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Dendrite structure

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Summary

Dendrites are extensions of the cell body of the neuron specialized for receiving and processing the vast majority of excitatory synaptic inputs. Dendrites exhibit enormously diverse forms. In many cases the shape of the dendritic arbor can be related to the mode of connectivity between neurons, with dendrites often ramifying in characteristic spatial domains where they receive specific inputs. At the ultrastructural level, dendrites are distinct from axons and astroglia processes, having a characteristic composition of subcellular organelles. Synapses occur directly on the shaft of some dendrites, but other dendrites have specialized enlargements and protrusions to receive synaptic input. These synaptic specializations also occur in many different forms. The use of serial electron microscopy to obtain detailed quantitative data on these structures has shown that different synaptic specializations have different intracellular organelles and synaptic compositions. Understanding the structural diversity of both dendritic arbors and synaptic specializations will be essential for understanding the intricacies of dendritic function and the contribution dendrites make to mental processes.

Introduction

What is the purpose of dendrites? Why do they exhibit such an overwhelming variety and complexity of shapes? How are their shapes related to neuronal function? Ramón y Cajal posed and, to a remarkable degree, answered these questions 100 years ago in his Histology of the Nervous System (Ramón y Cajal 1995). Ramón y Cajal established that the two types of neuronal processes, axons and dendrites, do not interconnect in anastomotic continuity. Neurons are independent entities. The many dendrites of a neuron receive electrical impulses from the axons of other neurons and conduct this activity to the neuron's own axon for transmission to other cells. This basic tenet is often referred to as the *neuron doctrine*.

Ramón y Cajal also saw that the complexity of dendrites reflects the number of connections that a neuron receives. Consider that a neuron without dendrites, having a roughly spherical cell body, has a very limited surface area for receiving inputs.

Increasing surface area by enlarging the cell body would mean prohibitive increases in cell and brain volume. Dendrites can be thought of as extensions of the cell body which provide increased surface area at much lower cell volumes. For example, 97% of the surface area of a motor neuron (excluding the axon) is dendritic (Ulfhake and Kellerth 1981). The dendrites have 370 000 μm^2 of surface area while occupying only 300 000 μm^3. To provide an equivalent surface, a spherical cell body would be 340 μm in diameter and consume 20 000 000 μm^3. The fact that 80% of the surface area of proximal dendrites of motor neurons are covered with synapses (Kellerth et al. 1979) suggests that this increased surface area is indeed valuable for increasing the number of inputs to a neuron.

Dendrites make relatively local connections as compared with the axon. The axon, emerging either from the soma or a dendrite, may extend to distant targets, up to a meter or more away from the cell body in some cases, (e.g. motor neurons and corticospinal projection neurons). Dendrites are rarely longer than 1-2 mm, even in the largest neurons, and are often much smaller (Table 1.1). In many neurons the diameter of dendrites at their origin from the cell body is proportional to the diameter of the cell body (Chen and Wolpaw 1994; Ulfhake and Kellerth 1981). Furthermore, these dendrites are tapered, such that the total length and the number of branches are correlated with the diameter of the proximal segment. Thus, larger neurons typically have both larger perikarya and more extensive dendritic fields (Table 1.1).

Ramón y Cajal argued that phylogenetic differences in specific neuronal morphologies support the relationship between dendritic complexity and number of connections. The complexity of many types of vertebrate neurons, including cerebellar Purkinje cells, cortical pyramidal cells, and mitral cells of the olfactory bulb, increases with increasingly complex nervous systems. These changes are driven both by the need to make more connections and by the need to make connections with additional cell types at specific locations. As expressed by Sholl (1956), it is the *mode of connectivity* between neurons that is the most critical property of their diverse morphologies.

Dendrite Arbors

Classification of morphologies is difficult because of the large number of different dendritic arborization patterns in the central nervous system. For this reason, contemporary expositions often fall back on the simple scheme originated by Ramón y Cajal, in which neurons are classified as *unipolar*, *bipolar*, and *multipolar*, based on the number and orientation of processes emanating from the cell body. Ramón y Cajal intended this only as an introduction, however, and developed a detailed classification to differentiate the wide variety of multipolar neurons. A more geometrical classification of dendritic arborizations will be useful for understanding the purposes of this diversity.

The primary contribution of dendrites to a neuron's mode of connectivity is through their characteristic branching and extension into specific spatial domains (Table 1.2). Axons from particular sources ramify within these domains, such that particular portions of the dendritic arbor receive specific inputs. A further charac-

Table 1.1 Typical dimensions of dendrites for a few types of neurons

Neuron	Average soma diameter (μm)	Number of dendrites at soma	Proximal dendrite diameter (μm)	Number of branch points	Distal dendrite diameter (μm)	Dendrite extent* (μm)	Total dendritic length (μm)
Cerebellar granule cell (cat)	7	4	1	0	0.2-2	15	60
Starburst amacrine cell (rhesus)	9	1	1	40	0.2-2	120	—
Dentate gyrus granule cell (rat)	14	2	3	14	0.5-1	300	3200
CA1 pyramidal cell (rat)	21						11 900
basal dendrites		5	1	30	0.5-1	130	5500
stratum radiatum		1	3	30	0.25-1	110	4100
stratum lacunosum-moleculare				15	0.25-1	500	2300
Cerebellar Purkinje cell (guinea pig)	25	1	3	440	0.8-2.2	200	9100
Principal cell of globus pallidus (human)	33	4	4	12	0.3-0.5	1000	7600
Meynert cell of visual cortex (macaque)	35						15 400
basal dendrites		5	3	—	—	250	10 200
apical dendrites		1	4	15	2-3	1800	5200
Spinal a-motoneuron (cat)	58	11	8	120	0.5-1.5	1100	52 000

* The average distance from the cell body to the tips of the longest dendrites.

Sources: Ito (1984); Mariani (1990); Claiborne et al. (1990); Bannister and Larkman (1995a); Rapp et al. (1994); Palay (1978); Yelnik et al. (1984); Ulfhake and Kellerth (1981)

teristic of dendritic branching patterns is the degree to which they fill the spatial domain of their arborization (Fig. 1.1). At one extreme, a dendrite connects a single remote target to the rest of the neuron. This is a *selective* arborization. At the other extreme, dendritic branches occupy most of the domain of arborization in a *space-filling* arborization. An example of this is the cerebellar Purkinje cell arbor that synapses with at least half of the parallel fiber axons that pass through it (Napper and Harvey 1991; Palay and Chan-Palay 1974). Most dendritic arborizations lie between the selective and space-filling varieties and are referred to as *sampling* arborizations.

