, at least some spines are formed from filopodia. In addition to their role in spine formation, filopodia may also be involved in spine elimination. Zuo et al. have shown that spines are often transformed into filopodia-like structures before undergoing elimination (Zuo et al., 2005a).

The turnover of spines has provoked a fundamental question: how stable are spines? Using repeated two-photon imaging, two independent groups have first addressed this question in young and adult animals (Grutzendler et al., 2002; Trachtenberg et al., 2002). Consistently, both groups found that spines are highly plastic in young animals and more spines are eliminated than formed during early development, leading to a developmental decrease in spine density (Grutzendler et al., 2002; Trachtenberg et al., 2002; Holtmaat et al., 2005; Zuo et al., 2005a). In addition, Zuo et al. (Zuo et al., 2005a) also found that the spine formation rate is largely constant from young to adult animals, but the elimination rate decreases gradually until they reach a value that is comparable to formation rate. Therefore, spines become more stable when animals mature. Although in general, both groups agree that the majority of spines in apical dendrites of layer 5 pyramidal neurons in the adult brain are stable for over weeks to months in different cortical regions (Grutzendler et al., 2002; Trachtenberg et al., 2002; Holtmaat et al., 2005; Zuo et al., 2005a), there is a lack of consensus in the degree of stability. For example, Gan group reported a high stability with more than 90% of spines remaining stable over 1 month (Grutzendler et al., 2002; Zuo et al., 2005a) in the adult cortex. However, Svoboda group found only 73% of spines persisted in the adult mouse visual cortex over 1 month (Holtmaat et al.,

2005). Methodological differences such as surgical preparation, sampling of different cell types or cortical regions, classification of dendritic protrusions, usages of different lines of animals, or even housing conditions could all contribute to the quantitative difference in spine turnover (Grutzendler et al., 2002; Trachtenberg et al., 2002; Holtmaat et al., 2005; Zuo et al., 2005a; Holtmaat et al., 2006; Majewska et al., 2006; Xu et al., 2007). Nevertheless, both groups and other labs agree that spines become more stable in adult animals and may form a physical substrate for circuit plasticity (Mizrahi et al., 2004; Holtmaat et al., 2005; Zuo et al., 2005a; Lee et al., 2006; Majewska et al., 2006).

Spine formation and elimination are not only related to development, but also associated with change in synaptic activity. Studies using cultured hippocampal slices have shown that new spine formation is correlated with the induction of LTP or enhanced synaptic activity (Collin et al., 1997; Engert and Bonhoeffer, 1999; Maletic-Savatic et al., 1999). Depending on the frequency of the activity, spines can undergo bi-directional changes. For example, low frequency stimulation can induce spine retractions in cultured slices, whereas theta burst stimulation can lead to new spine formation (Nagerl et al., 2004). Spine turnover is also influenced by a number of other factors such as temperature, hormonal and learning activity (Woolley et al., 1990; Moser et al., 1994; Kirov et al., 1999; Roelandse and Matus, 2004). Recent *in vivo* imaging studies have shown that experience-dependent activity appears to have differential effects on spine stability in young and adult animals. For example, whisker trimming or pharmacological blockage of NMDA receptors with MK-801 can change spine turnover rate in young animals (Zuo et al., 2005b; Holtmaat et al., 2006), but manipulation of sensory input in adult animals does not change spine turnover significantly (Mizrahi and Katz, 2003; Zuo et al., 2005b; Majewska et al., 2006). However, it should be noted that activity may modify other aspects of spine structure such as spine head volume or motility in adult animals (Lendvai et al., 2000; Majewska and Sur, 2003; Zuo et al., 2005a; Majewska et al., 2006). All these data suggest that spine turnover plays an important role in coordinating synaptic function.

Recent data suggest that circuit remodeling associated with spine turnover may also underlie functional recovery in neurological diseases. For example, Brown *et al*. (Brown et al., 2007) have shown that dendritic arbors undergo an extensive reorganization when animals recover from stroke. This large scale reorganization of dendritic branches is accompanied by a dramatic increase in spine turnover and a recovery of spine density. A recent study in Alzheimer's disease (AD) has shown that functional recovery can be achieved by restoring spine structure and density (Smith et al., 2009). These studies offer the hope for promoting functional recovery in neurological diseases by modulating spine structural plasticity.

5 Spine motility and structural modification in spine size and shape

This concept of spine motility was first proposed by Blomberg et al. (Blomberg et al., 1977; Sala, 2002). It refers to the ability of dendritic spines to move and accordingly change their morphology. Dendritic spines can undergo at least two types of motility: protrusive motility and/or head morphing (Tashiro and Yuste, 2004).

