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Overview on the Structure, Composition, Function, Development, and Plasticity of Hippocampal Dendritic Spines

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ABSTRACT: There has been an explosion of new information on the neurobiology of dendritic spines in synaptic signaling, integration, and plasticity. Novel imaging and analytical techniques have provided important new insights into dendritic spine structure and function. Results are accumulating across many disciplines, and a step toward consolidating some of this work has resulted in *Dendritic Spines of the Hippocampus.* Leaders in the field provide a discussion at the level of advanced undergraduates, with sufficient detail to be a contemporary resource for research scientists. Critical reviews are presented on topics ranging from spine structure, formation, and maintenance, to molecular composition, plasticity, and the role of spines in learning and memory. *Dendritic Spines of the Hippocampus* provides a timely discussion of our current understanding of form and function at these excitatory synapses. We asked authors to include areas of controversy in their papers so as to distinguish results that are generally agreed upon from those where multiple interpretations are possible. We thank the contributors for their insights and thoughtful discussions. In this paper we provide background on the structure, composition, function, development, plasticity, and pathology of hippocampal dendritic spines. In addition, we highlight where each of these subjects will be elaborated upon in subsequent papers of this special issue of *Hippocampus. Hippocampus 2000;10:501–511.*

KEY WORDS: synapse; ultrastructure; dendrite; filopodia; microscopy

STRUCTURE OF HIPPOCAMPAL DENDRITIC SPINES

Hippocampal pyramidal neurons, like neurons in other brain regions, have a variable assortment of spines and spine-like protrusions emerging from their dendrites. Dendritic spine structure at any single point in time reflects a dynamic structure that may undergo numerous changes in shape, both slowly and rapidly, over its lifetime. Neighboring spines, along even a short segment of dendrite, exhibit a broad range in spine morphologies Fig. 1, Table 1). In hippocampal area CA1, spine neck diameters range from 0.04–0.5 μm, while total spine length ranges from roughly 0.2–2 μm (Harris and Stevens, 1989). There is also more than a 50-fold difference among other spine dimensions that varies proportionately with synaptic and presynaptic parameters (Table 1, Fig. 1) (Harris and Kater, 1994; Lisman and Harris, 1993).

Dendritic spine shape varies over a continuum of morphologies from short to long, thin to thick-necked, headless to large pedunculated structures. The distribution of shapes is skewed toward thin spines in the adult brain. A *thin spine* has a total length greater than the neck diameter ending in a small bulbous head (<0.6 μm in diameter; Fig. 1b). *Stubby spines* are short and wide with no constriction in their necks (Fig. 1A). *Sessile spines* are longer than their diameter but have no bulbous head. *Mushroom spines* have a constricted neck and a large irregular head (>0.6 μm in largest diameter; Fig. 1B). In mature hippocampal areas CA1 and dentata, these four types of dendritic spines usually have only one synapse on their head. *Branched spines* have multiple heads that emerge from a shared origin. In hippocampal areas CA1 and dentata, each head of a branched spine synapses with a different presynaptic axon, while some heads have no presynaptic partners (Sorra et al., 1998; Trommald and Hulleberg, 1997). In contrast, different heads of the "thorny excresences," which are highly irregular and large spines on CA3 pyramidal cells, can be innervated by the same or different axonal boutons (Chicurel and Harris, 1992). Classifying spines first by their shape has proven useful to ensure that the full range in morphologies is sampled for three-dimensional reconstructions, and in determining whether shifts in spine morphology occur with experimental manipulations (Kirov et al., 1999; Sorra and Harris, 1998; Chicurel and Harris, 1992; Harris et al., 1992; Harris and Stevens, 1989).

Serial electron microscopy (EM) is needed to make these subtle distinctions in dendritic spine shape because their classification is often dependent on dimensions beyond the resolution of light microscopy. Fluorescence, confocal, or two-photon laser scanning microscopy enable observation of individual dendrite protrusions in living neurons, and in some cases spines can be distinguished from filopodia (see Methods in Parnass et al., this issue). Mature dendrites have so many spines (1–10 spines/μm) that profiles of neighboring spines often overlap one another and interfere with the study of spine shape. In addition, it is not possible to distinguish with