Many approaches have been used to characterize the density of dendritic arborizations (Uylings et al. 1975). Branch ordering schemes are frequently used, such as the *centrifugal method* wherein the dendrites emerging from the cell soma are primary, their first branches are secondary and so on, with increasing order until the tips are reached. Alternatively, the *Strahler method* might be used wherein the dendritic tips are all given the order number 1 and then branch numbers are increased sequentially towards the soma. The number of dendrite segments of each order characterizes the degree of branching of the arbor. A simpler scheme is to just count the number of branch points in the entire dendritic arbor. Such schemes

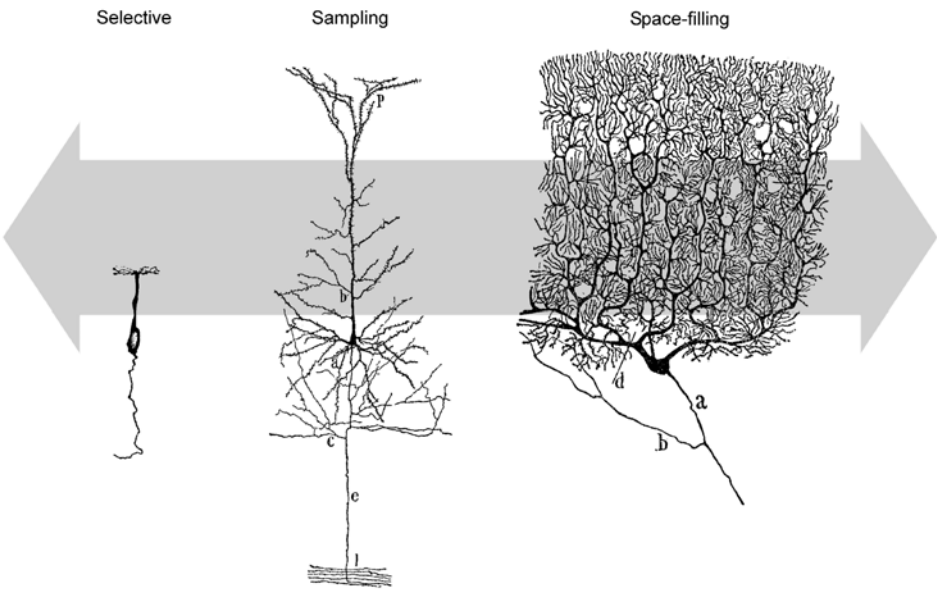


Fig. 1.5 The densities of dendritic arbors lie on a continuum of values. Differences in arbor density reflect differences in connectivity. At one extreme are selective arborizations in which each dendrite connects the cell body to a single remote target. An olfactory sensory cell is used to illustrate this. At the other extreme lie space-filling arborizations in which the dendrites cover a region, as with the cerebellar Purkinje cell. Intermediate arbor densities are referred to as sampling arborizations, as demonstrated by a pyramidal cell from cerebral cortex. (Drawings of neurons from Ramón y Cajal, 1995.)

Table 1.2 Some characteristic dendritic arborization patterns

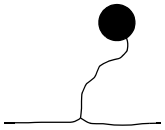
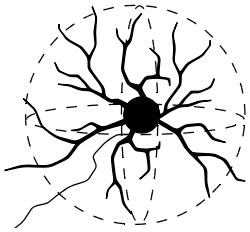
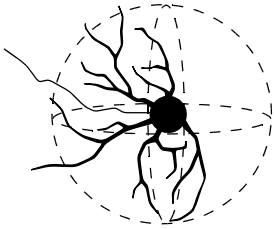
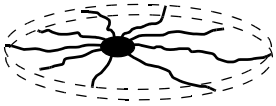
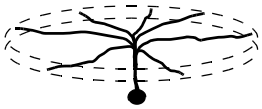
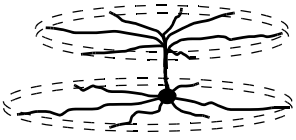
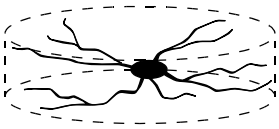
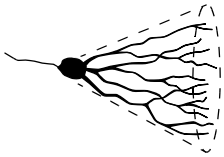
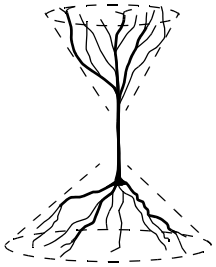
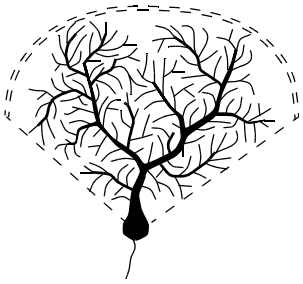
Pattern	Characteristics	Examples
Adendritic 	Cell body lacks dendrites	Dorsal root ganglion cells Sympathetic ganglion cells
Spindle radiation 	Two dendrites emerge from opposite poles of the cell body and have few branches	Lugaro cells Bipolar cells of cortex
Spherical radiation		
Stellate 	Dendrites radiate in all directions from cell body	Spinal neurons Neurons of subcortical nuclei (e.g. inferior olive, pons, thalamus, striatum) Cerebellar granule cells
Partial 	Dendrites radiate from cell body in directions restricted to a part of a sphere	Neurons at edges of "closed" nuclei (e.g. Clarke's column, inferior olive, vestibular nuclei)
Laminar radiation		
Planar 	Dendrites radiate from cell body in all directions within a thin domain	Retinal horizontal cells
Offset 	Plane of radial dendrites offset from cell body by one or more stems	Retinal ganglion cells
Multi 	Cell has multiple layers of radial dendrites	Retinal amacrine cells

Table 1.2 Some characteristic dendritic arborization patterns

Pattern	Characteristics	Examples
Cylindrical radiation 	Dendrites ramify from a central soma or dendrite in a thick cylindrical (disk-shaped) domain	Pallidal neurons Reticular neurons
Conical radiation 	Dendrites radiate from cell body or apical stem within a cone or paraboloid	Granule cells of dentate gyrus and olfactory bulb Primary dendrites of mitral cells of olfactory bulb Semilunar cells of piriform cortex
Biconical radiation 	Dendrites radiate in opposite directions from the cell body	Bitufted, double bouquet, and pyramidal cells of cerebral cortex Vertical cells of superior colliculus
Fan radiation 	One or a few dendrites radiate from cell body in a flat fan shape	Cerebellar Purkinje cells

provide a sense of how branched a neuron is, but do not indicate the degree to which they fill the space of their arborizations, an important factor when considering their potential for connectivity.