Much of our knowledge about spine motility comes from live cell imaging experiments (Dailey and Smith, 1996; Ziv and Smith, 1996; Fischer et al., 1998; Dunaevsky et al., 1999; Lendvai et al., 2000; Bonhoeffer and Yuste, 2002; Zhang and Murphy, 2004; Zuo et al., 2005a). These studies have found that rapid morphologic alterations of spines such as linear extensions, retractions and head morphing can occur on the order of minutes or even seconds (Dailey and Smith, 1996; Ziv and Smith, 1996; Fischer et al., 1998; Dunaevsky et al., 1999; Zhang and Murphy, 2004). It appears that spine motility is developmentally regulated (Dunaevsky et al., 1999; Zhang and Murphy, 2004). Young neurons have a higher spine motility than mature neurons. Nerverthereless, mature spines can still undergo constant movement. Spine motility can be changed by activity. For examples, activation of glutamate receptors with AMPA or NMDA can reduce spine motility (Fischer et al., 2000; Ackermann and Matus, 2003; Oray et al., 2006), and experience-dependent remodeling such as sensory deprivation can depress the protrusive motility of spines and filopodia (Lendvai et al., 2000). However, basal spine motility appears to be an intrinsic feature of neurons and is not determined by Ca^{2+}-dependent events, as bath application of BAPTA-AM has little effect on spine dynamics (Dunaevsky et al., 1999; Zhang and Murphy, 2004). Although these imaging studies have provided fundamental insight into the mechanisms regulating spine motility, the physiological roles of spine motility remain largely unclear.

One of the potential functions of spine motility may be related to spinogenesis and synaptogenesis. Motile spines may facilitate seeking for new synaptic contacts. As we known, spine precursors, or filopodia are highly dynamic and have very short lifetime (about 10 min) (Ziv and Smith, 1996). There are more filopodia than spines during early stages of development. As synapse formation progresses, most filopodia disappear and are replaced by more stable mature spines (Dunaevsky et al., 1999; Calabrese et al., 2006). The highly motile and short-lifed nature of filopodia suggests that developing dendritic protrusions may actively probe their environment for presynaptic terminals, thereby promoting synaptogenesis. Consistent with this, experiments in cultured neurons have shown that dendritic filopodia can initiate synaptic contact and be stabilized by the newly formed synaptic contact (Ziv and Smith, 1996; Zuo et al., 2005a). The stabilization of dendrtic protrusions by synaptic contact raises an

interesting question about whether spines are still able to move when connected by presynaptic terminals. Studies combining time-lapse imaging and immunocytochemistry and electron microscopy have reported that spines remain motile even with synaptic contacts (Fischer et al., 1998; Dunaevsky et al., 2001). These raise other interesting questions such as whether these synapses are functional and how synapses maintain relative synaptic strength with moving synaptic components. Later studies suggested that spines can continue to move even when a functional presynaptic terminal is present, thus functional presynaptic terminals may not necessarily arrest spine motility (Korkotian and Segal, 2001a, b; Deng and Dunaevsky, 2005). Importantly, presynaptic terminal seems quite stable, suggesting that postsynaptic spine has to morph around a presynaptic axonal varicosity (Dunaevsky and Mason, 2003; Deng and Dunaevsky, 2005). The mechanism underling spine motility in an established synapse remains to be determined. Presumablely, morphing of the postsynaptic structure may help explore new synaptic contacts or promote synapse maturation (Zito et al., 2009). In addition, dynamic change of spine with synaptic contacts may be associated with spine elimination and circuit remodeling, as morphological alteration and transformation often occur before spine undergoing elimination (Zuo et al., 2005a).

Another potential function of spine motility may be related to information processing and modulation of synaptic strength. Because the geometry of the spine is essential for signal integration and molecular compartmentalization, morphological alterations associated with spine motility may drive signal integration in the synapse (Bloodgood and Sabatini, 2005; Hayashi and Majewska, 2005). For example, volume change of spine head can cause a change in Ca^{2+} concentration and accordingly Ca^{2+} dynamics (Holcman et al., 2004; Nimchinsky et al., 2004; Noguchi et al., 2005). Similarly, a change in spine neck length or diameter may alter Ca^{2+} signal decay kinetics (Majewska et al., 2000; Grunditz et al., 2008; Bloodgood et al., 2009). In addition, because spine heads are filled with structural proteins and many other diffusible signaling molecules, spine motility could cause rearrangement of the spine matrix and signaling micro-domains. Moreover, reassembly of actin-related proteins and synaptic events associated with actin dynamics such as membrane trafficking and receptor recruitment could all be coupled with spine motility (Lippman and Dunaevsky, 2005; McKinney, 2005). Taken together, spine dynamics may be closely linked to synaptic events and understanding the mechanisms controling spine motility will likely provide fundamental insights into how the synapses process information.

