REPRINTED FROM

Elsevier's

Encyclopedia of

Neuroscience

2nd enlarged and revised edition

Edited by
George Adelman
Barry H. Smith

Editorial Manager
Jennifer De Pasquale

Visit the Encyclopedia's website for supplementary information and details regarding the CD-ROM version:

http://www.elsevier.com/locate/encneu

gated) are accompanied by an increase in citosolyc Ca^{2+}. Part of this ion, sometimes to a large extent, comes from intracellular stores (where it is originally in a bound form). And what is more fascinating is that these Ca^{2+} seem to move away from the site of the synapses, thus possibly forming some kind of dendritic gradient (we don't know yet if this is done by an active or passive process). Since an increase in intracellular Ca^{2+} will affect the properties of synaptic receptors as well as the electrical properties of the membrane, these findings obviously implicate the citosol in what has been considered up to now basically a membrane process, i.e., Neuronal Integration. On the other hand, due to the enormous and complementary interaction of active membrane properties and synaptic processes, it is obvious one cannot talk here of "hard-wiring" but that dendritic properties will bring instead a considerable amount of "plasticity" to this part of the neuron. Furthermore, the overwhelming complexity implied by these experimental facts indicates that some radically new theoretical ideas will be needed before a formal approach is again attempted.

Another important aspect of dendritic physiology is its relation to the electroencephalogram. Although the intimate mechanism of the latter is far from being clearly understood, it has been accepted for some time that PSPs, rather than spikes, are the main electrical events behind its genesis. One should add, in the light of what has been said about dendritic responses, that most of these "dendritic PSPs" should be considered the result of active dendritic responses and not just simple cable propagated potentials. The great wealth of dendritic electrical responses and the variety of dendrodendritic contacts that have been described (e.g., chemical synapse, tight junction, reciprocal synapses, dendritic bundles), raise the possibility of dendritic ensembles working together. In this context it is important to state that the role of extracellular current fields in the functioning of dendrites is still an open question, but it would seem to be the obvious mechanism in operation for the case of dendritic bundles. It is known that artificially applied weak DC fields can affect dendritic potentials without necessarily changing spike discharges. On the other hand, changes in firing patterns of neocortical mammalian cells, produced by stronger fields, can become long-lasting (sometimes longer than 3 h) when the DC field is applied for some time (10 to 20 min). A long-lasting dendritic gradient of some type is perhaps the mechanism behind these otherwise puzzling phenomena. Whether these field effects occur under normal conditions is not known, but the extracellular current values needed to obtain them are likely to be produced in physiological conditions requiring a degree of synchronization, as is the case for some stages of learning.

Further reading

Llinas RR, Sugimori M (1980): Electrophysiological properties of in vitro Purkinje cell dendrites in mammalian cerebellar slices. *J Physiol (Lond.)* 305:197–213

Llinas RR (1988): The intrisic electrophysiological properties of mammalian neurons: Insights into central nervous system function. *Science* 242:1654–1664

Lorente de No R, Condouris R (1959): Decremental conduction in peripheral nerve: Integration of stimuli in the neuron. *Proc Natl Acad Sci USA* 45:592–617

Midtgaard J (1994): Processing of information from different sources: Spatial synaptic integration in the dendrites of vertebrates CNS neurons. *Trends Neurosci* 17:166–173

Murphy TH, Baraban JM, Wier WG, Blatter LA (1994): Visualization of quantal synaptic transmission by dendritic calcium imaging. *Science* 262:529–531

Rall W (1977): Core conductor theory and cable properties of neurons. In: *Handbook of Physiology, Section 1: The Nervous System, vol. I, Part I*, Kandel ER, ed. Bethesda, MD: American Physiological Society, pp. 39–97

Regehr WG, Tank DW (1994): Dendritic calcium dynamics. *Curr Opin Neurobiol* 4:373–382

Sobel EC, Tank DW (1994): In vivo Ca^{2+} dynamics in a cricket auditory neuron: An example of chemical computation. *Science* 263:823–826

Spencer W. (1977): The Physiology of supraspinal neurons in mammals. In: *Handbook of Physiology, Section 1: The Nervous System, vol. I, Part II*, Kandel ER, ed. Bethesda, MD: American Physiological Society, pp. 969–1021

See also Dendrites, dendrodendritic interactions; Neuronal morphology; Neuron, cable properties; Purkinje cell electrophysiology; Synaptic transmission: facilitation etc.