Another measure, *fractal dimension*, can be used to quantify the degree to which an arborization fills its spatial domain. From basic geometry, linear objects have a dimension of 1, planar objects have a dimension of 2, and solid objects, such as a sphere, have a dimension of 3. In addition, there exist objects with non-integer dimensions, often called *fractal* objects, that fill a portion of the space in which they

are embedded. Dendritic arbors can be considered fractal on a limited scale (Smith et al. 1989). Selective arborizations have fractal dimensions close to unity while space-filling arborizations have fractal dimensions close to the dimension of the geometrical region they occupy. For instance, the fractal dimension of Purkinje cell dendritic arbors that fill the two-dimensional domain in which they ramify, is about 1.8 in mammals. In agreement with Ramón y Cajal's assessment of the phylogenetic trend in complexity, the fractal dimension of Purkinje cells increases with phylogeny, from a value of 1.13 in lamprey up to a value of 1.86 in humans (Takeda et al. 1992).

Sampling arborizations have fractal dimensions greater than 1 but much less than in the dimension of the spatial domain in which they arborize. For example retinal ganglion cells, which have essentially planar arbors, have a fractal dimension of approximately 1.5 (Fernandez et al. 1994; Wingate et al. 1992). To understand how the differences in fractal dimension relate to differences in connectivity, consider that a retinal ganglion cell with a sampling planar arbor covering 25 000 μm^2 receives only 2000 synapses (Sterling 1990), while a Purkinje cell with a space-filling planar arbor of 50 000 μm^2 receives 160 000 synapses (Harvey and Napper 1991).

Dendritic complexity can reflect a propensity for a neuron to make contacts with axons from a large number of cells or many connections with the axons of just a few cells. This depends of the axonal arborization pattern and the direction of axons relative to dendrites. For example, parallel fiber axons are orthogonal to the dendritic tree of the Purkinje cell, permitting few synapses per axon (Palay and Chan-Palay 1974). An ascending axon of a granule cell in the plane of the Purkinje arbor, however, makes as many as 17 synapses with a single Purkinje cell (Harvey and Napper 1991; Bower and Woolston 1983). Thus in brain regions where dendrites take on a characteristic orientation, the relative orientation of axons has a significant impact on connectivity.

Table 1.2 illustrates some characteristic dendrite arborization patterns ranging from *adendritic* ganglion cells, which have only a branched axon and no dendrites, to the dense *fan radiations* of cerebellar Purkinje cells. For instance, the slender neurons found throughout the brain may frequently be characterized as having a *spindle radiation*, since two sparsely-branching dendrites emerge from opposite poles of the cell body. The Lugaro cell of cerebellar cortex and the bipolar cell of cerebral cortex are examples of this pattern.

A common arborization pattern in the central nervous system is the *spherical radiation* (stellate) cells. These are found throughout the brain and spinal cord, and predominate in non-laminated subcortical nuclei such as the inferior olive, pontine nuclei, striatum, thalamus, etc. In most cases, stellate cells have sampling arborizations with many synapses along the length of each dendritic segment. Many nominally stellate neurons can be seen on closer inspection to come in characteristic patterns that are not uniformly spherical radiations. For instance, neurons near the border of a *closed* nucleus extend dendrites into only that part of the sphere that lies within the nucleus (partial spherical radiation; Table 1.2). More generally stellate neurons are often distinguishable by specific characteristics. Although attempts have been made to describe the variety of stellate types in general terms (Ramón-Moliner 1968), classification often comes down to individual characteristics. For example, in the ventral cochlear nucleus there is a unique set of descriptive morphologies: spher-

ical bushy, globular bushy, stellate, bushy multipolar, elongate, octopus, and giant (Ostapoff et al. 1994). These descriptors are not readily applicable to stellate neurons in other areas of the brain.

In some neurons, dendrites radiate in arbitrary directions from the cell body but are restricted to a planar region. This type of *laminar radiation* (see Table 1.2) is seen in horizontal cells of the retina (Kolb et al. 1994), and in some interneurons of cortex (Parra et al. 1988). Dendrites of retinal ganglion cells are laminar radiations offset by an apical stem. Nearly 20 kinds of retinal ganglion cells can be distinguished by their dendritic arborization patterns (Sterling 1990). Three basic types, alpha, beta, and gamma cells (Wingate et al. 1992), are easily distinguished physiologically (Fukuda et al. 1984). Apparently the pattern of dendritic arborization of these neurons contributes to their physiological differences. The contribution of morphology to physiology is examined in more detail in Chapters 8, 9, and 10.

Dendritic arbors that are truly stellate do not receive segregated inputs. In other words, the same types of axons contact all parts of the arbor. In brain areas where there are layers of cells and fibers, such as cerebral cortex, dendritic arborizations receive specific sources in specific spatial domains. For example, the arbors of some retinal ganglion cells lie in the outer third of the inner plexiform layer (Sterling 1990). These receive contacts from bipolar cells that respond to light turning off. Other retinal ganglion cells have arbors in the inner two thirds of the inner plexiform layer, receiving contacts from bipolar cells that respond to light turning on. The physiological differences between on- and off- ganglion cells arise in part from differences in their regions of dendritic arborization and sources of input.

Frequently, dendritic arbors ramify into more than one layer to access more than one type of afferent. Such is the case with the many multilaminar forms of retinal amacrine cells. At least 26 different types of amacrine cells can be identified based on their dendritic arborization patterns (Kolb et al. 1992; MacNeil and Masland 1998; Mariani 1990). As with ganglion cells, these morphological differences almost certainly denote differences in the computational roles of these neurons, but the functions of most amacrine cell types is not yet known.