Spine motility inevitably leads to changes in spine shape and/or volume. Because most spines are stable in adult animals, modifications of spine size and shape are the major forms of structural plasticity. As rapid morphological alterations can occur within minutes or even seconds, this form of structural plasticity may provide a potential mechanism for encoding short-term plasticity. It has been reported that the volume of the spine head is proportional to the number of *a*-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors and the size of the PSD (McKinney, 2005) (Harris and Stevens, 1989; Takumi et al., 1999; Matsuzaki et al., 2001; Passafaro et al., 2003). The latter is further correlated with the area of the presynaptic active zone, the number of docked vesicles and the neurotransmitter releasing probability per action. Thus, morphological changes associated with motility may imply a change in synaptic function. Many lines of evidences suggest that changes in spine size are tightly regulated by neuronal activity. For examples, uncaging glutamate near individual spines results in rapid spine enlargement of the stimulated spine (Matsuzaki et al., 2004). In cultured neurons, bursts of action potentials evoked in response to a depolarizing current pulse can cause fast spine contraction (Korkotian and Segal, 2001b). In some cases, spines can contract or enlarge depending on the intensity or frequency of the stimuli. For example, tetanic stimulation leads to rapid enlargement of the spine heads in cultured slices, whereas prolonged 1 Hz stimulation induces a decrease in spine head size (Okamoto et al., 2004; Zhou et al., 2004). Another study has shown that application of short pulses of glutamate to cultured hippocampal neurons can cause spines to shrink or elongate, depending on the stimulation intensity and duration (Korkotian and Segal, 1999). These data suggest that activity can induce rapid changes in spine structures, consistent with the idea that morphological modification may serve as a mechanism for short-term plasticity.

6 Structural abnormalities of dendritic spines in pathological conditions

Because spine structure is intimately associated with synaptic function, it is conceivable that abnormal spine structure may be associated with malfunction of the nervous system. Indeed, dendritic spine abnormalities have been described in many pathological conditions including Alzheimer's disease, Parkinson's disease, Huntington's disease, Down's syndrome, Fragile-X syndrome, epilepsy, Schizophrenia, prion disease, addiction, and stroke (reviewed by Fiala et al., 2002; Fuhrmann et al., 2007). Abnormal changes in spine density, size, shape, sprouting locations, as well as ultrastructure have all been reported in disease states. For example, changes in spine density have been observed in many diseases. Addictive drugs such as amphetamine and cocaine can induce an increase in spine density (Robinson and Kolb, 1999; Norrholm et al., 2003), while epilepsy can induce a decrease in spine density (Swann et al., 2000). It should be emphasized that spine density change may not necessarily

be correlated with disease symptom, as both increase and decrease in spine density can lead to simlar symptoms. For examples, in Down's syndrome, the most common cause of mental retardation, neurons have fewer dendritic branches, shorter basal dendrites and a decreased spine density (Takashima et al., 1981; Takashima et al., 1994). However, in Fragile-X syndrome, another leading cause of mental retardation, spine density is increased and many spines are long and thin characteristic of immature filopodia-like protrusions (Irwin et al., 2000). Perhaps, spine integrity, stability, and/or a balance between spine formation and elimination are more important for neuronal function than the absolute spine number. Nevertheless, some common pathological changes can occur in many neurological diseases. For examples, several chronic neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease that are associated with neuronal death often display a progressive loss of dendritic spines in the course of disease development (McNeill et al., 1988; Guidetti et al., 2001; Selkoe, 2002). In addition, disruption of spine integrity and aberrant spine morphology are oftern associated with pathogenesis and disease progression. In the case of Alzheimer's disease, dendrites near amyloid plaques always exhibit some degree of abnormality. Another good example is acute structural changes after stroke. It has been shown that spine integrity and structural abnormalities after stroke are highly correlated with the degree of ischemia (Fig. 2). In a moderate ischemic stroke model where blood flow was reduced about 50%, repeated imaging showed that dendritic spine structure is largely intact within the first 5 hours after stroke onset (Fig. 2a), suggesting modest reduction in blood flow is not associated with an immediate damage to synaptic structure (Zhang et al., 2005). In contrast, in a severe stroke where blood flow drops to less than 10%, rapid loss of spines and dendritic swelling occur within 10–30 min (Fig. 2b) (Zhang et al., 2005; Zhang and Murphy, 2007). Interestingly, swelling dendrites and lost spines can regain their original structure when reperfusion occurred in occluded vessels (Zhang et al., 2005; Murphy et al., 2008). More importantly, restore of synaptic structure can lead to a corresponding recovery of function (Murphy et al., 2008). In the case of intermediate ischemia, a gradual degeneration of spine structure are observed (Fig. 2c) (Zhang and Murphy, 2007). Consistent with this, in ischemic border region where there is only a partial reduction in blood supply, progressive loss of dendritic spines occurs over the

