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Balancing Structure and Function at Hippocampal Dendritic Spines

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Key Words

serial section transmission electron microscopy, long-term potentiation, long-term depression, development, morphological plasticity

Abstract

Dendritic spines are the primary recipients of excitatory input in the central nervous system. They provide biochemical compartments that locally control the signaling mechanisms at individual synapses. Hippocampal spines show structural plasticity as the basis for the physiological changes in synaptic efficacy that underlie learning and memory. Spine structure is regulated by molecular mechanisms that are fine-tuned and adjusted according to developmental age, level and direction of synaptic activity, specific brain region, and exact behavioral or experimental conditions. Reciprocal changes between the structure and function of spines impact both local and global integration of signals within dendrites. Advances in imaging and computing technologies may provide the resources needed to reconstruct entire neural circuits. Key to this endeavor is having sufficient resolution to determine the extrinsic factors (such as perisynaptic astroglia) and the intrinsic factors (such as core subcellular organelles) that are required to build and maintain synapses.

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INTRODUCTION

Since Golgi and Cajal first revealed the intricate structure of dendrites more than 100 years ago, scientists have pondered several questions: Why are dendritic spines distributed nonuniformly along dendrites? Why do dendrites become grossly distorted among individuals with severe neuropathology and mental retardation? Is the number of spines limited by size? Does the number reach saturation? Do more or less spiny dendrites have a greater capacity for plasticity? Which intrinsic and extrinsic features control dendritic plasticity or allow for homeostatic regulation? As protrusions with diverse lengths and shapes, spines allow more connections to form in a compact neuropil. A constricted neck compartmentalizes molecular signals in the spine head and imparts synapse specificity, promotes plasticity, and protects the parent dendrite from excitotoxicity. Spine shape can reflect different inputs in some brain regions such as the lateral nucleus of the amygdala, where cortical inputs synapse on thin spines and thalamic inputs synapse on mushroom spines (Humeau et al. 2005). Conversely, both thin and mushroom spines can synapse with the same CA3 inputs in the hippocampus (Harris & Stevens 1989). Furthermore, cerebellar Purkinje cell spines appear club-shaped even without synaptic input (Cesa & Strata 2005). Live imaging with two-photon microscopy has revealed rapid, activity-dependent spine turnover common during development, but as an animal matures more spines stabilize (Alvarez & Sabatini 2007). This form of imaging also reveals dynamic changes in the shapes of individual spines but is not of sufficient resolution to measure dimensions, count numbers, determine local subcellular or molecular composition, or identify exactly where synapses occur. Electron microscopy is needed to reveal these features (Harris et al. 2006, Rostaing et al. 2006, Masugi-Tokita & Shigemoto 2007). New approaches to combine light and electron microscopy are promising (Zito et al. 1999, Knott et al. 2006, Nagerl et al. 2007), although refinement is needed because the reaction products used to track the dendrites often obscure synapses and subcellular organelles.

This review concentrates on hippocampal dendritic spines. Spatial training (Moser et al. 1997) and exposure to enriched environments (Kozorovitskiy et al. 2005) alter hippocampal spine numbers. Long-term potentiation (LTP) alters spine number, shape, and subcellular composition in both the immature (Maletic-Savatic et al. 1999, Engert & Bonhoeffer 1999, Ostroff et al. 2002, Lang et al. 2004, Matsuzaki et al. 2004, Kopec et al. 2006, Nagerl et al. 2007) and the mature hippocampus (Van Harreveld & Fifkova 1975, Trommald et al. 1996, Popov et al. 2004, Stewart et al. 2005, Bourne et al. 2007b). Conversely, long-term depression (LTD) decreases spine number and size (Chen et al. 2004, Nagerl et al. 2004, Zhou et al. 2004). Structural spine plasticity in the hippocampus involves a change in the size and composition of the postsynaptic density (PSD); assembly and disassembly of actin filaments; exocytosis and endocytosis of glutamate

Thin spines: spines that have constricted necks and small heads

Mushroom spines: spines with constricted necks and heads exceeding 0.6 microns in diameter

LTP: long-term potentiation

LTD: long-term depression

PSD: postsynaptic density

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receptors and ion channels; regulation of local protein synthesis by redistribution of polyribosomes and proteasomes; dynamic repositioning of smooth endoplasmic reticulum (SER) and mitochondria; and metabolic and structural interactions between spines and perisynaptic astroglia. The extent and type of structural change depend partly on experimental methods, developmental age, and regional differences in synaptic organization. This review discusses factors that regulate spine structure and function during hippocampal synaptogenesis and plasticity (**Table 1**).

