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Dendritic Spines

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Abstract

Dendritic spines are important sites of excitatory synaptic transmission and changes in the strength of these synapses are likely to underlie important higher brain functions such as learning and memory. Spines form biochemical compartments for isolating reactions that occur at one synapse from those at other synapses thereby providing a possible way to ensure the specificity of connections between neurons in the brain.

Keywords: brain; neuron; dendrite; synapse; ultrastructure; plasticity

Spiny Projections from Dendrites Seen in the Light Microscope

Around the beginning of the twentieth century, Ramón y Cajal first discovered the tiny protrusions called dendritic spines that stud the surfaces of neurons throughout the brain. Figure 1a illustrates a pyramidal cell, so named for the shape of its cell body. From the apex emerges a long dendritic trunk, the apical dendrite, which gives rise to many lateral dendrites. Several basilar dendrites emerge from the base of the cell body. At higher magnification (Figure 1b) the dendritic spines become visible along these dendrites. Cajal noticed that the dendritic spines have a diversity of shapes and, in one of his classic treatises, he described the spines as 'Stalcheln und Dornen' in reference to the long spicule-like spines and the shorter thorn-like spines that could be distinguished with light microscopy. See also Dendrites, Neurons, and Ramón y Cajal, Santiago

[figure 1 below]

The Golgi silver-impregnation method (used to reveal the cell in Figure 1) is named after Camillo Golgi, who discovered it accidentally when some silver nitrate spilled on a brain he was dissecting. The Golgi method reveals about 1 in every 1000 neurons in its entirety, leaving the surrounding tissue unstained. If all of the cells were to be stained, then the tissue would be completely black and the individual cells would be indistinguishable from the surrounding cells. This Golgi preparation is identical to that which Cajal used more than a century ago and is still widely used to obtain a first estimate of what happens to dendritic spines under a variety of conditions. The disadvantage is that it is still not known why the method works and whether there is something special about the cells that stain. Nevertheless, much of our understanding about the diversity in neuronal structure has come from studying these beautiful preparations. See also Golgi, Camillo

From the beginning, Cajal postulated that the spines were the points of contact between cells. Later, Gray discovered, using electron microscopy, that dendritic spines are the major sites of excitatory electrochemical communication between neurons via synapses. Throughout most brain regions, more than 90% of all excitatory synapses occur on dendritic spines; understanding the function of dendritic spines remains one of the major questions in neurobiology. See also Electron Microscopy, Glutamatergic Synapses: Molecular Organisation, and Synapses

Modern studies of dendritic spines can be summarized around attempts to answer four key questions: How big are the spines and what do they contain? How do they interact with the structures that surround them in the brain? How are new spines generated, during development and in the adult nervous system? Are changes in spine structure involved in more global brain processes, such as learning and memory? Many new methods have been developed to answer these questions, including computer-assisted reconstruction from serial sections at the electron microscopic level and functional imaging using confocal and two-photon microscopy. In combination with electrophysiological analyses of neurons, these imaging approaches are beginning to give new insights into the functions of dendritic spines and their synapses. In addition, new molecular labels have made it possible to probe the identity of molecules that could mediate these functions in the dendritic spines. See also Confocal Microscopy, Imaging: An Overview, Learning and Memory, Molluscs: Learning and Memory, and Vertebrate Central Nervous System

Distinctive Structural Features of Dendritic Spines

Spine morphology

Dendritic spines have a wide variety of sizes, shapes and subcellular compositions, both within and across brain regions. Most spines can be classified by their shapes as stubby, thin or mushroom-shaped (Figure 2a). Occasionally, dendritic spines have multiple branches, each of which can be innervated by the same presynaptic axon or by different axons depending on brain region. Sometimes one or more of the spine branches have no presynaptic axon.