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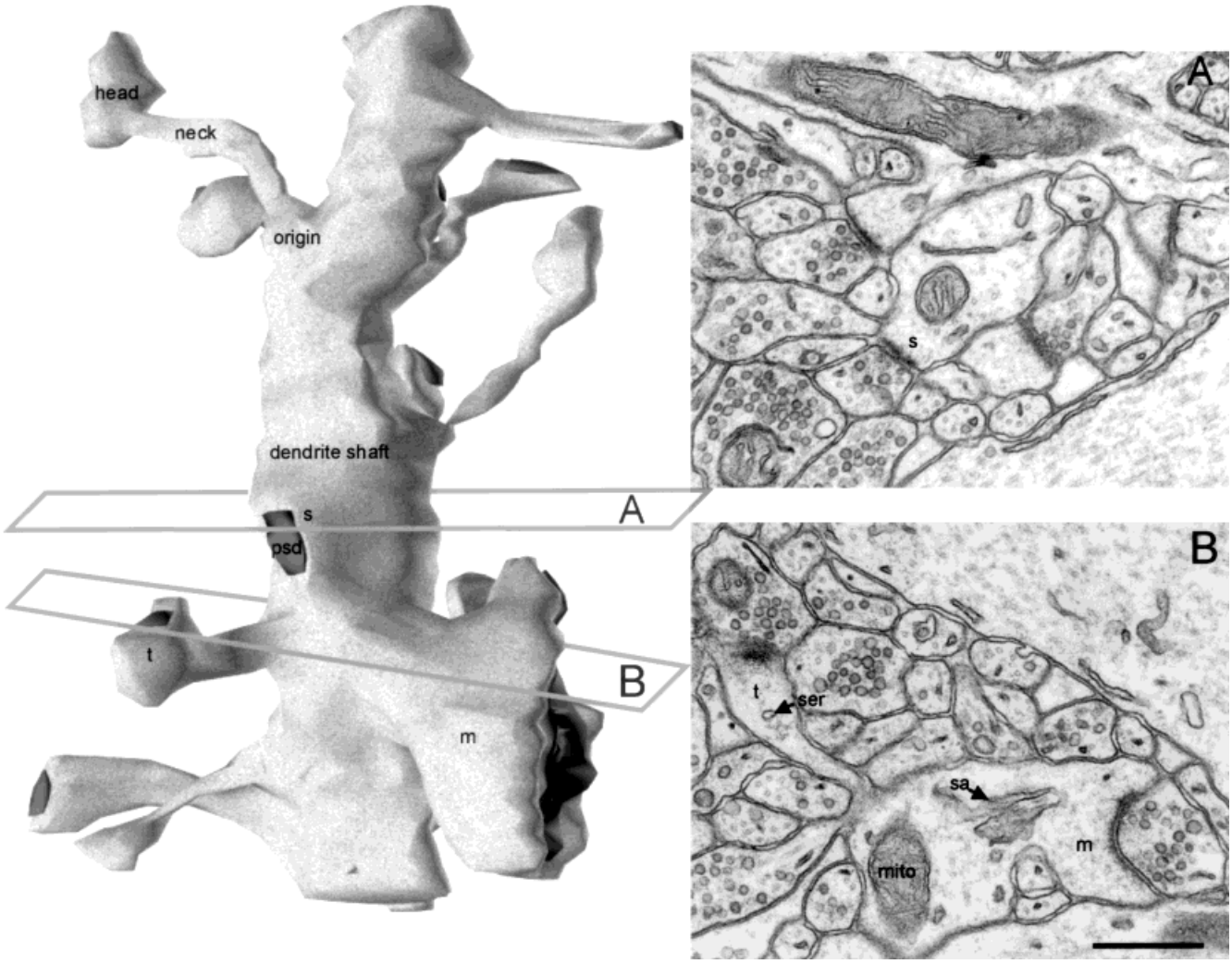

FIGURE 1. Reconstructed dendrite segment, dendritic spines, and representative electron micrographs (EM) from which the reconstruction was created (rat hippocampus, area CA1). A: Section 59 of the EM series, illustrating a stubby spine (s) with a macular postsynaptic density. B: Section 66 of the EM series, showing thin (t) and mushroom-shaped (m) spines along the same dendritic segment. Spine apparatus (sa) is present within the mushroom spine neck, as is a tubule of smooth endoplasmic reticulum (ser) within the thin spine. mito, mitochondrion within the dendrite. Scale bar (0.5 μm) is for A and B.

light microscopy whether dendritic protrusions have a synapse, especially on immature neurons (Fiala et al., 1998). Adding indicator dyes, such as those that respond to calcium influx, facilitates the interpretation that a dendritic protrusion is activated by a synapse, although nonsynaptic calcium channels cannot be ruled out as a possible source. Combining real-time imaging with post hoc serial electron microscopy of identified spines provides an unequivocal approach (see Mackenzie et al., 1999), although reliable labeling of synapses is needed to distinguish neighboring, "unaffected" spines at the EM level. Such an approach also makes it possible to identify whether changes in other subcellular components of the spine are involved. Several papers within this supplement provide further insight into current and future possibilities of combining experimental approaches to link dynamic spine structure with synapse location and composition (see Deller et al., Korkotian and Segal, Matus and Brinkhaus, Muller et al., Parnass et al., Smart and Halpain, Rao and Craig, and Zhang and Benson, this issue).

ORGANELLES IN DENDRITIC SPINES

Specific spine shapes are also associated with distinct synapse morphologies and subcellular organelles. Below, the structure of spine organelles is described, followed by a brief overview of their molecular composition.

Postsynaptic Density

Working from the synapse to the origin of the spine with the dendrite, the first organelle encountered is a dense thickening,

TABLE 1.

Ranges in Dimensions of Hippocampal Dendritic Spines and Their Synapses

	Dentate gyrus[a]	Area CA3[b]	Area CA1[c]
Neck diameter (μm)	0.09–0.54*	0.20–1.00	0.038–0.46
Spine length (μm)	0.20–1.78	0.60–6.50	0.160–2.13
Spine volume (μm^3)	0.003–0.23	0.13–1.83	0.004–0.56
Head volume only (μm^3)			0.003–0.55
Postsynaptic density area (μm^2)	0.003–0.23	0.01–0.60	0.008–0.54

*Ranges in neck diameter were calculated from published values of average cross-sectional area based on the formula πr^2.
[a]Trommald and Hulleberg, 1997.
[b]Harris and Kater, 1994; Chicurel and Harris, 1992.
[c]Harris and Stevens, 1989.

called the postsynaptic density (PSD). The PSD is attached under the surface of the spine membrane either at the top or side of the spine head, across from a vesicle-containing presynaptic axon. The PSD ranges in shape from a simple disc (macular PSD) or a perforated annulus (perforated PSD), to a highly irregular or segmented structure (Fig. 2). PSD dimensions are proportional to total spine volume, number of presynaptic vesicles, and quantity of organelles within the spine (Spacek and Harris, 1997; Harris et al., 1992).