Dendritic spines

Kristen M. Harris

1. Introduction

Around the turn of the century Ramon y Cajal (1893) first discovered the tiny protrusions called "dendritic spines" that stud the surfaces of neurons throughout the brain. He and his contemporary, Tanzi, postulated that changes in spine structure or number would be important factors in synapse formation during development and synapse modification during learning and memory in the mature nervous system. Later, Gray (1959) discovered with electron microscopy (EM) that dendritic spines are indeed the key postsynaptic targets of excitatory axons in most brain regions. Results from numerous studies are beginning to show evidence for alterations in dendritic spines during development, with learning and memory, and also with long-term potentiation, a physiological model that is widely studied as a candidate cellular mechanism of some forms of learning and memory.

2. Structure and composition of dendritic spines

2.1. Spine shapes

Dendritic spines assume striking differences in size, shape, and subcellular composition both within and across brain regions (Figure 1). Most spines are unbranched protrusions that can be classified by their stubby, thin, or mushroom shapes (Figure 2). Branched spines have multiple heads which in some brain regions are all innervated by a single axonal bouton (e.g., hippocampal area CA3) (Chicurel and Harris, 1992); in other brain regions the different heads of a branched spine are innervated by different axons (e.g., hippocampal area CA1 (Harris et al., 1992), Figure 2); and in rare cases some of the heads have no presynaptic partners while other heads are innervated by different axons (e.g., cerebellar Purkinje spiny branchlets) (Harris and Stevens, 1988).

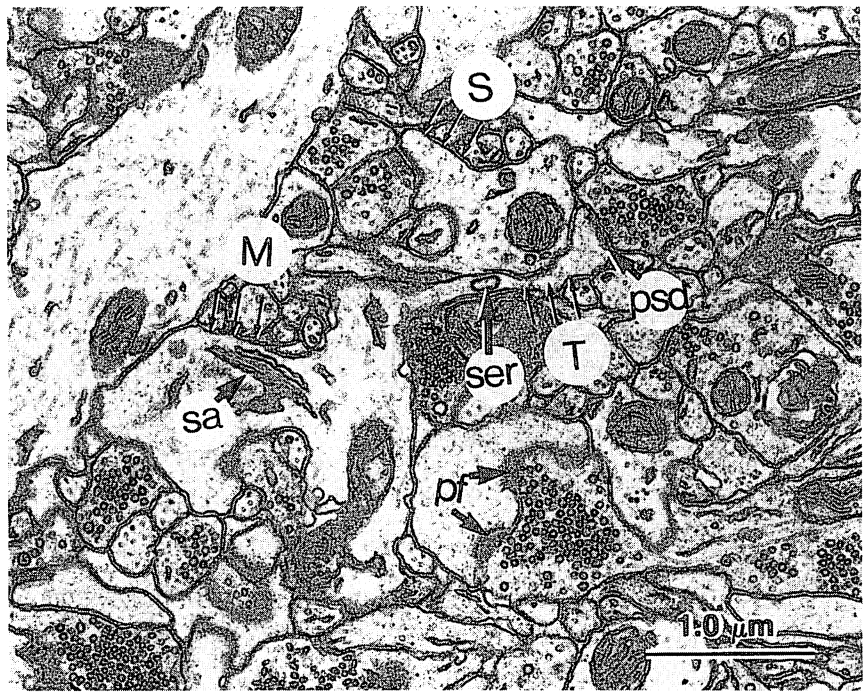

Figure 1. Electron micrograph of a section through dendritic spines in stratum radiatum of hippocampal area CA1. In this fortuitous section, three spines were sectioned parallel to their longitudinal axis revealing spines of the stubby (S), mushroom (M), and thin (T) morphologies. The postsynaptic density (PSD) occurs on the spine head (see T) immediately adjacent the synaptic cleft (c) and the 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 (pf) is evident on the head of another mushroom spine. Near to this spine is a large astrocytic process (A) identified by the glycogen granules and clear cytoplasm.