[figure 2 below]

Three-dimensional reconstructions of dendritic spines have revealed their total size to range more than 100-fold. Neighbouring spines on the same short segment of dendrite can express this full range of dimensions (Figure 2b). This finding provided the first clue that individual spines might act as separate units.

For all spines, the postsynaptic density occupies only about 10–15% of the total spine surface area, suggesting that the nonsynaptic membrane must be present in a particular proportion to support synaptic function. In addition, the volume and surface area of the spine are proportional to the area of the synapse on its head, to the volume of smooth endoplasmic reticulum it contains and to the number of vesicles in the presynaptic bouton.

Synapses

As indicated above, dendritic spines are the major postsynaptic target for excitatory synapses throughout the central nervous system. These excitatory synapses are characterized by a thickened postsynaptic density (PSD) occurring on the spine head, across from a presynaptic axon containing round clear vesicles (Figure 2a). Three-dimensional reconstruction from serial electron microscopy reveals that some of these PSDs are uniform discs, referred to as macular PSDs. Other PSDs have electron-lucent regions, which create the appearance of perforations in the PSD, and these synapses are termed perforated PSDs (Figure 2a). Perforated PSDs occur preferentially on the large mushroom-shaped dendritic spines. Over 30 different proteins, known to be involved in synaptic transmission or maintaining the integrity of the synapse, have been identified in the PSD. See also Animal Cell Separation and Subcellular Fractionation, and Synapse Formation

In some brain regions a second synapse occurs directly on the spine neck. This second synapse differs from the primary excitatory synapse. Its structure is different, in that there is not a thickened PSD and the presynaptic bouton contains smaller, round and flattened vesicles. Immunostaining shows these synapses to contain inhibitory and modulatory substances that could alter the strength of the excitatory synapse occurring on the spine head. See also Neurotransmitter Release from Presynaptic Terminals, and Synaptic Vesicles: Methods for Preparation

Localization of organelles

Smooth endoplasmic reticulum (SER) is an organelle that is likely to be involved in sequestering calcium. Depending on the particular brain regions, few, many, or most of the dendritic spines contain SER (Figure 2a). For example, only about 14% of the hippocampal CA1 spines contain SER, and most of it occurs laminated with dense-staining material into a structure known as the spine apparatus (as in Figure 2a) in the large, complex spines. In contrast, nearly 100% of the cerebellar Purkinje spines contain SER in a tubular network. Polyribosomes are also present in or near the base of some dendritic spines (Figure 2b), suggesting that local protein synthesis of dendritic messenger ribonucleic acids (mRNAs) can occur in the spines. Synaptic plasticity such as that which occurs during long-term potentiation or learning and memory, can shift the distribution of polyribosomes into spines. Similarly, endosomal compartments including coated pits and vesicles, large vesicles, tubules and multivesicular bodies are restricted to a subpopulation of dendritic spines that differs from spines that contain SER. Mitochondria rarely occur in dendritic spines and are usually restricted to those that are very large, complex and highly branched. However, during periods of active synapse formation and remodelling in cultured neurons, mitochondria can localize to smaller dendritic spines. See also Cell Staining: Fluorescent Labelling of the Endoplasmic Reticulum, Eukaryotic Ribosomes: Assembly, Messenger RNA: Interaction with Ribosomes, and Protein Export from Endoplasmic Reticulum to the Cytosol: *In Vitro* Methods

Cytoskeleton

In the dendrite proper, microtubules are a prominent cytoskeletal element, involved in basic structure as well as the transport of organelles, such as mitochondria and vesicles containing membrane associated proteins. In contrast, the cytoskeleton of dendritic spines is usually devoid of microtubules except for the very largest spines in a few brain regions, such as hippocampal area CA3. Spine cytoplasm is characterized instead by a loose network of filaments comprised of actin and actin-binding proteins. The actin filaments are longitudinally situated in the spine neck, while those in the head are organized into a lattice. The actin filaments have been thought to provide both the scaffolding for supporting spine shape and a mechanism whereby the shape can be rapidly altered in a calcium-dependent fashion. Molecules found in the spine cytoplasm which could bind with the actin cytoskeleton, usually in a calcium-dependent manner, include calmodulin, myosin, brain spectrin (fodrin), microtubule-associated protein (MAP)-2 and a host of synaptic molecules located in the PSD, such as α-actinin, which may be crucial for mediating changes in the strength of synaptic transmission. See also Actin and Actin Filaments, Axonal Transport and the Neuronal Cytoskeleton, Cytoskeleton, Hippocampus, and Tubulin and Microtubules