STRUCTURE AND COMPOSITION OF DENDRITIC SPINES

In the hippocampus, spines vary greatly in size and shape even along short dendritic segments (**Figure 1**). Most spines have constricted necks and are either mushroom shaped with heads exceeding 0.6 microns in diameter or thin shaped with smaller heads (Harris et al. 1992). Other spines are stubby protrusions with head widths equal to neck lengths, branched protrusions with two or more heads, or single protrusions with multiple synapses along the head and neck. These features provide measurably distinct shape categories (**Figure 1*a***) that might reflect functional histories of the spines. Mushroom spines have larger, more complex PSDs (Harris et al. 1992) with a higher density of glutamate receptors (Matsuzaki et al. 2001, Nicholson et al. 2006). Larger spines are more likely to have SER (Spacek & Harris 1997), polyribosomes (Ostroff et al. 2002, Bourne et al. 2007b), endosomal compartments (Cooney et al. 2002, Park et al. 2006), and perisynaptic astroglia (Witcher et al. 2007). These features suggest that larger spines are functionally stronger in their response to glutamate, local regulation of intracellular calcium, endosomal recycling, protein translation and degradation, and interaction with astroglia. Smaller spines may be more flexible, rapidly enlarging or shrinking in response to subsequent activation (Bourne & Harris 2007).

Postsynaptic Density

Spine heads provide a local biochemical compartment where ions and signaling molecules become concentrated following synaptic activation. The PSD is an electron-dense thickening on spine heads that is apposed to the presynaptic active zone. The PSD contains hundreds of proteins including NMDA (N-methyl-d-aspartate), AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate), and metabotropic glutamate receptors; scaffolding proteins such as PSD-95; and signaling proteins such as calcium/calmodulin-dependent kinase II (CamKII) (Okabe 2007). The PSD surfaces vary from small discs to large irregular shapes that can be perforated by electron lucent regions. Differences in PSD dimensions can reflect distance-dependent differences in dendritic function (Magee & Johnston 2005). Relatively more of the distal synapses on CA1 pyramidal cells have perforated synapses; however, perforated synapses associated with the distal input of entorhinal cortex host a lower density of AMPA receptors than do perforated synapses at proximal CA3 input of the same CA1 cells (Nicholson et al. 2006). PSDs appear larger and are more likely to have perforations shortly after the induction of LTP (Geinisman et al. 1991, Toni et al. 1999, Mezey et al. 2004, Popov et al. 2004, Dhanrajan et al. 2004, Stewart et al. 2005), consistent with the idea that perforations are transient structural perturbations responding to activation (Lisman & Harris 1994, Sorra et al. 1998, Fiala et al. 2002, Spacek & Harris 2004). Larger spines with more AMPA and NMDA receptors in the PSD are more sensitive to glutamate (Takumi et al. 1999a,b; Matsuzaki et al. 2001). Small "silent" spine synapses contain only NMDA receptors, and LTP activates them with exocytic insertion of AMPA receptors (Isaac et al. 1995, Liao et al. 1995, Liao et al. 1999, Petralia et al. 1999, Lu et al. 2001, Park et al. 2004, Kopec et al. 2006). AMPA receptors must be constitutively exchanged to sustain the newly active spines; fortunately, lateral diffusion of AMPA receptors out of a spine is limited by the constricted

SER: smooth endoplasmic reticulum

Stubby spines: spines that have head widths equal to the neck length

NMDA: N-methyl-d-aspartate, glutamate receptor

AMPA: α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate, glutamate receptor

CamKII: calcium/calmodulin-dependent kinase II

Perforated synapse: PSD surface is irregularly shaped with electron lucent region(s) dividing it

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Table 1 Molecular mediators of spine morphology