2.2. Synapses

Usually an asymmetric synapse with a thick postsynaptic density (PSD) occurs on the spine head across from the presynaptic axon which contains round clear vesicles (Figure 1). Serial EM reconstruction reveals macular PSDs on all of the different spine shapes while perforated PSDs are specifically associated with larger mushroom-shaped dendritic spines. Some spines also have a symmetric, inhibitory synapse located on the spine neck, though the presence of this second synapse is not universal and in several brain regions, none of the spines have a second synapse. Over 30 proteins have been identified (Kennedy et al., 1983; Walsh and Kuruc, 1992) in subcellular fractions from the brain that are highly enriched in PSDs including: neuroreceptor glycoproteins, protein kinases, structural and mechanochemical proteins, proteins involved in endocytosis, and proteins involved in the glycolytic pathway.

2.3. Organelles

Most spines contain smooth endoplasmic reticulum (SER in Figure 1), an organelle that is likely to be involved in membrane synthesis and sequestering of calcium. The volume of the SER is proportional to spine volume and PSD area, and occupies about 10–20% of the total spine volume. The larger and more complex spines contain sacs of SER laminated with dense-staining material into a structure known as the spine apparatus (sa in Figure 2). Three-dimensional reconstructions have revealed polyribosomes in 80–90% of dendritic spines. Mitochondria rarely occur in dendritic spines and are typically restricted to the very complex or very large or highly branched dendritic spines. Similarly, multivesicular bodies, are restricted to large spines or the dendritic shafts at the base of dendritic spines (KH, personal observations). Coated vesicles are occasionally found in dendritic spines of the normal brain and their frequency increases during synaptogenesis.

2.4. Cytoskeleton and cytoplasm

The cytoskeleton of dendritic spines is characterized by a loose network of filaments. It is distinguished from the dendritic cytoskeleton by the near absence of microtubules, except for an occasional microtubule in the largest and most complex spines. The filamentous network of spine cytoplasm is comprised of actin and many actin-regulating proteins. The actin filaments of the spine neck are longitudinally situated while those in the head are organized into a dense lattice surrounding the SER or spine apparatus. This organization of the actin filaments suggests that they provide the scaffolding for the basic spine structure. Other molecules found in the spine cytoplasm which may interact with the actin cytoskeleton, usually in a calcium dependent manner, include: calmodulin, myosin, brain spectrin (fodrin) and MAP-2.

2.5. Presynaptic vesicles

The boutons associated with dendritic spines have numerous round clear vesicles which contain glutamate and their membranes are likely to contain specific molecules involved in vesicle formation, docking and release. On the presynaptic membrane, is the presynaptic grid that is characterized by dense-staining projections on the cytoplasmic side of the membrane. These projections may be the equivalent of the actin-like filaments seen in rapid-frozen material and are thought to be the "vesicle docking" sites. The presynaptic vesicles congregate in the vicinity of the presynaptic grid though many also occur throughout the bouton (Figure 2). The total number of vesicles in completely reconstructed axonal boutons ranges from