Presynaptic vesicles

The axonal boutons which form synapses with dendritic spines have numerous round clear vesicles (Figure 2a). The membrane surrounding the vesicles contains specific molecules involved in filling the vesicles with neurotransmitter, docking them with the presynaptic membrane and fusing the vesicle with the membrane, thereby releasing the neurotransmitter, usually glutamate, into the synaptic cleft. The total number of vesicles can range from as few as 1–3 to more than 2000 in each axonal bouton. This number is proportional to spine volume, the volume of the SER and the area of the PSD on the dendritic spine. An area of active research is to determine how variation in vesicular size, composition and distribution influences the properties of synaptic transmission at dendritic spine synapses. See also Synapse Formation, Synaptic Vesicle Fusion, Synaptic Vesicle Proteins, and Synaptic Vesicle Traffic

Synaptic cleft

Between the membranes of the presynaptic axon and the postsynaptic dendritic spine is a gap, the synaptic cleft, which is about 10–20 nm wide and is filled with a dense-staining material. The composition of this dense-staining material is not known; however, it is likely to contain cell adhesion molecules which span the two membranes and serve both structural and molecular signalling functions.

Connections between dendritic spines and astrocytic processes

Astrocytes are glial cells in the central nervous system which are involved in regulating ions, glucose and neurotransmitter concentration in the extracellular space (Figure 2a). In some brain regions, such as the cerebellum, astrocytic processes surround the spine and presynaptic axon, thereby tightly controlling the escape of molecules from the synaptic cleft. At some spines the astrocytic processes also form cell adhesion junctions

where there can be direct signalling between the spines and astroglia during synaptic transmission. Extensive projections of astroglia throughout the neuropil position them to scale synaptic responses at the level of entire neuronal networks. Another important role of the astrocytes is to protect the neuron from calcium-induced neurotoxicity. This regulation could also be aided by SER, which is found on either side of the cell adhesion junctions between spines and the astrocytic processes.

In addition to affecting the physiological properties of synapses, astroglia can also regulate the structure of dendritic spines in response to synaptic activity. Astroglial processes tend to be found around larger and presumably more mature synapses, while areas that have undergone recent spinogenesis tend to be devoid of astroglia. Thus in the mature brain, astroglia may be involved in enhancing the stability of spines. Interactions between cell surface molecules and the release of various soluble factors by astroglia may be of crucial importance to the turnover and structural alteration of spines observed with synaptic plasticity. See also Astrocytes and Brain Signalling

Dendritic Spines Enhance Connectivity

With the evolution of the brain, the increase in synaptic density had to be accompanied by a significant reorganization of the neuropil. Dendritic spines permit dendrites to synapse with neurons 1–2 μm away, which allows for more synapses in a densely packed neuropil (Figure 3a). Even some invertebrate neurons exhibit spine-like structures, indicating dendritic spines appeared well before the evolution of the complex mammalian brain. Consider the simple case of an orthogonal relationship between dendrites and axons (Figure 3b, left side). There can only be two synapses on either side of the dendrite in any given plane without the presence of spines. Dendrites with spines can reach beyond their immediate perimeter to connect with axons in nearby rows, thereby at least doubling the density of possible connections. In addition, the shape of dendritic spines allows efficient interdigitation between neighbouring processes, thus achieving the high synapse-packing density in the neuropil (Figure 3b, right side).