Protein	Function	References
PSD-95	Stabilizes nascent spines and anchors receptors and scaffolding proteins at the synapse.	Ehrlich et al. 2007, Marrs et al. 2001, Okabe et al. 2001
CamKII	Increases the thickness of the PSD and phosphorylates signaling molecules involved in plasticity.	Aakalu et al. 2001; Havik et al. 2003; Kennedy et al. 1983, 1990; Liao et al. 1995; Lledo et al. 1995; Martone et al. 1996; McGlade-McCulloh et al. 1993; Ouyang et al. 1997, 1999; Pettit et al. 1994
Actin	Regulates the extension of filopodia and mediates the expansion of spine heads with LTP and the shrinkage of spine heads with LTD.	Chen et al. 2004, Fukazawa et al. 2003, Matus 2000, Kim & Lisman 1999, Krucker et al. 2000, Lin et al. 2005, Nagerl et al. 2004, Ouyang et al. 2005, Star et al. 2002, Zhou et al. 2004
Profilin	Promotes activity-dependent actin polymerization and stabilizes actin.	Ackermann & Matus 2003, Ethell & Pasquale 2005, Tada & Sheng 2006
Cofilin	Depolymerizes actin filaments, but LTP or learning-induced phosphorylation decreases its affinity for actin, promoting polymerization and spine enlargement.	Chen et al. 2007, Fedulov et al. 2007
Rap1/AF-6	Elongates spines and removes AMPA receptors with activation, whereas inactivation enlarges spines and recruits AMPA receptors.	Xie et al. 2005, Zhu et al. 2002
Myosin IIb	Stabilizes mushroom spines.	Ryu et al. 2006
Myosin VI	Regulates clathrin-mediated endocytosis of AMPA receptors.	Osterweil et al. 2005
Synaptopodin	Binds to the spine apparatus and may mediate interactions between the actin cytoskeleton and calcium signaling. Synaptopodin-deficient mice have normal spine morphology and density, but all spines lack a spine apparatus.	Deller et al. 2007
Telencephalin	Slows the development of dendritic spines with overexpression, whereas deletion accelerates the spine development, suggesting a role in maintaining filopodia during development.	Matsuno et al. 2006
SynGAP	Maintains filopodia during development and localizes to the synapse to negatively regulate Ras signaling pathways, which promote spine formation and growth.	Chen et al. 1998, Kim et al. 1998, Krapivinsky et al. 2004, Oh et al. 2004, Vazquez et al. 2004
miR-134	Negatively regulates spine development by inhibiting translation of Limk1. Overexpression of miR-134 results in a decrease of spine volume.	Schratt et al. 2006
N-cadherin	Stabilizes mature synapses and regulates spine morphology and synaptic efficacy.	Abe et al. 2004, Bozdagi et al. 2000, Kosik et al. 2005, Nuriya & Huganir 2006, Tai et al. 2007, Togashi et al. 2002
EphB/EphrinB	Clusters receptors and mediates spine morphology by recruiting molecules involved in actin polymerization.	Contractor et al. 2002, Dalva et al. 2000, Irie & Yamaguchi 2004, Grunwald et al. 2004, Penzes et al. 2003
EphA/EphrinA	Regulates neuro-glial signaling and induces the retraction of spines. Expression decreases during development and is inactive in mature brains, suggesting a potential role in synaptic pruning.	Allen & Barres 2005, Grunwald et al. 2004, Murai et al. 2003

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spine neck (Adesnik et al. 2005, Ashby et al. 2006). AMPA receptors can also be actively removed via endocytosis during LTD (Beattie et al. 2000, Man et al. 2000, Snyder et al. 2001, Xiao et al. 2001, Lee et al. 2002, Brown et al. 2005). Both exo- and endocytic processes alter spine shape. Because the PSD's size is well correlated with spine head volume and the number of presynaptic vesicles (Harris & Stevens 1989, Harris et al. 1992), there is likely a trans-synaptic mechanism to coordinate them during plasticity (Lisman & Harris 1993, Spacek & Harris 2004).

Actin Cytoskeleton

Spine formation and morphology are regulated by actin filaments (Matus 2000, Zito et al. 2004). Filamentous actin (F-actin) forms organized bundles in spine necks, and altered polymerization-depolymerization states accompany changes in head shapes (Star et al. 2002). Induction of LTP briefly depolymerizes actin filaments (Ouyang et al. 2005), whereas maintenance of LTP and sustained spine enlargement require polymerization of F-actin (Kim & Lisman 1999, Krucker et al. 2000, Fukazawa et al. 2003, Lin et al. 2005). In contrast, LTD results in the depolymerization of actin and spine elongation or shrinkage of spine heads (Chen et al. 2004, Nagerl et al. 2004, Zhou et al. 2004). The actin cytoskeleton is regulated by actin-binding proteins (Ethell & Pasquale 2005, Tada & Sheng 2006). Profilin is a promoter of actin polymerization that could facilitate LTP-induced actin assembly and spine enlargement (Ackermann & Matus 2003). Cofilin is an actin-binding protein that causes actin depolymerization; induction of LTP or exposure to enriched environments causes phosphorylation-mediated inhibition of cofilin and promotes spine enlargement (Chen et al. 2007, Fedulov et al. 2007). Rap1 is an actin-binding protein that localizes AF-6 to the synaptic membrane, where it induces rearrangement of actin filaments and promotes removal of AMPA receptors (Xie et al. 2005) and spine elongation, a morphological correlate of LTD (Zhu et al. 2002). Conversely, inactivation of Rap1 releases AF-6 from the synaptic membrane to regulate a different pool of actin filaments that promote recruitment of AMPA receptors to the synapse and spine enlargement with LTP (Xie et al. 2005). Myosins IIb and VI are motor proteins enriched in the PSD that translocate along, and regulate contractility of, actin filaments and spine shape (Osterweil et al. 2005, Ryu et al. 2006). Myosin VI–deficient spines have disrupted clathrin-mediated endocytosis of AMPA receptors, suggesting a role in LTD (Osterweil et al. 2005).