Smooth Endoplasmic Reticulum (SER) and Polyribosomes

SER is an organelle of elongated, flattened, or enlarged cisternae found in about half of the hippocampal dendritic spines. Spine SER is continuous with SER of the dendrite (Spacek and Harris, 1997). SER likely regulates the concentration of calcium in spines (see Spine Functions, below). In about 1 in 15 mature dendritic spines, the SER elaborates into a structure called the "spine apparatus" (Fig. 1B; see also Deller et al., this issue; Spacek and Harris, 1997; Westrum et al., 1980). In hippocampal area CA1, the spines containing a spine apparatus are large and mushroom-shaped, with a perforated or irregular PSD (Spacek and Harris, 1997). The spine apparatus is composed of stacks of SER laminated with densely stained material. Polyribosomes, rough endoplasmic reticulum (RER), and smooth vesicles are also frequently in spines with a spine apparatus (see Synapse Web, Boston University, http://synapses.bu.edu). The function of the spine apparatus is unknown. However, its ultrastructure suggests that it may be involved in the synthesis of membrane-bound proteins and their transport, similar to the RER and Golgi apparatus in the cell soma. Polyribosomes also occur freely in the dendritic spine cytoplasm (see Fig. 3E) (Chicurel et al., 1993; Steward and Reeves, 1988; Steward and Levy, 1982; Synapse Web, Boston University, http://synapses.bu.edu).

Endosomal-Lysosomal Pathway

Coated vesicles, endosomes, and multivesicular bodies are also found, particularly in the large dendritic spines (Spacek and Har-

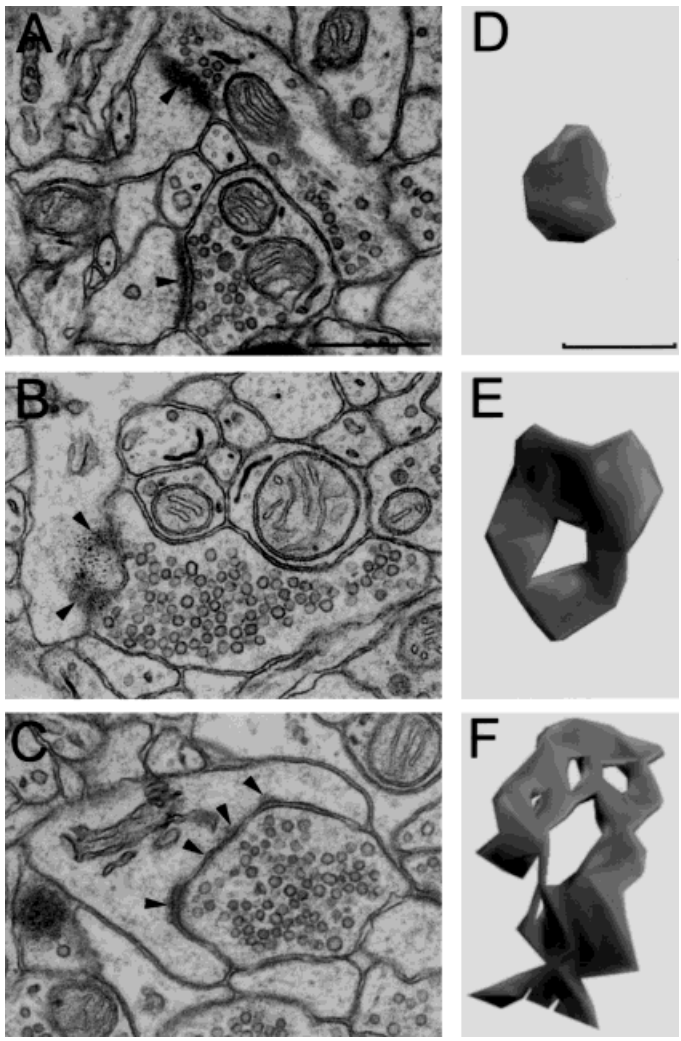

FIGURE 2. Diversity in postsynaptic densities (PSDs) on hippocampal dendritic spines. Electron micrographs of a macular (A), perforated (B), and segmented (C) PSD. Arrowheads indicate dark-staining PSD from the postsynaptic side of the synapse. D–F: Three-dimensional reconstructions, showing a full range of PSD morphologies. Reconstructions are illustrated en face. Scale bar in A and D, 0.5 μm.