In many regions, such as the retina, there is an enormous variety of distinct neuronal shapes, but in other brain regions there appear to be relatively few. One example of the latter is the globus pallidus of primates in which small interneurons appear to be infrequent. Principal components analysis reveals that the large pallidal neurons belong to a single population (Yelnik et al. 1984). The dendrites of these neurons fill cylindrical spatial domains approximately 15001000 μm in diameter and 250 μm thick (Tables 1.1 and 1.2). These dendritic disks are parallel to the boundaries of the globus pallidus and thus perpendicular to incoming striatal axons, such that each neuron receives a wide distribution of inputs.

Pyramidal cells often extend dendrites into two distinct conical arbors, an apical one and a basal one. This configuration corresponds to a *biconical radiation* (Table 1.2) and may be characterized by different afferents contacting the basal versus apical domains. Pyramidal cells provide a good example of how arborization patterns depend on the cell body location relative to preferred input sources. The length of an apical dendrite of a cortical neuron depends on how far the cell body is from the outermost (e.g. plexiform) layer in which it ramifies its apical tuft. Cells very near the outermost layer usually do not have an apical stem at all, since one is

not required to reach the appropriate axonal contacts (Ramón y Cajal 1995). The dendritic arbors of pyramidal cells are sampling arborizations (Porter et al. 1991). Since the direction of dendrites relative to that of afferent axons varies, pyramidal cells may receive many synapses from a single axon which runs parallel to a dendritic segment or few synapses from axons which traverse its dendrites perpendicularly (Sholl 1956; Sorra and Harris 1993; see also Fig. 1.2b).

Afferents sometimes traverse the apical stem dendrite of pyramidal cells, in which case additional dendritic branches emanate from the apical stem in a *cylindrical radiation*. This occurs, for example, in the large pyramidal cells of hippocampal area CA1 (Fig. 1.2a). Here, the apical tuft arborizes in stratum lacunosum-moleculare and receives perforant path input from entorhinal cortex. The middle arbor in stratum radiatum receives the Schaffer axon collaterals from CA3 pyramidal cells. The basal cone extends into stratum oriens where it receives afferents from a more proximal part of CA3 (Amaral and Witter 1989). A CA1 pyramidal cell may be characterized as having three different spatial domains of dendritic arborization, an apical cone, a basal cone, and a central cylinder, each with different sampling densities. A similar pattern is frequently seen in neocortical pyramidal cells such as those of visual cortex (Feldman and Peters 1978).

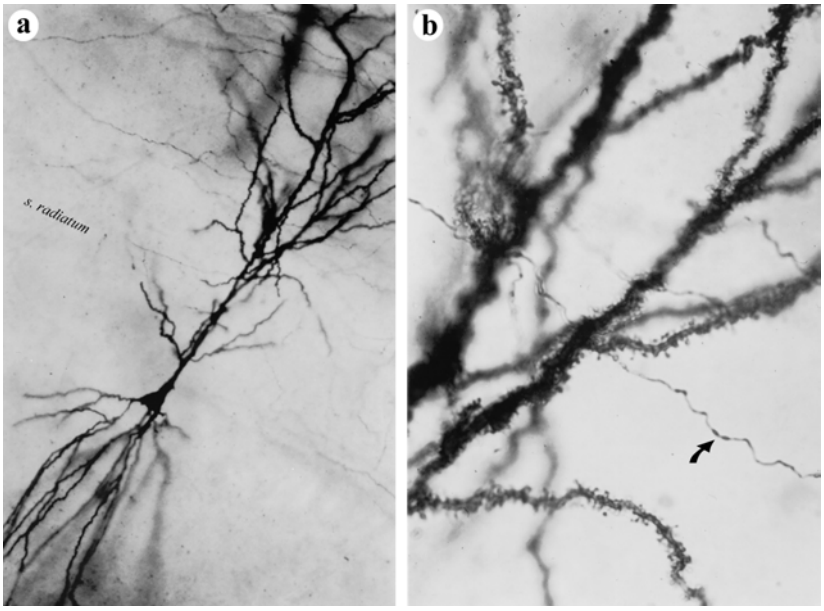


Fig. 1.2 A pyramidal cell from area CA1 of the rat hippocampus silver-impregnated using the Golgi method. This and subsequent figures are from the brains of adult rats. a. At low magnification the basal and apical dendrites can be seen to ramify into conical domains. Additional dendrites extend obliquely from the apical stem in stratum radiatum. b. At higher magnification numerous spines can be seen extending from the dendrites. A thinner, nonspiny process (arrow) recognizable as an axon passes nearby.

Table 1.2 summarizes some common arborization patterns but it is far from exhaustive. Just as pyramidal cells may have cylindrical radiations from the apical dendrite, many other arbors can be characterized by elaborations on or combinations of the basic patterns of Table 1.2. For instance, it is common for the apical stem of pyramidal cells in CA1 to bifurcate midway through stratum radiatum, each branch giving rise to an apical tuft (Bannister and Larkman 1995). Similarly, the apical stems in mitral and tufted cells of the olfactory bulb may be branched with a tuft on the end of each branch. Thus, a *branched conical radiation* might be included in Table 1.2. Mitral cells may also exhibit a laminar radiation of secondary dendrites from the soma (Kishi et al. 1982). Another example is the giant pyramidal cell referred to as a Betz cell. This cell has an essentially stellate arbor around the cell body as well as an apical cone ramifying in the outermost layers of cortex (Ramón y Cajal 1995).

It is important to note that dendrites are not completely static structures. Individual dendrites can extend or retract over periods of days to weeks (Purves et al. 1986; Stern and Armstrong 1998). Much modern research into the cellular basis of learning and memory has focused on activity-dependent changes in the strength of synapses, an idea as old as the neuron doctrine itself (Tanzi 1893). But Ramón y Cajal thought that synaptic plasticity alone could not explain the slow acquisition and long-term retention of the complex skills of an expert pianist or mathematician (Ramón y Cajal 1995). He suggested that learning also involves the growth of neuronal processes, establishing new communication pathways between neurons and brain regions that were not connected before. Recent research (Chapter 13) has reawakened interest in the intriguing possibility that continual changes in the dendritic arbor could play an important role in brain function.

Intracellular structure of dendrites

Electron microscopy reveals that the contents of large proximal dendrites are similar to those of the perikaryon from which they arise (Fig. 1.3). Perikaryal organelles such as the Golgi apparatus and the granular (or rough) endoplasmic reticulum extend into the proximal dendrites, reinforcing the view that dendrites are extensions of the cell body. These characteristically perikaryal organelles diminish however, with increasing distance from the cell body and decreasing dendrite diameter.