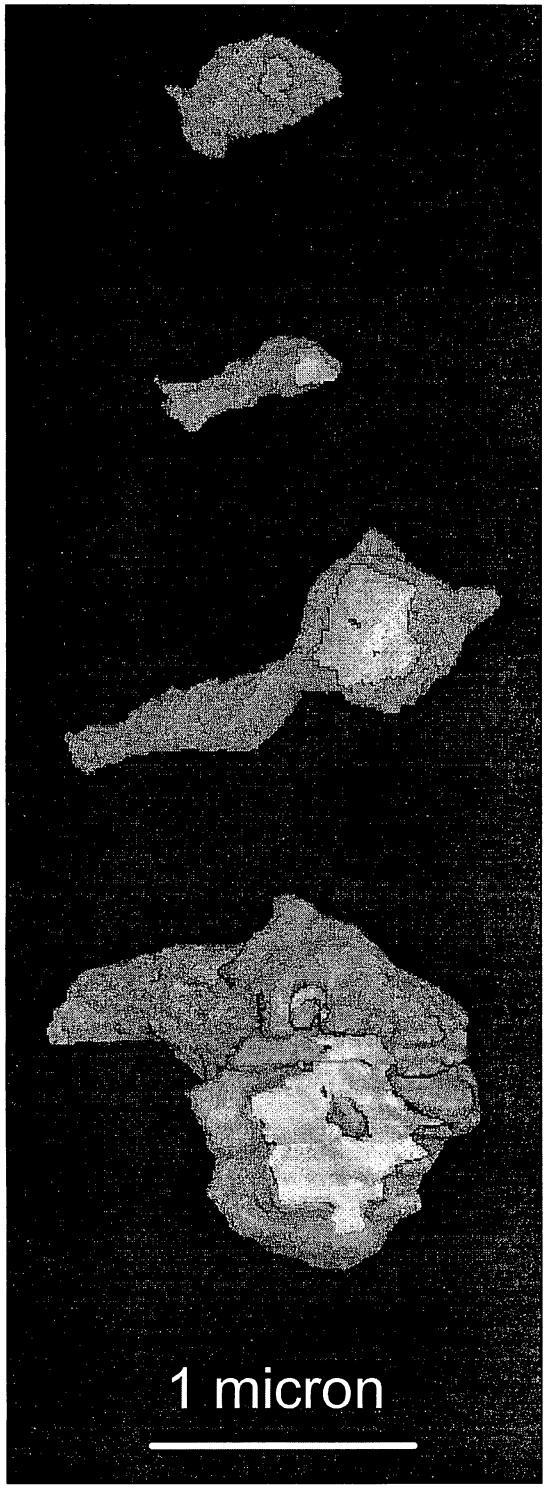

Figure 2. Three-dimensional reconstructions of stubby, thin, and 2 mushroom-shaped dendritic spines from hippocampal area CA1. PSDs are reconstructed in white, the spines are gray. The larger PSD has a larger perforation (gray area in the center of the PSD).

38–1234 for cerebellar spines and 3–1606 for CA1 spines. This number is proportional to spine volume, SER volume, and the area of the PSD on dendritic spines of both regions. It will be important to determine whether variation in vesicular size, composition, and distribution with respect to the synaptic cleft influences the properties of synaptic transmission at dendritic spine synapses.

2.6. Synaptic cleft

Between the pre- and postsynaptic membranes is the synaptic cleft, a region where the extracellular space widens slightly to about 10–20 nm and is filled with a dense-staining material. The composition of the synaptic cleft has not yet been delineated, however current data suggest that it is comprised of cell surface molecules involved in cell-cell adhesion such as integrin-like and neural cell-adhesion molecules, and in molecules such as agrin that are involved in synaptic receptor localization.

2.7. Neighboring astrocytic processes

Dendritic spines occur in close association with tiny astrocytic processes ranging from a complete surrounding of the synaptic complex, as is often seen at cerebellar dendritic spines, to the less conspicuous interdigitation of astrocytic profiles amongst synapses as in the hippocampus. This close association between dendritic spines and neighboring astrocytes may be a key factor in controlling the extracellular concentrations of glutamate, and facilitate the localization of the effect of evoked glutamate release specifically to the synaptic cleft of the activated synapse. In this way, the astrocytic processes are likely to be involved directly in normal synaptic transmission as well as indirectly by preventing glutamate induced cytotoxicity.

3. General relationships between the structure and composition of dendritic spines

There is at least a 100-fold variation in dendritic spine and synaptic dimensions. The differences in spine and synapse morphology and composition have been hypothesized to reflect different synaptic histories due to developmental and use-dependent mechanisms. Despite these gross differences several general principles have emerged from quantitative measurements through serial EM reconstruction. First, for all spines, the PSD occupies only about 10% of the total spine surface area suggesting that the non-synaptic membrane must be present in a particular proportion to support synaptic function. Second, the volume and surface area of the spine is proportional to the area of the PSD on its head, to the volume of smooth endoplasmic reticulum it contains, and to the number of vesicles in the presynaptic bouton. Third, computer simulations have revealed that most of the spine necks are sufficiently wide and short that charge transfer to the postsynaptic dendrite is 85–100% complete within 100 ms after the initiation of a synaptic event, given reasonable values for synaptic conductance. 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 NMDA class of glutamate receptors. Fourth, the spine neck constrictions are sufficiently narrow to slow diffusion of calcium from the activated synapses so that its concentration may build up to levels that activate second messenger cascades thereby altering subsequent synaptic efficacy. This biochemical compartmentalization in spine heads may also serve an important role in restricting calcium from the postsynaptic dendrite thereby preventing excitotoxic cell damage such as microtubule breakdown and mitochondrial swelling. Since dendritic spines rarely have microtubules or mitochondria, a high calcium concentration in the spine head is less likely to have these detrimental effects.