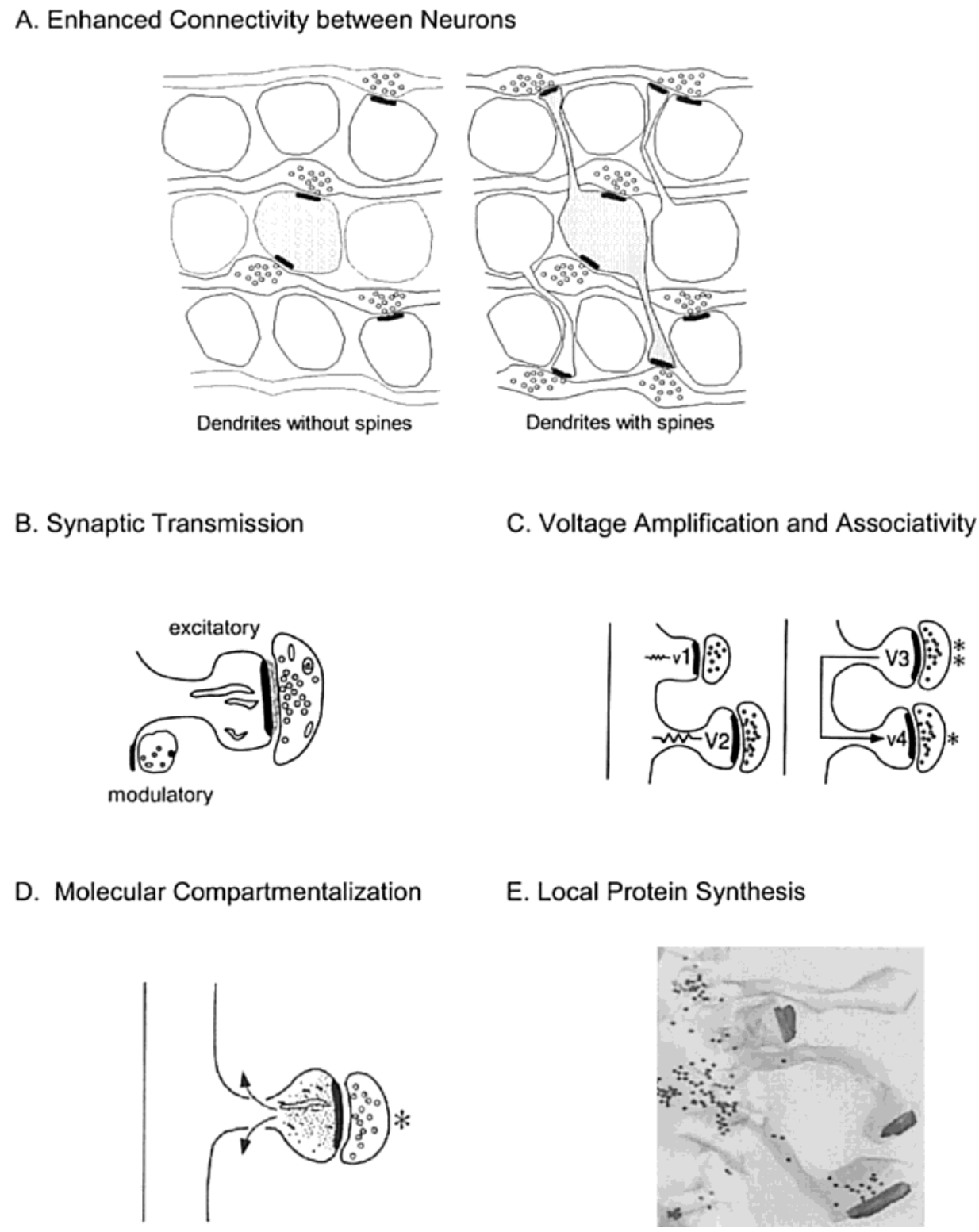

FIGURE 3. Dendritic spine function. A: Spines exist to increase the packing density of synapses. Schematic illustrates a cross section through two dendrites (shaded), one without and one with dendritic spines. Convolution and interdigitation of dendrite, axon, and spine membranes support more synapses. B: Spines exist as principal sites of excitatory synaptic transmission. C: Spines exist to amplify electrical potential at the synapse and promote associativity among neighboring synapses. Spine shape and resistance of the spine neck may influence potential (V) generated by synaptic activation. D: Spines exist as molecular compartments. Smooth endoplasmic reticulum (tubules), calcium, and a myriad of other signaling mechanisms (stippling) are recruited in response to synaptic activation (asterisk). E: Three-dimensional reconstruction of thin spines emerging from a dendrite. Polyribosomes (black dots) are most frequent at the base of dendritic spines, although they can also occur within them (see thin spine at bottom). Areas of synaptic membrane are shown in dark gray (rat hippocampus, area CA1).

ris, 1997). Endosomes are distinguished from the SER by their more tubular structure and a direct connection with coated vesicles and multivesicular bodies. Thus, local degradation of proteins can occur within dendritic spines.

Mitochondria

Mitochondria are conspicuously absent from most dendritic spines, though they are abundant within dendrites (Fig. 1). In the hippocampus, mitochondria have only been detected in the largest, complex spines of area CA3 (Chicurel and Harris, 1992). To generate the energy needed for signal transduction in the spine, ATP from dendritic mitochondria may diffuse into the spine, or glycolytic production of ATP may occur directly at the synapse (Wu et al., 1997).