The cytoskeleton of dendrites is composed of microtubules, neurofilaments, and actin filaments. Microtubules are long, thin structures, approximately 24 nm in diameter, oriented to the longitudinal axis of the dendrite. In regions of the dendrite free of large organelles, they are found in a regular array at a density of 50-150 / μm2 (Fig. 1.4). Microtubules are typically spaced 80-200 nm apart, except in places where mitochondria or other organelles squeeze in between them. Microtubules are the "railroad tracks" of the cell and they play an important role in the transport of mitochondria and other organelles (Overly et al. 1996).

Axons also contain microtubules, usually with closer spacing than in dendrites. However, the fine processes of glia do not contain microtubules ordered in a regular array. Glial processes are highly irregular, extending protrusions into narrow crevices between axonal and dendritic processes (Fig. 1.4). Axons tend to maintain a

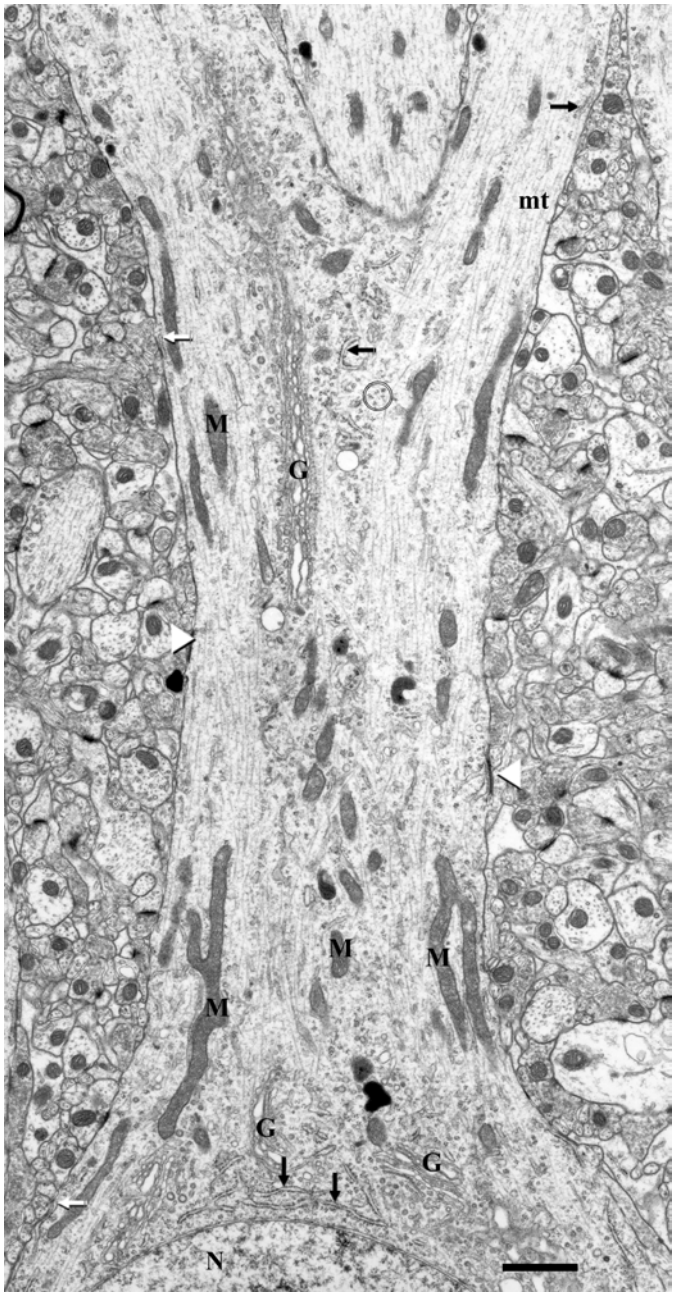


Fig. 1.3 Perikaryal organelles extend into the apical dendrite of a CA1 pyramidal cell to the first branch point. The smaller branch at the right shows fewer of the characteristically perikaryal organelles. Nucleus (N), granular endoplasmic reticulum (black arrows), Golgi apparatus (G), polyribosomes (circled), mitochondria (M), microtubules (mt), hypolemmal endoplasmic reticulum (white arrows), subsurface cisternal junctions of endoplasmic reticulum (white arrow heads). Scale bar: 1 μm.

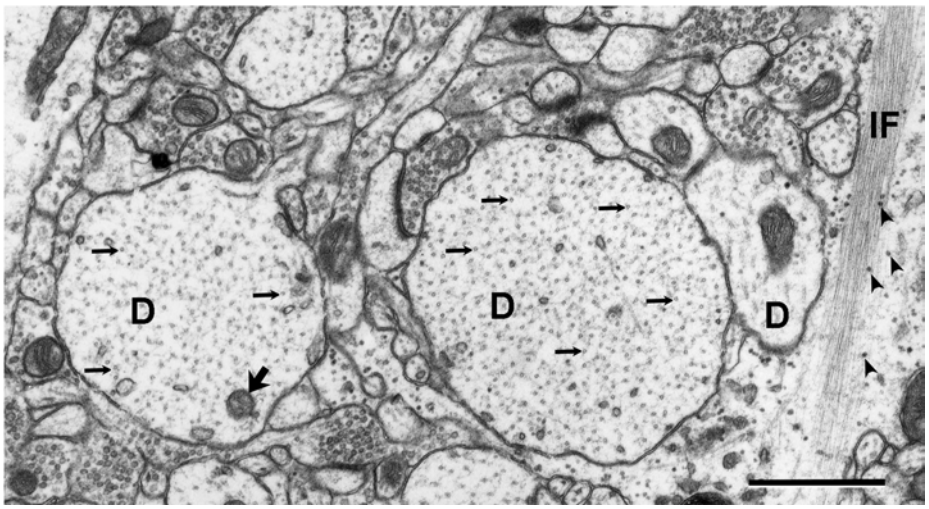


Fig. 1.4 The regular array of microtubules (small arrows) is clearly visible in the large dendrites (D) shown in cross-sectioned. A cross-sectioned mitochondrion (large arrow) is visible. A glia process is readily identified by the presence of numerous glycogen granules (arrow heads) and a bundle of intermediate filaments (IF). Scale bar: 1 μm.

consistent, convex cross-sectional shape except where they expand into varicosities containing mitochondria and/or synaptic vesicles. Small dendrites tend to be more irregular in cross-section than axons, while still maintaining convexity as compared with glia. The ultrastructure of glia also differs from that of axons and dendrites in that glia characteristically contain glycogen granules and bundles of intermediate filaments (Fig. 1.4).