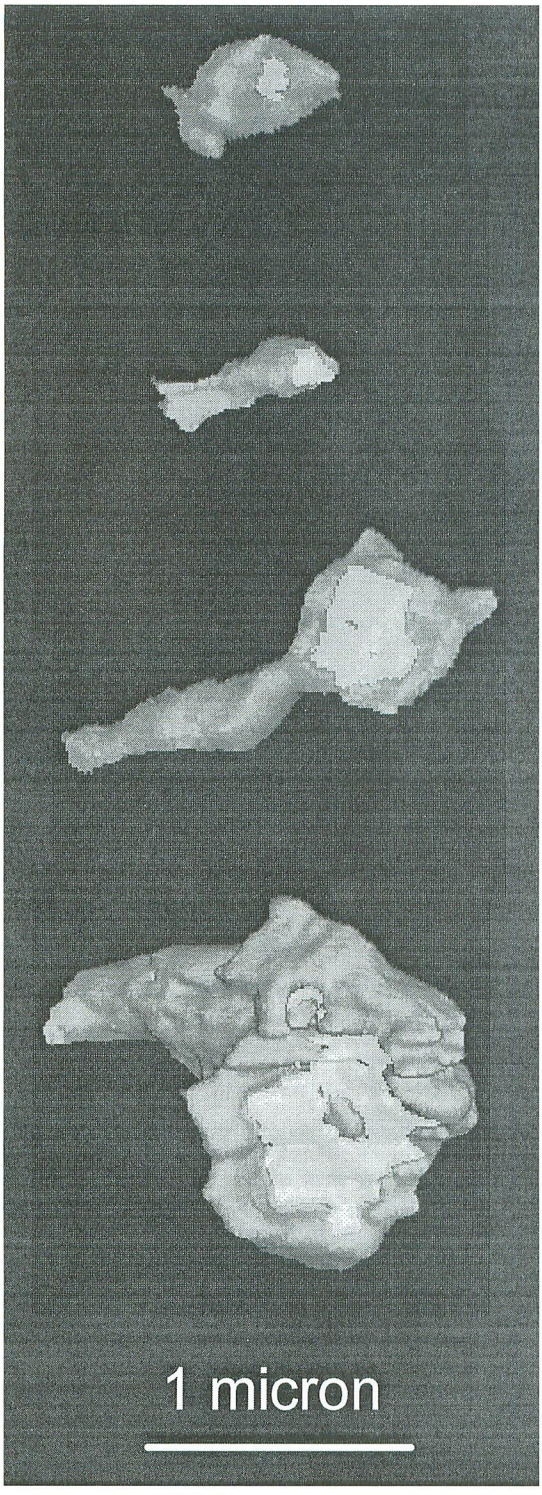

Figure 2. Three-dimensional reconstructions of stubby, thin, and 2 mushroom-shaped dendritic spines from hippocampal area CA1. PSDs are reconstructed in white, the spines are gray. The larger PSD has a larger perforation (gray area in the center of the PSD).

38–1234 for cerebellar spines and 3–1606 for CA1 spines. This number is proportional to spine volume, SER volume, and the area of the PSD on dendritic spines of both regions. It will be important to determine whether variation in vesicular size, composition, and distribution with respect to the synaptic cleft influences the properties of synaptic transmission at dendritic spine synapses.

2.6. Synaptic cleft

Between the pre- and postsynaptic membranes is the synaptic cleft, a region where the extracellular space widens slightly to about 10–20 nm and is filled with a dense-staining material. The composition of the synaptic cleft has not yet been delineated, however current data suggest that it is comprised of cell surface molecules involved in cell-cell adhesion such as integrin-like and neural cell-adhesion molecules, and in molecules such as agrin that are involved in synaptic receptor localization.

2.7. Neighboring astrocytic processes

Dendritic spines occur in close association with tiny astrocytic processes ranging from a complete surrounding of the synaptic complex, as is often seen at cerebellar dendritic spines, to the less conspicuous interdigitation of astrocytic profiles amongst synapses as in the hippocampus. This close association between dendritic spines and neighboring astrocytes may be a key factor in controlling the extracellular concentrations of glutamate, and facilitate the localization of the effect of evoked glutamate release specifically to the synaptic cleft of the activated synapse. In this way, the astrocytic processes are likely to be involved directly in normal synaptic transmission as well as indirectly by preventing glutamate induced cytotoxicity.