Cytoskeleton

Hippocampal dendritic spines have an actin-based cytoskeleton that is distinguished from dendritic cytoskeleton by the absence of microtubules and intermediate filaments (Kaech et al., 1997; Markham and Fifkova, 1986; Cohen et al., 1985; Matus et al., 1982). Occasionally, the larger CA3 dendritic spines have one or more microtubules within them (Chicurel and Harris, 1992). The cytoskeleton in spines, as is the case for many actin-based structures, participates in rapid changes in form. Rao and Craig (this issue) compare the spine cytoskeleton to other actin-based structures including lamellopodia, filopodia, microvilli, and stereocilia.

A major extension of this research is to determine the molecular basis of spine motility. Smart and Halpain (this issue) discuss relevant "pools" of actin filaments, and growing numbers of actin-regulatory proteins are reviewed. Matus and Brinkhaus (this issue) present findings to the effect that different glutamate receptors interact with spine motility. Synaptopodin, a novel cytoskeletal protein, is uniquely positioned to influence spine dynamics and is discussed by Deller et al. (this issue). In addition, Rac signal transduction is a likely pathway by which extracellular cues are transduced to intracellular signals, resulting in changes to spine shape (Nakayama and Luo, this issue). Collectively, these data provide insight into whether actin-based changes in spine form alter synapse function.

MOLECULAR COMPOSITION OF DENDRITIC SPINES AND THEIR SYNAPSES

Several papers in this issue provide detailed analyses of the molecular composition and function in dendritic spines (see Zhang and Benson; Rao and Craig). Here we provide a brief overview in relationship to the structural components described above.

Synaptic Membrane

Dendritic spines contain a complex mixture of ions, lipids, proteins, and other signaling molecules. The most widely studied proteins have been those in the PSD. Hippocampal PSDs contain receptors, calcium/calmodulin-dependent kinase II (CaMK II), and a myriad of signaling and structural proteins (Walikonis et al., 2000; Ziff, 1999; Kennedy, 1998). For example, there are at least four distinct classes of glutamate receptors including, N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), kainate, and metabotropic glutamate receptors (mGluRs), which occur at discrete locations within the synaptic membrane (Racca et al., 2000; Nusser et al., 1998; Baude et al., 1995). NMDA receptors are located in the center of the PSD and are found at most hippocampal synapses (Racca et al., 2000). AMPA glutamate receptors are more evenly distributed across the surface of the PSD, though they are detected in fewer hippocampal synapses, especially during development (Lujan et al., 1996). Metabotropic glutamate receptors cluster at the outer edges of the PSD and are detected in about half of the hippocampal synapses (Lujan et al., 1996).

Cell-Adhesion Junctions

Cell-adhesion junctions, also known as "puncta adherentia," occur between the presynaptic axon and postsynaptic dendritic spine at the edges of the PSD in about 33% of CA1 synapses (Spacek and Harris, 1997). Puncta contain molecules distinct from the PSD such as the neural-cell adhesion molecule (NCAM), cadherins, catenins, and nexilin (Ohtsuka et al., 1998; Uchida et al., 1996). The mGluRs also occur at the edges of the PSD close to (or at) the puncta adherens. Puncta adherens can be confluent with SER in the spines. Hence, mGluRs and their associated Homer proteins are positioned to trigger release of Ca^{2+} from SER, via phosphinositide or ryanodine receptors on the SER (Fagni et al., 2000; Tu et al., 1998; Brakeman et al., 1997).

Receptor Clustering and Targeting Molecules

In addition to receptors, the PSD contains specific proteins that bind receptors. The PSD-95 protein and guanylate kinase-associated proteins (GKAPs) are major contributors to glutamate receptor clustering on the spine head (Kim and Huganir, 1999; Rao et al., 1998; Kim et al., 1997). Other clustering proteins have been identified and are differentially associated with either the NMDA, AMPA, or metabotropic glutamate receptors. For instance, PSD-95/SAP90, PSD-93/Chapsyn, and SAP-102 have been identified and bind directly to NMDA receptor subunits (Brenman et al., 1996; Kim et al., 1996; Lau et al., 1996; Muller et al., 1996; Kornau et al., 1995; Cho et al., 1992; Kistner et al., 1993). On the other hand, SAP97, another member of the "synapse-associated" family of proteins, binds to AMPA receptors in vitro (Leonard et al., 1998). Other protein-protein interactions relevant to receptor targeting are being uncovered both early in development and in adults (Sans et al., 2000; Rao et al., 1998). Rao and Craig (this issue) review a model of PSD assembly at developing hippocampal synapses.

Thus the diversity in composition of organelles and molecules among dendritic spines provides evidence for their functional diversity.

DENDRITIC SPINE FUNCTIONS

Spines Increase the Packing Density of Synapses (Fig. 3A)

Dendritic spines likely evolved to support the vast number of synapses that occur between individual neurons (Fiala and Harris, 1999). Flatworms (*Planaria*) are the simplest organisms possessing bilateral symmetry and a primitive brain. Several different types of planarian neurons have dendritic spines (Reuter and Gustafsson, 1995; Sarnat and Netsky, 1985; Keenan et al., 1981). Other invertebrate neurons also exhibit spine-like structures including honeybee Kenyon cells, and neurons of the squid giant synapse (Brandon and Coss, 1982; Young, 1973), and thus dendritic spines appeared well before the evolution of complex mammalian brains. Dendritic spines allow dendrites to reach beyond their surface to synapse with axons 1–2 μm away. In neuropil densely packed with axons and dendrites, the extension of dendritic spines allows increased synaptic density. Consider the simple case of an orthogonal relationship between dendrites and axons (Fig. 3A). In any one plane there can be only two synapses, one on each side of a dendrite without spines. Dendrites with spines can reach beyond to connect with axons in adjacent rows, thereby at least doubling the density of possible connections. In addition, the dendritic spines allow efficient interdigitation between neighboring processes, thereby achieving the high synapse packing density in the neuropil.