[figure 3 below]

Dendritic Spines as Electrical Compartments

Amplification of voltage in spine head

The constriction in dendritic spine necks poses a small resistive barrier thereby amplifying the depolarization attained in the immediate vicinity of the synapse, in contrast to that which would be generated if the synapse occurred directly on the wide dendritic shaft (Figure 3c). Computer simulations have revealed that most of the spine necks are sufficiently wide and short so that charge transfer to the postsynaptic dendrite is 85–100% completed within 100 ms after the initiation of a synaptic event. The time delay in charge transfer is sufficient, however, to provide a transient amplification of voltage at the spine synapse which may facilitate opening of voltage-dependent channels in the spine head, such as the calcium-channel associated with the *N*-methyl-D-aspartate (NMDA) class of glutamate receptors. See also Learning and Memory, NMDA Receptors, and Voltage-gated Potassium Channels

Sharing of postsynaptic potential

A long-standing hypothesis has been that the narrow dimensions of the spine neck would attenuate current flow between the spine head and the dendrite. Morphological evidence suggests, however, that most spine necks are not thin and long enough to significantly reduce the charge transferred to the parent dendrite. Current electrophysiological evidence from hippocampal CA1 cells suggests that the mean synaptic conductance for a minimal evoked response is 0.21±0.12 ns, such that the current generated by release of 10–20 quanta would likely be fully transmitted to the postsynaptic dendrite. Thus the constriction in the spine neck is not sufficient to prevent addition of voltage changes among coactivated synapses. Other models endow the spine with active membrane that would further enhance the sharing of postsynaptic potentials among neighbouring spines (Figure 3c). See also Membrane Potential

Dendritic Spines as Biochemical Compartments

Compartmentalization of calcium has now been demonstrated in the heads of dendritic spines under a variety of conditions. Two features of spines help to achieve localization of this second messenger in spine heads at least for a short time: (1) the spine neck could provide a narrow diffusion path and (2) a rise in spine calcium could cause release from SER, the intracellular calcium stores thereby amplifying the calcium signal. Biochemical compartmentalization in spine heads may also serve an important role in restricting calcium from the postsynaptic dendrites and preventing excitotoxic cell damage such as microtubule breakdown and mitochondrial swelling. Since dendritic spines rarely have microtubules or mitochondria, high calcium concentrations in the spine head is less likely to have these detrimental effects. Not all spine morphologies would be expected to restrict diffusion, and only some spines have internal stores. A recent study that utilized caged glutamate to activate NMDA receptors and a low-affinity Ca^{2+} indicator (to minimize the perturbation of endogenous Ca^{2+} buffering) indicates that small spines with narrow necks exhibit large, isolated increases in $[Ca^{2+}]_i$. However, the necks of larger spines allow for a greater efflux of Ca^{2+} into the dendritic shaft at the base of the spine. Perhaps only a subset of spines, or alternatively all spines, but only at a restricted time during their lifetime, achieve the compartmentalization of calcium, whether in spines or along a short segment of dendrite and its associated spines. See also Calcium and Neurotransmitter Release, and Fluorescent Probes Used for Measuring Intracellular Calcium

The specific localization of voltage-dependent calcium channels is also an important factor in determining which components of the dendritic arbour will compartmentalize and utilize relatively high concentrations of calcium. Whether spines preferentially sequester other second messengers remains to be determined. Certainly those tethered to the PSD are prevalent in spines, but further work is needed to determine how they are targeted to spines and whether compartmentalization in the spine head is a crucial element in their regulation. Recent evidence suggests that synaptic activity can create a bidirectional barrier to the diffusion of proteins, indicating a synapse-specific mechanism to amplify the biochemical signals necessary for establishing plasticity (Figure 3d). In addition, the presence of polyribosomes in some spines could provide the necessary machinery for generating plasticity-related proteins locally (Figure 2b).