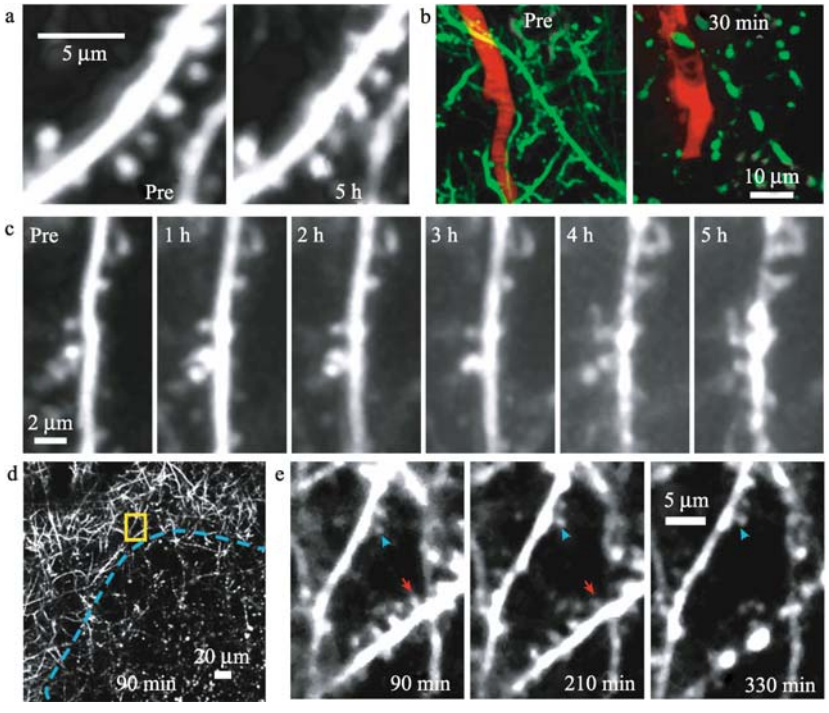

Fig. 2 Spine integrity and structural abnormalities after stroke are associated with the degree of ischemia. **(a)** There is no apparent change in spine structure within the first 5 h in a moderate ischemic stroke model where blood flow is reduced about 50%. **(b)** Rapid loss of spines and dendritic swelling is observed in a severe stroke where blood flow drops to less than 10%. Dendritic structure (green) is completely lost within 30 min. **(c)** A gradual degeneration of spine structure occurs in an intermediate ischemia. **(d)** Image of dendritic structure 90 min after ischemia. Note the sharp border (blue line, visualized as a rapid transition from relatively normal dendritic structure to beaded and swollen structure) between the core heavily clotted region and the relatively intact region. **(e)** A magnified view of the yellow boxed region in **(d)** showing progressive loss of dendritic spines in ischemic border region. Note a stable spine (blue arrowhead) and a lost spine (red arrowhead) 5.5 h after stroke near the border region. Pre: Pretreatment. Panels a–b are modified from Zhang et al. (Zhang et al., 2005) with permission and c–e are adapted from Zhang et al. (Zhang and Murphy, 2007) with permission.

first few hours after stroke onset (Fig. 2d and 2e) (Zhang and Murphy, 2007). These data suggest that structural abnormalities of dendritic spines can be used as indicators of disease severity and progression, and information about spine morphology and dynamics may contribute to the diagonosis and treatment of the neurological disorders.

7 Conclusions

Abundant experimental data suggest that spine can undergo various morphological changes. It is now clear that the morphological alterations may play essential roles in synaptic plasticity and function. Recent development of *in vivo* imaging techniques has greatly improved our knowledge of spine structural plasticity. However, many fundamental questions remain to be answered. For example, what controls the lifetime of individual spines? This question is important becaue the lifetime of spines can shift the balance between spine formation and elimination and ultimately affect the stability and plasticity of the neural circuit. Because spine density change (increase or decrease) often lead to malfunction of the nervous system as we observed in many pathological conditions, it may be important for the brain to maintain a balance between stability and plasticity. Other related questions are: How does spine turnover contribute to learning and memory? Is it possible to manipulate spine structural plasticity?

As most spines do not turnover in the adult brain, alterations in spine shapes or sizes may be the major forms of structural plasticity in adult animals. Although activity and experience have been related to these forms of structural plasticity, many questions remain. For example, do spine dynamics affect information storage? Although a vast majority of spines are stable in adult brain and they may serve as a physical substrate for long-term information storage, it is conceivable that memory will not last if the relative synaptic strength cannot be maintained in a neural circuit. How is the relative synaptic strength maintained in a synapse with a motile postsynaptic spine? Answers to these questions will eventually help us understand how the brain encodes and stores information.

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References

Ackermann M, Matus A (2003). Activity-induced targeting of profilin and stabilization of dendritic spine morphology. Nat Neurosci, 6: 1194–1200

Adams I, Jones D G (1982). Quantitative ultrastructural changes in rat cortical synapses during early-, mid- and late-adulthood. Brain Res, 239: 349–363

Ashby M C, Maier S R, Nishimune A, Henley J M (2006). Lateral diffusion drives constitutive exchange of AMPA receptors at dendritic spines and is regulated by spine morphology. J Neurosci, 26: 7046–7055

Blomberg F, Cohen R S, Siekevitz P (1977). The structure of postsynaptic densities isolated from dog cerebral cortex. II. Characterization and arrangement of some of the major proteins within the structure. J Cell Biol, 74: 204–225

Bloodgood B L, Sabatini B L (2005). Neuronal activity regulates diffusion across the neck of dendritic spines. Science, 310: 866–869

Bloodgood B L, Giessel A J, Sabatini B L (2009). Biphasic synaptic Ca influx arising from compartmentalized electrical signals in dendritic spines. PLoSBiol, 7: e1000190

Bonhoeffer T, Yuste R (2002). Spine motility. Phenomenology, mechanisms, and function. Neuron, 35: 1019–1027

Bourne J N, Harris K M (2008). Balancing structure and function at hippocampal dendritic spines. Annu Rev Neurosci, 31: 47–67