Spines Are Sites for Excitatory Synaptic Input (Fig. 3B)

Hippocampal spines are primarily sites of excitatory glutamatergic synaptic transmission (Fig. 3B). Hippocampal spines differ from spines in other brain regions (Groves et al., 1994; de Zeeuw et al., 1990; Gerfen, 1988; Spacek and Hartmann, 1983), because they rarely have inhibitory or peptidergic modulatory synapses on them (Trommald and Hulleberg, 1997; Harris and Stevens, 1989). Instead, these modulatory synapses tend to be located on the neighboring dendritic shaft or cell soma in the hippocampus.

Spine Neck Constrictions Amplify Voltage at the Synapse and Facilitate Associativity Between Synapses (Fig. 3C)

Many biophysical models suggest that spine necks can slow charge-transfer from the synapse to the parent dendrite (Segev and Rall, 1988, 1998). Hence there is a larger potential in the spine head for a transient period after synaptic activation which facilitates the opening of voltage-dependent channels. Most spines are not long or thin enough to prevent the eventual transfer of charge from the synapse to the parent dendrite, where it would be transferred to neighboring spine synapses (Svoboda et al., 1996; Harris and Stevens, 1989). This shared potential could facilitate associativity during weak and strong coactivation among neighboring spine synapses (Shepherd, 1996; Harris and Kater, 1994).

Spines Provide Synapse Specificity Via Molecular Compartmentalization and Local Protein Synthesis (Fig. 3D,E)

Imaging experiments show that spines compartmentalize calcium such that localized changes in intracellular calcium at an active synapse do not spread to neighboring inactive synapses (Yuste and Denk, 1995; Guthrie et al., 1991; Muller and Connor, 1991). Spine shape and size likely contribute to differences in calcium kinetics (see Korkotian and Segal, this issue; Majewska et al., 2000), and these kinetic differences translate into different signaling events at the synapse. Such localized changes in spine calcium result from influx through voltage-gated or ligand-gated ion channels (e.g., NMDA receptors), or release from intracellular stores (SER). Depending on the source or change in intraspine calcium, different signaling mechanisms may be evoked (Berridge, 1998). Recent evidence suggests that elevated calcium is sufficient to alter spine length, thereby coupling compartmentalization with an overall change in spine structure (Korkotian and Segal, 1999).

Polyribosomes localized to postsynaptic sites provide a substrate for local and spine-specific translation of proteins (Fig. 3E). Certain patterns of synaptic activation regulate rapid targeting of receptor proteins to dendritic spines (Shi et al., 1999). Perhaps a polyadenylation signal regulates protein synthesis within, and/or mRNA translocation to certain spines and not others (Wells et al., 2000).

FORMATION OF DENDRITIC SPINES

Spine Formation During Development

Hippocampal dendrites display numerous filopodia, some of which have synapses on them during the first 2–3 postnatal weeks (Fiala et al., 1998; Papa and Segal, 1996; Ziv and Smith, 1996). Filopodia are dendritic specializations that can be difficult to distinguish from dendritic spines at the light microscopic level (including confocal and two-photon laser scanning microscopy). Electron microscopic evaluation shows that filopodia are typically long and have a darker cytoplasm than spines. In addition, filopodia usually end in a pointy rather than a bulbous head, and can be much longer than mature dendritic spines (Fiala et al., 1998). In long-term organotypic cultures, filopodia extend and retract with a half-life of about 10 min (Wong and Wong, 2000; Dailey and Smith, 1996; Ziv and Smith, 1996). Recent studies show that filopodia are also quite transient in acute hippocampal slices (Parnass et al., this issue) and in the intact cortex from young animals (Lendvai et al., 2000). Even when filopodia are relatively abundant during the early postnatal period, only about 25% of synapses occur on them; the other 75% occur directly on dendritic shafts. These findings suggest that filopodia are precursors to shaft synapses, which then mature into dendritic spines (Fig. 4) (Fiala et al., 1998; Harris et al., 1992).

Spine Formation in the Mature Hippocampus

Mature hippocampal neurons also produce new dendritic spines. For example, new dendritic spines are generated within a