Synaptic Activity and Structural Plasticity of Dendritic Spines

Spine stability and turnover

The stability of spines largely depends on the level of synaptic activity and the developmental stage of the neuron. In immature neurons, spines and filopodia turnover rapidly as connections are formed and stabilized. Only a small amount of glutamate is required to stabilize a spine. Excitotoxicity resulting from too much glutamate can result in the disappearance of spines, while a block of synaptic transmission can result in robust spinogenesis, particularly on mature neurons following traumatic injury or exposure to cold temperatures as occurs during hibernation and some surgical and experimental procedures. The appearance and disappearance of spines may reflect the capacity of mature neurons for recuperative synaptogenesis or a form of synaptic scaling, a homeostatic mechanism that ensures that the output of a postsynaptic cell remains constant despite alterations in synaptic input. In contrast, young neurons do not exhibit spinogenesis with blocked transmission, but rather insert more receptors to maintain synaptic homeostasis.

Brain regions also differ in the amount of synaptic turnover that occurs with the modulation of sensory experience. Recent technological advances have allowed dendritic spines of the somatosensory cortex to be imaged *in vivo* for periods of time ranging from a few hours to a few months. Small dendritic protrusions (thin spines or filopodia) appear and disappear in an experience-dependent manner associated with synapse formation or elimination, while larger spines persist for months. The effect of sensory experience on synapse number depends on the rates of synapse formation and elimination at different developmental stages, and the percentage of stable spines increases with age.

Structural synaptic plasticity at dendritic spines

Results from many studies suggest that spines undergo changes in structure with synaptogenesis during development, with the behavioural changes associated with learning and memory, and under pathological conditions associated with neural dysfunction. During development, the number of synapses and dendritic spines increases steadily and in some cortical regions of higher mammals, the total number of spines appears to peak during adolescence, declining to a plateau in early adulthood. This peak is thought to occur during some critical period and its duration is lengthened by preventing synaptic activation in the brain, suggesting that synaptic transmission mediates the pruning of excess synapses. See also Developmental Biology of Synapse Formation

Long-term potentiation (LTP) is a cellular model of learning and memory that has been extensively investigated regarding changes in spine and synapse structure. LTP is expressed as an enhanced synaptic response following a brief, high-frequency stimulation of the synapses. Two key structural changes would contribute to a potentiated synaptic response: an increase in the number of spines or an increase in the size of synapses with LTP. Several studies in the hippocampus over the last 30 years have attempted to link structural alterations of the synapse to the increase in synaptic

strength, but the results remain controversial, particularly in the adult brain. Early studies describe an input-specific increase in spine volume and a shortening of spines accompanied by an enlargement of the spine neck. Overall spine density and branched spines in particular are increased 30 min after the *in vivo* induction of LTP in the hippocampus, although the increase in branched spines may be due to high-frequency stimulation alone, even in the absence of LTP. While there has been some speculation that branched spines might arise from the splitting of individual potentiated spines, careful three-dimensional reconstructions of the neuropil have revealed that branched spines never synapse on the same axonal bouton. In addition, the number of neuronal and dendritic processes that pass between the branches argues against the idea of spine splitting. An alternative hypothesis suggests that branched spines arise from the formation of new protrusions called filopodia which can be initiated by the enhanced synaptic activity, navigate between neighbouring processes to find a presynaptic partner and then become dendritic spines. In any case, the majority of morphological alterations that have been attributed to *in vivo* induction of LTP have included more subtle changes such as increases in the concavity of spine heads and an increase in PSD area, as well as an increase in the ratio of perforated to nonperforated PSDs. Because perforated PSDs tend to occur in mushroom spines, this change could indicate an alteration in spine morphology if potentiation results in a shift from thin spines to mushroom spines. Spine and PSD enlargement are also associated with the translocation of polyribosomes into spines following the induction of LTP in acute PN15 hippocampal slices. Given that the maintenance of LTP is dependent on the synthesis of new proteins, the presence of polyribosomes in a subset of spines may provide an indication of which spines underwent potentiation. See also Long-term Depression and Depotentiation, and Long-term Potentiation