ssTEM: serial section transmission electron microscopy

Recycling Endosomes

LTP requires exocytosis-mediated insertion of AMPA receptors (Lu et al. 2001, Park et al. 2004, Kopec et al. 2006) and is accompanied by endocytosis of Kv4.2 subunits of voltage-gated A-type K^+ channels, which enhances local dendritic excitability (Kim et al. 2007). Patches of preassembled clathrin provide hot spots of endocytosis along spine and dendritic membranes (Blanpied et al. 2002, Racz et al. 2004). Spine shape is regulated by recycling endosomes, and blocking this pathway results in significant spine loss (Park et al. 2006). Following the induction of LTP, live imaging and serial section transmission electron microscopy (ssTEM) revealed translocation into spines of endosomes having sufficient surface area to provide an abundant resource for spine growth. Two membrane pools were identified: recycling endosomes with tubules, vesicles, and clathrin-coated pits or buds and large amorphous vesicular clumps (AVC). Quantification suggested that AVCs provided membrane for new or enlarged spines, and recycling endosomes maintained them. LTD results in AMPA receptor internalization and reduced spine and synapse size (Man et al. 2000, Chen et al. 2004, Nagerl et al. 2004, Zhou et al. 2004, Brown et al. 2005). Interference with this AMPA receptor internalization leads to excitotoxicity via increased sensitivity to glutamate and eventual spine loss (Halpain et al. 1998, Hasbani et al. 2001). Thus, exo- and endocytosis must maintain an

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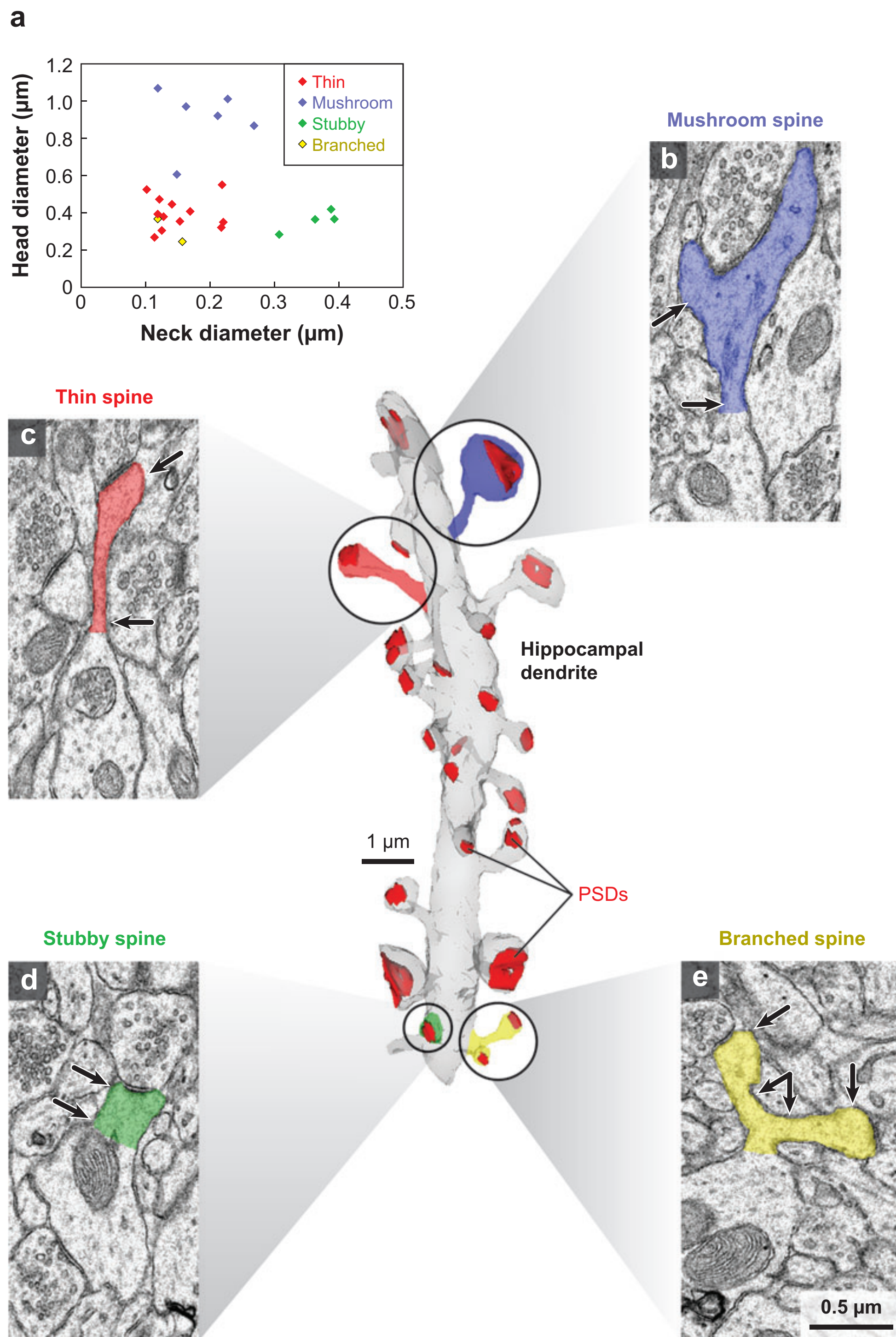

activity-dependent balance to fine-tune the physiological and structural responses of spines to synaptic plasticity.