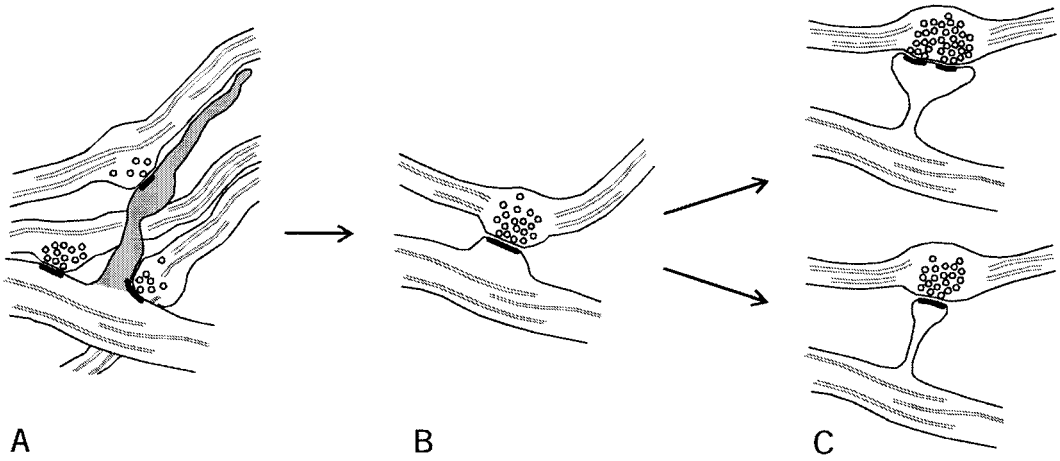

FIGURE 4. Spine formation during development. Possible mechanisms by which filopodia support stubby/shaft synapse or spine formation. A: Synapses form on the receptive surface of filopodia (gray). B: Filopodia retract, followed by stabilization of the synapse on a stubby protrusion. C: Synapse stabilization ensues via maturation of a dendritic spine.

few hours after preparing adult hippocampal slices compared to perfusion-fixed hippocampus in vivo (Kirov and Harris, 1999; Kirov et al., 1999). New spines form and regress during estrus in the cycling female rat (Woolley and McEwen, 1993; Woolley et al., 1990), and during hibernation and awakening (Popov et al., 1992). Environmental enrichment leads to the preservation or formation of more dendritic spines (Rampon et al., 2000). Where spine formation on mature neurons has been studied with serial EM, the new spines are consistently found to make synapses with preexisting axonal boutons, forming structures called multiple synapse boutons. It remains to be determined whether synaptogenesis in the mature brain also involves transient filopodia.

PLASTICITY IN DENDRITIC SPINE STRUCTURE

Plasticity describes changes in dendritic spine number or morphology. Both the type and degree of plasticity may differ with age, brain region, and experimental conditions. It is also important to distinguish the motility of existing dendritic spines from the formation of new dendritic spines or protrusions (as described above), because motility at existing spines certainly has functional implications quite different from the formation or loss of dendritic spines.

Long-Term Potentiation

Long-term potentiation (LTP) is a long-lasting enhancement of synaptic transmission, widely thought to be a candidate learning and memory mechanism mediated in part by changes in spine number or structure (Malenka and Nicoll, 1999; Bliss and Collingridge, 1993; Bliss and Lomo, 1973). During development, new dendritic protrusions form in the vicinity of local synaptic potentiation and last for at least an hour and up to several hours in vitro (Engert and Bonhoeffer, 1999; Maletic-Savatic et al., 1999). In contrast, no long-lasting change in total spine number occurs after LTP in mature neurons (Sorra and Harris, 1998), but instead mature neurons undergo extensive spine proliferation when synapses are globally silenced (Fig. 5) (Kirov and Harris, 1999). At the other extreme, intense activation of immature or mature hippocampal neurons leads to a loss of dendritic spines (Korkotian and Segal, 1999; Halpain et al., 1998; Jiang et al., 1998; Drakew et al., 1996).

Historically it has been difficult to ascertain the morphological basis of LTP, because newly potentiated synapses cannot be distinguished from previously potentiated, depressed, or inactive synapses (Sorra and Harris, 1998). Clearly an unbiased anatomical marker of synapses reflecting these variable states of activation is needed. A first step towards activity-dependent labeling of synapses for serial electron microscopy that have undergone LTP was recently completed (see Muller et al., this issue). The approach involved detection of a calcium precipitate in the spine apparatus (e.g., SER) of activated synapses. As pointed out by the investigators, the study was limited to the evaluation of spines that contain a spine apparatus (~10% of spines), because only these show a detectable increase in the calcium precipitate. By 10 min after onset of potentiation, there began a transient upregulation of perforated synapses lasting about 30 min. Later, the frequency of synapses on multiple synapse boutons increased. While this research provides new insights about a small subset of hippocampal synapses, a label is needed to mark the activation or potentiation status of all synapses to unravel the role of spine structural plasticity with LTP.

Learning and Memory

The concept of synaptic and spine plasticity as a mechanism of learning and memory was first introduced over a century ago. Modern gene-targeting approaches have produced mice lacking AMPA or NMDA receptor subunits (Rampon et al., 2000; Tang et al., 1999; Zamanillo et al., 1999). Mice lacking AMPA receptor