Although quite a bit of uncertainty still surrounds the set of structural changes associated with LTP, it appears likely that the effect is selective to potentiated synapses and that changes in a tissue will be correlated with the numbers of stimulated axons and dendrites. Nevertheless, there is evidence that LTP-inducing stimuli can result in increases in spine size and number and may involve the remodelling of the PSD and the translocation of organelles into activated spines. All of these changes could form the basis of long-lasting changes in synaptic strength.

Summary

Although much is now known about the diversity in the structure of dendritic spines and their synapses, much remains to be learned about how variation in structure might be involved in variation in synaptic function. The challenge for the next generation of neuroscientists will be to discover the full range of molecules residing in dendritic spines and whether the compartments formed by the spines are crucial for the molecular function. Ultimately we will need to learn exactly how the spine compartments work in conjunction with signalling the cell nucleus when changes in synaptic input have occurred. Obtaining this understanding will be important for elucidating the causes of mental retardation where dendritic spines are drastically affected, either remaining as immature, long and thin structures or disappearing all together.

End Notes

Based in part on the previous version of this Encyclopedia of Life Sciences (ELS) article, Dendritic Spines by Kristen M Harris.

Further Reading

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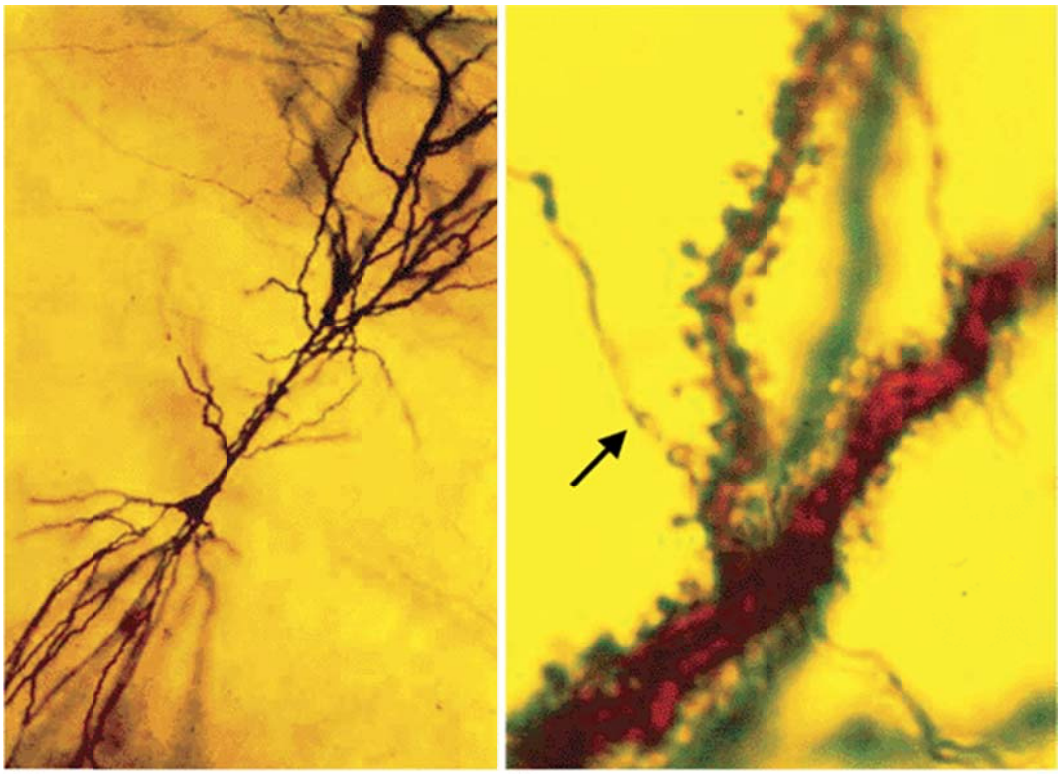