Smooth endoplasmic reticulum (SER) is an organelle found throughout dendrites which is thought to be involved in the regulation of calcium. SER in aldehyde-fixed brain tissue usually appears as flattened compartments (cisternae) with a clear interior, which are occasionally swollen depending on the state of the tissue or quality of preservation. These cisternae are bounded by a wavy membrane (Fig. 1.5a). Hypolemmal cisternae are those parts of the SER network which lie just beneath the plasmalemma. Often these cisternae form characteristic junctions (Fig. 1.3) that could give access to the extracellular space (Henkart et al. 1976). In the three-dimensional view obtained by reconstruction from serial sections (Fig. 1.5b), the cisternae of SER form a continuous reticulum throughout the dendrites (Harris and Stevens 1988, 1989; Martone et al. 1993; Spacek and Harris 1997).

Organelles of the early endosomal pathway involved in membrane protein sorting and recycling are common in dendrites. *Recycling endosomes* appear as tubular compartments that are not part of a reticulum (Fig. 1.5a). These can be distinguished from SER by their darker interior, more uniform diameter, and the frequent occurrence of specialized coats at the ends of the tubule. These coated ends may represent sites of budding of recycling vesicles bound for the plasmalemma

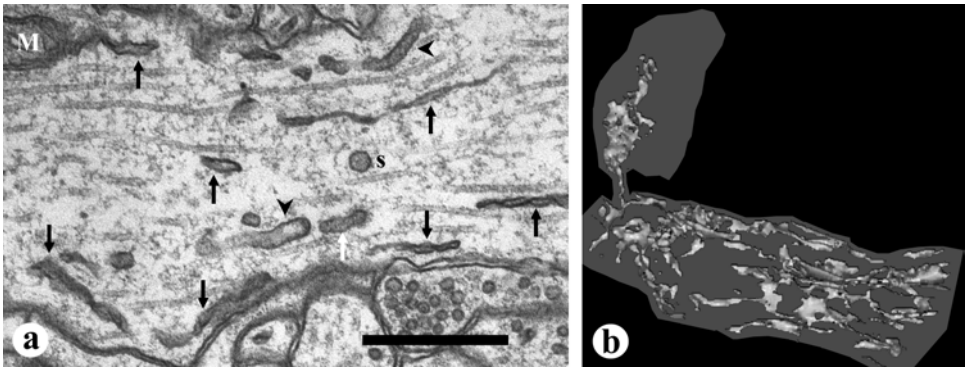


Fig. 1.5 The smooth endoplasmic reticulum (SER) forms a continuous compartment in dendrites. a. Pieces of SER appear as thin cisternae with wavy membranes (black arrows). SER cisternae can be seen in continuity with the outer membrane of mitochondria (M). (See also Spacek and Lieberman, 1980). Endosomal compartments (black arrow heads) are tubes which do not connect in a reticulum throughout the dendrite. These have a uniform diameter and dark, grainy interior. Recycling endosomes frequently display a coated tip at one end (white arrow). The spherical vesicle (s) with its dark interior is related to the endosomal compartments, but it is unclear whether it will merge with or has just budded from a recycling endosome. Scale: 0.5 μm. b. Three-dimensional reconstruction of the SER in a different dendrite and spine reveals the interconnectivity of the cisternae.

(Bauerfeind et al. 1996). *Sorting endosomes* can be identified by the occurrence of similar tubular compartments connected to larger, spherical organelles with interior vesicles (Gruenberg and Maxfield 1995). These spherical compartments mature into *multivesicular bodies*, separate from the sorting endosome, and are transported to the cell body for processing in late endosomes and lysosomes (Parton et al. 1992). Thus, multivesicular bodies in dendrites occur alone or in conjunction with the sorting endosome compartments (Fig. 1.6). In three dimensions the later complex can be seen to emanate many tubular profiles with coated tips (Fig. 1.6b).

Coated pits and vesicles representing the initial step in endocytosis are frequently seen in dendrites (Fig. 1.7a). The cytoplasmic coat is composed of *clathrin* (Brodsky 1988) giving it a distinctive periodic structure recognizable as the same coat found on the tips of early endosomes. Clathrin coated vesicles uncoat less than a minute after their formation from a coated pit (Fine and Ockleford 1984). For this reason coated vesicles are only found in the vicinity of their locus of generation within the dendrite. Coated vesicles and coated pits occur more frequently in dendrites during development (Altman 1971) and during periods of synaptic remodeling (McWilliams and Lynch 1981).

Ribosomes are sites of protein synthesis within cells. Free ribosomes, those not attached to ER, occur throughout the cytoplasm of dendrites at a very low density compared to the perikaryon. Frequently, they are closely clustered into groups of 3 to 30 (Fig. 1.7b), called *polyribosomes* (Steward and Reeves 1988). Groups of polyribosomes often occur together in dendrites, especially at the branch points. In contrast to dendrites, axons are generally devoid of ribosomes, suggesting that new

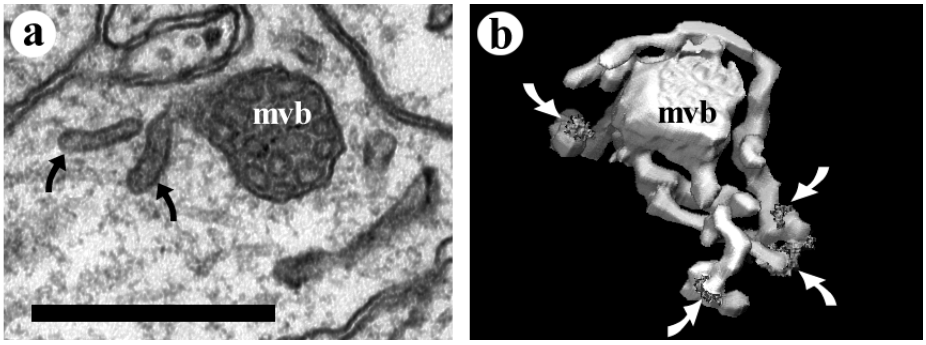


Fig. 1.6 Sorting endosomes form complex structures which include multivesicular bodies. a. A multivesicular body (mvb) with its connected tubular compartments of sorting endosome (arrows) in a hippocampal pyramidal cell dendrite. Scale: 0.25 μm. b. Three-dimensional reconstruction of a sorting endosome from a different dendrite. The tubular sorting compartments often end in coated tips (arrows) with the same appearance as in Fig. 1.5a. The top of the multivesicular body (mvb) is removed to reveal the interior vesicles.