Brown C E, Li P, Boyd J D, Delaney K R, Murphy T H (2007). Extensive turnover of dendritic spines and vascular remodeling in cortical tissues recovering from stroke. J Neurosci, 27: 4101–4109

Calabrese B, Wilson M S, Halpain S (2006). Development and regulation of dendritic spine synapses. Physiology (Bethesda), 21: 38–47

Catsicas M, Allcorn S, Mobbs P (2001). Early activation of Ca(2 +)-permeable AMPA receptors reduces neurite outgrowth in embryonic chick retinal neurons. J Neurobiol, 49: 200–211

Chicurel M E, Harris K M (1992). Three-dimensional analysis of the structure and composition of CA3 branched dendritic spines and their synaptic relationships with mossy fiber boutons in the rat hippocampus. J Comp Neurol, 325: 169–182

Cingolani L A, Goda Y (2008). Actin in action: the interplay between the actin cytoskeleton and synaptic efficacy. Nat Rev Neurosci, 9: 344–356

Collin C, Miyaguchi K, Segal M (1997). Dendritic spine density and LTP induction in cultured hippocampal slices. J Neurophysiol, 77: 1614–1623

Dailey M E, Smith S J (1996). The dynamics of dendritic structure in developing hippocampal slices. J Neurosci, 16: 2983–2994

Deng J, Dunaevsky A (2005). Dynamics of dendritic spines and their afferent terminals: spines are more motile than presynaptic boutons. Dev Biol, 277: 366–377

Dunaevsky A, Mason C A (2003). Spine motility: a means towards an end? Trends Neurosci, 26: 155–160

Dunaevsky A, Blazeski R, Yuste R, Mason C (2001). Spine motility with synaptic contact. Nat Neurosci, 4: 685–686

Dunaevsky A, Tashiro A, Majewska A, Mason C, Yuste R (1999). Developmental regulation of spine motility in the mammalian central nervous system. Proc Natl Acad Sci U S A, 96: 13438–13443

Engert F, Bonhoeffer T (1999). Dendritic spine changes associated with hippocampal long-term synaptic plasticity. Nature, 399: 66–70

Ethell I M, Pasquale E B (2005). Molecular mechanisms of dendritic spine development and remodeling. Prog Neurobiol, 75: 161–205

Fiala J C, Spacek J, Harris K M (2002). Dendritic spine pathology: cause or consequence of neurological disorders? Brain Res Brain Res Rev, 39: 29–54

Fiala J C, Feinberg M, Popov V, Harris K M (1998). Synaptogenesis via

dendritic filopodia in developing hippocampal area CA1. J Neurosci, 18: 8900–8911

Fischer M, Kaech S, Knutti D, Matus A (1998). Rapid actin-based plasticity in dendritic spines. Neuron, 20: 847–854

Fischer M, Kaech S, Wagner U, Brinkhaus H, Matus A (2000). Glutamate receptors regulate actin-based plasticity in dendritic spines. Nat Neurosci, 3: 887–894

Fuhrmann M, Mitteregger G, Kretzschmar H, Herms J (2007). Dendritic pathology in prion disease starts at the synaptic spine. J Neurosci, 27: 6224–6233

Garner C C, Kindler S (1996). Synaptic proteins and the assembly of synaptic junctions. Trends Cell Biol, 6: 429–433

Gomez T M, Robles E, Poo M, Spitzer N C (2001). Filopodial calcium transients promote substrate-dependent growth cone turning. Science, 291: 1983–1987

Gray E G (1959a). Electron microscopy of synaptic contacts on dendrite spines of the cerebral cortex. Nature, 183: 1592–1593

Gray E G (1959b). Axo-somatic and axo-dendritic synapses of the cerebral cortex: an electron microscope study. J Anat, 93: 420–433

Gray E G, Guillery R W (1963). A Note on the Dendritic Spine Apparatus. J Anat, 97: 389–392

Grunditz A, Holbro N, Tian L, Zuo Y, Oertner TG (2008). Spine neck plasticity controls postsynaptic calcium signals through electrical compartmentalization. J Neurosci, 28: 13457–13466

Grutzendler J, Kasthuri N, Gan WB (2002). Long-term dendritic spine stability in the adult cortex. Nature, 420: 812–816

Guidetti P, Charles V, Chen E Y, Reddy P H, Kordower J H, Whetsell W O, Jr., Schwarcz R, Tagle D A (2001). Early degenerative changes in transgenic mice expressing mutant huntingtin involve dendritic abnormalities but no impairment of mitochondrial energy production. Exp Neurol, 169: 340–350

Harris K M (1999). Structure, development, and plasticity of dendritic spines. Curr Opin Neurobiol, 9: 343–348

Harris K M, Stevens J K (1989). Dendritic spines of CA 1 pyramidal cells in the rat hippocampus: serial electron microscopy with reference to their biophysical characteristics. J Neurosci, 9: 2982–2997

Harris K M, Kater S B (1994). Dendritic spines: cellular specializations imparting both stability and flexibility to synaptic function. Annu Rev Neurosci, 17: 341–371