Polyribosomes and Proteasomes

Dendritic spine response to synaptic plasticity relies on spines' ability to regulate protein synthesis and degradation. Treatment with anisomycin prevents spine enlargement during LTP (Fifkova et al. 1982, Kelleher et al. 2004). Other findings show that polyribosomes, the machinery necessary to translate proteins, occur at the base of dendritic spines (Steward & Levy 1982) and preferentially redistribute into dendritic spines with enlarged heads and synapses during LTP (Ostroff et al. 2002, Bourne et al. 2007b). Which plasticity-related proteins could be translated by these local polyribosomes to increase the PSD size? One candidate is CamKII, a cytoplasmic protein highly enriched in the PSD (Kennedy et al. 1983, 1990; Otmakhov et al. 2004). CamKII becomes autophosphorylated (Miller & Kennedy 1986) following activation and can regulate glutamate receptors both directly and indirectly long after calcium levels have returned to baseline during LTP (McGlade-McCulloh et al. 1993, Pettit et al. 1994, Liao et al. 1995, Lledo et al. 1995). Furthermore, the mRNA transcripts for CamKII are present in dendrites (Martone et al. 1996, Havik et al. 2003), and translation of CamKII is upregulated (Ouyang et al. 1997, Ouyang et al. 1999, Aakalu et al. 2001) and more CamKII is present in the PSD after LTP (Otmakhov et al. 2004). Induction of LTD through activation of metabotropic glutamate receptors (mGluRs) is dependent on protein synthesis in adolescent but not neonatal rats (Huber et al. 2001, Nosyreva & Huber 2005). Stimulation of mGluRs in synaptoneurosomes triggers the aggregation of polyribosomes and the translation of proteins, including the fragile X mental retardation protein (Weiler et al. 1997), although the dendritic distribution of polyribosomes following induction of LTD has not yet been examined.

mGluR: metabotropic glutamate receptor

Rough endoplasmic reticulum (RER) and Golgi have been identified in dendrites, where they could locally synthesize and regulate integral membrane proteins (Steward & Reeves 1988, Gardiol et al. 1999, Cooney et al. 2002, Horton & Ehlers 2004, Grigston et al. 2005). One intriguing possibility is that the enigmatic spine apparatus, which occurs in ∼10%–15% of mature hippocampal spines (Spacek & Harris 1997), may also be an extension of the Golgi apparatus (Pierce et al. 2000). Localized synthesis of the GluR1 and GluR2 subunits for AMPA glutamate receptors has been demonstrated in hippocampal dendrites (Kacharmina et al. 2000, Ju et al. 2004, Grooms et al. 2006), and the mRNAs for other integral membrane and secretory proteins are found throughout the dendritic arbor (Steward & Schuman 2003).

Maintenance of LTP also relies on proteasomes to degrade proteins (Fonseca et al. 2006, Karpova et al. 2006). Lysosomes and

Figure 1

Variability in spine shape and size. A three-dimensional reconstruction of a hippocampal dendrite (*gray*) illustrating different spine shapes including mushroom (*blue*), thin (*red*), stubby (*green*), and branched (*yellow*). PSDs (*red*) also vary in size and shape. (*a*) A graph plotting the ratio of head diameters to neck diameters for the spines on the reconstructed dendrite. Spine heads were measured at their widest point parallel to the PSD, and spine necks were measured just above the base of the spine to give a uniform location of measurement across all spines. Mushroom spines (*blue diamonds*), stubby spines (*green diamonds*), and thin spines (*red diamonds*) segregated into distinct groups. Both branches of the branched spine were of a thin shape and were situated among the thin spine dimensions (*yellow diamonds*). (*b*) An example of a mushroom spine (*blue*) with a head diameter exceeding 0.6 microns and a narrow neck. (*c*) An example of a thin spine (*red*) with a small head and narrow neck. (*d*) An example of a stubby spine (*green*) with an equal head and neck diameter and an overall length that equals its width. (*e*) An example of a branched spine (*yellow*) where both branches are thin spines. Scale bar = 0.5 μm, and arrows indicate where the head and neck diameters were measured for each spine in *b*–*e*.