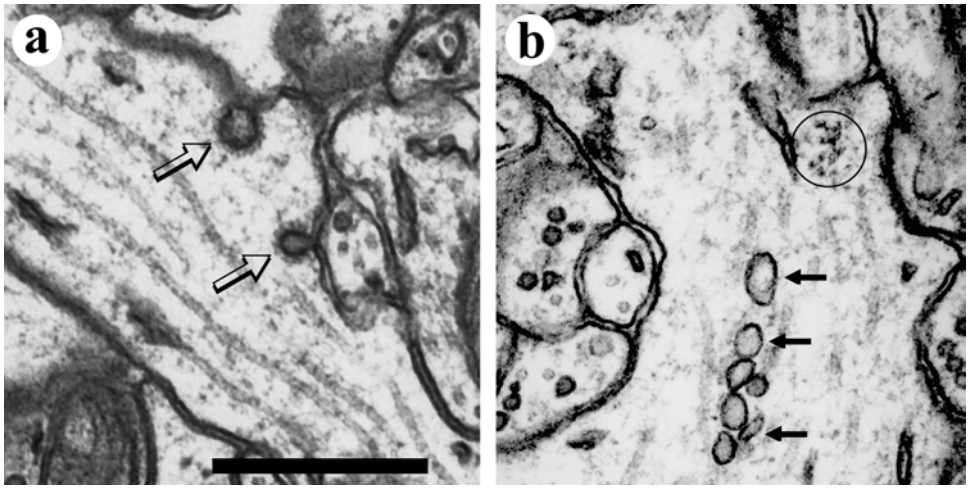


Fig. 1.7 Some other ultrastructural features frequently found in distal dendrites. a. Clathrin coated pits (arrows) are the initial step in the endosomal pathway. These pits may form into vesicles destined for recycling endosomes. b. This section of dendrite contains polyribosomes (circled) and a string of large, clear vesicles (arrows) similar in appearance to strings of vesicles in the Golgi apparatus. Scale: 0.5 μm.

proteins are transported from the cell body rather than manufactured within the axon.

Mitochondria in dendrites are usually elongated and oriented with their long axis parallel to the microtubules. Given their likely roles in calcium signalling and prevention of excitotoxicity (Miller 1998), it is interesting that mitochondria are not distributed uniformly throughout the dendritic arbor. Larger, proximal dendrites have fewer mitochondria per unit of cross-sectional area than thinner distal dendrites (Peters et al. 1991). For example, in stratum radiatum of area CA1 mitochondria comprise about 2% of intracellular space in the apical stem dendrites, while filling 13% of the thinnest branches in the apical tuft (Nafstad and Blackstad 1966).

Synaptic specializations of dendrites

Although a dendrite is adjacent to many axons and other dendrites throughout its length, functional connectivity occurs at specialized sites where neurons communicate. These are called *synapses*. "Synapses" is the plural of synapsis, a term first employed by Foster and Sherrington (Foster 1897). Synapsis means "connection" (Murray et al. 1919), apropos for the site of connectivity between neurons. In modern usage, the singular of synapses is usually expressed as *synapse*. Synapses are made on the surface of the dendrite, so called *shaft* synapses, but many synapses lie on specialized enlargements of or protrusions from the dendrites (Table 1.3). Shaft synapses are only 5% of all synapses on the pyramidal cell dendrites in stratum radiatum (Harris et al. 1992; Kirov et al. 1999).

An example of a synaptic specialization of a dendrite is found in amacrine cells of the retina. The dendrites of AI amacrine cells are not tapered in the same way as motoneurons. They are very thin and have numerous *varicosities* or swellings at contacts with rod bipolar cells (Ellias and Stevens 1980). The varicosities receive synapses from rod bipolar cells. In addition, these varicosities contain synaptic vesicles and make reciprocal synapses on the rod bipolar cells. There are other examples of presynaptic dendrites in the nervous system, such as in granule, mitral and tufted cells of the olfactory bulb, although these do not necessarily have similar varicosities.

Filopodia are another synaptic specialization of dendrites. All neurons exhibit dendritic filopodia transiently during development (Morest 1969). As discussed in Chapter 1, filopodia appear to play a role in synaptogenesis, making numerous nascent synaptic contacts (Fiala et al. 1998). Filopodia are rarely seen on dendrites in normal adult brain, perhaps because such long protrusions are not required for establishing new contacts. Adult neuropil is densely backed with axonal boutons, such that only a short dendritic outgrowth is required for a dendrite to encounter a new presynaptic partner.

The most common synaptic specializations of dendrites are *simple spines*. Spines are protrusions from the dendrite of usually no more than 2 μm, often ending in a bulbous head attached to the dendrite by a narrow stalk or neck (Fig. 1.2b, 1.8). Simple spines are frequent on the dendrites of cerebral pyramidal cells, striatal neurons, granule cells of the dentate gyrus, cartwheel cells of the dorsal cochlear nucleus, and cerebellar Purkinje cells, to name a few *spiny* neurons. More generally