(a) (b)

Figure 1. Pyramidal cell in hippocampal area CA1 of the rat brain showing the typical appearance of the principal excitatory neurons that occur throughout the brain. (a) The low-magnification view of these cells shows an apical dendrite projecting towards the upper left quadrant of the figure. Many lateral dendrites emerge from the large apical dendrite. Several basillar dendrites project from the base of the cell soma. Dendritic spines are the tiny projections that stud the surface of these dendrites in both the apical and basillar dendritic arbour. (b) A higher magnification view of the dendrites reveals the tiny spines a thin axon (arrow) passing through the dendritic arbour.

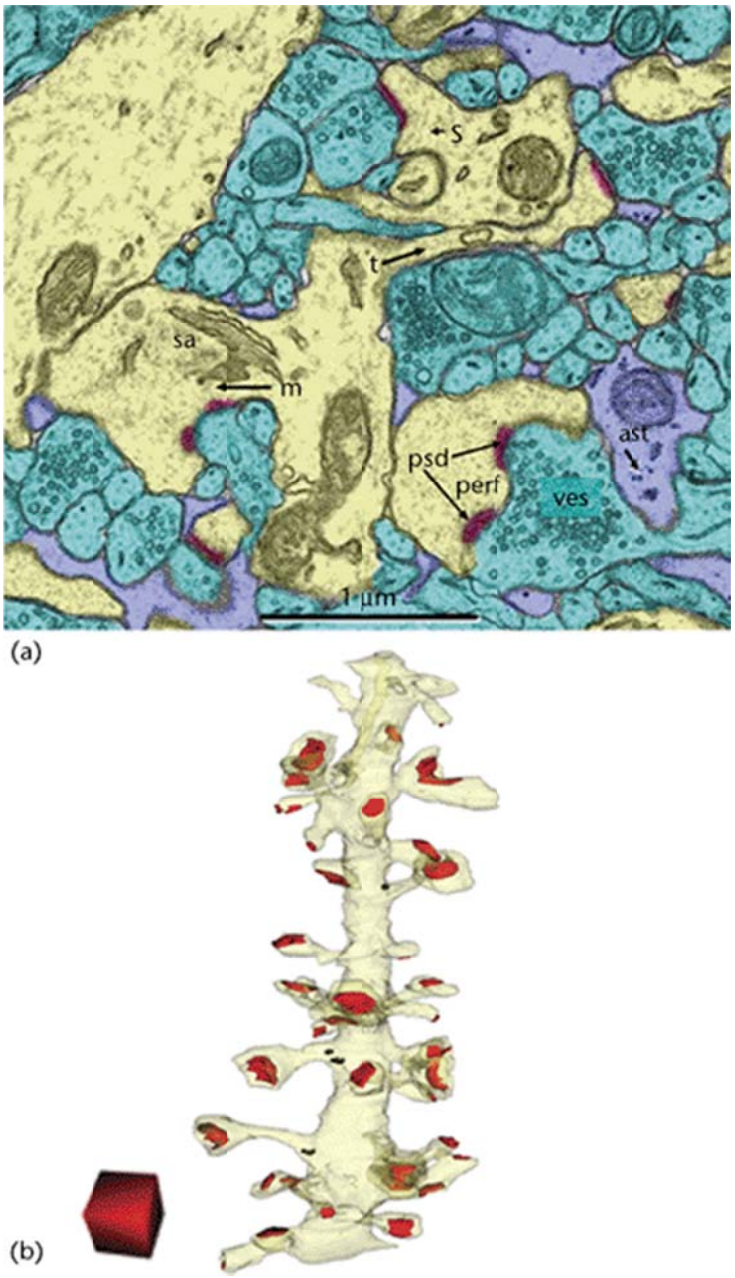

Figure 2. (a) Electron micrograph of a section through dendritic spines in stratum radiatum of hippocampal area CA1 that has been colour coded to identify dendrites (yellow), axons (green) and astroglia (purple). In this fortuitous section, three spines were sectioned parallel to their longitudinal axis revealing spines of the stubby (S), mushroom (m) and thin (t) morphologies. The postsynaptic density (PSD) occurs on the spine head (see t) immediately adjacent the synaptic cleft (c) and to a presynaptic axonal bouton