Harris K M, Jensen F E, Tsao B (1992). Three-dimensional structure of dendritic spines and synapses in rat hippocampus (CA1) at postnatal day 15 and adult ages: implications for the maturation of synaptic physiology and long-term potentiation. J Neurosci, 12: 2685–2705

Hayashi Y, Majewska A K (2005). Dendritic spine geometry: functional implication and regulation. Neuron, 46: 529–532

Hering H, Sheng M (2001). Dendritic spines: structure, dynamics and regulation. Nat Rev Neurosci, 2: 880–888

Higley M J, Sabatini B L (2008). Calcium signaling in dendrites and spines: practical and functional considerations. Neuron, 59: 902–913

Holcman D, Schuss Z, Korkotian E (2004). Calcium dynamics in dendritic spines and spine motility. Biophys J, 87: 81–91

Holtmaat A, Wilbrecht L, Knott G W, Welker E, Svoboda K (2006). Experience-dependent and cell-type-specific spine growth in the neocortex. Nature, 441: 979–983

Holtmaat A J, Trachtenberg J T, Wilbrecht L, Shepherd G M, Zhang X, Knott G W, Svoboda K (2005). Transient and persistent dendritic spines in the neocortex *in vivo*. Neuron, 45: 279–291

Hoyt K R, Arden S R, Aizenman E, Reynolds I J (1998). Reverse Na +/ Ca2 + exchange contributes to glutamate-induced intracellular Ca2 + concentration increases in cultured rat forebrain neurons. Mol Pharmacol, 53: 742–749

Irwin S A, Galvez R, Greenough W T (2000). Dendritic spine structural anomalies in fragile-X mental retardation syndrome. Cereb Cortex, 10: 1038–1044

Kirov S A, Sorra K E, Harris K M (1999). Slices have more synapses than perfusion-fixed hippocampus from both young and mature rats. J Neurosci, 19: 2876–2886

Koch C, Zador A (1993). The function of dendritic spines: devices subserving biochemical rather than electrical compartmentalization. J Neurosci, 13: 413–422

Korkotian E, Segal M (1999). Bidirectional regulation of dendritic spine dimensions by glutamate receptors. Neuroreport, 10: 2875–2877

Korkotian E, Segal M (2001a). Regulation of dendritic spine motility in cultured hippocampal neurons. J Neurosci, 21: 6115–6124

Korkotian E, Segal M (2001b). Spike-associated fast contraction of dendritic spines in cultured hippocampal neurons. Neuron, 30: 751–758

Lauer M, Senitz D (2006). Dendritic excrescences seem to characterize hippocampal CA3 pyramidal neurons in humans. J Neural Transm, 113: 1469–1475

Lee W C, Huang H, Feng G, Sanes J R, Brown E N, So P T, Nedivi E (2006). Dynamic remodeling of dendritic arbors in GABAergic interneurons of adult visual cortex. PLoS Biol, 4: e29

Lendvai B, Stern E A, Chen B, Svoboda K (2000). Experience-dependent plasticity of dendritic spines in the developing rat barrel cortex in vivo. Nature, 404: 876–881

Li Z, Okamoto K, Hayashi Y, Sheng M (2004). The importance of dendritic mitochondria in the morphogenesis and plasticity of spines and synapses. Cell, 119: 873–887

Lin B, Kramar E A, Bi X, Brucher F A, Gall C M, Lynch G (2005). Theta stimulation polymerizes actin in dendritic spines of hippocampus. J Neurosci, 25: 2062–2069

Lippman J, Dunaevsky A (2005). Dendritic spine morphogenesis and plasticity. J Neurobiol, 64: 47–57

Lohmann C, Wong RO (2005). Regulation of dendritic growth and plasticity by local and global calcium dynamics. Cell Calcium, 37: 403–409

Majewska A, Sur M (2003). Motility of dendritic spines in visual cortex in vivo: changes during the critical period and effects of visual deprivation. Proc Natl Acad Sci U SA, 100: 16024–16029

Majewska A, Tashiro A, Yuste R (2000). Regulation of spine calcium dynamics by rapid spine motility. J Neurosci, 20: 8262–8268

Majewska A K, Newton J R, Sur M (2006). Remodeling of synaptic structure in sensory cortical areas in vivo. J Neurosci, 26: 3021–3029

Maletic-Savatic M, Malinow R, Svoboda K (1999). Rapid dendritic morphogenesis in CA1 hippocampal dendrites induced by synaptic activity. Science, 283: 1923–1927

Marrs G S, Green S H, Dailey M E (2001). Rapid formation and remodeling of postsynaptic densities in developing dendrites. Nat Neurosci, 4: 1006–1013

Matsuzaki M, Honkura N, Ellis-Davies G C, Kasai H (2004). Structural

basis of long-term potentiation in single dendritic spines. Nature, 429: 761–766

Matsuzaki M, Ellis-Davies G C, Nemoto T, Miyashita Y, Iino M, Kasai H (2001). Dendritic spine geometry is critical for AMPA receptor expression in hippocampal CA1 pyramidal neurons. Nat Neurosci, 4: 1086–1092