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Filopodia: dynamic protrusions from dendrites that may become spines

multivesicular bodies also occur in dendritic spines (Spacek & Harris 1997, Cooney et al. 2002). It will be interesting to learn whether the balance of protein synthesis and degradation is shifted depending on whether a synapse is potentiated or depressed.

SER

Many dendritic spines contain SER, which likely regulates calcium. SER is present in all dendritic spines of cerebellar Purkinje neurons (Harris & Stevens 1988) but in less than half of cortical or hippocampal spines (Spacek 1985a, Spacek & Harris 1997). Calcium influx can trigger release from SER, thereby extending its elevation in stimulated spine heads (Sabatini et al. 2001). The elevated calcium facilitates remodeling of the actin cytoskeleton (Oertner & Matus 2005). Laminae of SER and dense-staining material form a spine apparatus in ~10%–20% of hippocampal and cortical spines. Synaptopodin is an actin-associated protein that occurs in the spine apparatus, and mice lacking synaptopodin also lack a spine apparatus and display deficits in synaptic plasticity (Deller et al. 2007). SER can shift throughout the dendrite (Toresson & Grant 2005), and it will be interesting to learn whether these dynamics are influenced by synaptic plasticity.

Mitochondria

Mitochondria are abundant in dendritic shafts, and the ATP they produce likely diffuses into spines to provide energy for signal transduction. In contrast, mitochondria are rarely found in dendritic spines and are usually restricted to very large and complex spines, such as the branched spines or "thorny excrescences" located on proximal dendrites of CA3 pyramidal cells (Chicurel & Harris 1992). In cultured neurons from area CA1, mitochondria occasionally migrate into some dendritic spines during periods of intense synaptic remodeling (Li et al. 2004). The enzymes involved in the glycolic generation and regulation of ATP have been localized to isolated PSDs, suggesting a mechanism for direct synthesis of ATP at individual synapses even in the absence of mitochondria in spines (Rogalski-Wilk & Cohen 1997, Wu et al. 1997). Synaptic ATP could provide an energy source for signaling via protein kinases found at the PSD, such as protein kinase A, protein kinase C, and CamKII, and for local protein synthesis by polyribosomes. Although enzymes localized to the PSD are a potentially important source of ATP, it would be interesting to know whether the distances between dendritic mitochondria and spines are altered in response to input-specific plasticity, such as LTP and LTD.

THE FORMATION AND STABILIZATION OF NEW SPINES

New spines are formed in the hippocampus during development and some forms of adult plasticity. Filopodia are nonsynaptic or multisynaptic, actin-rich protrusions with pointy tips (Fiala et al. 1998) that tend to be transient and last ~10 min during development (Ziv & Smith 1996). With maturation, the density of the neuropil increases and additional mechanisms may be required for new spines to find, compete for, and maintain presynaptic partners.

Development

During the first few weeks of postnatal life, hippocampal dendrites have numerous filopodia (Papa & Segal 1996, Ziv & Smith 1996, Fiala et al. 1998). Some filopodia become spines with synapses (Marrs et al. 2001), whereas others withdraw into the dendrite to form synapses on the dendritic shaft (Fiala et al. 1998, Marrs et al. 2001). These shaft synapses either reemerge as spines or are preferentially eliminated later in life (Harris 1999, Bourne & Harris 2007).

Stabilization of hippocampal spines requires assembly of pre- and postsynaptic elements, although the timing of these events may vary (Harris et al. 2003, Ostroff & Harris 2004, Risher et al. 2006, Nagerl et al. 2007). Dense

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core vesicles containing piccolo and bassoon appear in axonal processes within 2 days and cluster along dendritic profiles by 4 days in vitro in cultured hippocampal neurons, which suggests that presynaptic active zones are prepackaged (Zhai et al. 2001, Shapira et al. 2003). PSD-95 is necessary to stabilize the spine, as evidenced by RNAi knockdowns that cause spine loss (Ehrlich et al. 2007). Assembly of PSD-95 is spatially and temporally correlated with spine morphogenesis (Marrs et al. 2001) and the clustering of presynaptic vesicle proteins (Okabe et al. 2001). Stabilization of dendritic spines also relies on the insertion and activation of glutamate receptors; AMPA receptor activation in particular decreases spine motility and stabilizes spine shape (Fischer et al. 2000). Blocking NMDA receptor signaling does not affect the emergence or density of spines during development (Rao & Craig 1997, Kirov et al. 2004a, Alvarez et al. 2007), but knocking down NMDA receptors through RNA interference (RNAi) results in increased spine motility and eventual elimination (Alvarez et al. 2007).