that is filled with round vesicles (v). This t spine contains a small tube of smooth endoplasmic reticulum (ser) in its neck. In the m spine a spine apparatus (sa) is visible. A perforated postsynaptic density (perf) is evident on the head of another mushroom spine. Near to this spine is a large astrocytic process (ast) identified by the glycogen granules and clear cytoplasm. (b) A three-dimensional reconstruction of a dendrite showing a variety of spine and synapse shapes and the presence of polyribosomes (black spheres) at the base of the spines. Scale cube=1 μm^3.

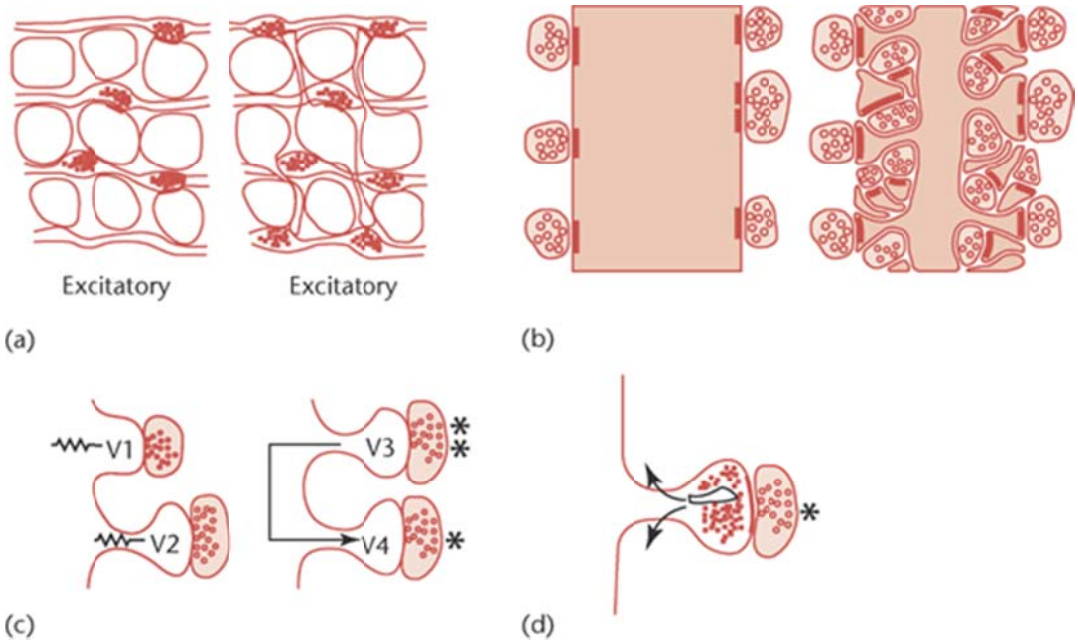

Figure 3. (a) Spines increase the packing density of synapses. Schematic illustrates a cross-section through two dendrites, one without and one with dendrites spines. Convolution and interdigitation of dendrite, axon and spine membranes support more synapses. (b) The presence of spines also allows for an increase in synaptic density without increasing the overall volume of the brain. (c) Spines exist to amplify electrical potential at the synapse and promote associativity among neighbouring 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 signalling mechanisms (stippling) are recruited in response to synaptic activation (asterisk).