Matus A (2000). Actin-based plasticity in dendritic spines. Science, 290: 754–758

Matus A, Brinkhaus H, Wagner U (2000). Actin dynamics in dendritic spines: a form of regulated plasticity at excitatory synapses. Hippocampus, 10: 555–560

McKinney R A (2005). Physiological roles of spine motility: development, plasticity and disorders. Biochem Soc Trans, 33: 1299–1302

McNeill T H, Brown S A, Rafols J A, Shoulson I (1988). Atrophy of medium spiny I striatal dendrites in advanced Parkinson's disease. Brain Res, 455: 148–152

Mizrahi A, Katz L C (2003). Dendritic stability in the adult olfactory bulb. Nat Neurosci, 6: 1201–1207

Mizrahi A, Crowley J C, Shtoyerman E, Katz LC (2004). High-resolution in vivo imaging of hippocampal dendrites and spines. J Neurosci, 24: 3147–3151

Moser M B, Trommald M, Andersen P (1994). An increase in dendritic spine density on hippocampal CA1 pyramidal cells following spatial learning in adult rats suggests the formation of new synapses. Proc Natl Acad Sci U SA, 91: 12673–12675

Murphy T H, Li P, Betts K, Liu R (2008). Two-photon imaging of stroke onset in vivo reveals that NMDA-receptor independent ischemic depolarization is the major cause of rapid reversible damage to dendrites and spines. J Neurosci, 28: 1756–1772

Nagerl U V, Eberhorn N, Cambridge S B, Bonhoeffer T (2004). Bidirectional activity-dependent morphological plasticity in hippocampal neurons. Neuron, 44: 759–767

Niell C M, Meyer M P, Smith S J (2004). In vivo imaging of synapse formation on a growing dendritic arbor. Nat Neurosci, 7: 254–260

Nimchinsky E A, Sabatini B L, Svoboda K (2002). Structure and function of dendritic spines. Annu Rev Physiol, 64: 313–353

Nimchinsky E A, Yasuda R, Oertner T G, Svoboda K (2004). The number of glutamate receptors opened by synaptic stimulation in single hippocampal spines. J Neurosci, 24: 2054–2064

Noguchi J, Matsuzaki M, Ellis-Davies G C, Kasai H (2005). Spine-neck geometry determines NMDA receptor-dependent Ca2 + signaling in dendrites. Neuron, 46: 609–622

Norrholm S D, Bibb J A, Nestler E J, Ouimet C C, Taylor J R, Greengard P (2003). Cocaine-induced proliferation of dendritic spines in nucleus accumbens is dependent on the activity of cyclin-dependent kinase-5. Neuroscience, 116: 19–22

Oertner T G, Matus A (2005). Calcium regulation of actin dynamics in dendritic spines. Cell Calcium, 37: 477–482

Okamoto K, Nagai T, Miyawaki A, Hayashi Y (2004). Rapid and persistent modulation of actin dynamics regulates postsynaptic reorganization underlying bidirectional plasticity. Nat Neurosci, 7: 1104–1112

Oray S, Majewska A, Sur M (2006). Effects of synaptic activity on dendritic spine motility of developing cortical layer v pyramidal neurons. Cereb Cortex, 16: 730–741

Passafaro M, Nakagawa T, Sala C, Sheng M (2003). Induction of dendritic spines by an extracellular domain of AMPA receptor subunit GluR2. Nature, 424: 677–681

Peters A, Kaiserman-AbramofI R (1970). The small pyramidal neuron of the rat cerebral cortex. The perikaryon, dendrites and spines. Am J Anat, 127: 321–355

Rakic P, Bourgeois J P, Eckenhoff M F, Zecevic N, Goldman-Rakic P S (1986). Concurrent overproduction of synapses in diverse regions of the primate cerebral cortex. Science, 232: 232–235

Ramon y Cajal S (1888). Estructura de los centros nervioso de las aves. Rev Trim Histol Norm Pat, 1: 1–10

Ramon y Cajal S (1899a). La Textura del sistema nervioso del hombre y de los vertebrados. Moya: Madrid

Ramon y Cajal S (1899b). Reglas y consejos sobre investigacion biologica. Imprenta de Fontanet: Madrid

Rao A, Craig A M (2000). Signaling between the actin cytoskeleton and the postsynaptic density of dendritic spines. Hippocampus, 10: 527–541

Robinson T E, Kolb B (1999). Alterations in the morphology of dendrites and dendritic spines in the nucleus accumbens and prefrontal cortex following repeated treatment with amphetamine or cocaine. Eur J Neurosci, 11: 1598–1604

Roelandse M, Matus A (2004). Hypothermia-associated loss of dendritic spines. J Neurosci, 24: 7843–7847

Sala C (2002). Molecular regulation of dendritic spine shape and function. Neurosignals, 11: 213–223

Segal I, Korkotian I, Murphy D D (2000). Dendritic spine formation and pruning: common cellular mechanisms? Trends Neurosci, 23: 53–57

Selkoe D J (2002). Alzheimer's disease is a synaptic failure. Science, 298: 789–791