Synaptogenesis requires that filopodia be maintained long enough to find appropriate presynaptic partners. Telencephalin is an adhesion molecule of the Ig superfamily and SynGAP is a Ras-GTPase activating protein; both of these proteins maintain filopodia in a dynamic state during synaptogenesis, and mice deficient in either protein show accelerated spine development and larger spine heads (Vazquez et al. 2004, Matsuno et al. 2006). Once filopodia become spines, telencephalin relocates to the dendritic shaft and is replaced with adhesion molecules, N-cadherin and α-catenin, which stabilize the new spine (Bozdagi et al. 2000, Togashi et al. 2002, Abe et al. 2004). SynGAP remains at the synapse and is bound to PSD-95 through its PDZ (PSD-95/Discs large/zona occludens-1) domain (Chen et al. 1998, Kim et al. 1998). Activation of NMDA receptors alters the phosphorylation state of different SynGAP isoforms, linking NMDA receptor activation and Ras signaling pathways (Chen et al. 1998, Krapivinsky et al. 2004, Oh et al. 2004).

Spinogenesis is also regulated by microRNAs, small noncoding RNAs that control the translation of messenger RNAs. miR-134 is a brain-specific microRNA localized to dendritic spines that negatively regulates spine size by inhibiting protein kinase Limk1 translation (Schratt et al. 2006). Treatment with brain-derived neurotrophic factor (BDNF) relieves miR-134-mediated inhibition of Limk1 translation, which suggests that synaptic stimuli and extracellular signals can regulate spine development through local translation mechanisms.

RNAi: ribonucleic acid interference

Spinogenesis in the Mature Hippocampus

Filopodia are rarely observed in the mature hippocampus; however, blocking synaptic transmission in mature hippocampal slices triggers filopodia and new spines in an apparent attempt to compensate for the loss of synaptic input (Kirov & Harris 1999). Chilling hippocampal slices during preparation results in an immediate disappearance of spines, but upon rewarming new spines proliferate beyond levels found in vivo (Kirov et al. 1999, Kirov et al. 2004b). Instead, if slices are prepared rapidly at room temperature, then spine density matches that found in perfusion-fixed hippocampus even several hours later (Bourne et al. 2007a). Hibernating ground squirrels also show substantial spine loss at near-freezing temperatures, but rapid spinogenesis occurs within minutes of awakening and return to warmer body temperatures (Popov et al. 1992, Popov & Bocharova 1992). Telencephalin levels remain high in adulthood, suggesting an ongoing involvement in transforming filopodia to new spines in the mature brain (Matsuno et al. 2006).

Adhesion and Trans-Synaptic Signaling

Cell-adhesion molecules, such as N-cadherins, catenins, neurexins, and neuroligins, and Ephs

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and ephrins begin to cluster on the pre- and postsynaptic sides and help stabilize the nascent spines and their synapses (Calabrese et al. 2006). N-cadherin is an adhesive molecule that links pre- and postsynaptic elements through calcium-dependent homophilic interactions. N-cadherin and β-catenin form a calcium-regulated complex with AMPA receptors, and overexpression of N-cadherin increases the surface expression of the AMPA receptor subunit GluR1 (Nuriya & Huganir 2006, Tai et al. 2007). NMDA receptor activation increases the concentration of unphosphorylated β-catenin and inhibits endocytosis of N-cadherin (Tai et al. 2007). N-cadherin also regulates spine morphology via its binding proteins, α- and β-catenin, which interact with the actin cytoskeleton (Kosik et al. 2005). Thus synaptic activity stabilizes synapse structure via N-cadherin, which in turn recruits AMPA receptors and maintains synaptic efficacy. Prolonged stability of N-cadherin abolishes NMDA receptor–induced LTD, perhaps because N-cadherin prevents the internalization of AMPA receptors associated with synaptic depression (Tai et al. 2007).

Eph receptor–ephrin binding results in multimeric clusters that bridge juxtaposed cell surfaces and mediate cell-cell adhesion and bidirectional signaling. Trans-endocytosis of the eph-ephrin complex loosens the adhesion between the pre- and postsynaptic elements, which may permit structural synaptic plasticity. EphB receptors directly associate with NMDA receptors at synapses, and ephrinB-induced activation of EphB receptors causes NMDA receptor clustering (Dalva et al. 2000). At the mossy fiber synapse in CA3, postsynaptic EphB2 receptors interact with a PDZ-domain protein, glutamate receptor interacting protein (GRIP), to mediate AMPA receptor-dependent LTP (Contractor et al. 2002). EphB2 also associates with the GTP exchange factors intersectin and kalirin (Penzes et al. 2003, Irie & Yamaguchi 2004). The intersectin-Cdc42-Wasp-actin and kalirin-Rac-Pak-actin pathways may regulate the EphB receptor–mediated morphogenesis and maturation of dendritic spines in cultured hippocampal and cortical neurons. Perhaps the interaction of presynaptic ephrins with postsynaptic Eph receptors coordinates the establishment of the well-known correlation between presynaptic vesicle number and postsynaptic size during structural synaptic plasticity.