3. General relationships between the structure and composition of dendritic spines

There is at least a 100-fold variation in dendritic spine and synaptic dimensions. The differences in spine and synapse morphology and composition have been hypothesized to reflect different synaptic histories due to developmental and use-dependent mechanisms. Despite these gross differences several general principles have emerged from quantitative measurements through serial EM reconstruction. First, for all spines, the PSD occupies only about 10% of the total spine surface area suggesting that the non-synaptic membrane must be present in a particular proportion to support synaptic function. Second, the volume and surface area of the spine is proportional to the area of the PSD on its head, to the volume of smooth endoplasmic reticulum it contains, and to the number of vesicles in the presynaptic bouton. Third, computer simulations have revealed that most of the spine necks are sufficiently wide and short that charge transfer to the postsynaptic dendrite is 85–100% complete within 100 ms after the initiation of a synaptic event, given reasonable values for synaptic conductance. 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 NMDA class of glutamate receptors. Fourth, the spine neck constrictions are sufficiently narrow to slow diffusion of calcium from the activated synapses so that its concentration may build up to levels that activate second messenger cascades thereby altering subsequent synaptic efficacy. This biochemical compartmentalization in spine heads may also serve an important role in restricting calcium from the postsynaptic dendrite thereby preventing excitotoxic cell damage such as microtubule breakdown and mitochondrial swelling. Since dendritic spines rarely have microtubules or mitochondria, a high calcium concentration in the spine head is less likely to have these detrimental effects.

4. Functions of dendritic spines

4.1. Postsynaptic targets

Evaluation of dendritic spine structure readily reveals them to be the major site of excitatory synaptic input, and occasionally inhibitory/modulatory synapses form on the heads, necks or at the bases of dendritic spines. An inhibitory input on spines could act to "veto" or modify the strength of the excitatory input. Since most dendritic spines have a single excitatory synapse on their head, more spines means more synapses and accordingly more point-to-point connections in a neuronal ensemble involving spiny neurons. Thus, one function of spines is the preservation of the individuality of inputs.

4.2. Expanded reach to presynaptic axons

It had been postulated by Ramon y Cajal that spines could increase the surface area available for new synapses to form, however, most of the dendritic shaft between spines does not have synapses and ample room is available for more synapses to occur even in the absence of more dendritic spines. Spines do allow relatively thin dendrites to reach multiple axons as they weave through the neuropil. For nonspiny dendrites to attain the same reach to the meandering axons they would need to be thicker than spiny dendrites (which typically they are), and to occupy a significantly greater volume of the neuropil. Thus, spiny dendrites allow more synaptic connections to be compacted into a limited brain volume.

4.3. Amplification of voltage in spine head

The constriction in dendritic spine necks, if it poses even a slight resistive barrier, results in an amplification of the depolarization attained in the immediate vicinity of the synapse, relative to that which would be generated if the synapse occurred directly on the dendritic shaft. Thus, spine neck constriction could facilitate the opening of voltage-dependent channels located on the spine head in response to a lower synaptic activation than would be required to depolarize synapses on nonspiny dendrites.

4.4. Sharing of postsynaptic potential

A long-standing hypothesis has been that the narrow dimensions of the spine neck will 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 reduce, significantly, the charge transferred to the parent dendrite, if the conductance changes at the synapse are less than 5 ns. 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, spines should permit the addition of voltage changes amongst co-activated synapses via the dendrites connecting them. Other models endow the spine with active membrane which would further enhance the sharing of postsynaptic potentials among neighboring spines.

4.5. Biochemical compartmentalization

Mathematical modeling provides plausible insights into how calcium compartmentalization could occur in the absence of an absolute barrier to diffusion between spines and dendrites. Three conditions could achieve localization of this second messenger: (1) the spine neck could provide a narrow diffusion path, which limits calcium ion flux into or out of some spine heads; (2) even a small rise in spine calcium could cause a controlled release from intracellular calcium stores thereby amplifying the calcium signal; and finally (3) only a very few calcium pumps would be required to extrude the few calcium ions that might diffuse through the limited volume of the spine neck from even micromolar concentrations in the spine head. Not all spine morphologies would be expected to restrict diffusion. Similarly, it is plausible that the distribution of intracellular calcium stores and pumps is not the same on all spines and dendrites. For example, only the large mushroom shaped dendritic spines have laminated spine apparatuses, while the smaller thin spines have only a thin tube of SER (see Figure 2, above). Perhaps only a subset of spines, or alternatively all spines, but only at a restricted time during their developmental history, achieve the compartmentalization required to confer this specificity. Recent visualization of events within living hippocampal dendritic spines has provided direct confirmation of these predictions; however, at cerebellar spiny branchlets, the calcium compartment may in fact be a short segment of dendrite and its associated spines. Thus, the specific localization of voltage-dependent calcium channels may also be an important factor in determining which components of the dendritic arbor sequester high concentrations of calcium and other synaptically-active molecules.