Shepherd G M (1996). The dendritic spine: a multifunctional integrative unit. J Neurophysiol, 75: 2197–2210

Shepherd G M (2004). The Synaptic Organization of the Brain, Fifth Edition. New York: Oxford University Press

Smith D L, Pozueta J, Gong B, Arancio O, Shelanski M (2009). Reversal of long-term dendritic spine alterations in Alzheimer disease models. Proc Natl Acad Sci U S A, 106: 16877–16882

Sorra K E, Harris K M (2000). Overview on the structure, composition, function, development, and plasticity of hippocampal dendritic spines. Hippocampus, 10: 501–511

Spacek J, Harris K M (1997). Three-dimensional organization of smooth endoplasmic reticulum in hippocampal CA1 dendrites and dendritic spines of the immature and mature rat. J Neurosci, 17: 190–203

Star E N, Kwiatkowski D J, Murthy V N (2002). Rapid turnover of actin in dendritic spines and its regulation by activity. Nat Neurosci, 5: 239–246

Steward O, Schuman E M (2001). Protein synthesis at synaptic sites on dendrites. Annu Rev Neurosci, 24: 299–325

Svoboda K, Mainen Z F (1999). Synaptic [Ca2 +]: intracellular stores spill their guts. Neuron, 22: 427–430

Swann J W, Al-Noori S, Jiang M, Lee C L (2000). Spine loss and other dendritic abnormalities in epilepsy. Hippocampus, 10: 617–625

Tada T, Sheng M (2006). Molecular mechanisms of dendritic spine morphogenesis. Curr Opin Neurobiol, 16: 95–101

Takashima S, Becker L E, Armstrong D L, Chan F (1981). Abnormal neuronal development in the visual cortex of the human fetus and infant with down's syndrome. A quantitative and qualitative Golgi

study. Brain Res, 225: 1–21

Takashima S, Iida K, Mito T, Arima M (1994). Dendritic and histochemical development and ageing in patients with Down's syndrome. J Intellect Disabil Res, 38 (Pt3): 265–273

Takumi Y, Ramirez-Leon V, Laake P, Rinvik E, Ottersen O P (1999). Different modes of expression of AMPA and NMDA receptors in hippocampal synapses. Nat Neurosci, 2: 618–624

Tarrant S B, Routtenberg A (1977). The synaptic spinule in the dendritic spine: electron microscopic study of the hippocampal dentate gyrus. Tissue Cell, 9: 461–473

Tashiro A, Yuste R (2004). Regulation of dendritic spine motility and stability by Rac1 and Rho kinase: evidence for two forms of spine motility. Mol Cell Neurosci, 26: 429–440

Trachtenberg J T, Chen B E, Knott G W, Feng G, Sanes J R, Welker E, Svoboda K (2002). Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex. Nature, 420: 788–794

Westrum L E, Jones D H, Gray E G, Barron J (1980). Microtubules, dendritic spines and spine appratuses. Cell Tissue Res, 208: 171–181

Wong W T, Wong R O (2001). Changing specificity of neurotransmitter regulation of rapid dendritic remodeling during synaptogenesis. Nat Neurosci, 4: 351–352

Woolley C S, Gould E, Frankfurt M, McEwen B S (1990). Naturally occurring fluctuation in dendritic spine density on adult hippocampal pyramidal neurons. J Neurosci, 10: 4035–4039

Xu H T, Pan F, Yang G, Gan W B (2007). Choice of cranial window type for in vivo imaging affects dendritic spine turnover in the cortex. Nat Neurosci, 10: 549–551

Yuste R, Bonhoeffer T (2004). Genesis of dendritic spines: insights from ultrastructural and imaging studies. Nat Rev Neurosci, 5: 24–34

Zhang S, Murphy T H (2004). Ca(2 +)-independent spine dynamics in cultured hippocampal neurons. Mol Cell Neurosci, 25: 334–344

Zhang S, Murphy T H (2007). Imaging the impact of cortical microcirculation on synaptic structure and sensory-evoked hemodynamic responses in vivo. PLoS Biol, 5: e119

Zhang S, Boyd J, Delaney K, Murphy T H (2005). Rapid reversible changes in dendritic spine structure in vivo gated by the degree of ischemia. J Neurosci, 25: 5333–5338

Zhou Q, Homma K J, Poo M M (2004). Shrinkage of dendritic spines associated with long-term depression of hippocampal synapses. Neuron, 44: 749–757

Zito K, Scheuss V, Knott G, Hill T, Svoboda K (2009). Rapid functional maturation of nascent dendritic spines. Neuron, 61: 247–258

Ziv N E, Smith S J (1996). Evidence for a role of dendritic filopodia in synaptogenesis and spine formation. Neuron, 17: 91–102

Zuo Y, Lin A, Chang P, Gan W B (2005a). Development of long-term dendritic spine stability in diverse regions of cerebral cortex. Neuron, 46: 181–189

Zuo Y, Yang G, Kwon E, Gan W B (2005b). Long-term sensory deprivation prevents dendritic spine loss in primary somatosensory cortex. Nature, 436: 261–265