Trans-synaptic signaling may also be mediated by the formation of spinules. Spinules are double-membrane structures that emerge primarily from dendritic spines into presynaptic or neighboring axons or astroglial processes (Spacek & Harris 2004). Spinules are likely involved in active trans-endocytosis, as evidenced by the presence of clathrin-like coats along the cytoplasmic surface of the engulfing structure, such as the presynaptic axons, across from the spinule tip. In particular, this trans-endocytosis could be the morphological correlate of retrograde signaling via cell surface molecules such as Ephs and ephrins, which must remain in the plasma membrane while signaling. Spinules may also be involved in remodeling the postsynaptic membrane, as suggested by their transient increase shortly after LTP induction (Applegate & Landfield 1988, Schuster et al. 1990, Geinisman et al. 1993, Toni et al. 1999).

Perisynaptic Astroglia

The development and stabilization of synapses also require astroglia (Allen & Barres 2005). Astroglia form nonoverlapping domains in the hippocampus and cortex, and a single astrocyte contacts hundreds of dendrites and thousands of synapses, which suggests that it coordinates multiple neuronal networks (Bushong et al. 2002, Halassa et al. 2007). Transient interactions between the ephrin-A3 ligand and the EphA4 receptor regulate the structure of excitatory synaptic connections through neuroglial cross talk (Murai et al. 2003, Grunwald et al. 2004). Activation of EphA4 by ephrin-A3 induces spine retraction, whereas inhibiting ephrin/EphA4 interactions distorts spine shape and organization (Murai et al. 2003). Expression of EphA4 decreases during maturation,

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suggesting its role in synaptic elimination and connection refinement. Astrocytes also secrete soluble factors such as thrombospondins and cholesterol, which influence spine formation and synapse maturation (Ullian et al. 2004, Christopherson et al. 2005). In the mature neocortex and hippocampus, fewer than half the synapses have perisynaptic astroglial processes (Spacek 1985b, Ventura & Harris 1999); however, synapses with astroglial processes at their perimeter are larger and presumably more effective than those without (Witcher et al. 2007). Synapse size is associated with the presence of an astroglial process juxtaposed to the postsynaptic spine and/or the synaptic cleft, not with the degree to which the astroglial process surrounds the synapse. Even the largest hippocampal or neocortical synapses might have only a small fraction of their perimeters surrounded by an astroglial process, which suggests that cross talk via spillover of neurotransmitters between synapses might be functionally significant. Thus, interactions between cell surface molecules and the release of various soluble factors by astroglia may be crucially important to the turnover and enlargement of spines observed with synaptic plasticity.

CONCLUSIONS

Modern molecular biology, electrophysiology, and imaging studies have provided many insights into the mechanisms of the morphological alterations undergone by dendritic spines during development and synaptic plasticity. Nevertheless, fundamental structural questions remain. Presently, only three-dimensional (3D) reconstruction from ssTEM provides sufficient resolution to determine how intrinsic and extrinsic factors might interact to control the structure and function of spines and synapses. Advances in imaging and computing technologies may soon provide resources to reconstruct entire neural circuits (e.g., projectomes or connectomes; Kasthuri & Lichtman 2007). It is not sufficient, however, to have just the wiring diagram because we also need to know what controls the switches. Determining the extrinsic factors that regulate connectivity along dendrites and axons and the intrinsic factors that regulate the availability of core subcellular structures required to build and maintain synapses is necessary to formulate a comprehensive understanding of neural circuits that underlie perception, memory, and cognition.

SUMMARY POINTS

1. Dendritic spines are complex biochemical compartments that integrate individual synaptic inputs into complex neural networks.
2. Dendritic spines in the hippocampus undergo genesis, elimination, and structural modification in response to a variety of stimuli.
3. Spines coordinate the activation of glutamate receptors with calcium regulation, cytoskeletal remodeling, membrane trafficking, protein synthesis and degradation, and trans-synaptic signaling.
4. The dynamic balance of the molecular machinery within spines is manifested by morphological changes in spine shape and density and by the translocation of necessary organelles into and out of spines.
5. Although light level microscopy can provide information on real-time dynamics of spines and proteins, ssTEM is required to detect small but crucial changes in spine dimensions and interspine spacing and the presence and distribution of subcellular organelles and perisynaptic astroglia.

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FUTURE ISSUES

1. Investigators must determine whether the mechanisms underlying the outgrowth and stabilization of new spines during plasticity in the mature hippocampus are the same as those regulating synaptogenesis during development.
2. We must also refine the methods used to correlate gross morphological changes observed at the light level with subtle ultrastructural changes observed with ssTEM and develop new strategies to label individual cells, dendrites, and spines in an unobtrusive manner.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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