5. Structural synaptic plasticity at dendritic spines

As implied in the description of dendritic spine and synaptic composition earlier, several molecular mechanisms exist that could mediate rapid short term and long term changes in spine and synaptic morphology. For example, glutamate and its analogues activate proteolysis of brain spectrin (fodrin) by the neuron specific protease, calpain I. Degradation of fodrin, a structural protein of the (spine) cytoskeleton, could allow the spine to undergo shape changes, possibly in response to growth of the synapse. The state of actin polymerization is regulated by calcium concentration, and determines the viscosity of the spine cytoplasm. The actin filaments are transient structures which can change rapidly in response to the calcium-activated second messenger systems involving stimulation of phosphorylation by calmodulin. Actin could serve to stabilize spine structure through its binding to the sub-plasmallemal cytoskeleton or to alter spine structure through "contraction".

Average spine and synaptic dimensions have been compared in preparations that have undergone plasticity with those in preparations that have not. Several results suggest that spines undergo changes in structure with synaptogenesis during development, with the behavioral changes associated with learning and memory, and under pathological conditions associated with neural dysfunction. Considerable evidence has accumulated to suggest that changes in spine and synaptic structure occur during long-term potentiation (LTP) though controversy remains as to whether new spines and synapses form or if the geometries of existing spines and synapses change. For example, in hippocampal area dentata, some results suggest that dendritic spines swell during LTP along with a change in the morphology of existing PSDs. In contrast, results from other studies suggest a doubling in total spine number, more branched spines, and more spines with wide necks during LTP. In hippocampal area CA1, no significant changes in overall spine density have been detected though there is evidence for spine "rounding" and an increase in the frequency of stubby dendritic spines. Except for extremely fortuitous sections (like the one shown in Figure 2, above), the morphology of most spines can not be identified on a single section and therefore, no data exist in these studies on the fate of the predominant thin, mushroom, and branched dendritic spines during LTP. Several new approaches are under development to ascertain which structural effects are specific to synaptic plasticity such as LTP and which structural effects occur with other forms of synaptic activity. These approaches include the combination of confocal microscopy of living dendrites followed by serial EM reconstruction to identify and mea-

sure the activated synapses. In addition, more robust sampling procedures such as the "series sample method" and the Dissector methods have been developed to make the appropriate distinctions between changes in size and number of synapses. As these new approaches are applied to the problem of synaptic plasticity they should help to resolve whether changes in the structure and/or number of particular spines and synapses are involved in the functional synaptic plasticity.

References

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

Gray EG (1959): Axo-somatic and axo-dendritic synapses of the cerebral cortex: An electron microscopic study. *J Anat* 93:420–433

Harris KM, Stevens JK (1988): Dendritic spines of rat cerebellar Purkinje cells: Serial electron microscopy with reference to their biophysical characteristics. *J Neurosci* 8:4455–4469

Harris KM, Jensen FE, Tsao, B (1992): Three-dimensional structure of dendritid spines and synapses in rat hippocampus (CA1): At postnatal day 15 and adult ages: Implications for the maturation of synaptic physiology and long-term potentiation

Kennedy MB, Bennett MK, Erondu NE (1983): Biochemical and immunochemical evidence that the "major postsynaptic density protein" is a subunit of a calmodulin-dependent protein kinase. *Proc Natl Acad Sci USA* 80:7357–7361

Ramon y Cajal S (1893): *Neue Darstellung vom Histologischen Bau des Centralnervensystems.* Archiv fur Anatomie und Entwickelungsgeschichte. Anatomische abteilung des archives fur anatome und physiologie: pp. 319–428

Walsh MJ, Kuruc N (1992): The postsynaptic density: Constituent and associated proteins characterized by electrophoresis, immunoblotting and peptide sequencing. *J Neurochem* 59:667–678

Further reading

Eilers J, Augustine GJ, Konnerth A (1995): Subthreshold synaptic Ca^{2+} signalling in fine dendrites and spines of cerebellar Purkinje neurons. *Nature* 373:155–158