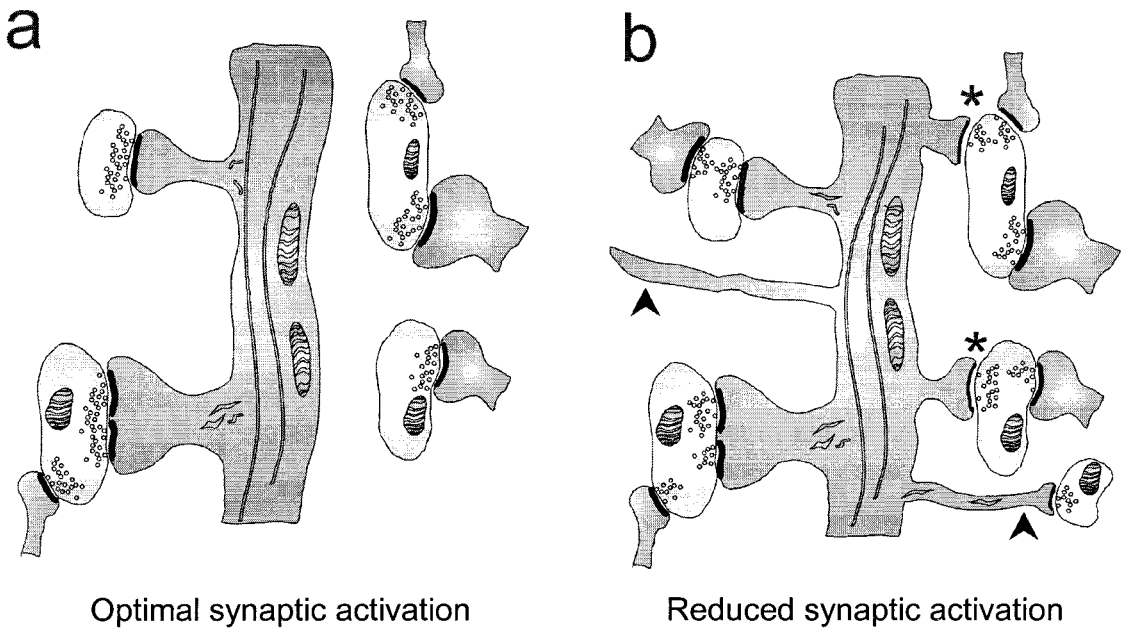

FIGURE 5. Spine plasticity in the mature brain. Dendritic spines and their synapses are (a) stable or (b) change their frequency based on the level of activation within the neuropil. b: Reduced synaptic activation leads to new spines (lower arrowhead) and/or filopodia (upper arrowhead), and more synapses on multiple synapse boutons (asterisks).

subunit GluR-A appear to develop normal hippocampal synapses that do not express LTP, yet spatial learning is preserved (Zamanillo et al., 1999). Mice that selectively lose NMDA-receptor expression in hippocampus also fail to express LTP and exhibit profound impairment during learning and memory tasks (Rampon et al., 2000; McHugh et al., 1996; Tsien et al., 1996). This deficit, however, appears to be overcome by rearing NMDA receptor knockout mice in "enriched" environments that produce more dendritic spines in an NMDA-independent fashion (Rampon et al., 2000). Implications for these findings are discussed further by Rampon and Tsien (this issue).

Spine Pathology

Dendritic spines are absent or their structure is grossly distorted in the brains of individuals suffering from a variety of neurological diseases, including developmental disorders that lead to mental retardation such as Down's syndrome, inherited metabolic diseases, fetal alcohol syndrome, and fragile X syndrome (Comery et al., 1997; Kamei et al., 1992; Hinton et al., 1991; Huttenlocher, 1991; Ferrer and Gullotta, 1990; Takashima et al., 1981, 1989; Galofre et al., 1987; Becker et al., 1986; Suetsugu and Mehraein, 1980; Marin-Padilla, 1972, 1976; Purpura, 1974, 1975). One common feature in these developmental conditions is a failure to convert from filopodia to dendritic spines, leaving the adult dendrites in an immature state. On the other extreme later in life, dendritic spines are lost or distorted after seizures, strokes, dementia, brain tumors, and chronic alcoholism (Jiang et al., 1998; Belichenko and Dahlstrom, 1995; Multani et al., 1994; Ferrer et al., 1991; Catala et al., 1988; Spacek, 1987; Scheibel et al., 1974). These pathological differences amplify the important role for maturation of dendritic spine morphology in normal brain function. Spine loss and other dendritic abnormalities in epilepsy are presented in detail in this issue by Swann et al. Synaptic modifications due to transient ischemia are discussed by Martone et al. (this issue).

One explanation for such neuropathology is that dendritic spines may protect neurons from excitotoxicity by isolating elevated calcium to the vicinity of the synapse, where it is needed for signal transduction. Ion exchangers, smooth endoplasmic reticulum, and cytoplasmic buffers could modulate calcium levels in the spines, thereby protecting the neuron. When seizures or other excessive activation overcomes the calcium-buffering capacity of a spine, it may retract with subsequent loss of spines and synaptic function (Segal et al., 2000; Segal, 1995).

CONCLUSIONS

Dendritic spines come in a wide diversity of shapes and corresponding molecular compositions, leading to the hypothesis that different spines serve different functions. Our interpretation of conflicting data in the literature regarding spine formation and plasticity is that the developmental stage of a neuron interacts with the capacity for plasticity under a variety of conditions, such as level of synaptic activation. Recent evidence suggests that filopodial formation and retraction are responsive to synaptic activity. Early during development, the emergence of new dendritic spines seems to be facilitated by long-term

potentiation. In contrast, dendritic spines proliferate on mature neurons, when synaptic activity is reduced or blocked. Potentiation may selectively preserve those spines with strengthened synapses, while excessive activation eliminates mature spines. With regard to future research on dendritic spines, further studies are needed to establish for how long newly formed dendritic spines and their synapses remain structurally intact before they are incorporated into a functional network or eliminated.

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