Fifkova E (1985): Actin in the nervous-system. *Brain Res Rev* 9:187–215

Guthrie PB, Segal M, Kater SB (1991): Independent regulation of calcium revealed by imaging dendritic spines. *Nature* 354:76–80

Harris KM, Kater SB (1994): Dendritic spines: Cellular specializations imparting both stability and flexibility to synaptic function. *Annu Rev Neurosci* 17:341–371

Harris KM, Stevens JK (1989): Dendritic spines of CA1 pyramidal cells in the rat hippocampus: Serial electron microscopy with reference to their biophysical characteristics. *J Neurosci* 9:2982–2997

Jaffe DB, Fisher SA, Brown TH (1994): Confocal laser scanning microscopy reveals voltage-gated calcium signals within hippocampal dendritic spines. *J Neurobiol* 25:220–233

Muller W, Connor JA (1991): Dendritic spines as individual neuronal compartments for synaptic Ca^{2+} responses. *Nature* 354:73–76

Peters A, Palay SL, Webster Hd (1991): *The Fine Structure of the Nervous System: The Neurons and Supporting Cells.* Philadelphia, London, Toronto: W.B. Saunders, Co.

Tanzi E (1893): Fatti e le induzioni nell'odierna istologia del sistema nervoso. *Riv Sperim Freniatria Med Leg* 19:419–472

Wallace C, Hawrylak N, Greenough WT (1991): Studies of synaptic structural modifications after long-term potentiation and kindling: Context for a molecular morphology. In: *Long-Term Potentiation: A Debate of Current Issues*, Baudry M, Davis JL, eds. Boston, MA: The MIT Press, pp. 189–232

Wilson CJ (1984): Passive cable properties of dendritic spines and spiny neurons. *J Neurosci* 4:281–297

See also Dendrites, dendrodendritic interactions; Dendrites, physiology; Dendritic spines, pathology and changes with age; Synapse, postsynaptic density; Synaptic plasticity; Synapse, morphology; Postsynaptic mechanisms

Dendritic spines, pathology and changes with age

Eva Fifková

Dendritic spines were first observed by Ramón y Cajal in the light microscope, and by Gray in the electron microscope. Spines are appendage-like outgrowths of the dendrites with an enlarged terminal part – the spine head carrying a synaptic contact and a slender stalk connecting the head with the parent dendrite. The stalk varies in width but it is always quite narrow in comparison with the head. The spine head varies in shape and size; some spines may have more than one head. In the hippocampus and the dentate fascia, there are sometimes one or two small protrusions emanating from the spine head into the axon terminal contacting the dendritic spine. These protrusions, called spinules, originate within the region of synaptic apposition. Three dimensional reconstructions were done for striatal and hippocampal spines. The spine synapse is conspicuous by its prominent postsynaptic density, giving it an asymmetric appearance in the electron microscope. The contact-making axon terminal has a uniform population of round, clear vesicles. These two features are considered to be morphological characteristics of excitatory synapses. The majority of axospinous synapses was shown to be excitatory. The spine may have a second synapse, as in the striatum, dentate fascia, cerebral cortex and medial accessory olive. It is positioned either on the head near to its junction with the stalk or on the stalk itself. Axon terminals of these synapses contain pleomorphic synaptic vesicles and form symmetrical junctional specializations. Recently it has been shown in the dentate fascia and medial accessory olive that these terminals are immunoreactive for GABA. While the prevailing population of spines is postsynaptic, dendritic spines of the granule cells of the olfactory bulb may also be presynaptic, containing synaptic vesicles and making reciprocal synapses with dendrites of mitral cells.

Dendritic spines are found on many types of neurons of the cerebral and cerebellar cortex, hippocampus, dentate fascia, striatum, olfactory bulb, thalamus, substantia gelatinosa, vestibular nucleus, medial accessory olive, and subfornical organ. Although spines are mostly associated with dendrites, they were also observed on perikarya of the vestibular, cochlear, cuneate, oculomotor, and red nuclei and on the initial segment of cortical pyramidal neurons. Within a defined brain region, dendritic spines may occur only on certain populations of neurons, while others may be spine free. In general, spiny neurons tend to be principal neurons of a region, while nonspiny neurons form local interneurons. Some brain pathways terminate solely on dendritic spines, while others seem to avoid them. In regions, like the cerebral cortex, hippocampus, and dentate fascia, large