Table 1.3 Synaptic specializations of dendrites

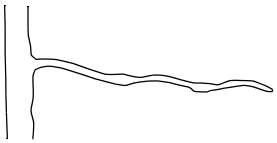
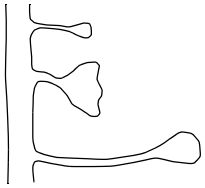
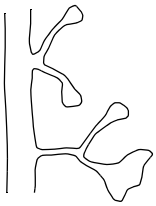
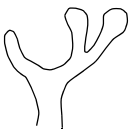
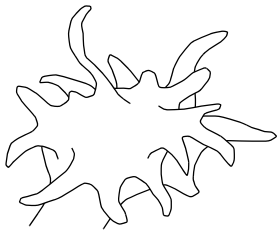
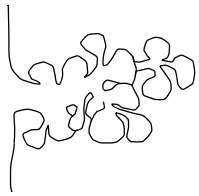
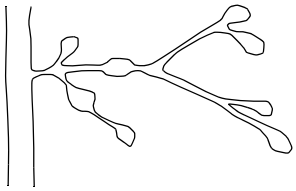
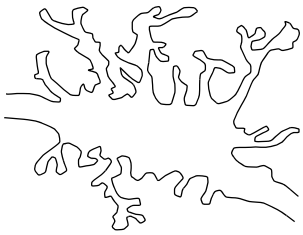
Pattern	Characteristics	Examples
Varicosity 	An enlargment in a thinner dendrite associated with synaptic contacts	Retinal amacrine cells
Filopodium 	A long, thin protrusion with a dense actin matrix and few internal organelles	Normally only seen during development
Simple Spine		
Sessile 	Synaptic protrusions without a neck constriction	
	Stubby spine	Pyramidal cells of cortex
	Crook thorn	Cerebellar dentate nucleus
Pedunculated 	Bulbous enlargement at tip	
	Thin spine	Pyramidal cells of cortex
	Mushroom spine	Pyramidal cells of cortex
	Gemmule	Olfactory bulb granule cell
Branched Spine 	Each branch has a unique presynaptic partner and each branch has the shape characteristics of a simple spine	CA1 pyramidal cells Granule cells of dentate gyrus Cerebellar Purkinje cells
Claw Ending 	Synaptic protrusions at the tip of the dendrite associated with one or more glomeruli	Granule cells of cerebellar cortex and dorsal cochlear nucleus

Table 1.3 Synaptic specializations of dendrites

Pattern	Characteristics	Examples
Brush Ending 	Spray of complex dendritic protrusions at the end of dendrite that extends into glomerulus and contains presynaptic elements	Unipolar brush cells of cerebellar cortex and dorsal cochlear nucleus
Thorny Excrescence 	Densely lobed dendritic protrusion into a glomerulus	Proximal dendrites of CA3 pyramidal cells and dentate gyrus mossy cells
Racemose Appendage 	Twig-like branched dendritic appendages that contain synaptic varicosities and bulbous tips	Inferior olive Relay cells of lateral geniculate nucleus
Coralline Excrescence 	Dendritic varicosity extending numerous thin protrusions, velamentous expansions and tendrils	Cerebellar dentate nucleus Lateral vestibular nucleus

neurons are classified as spiny, *sparsely spiny*, and *nonspiny* (or *smooth*) according to the density of simple spines on their dendrites (Peters and Jones 1984). Such a classification is complicated by the fact that different dendrites of a given neuron may exhibit widely different spine densities (Feldman and Peters 1978). Even along the length of a dendritic segment, spine densities can vary widely. Nominally nonspiny dendrites often exhibit a few simple spines.

Determining the density of spines on dendrites is difficult because of their small size. With light microscopy, the dendrite obscures spines that lie above or below it

in the section such that only the spines extending laterally can be accurately counted. Nor is this problem completely remedied by three-dimensional confocal microscopy. To compensate, many studies have applied correction factors for hidden spines (Bannister and Larkman 1995b; Trommald et al. 1995). A more accurate estimate of spine density can be obtained using serial electron microscopy (EM). By reconstructing cross-sectioned dendrites from EM (Fig. 1.8), all spines, including the shortest ones, can be counted. In addition, serial EM allows the accurate determination of spine dimensions as described below.

When the spine density on the dendrites of CA1 pyramidal cells is estimated, different values are obtained for different regions of the arbor. Spines are most dense on the lateral branches of the apical stem in stratum radiatum where they average about 3 per μm of dendrite as measured by both serial EM (Harris et al. 1992) and by light microscopy with correction (Bannister and Larkman 1995b; Trommald et al. 1995). On the dendrites of the apical and basal cones there are 1.4 spines/μm and 2.4 spines/μm, respectively (Bannister and Larkman 1995b). In total, CA1 pyramidal cells have ~30 000 spines, with 50% of them located in stratum radiatum and 40% in stratum oriens. By comparison, pyramidal cells of visual cortex are much less spiny. Total counts of only 15 000 spines are obtained for large pyramidal cells in visual cortex, with a maximum density of 1.5 spines/μm (Larkman 1991). Much higher spine densities (7.2 spines/μm) are found on certain neostriatal neurons (Graveland et al. 1985). The spiniest neuron in the brain may be the cerebellar Purkinje cell,

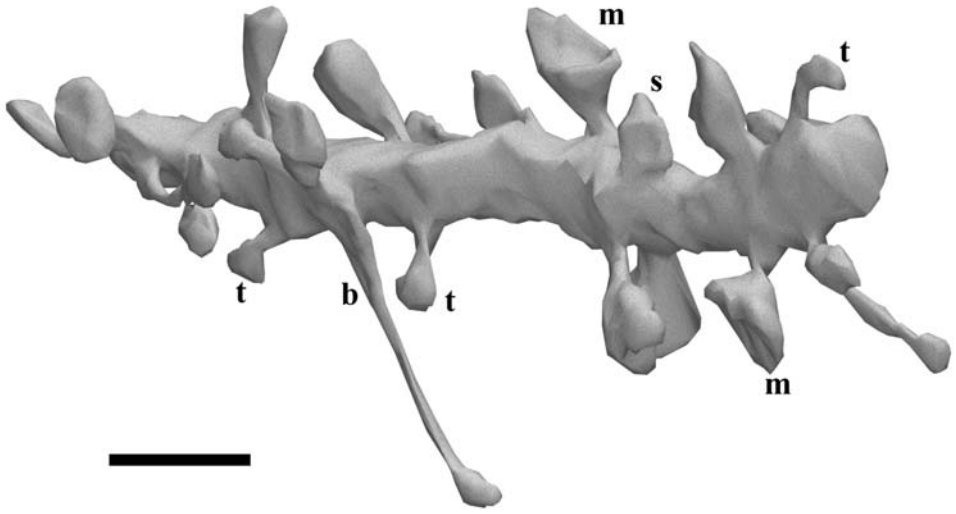


Fig. 1.8 This segment of spiny dendrite from stratum radiatum of area CA1 was reconstructed from 71 serial section electron micrographs (Harris and Stevens 1989). The 7 μm segment has 17 simple spines and 3 branched spines for a total of 23 spine heads. In evidence are stubby (s), thin (t), and mushroom (m) spine shapes. Although this view of the dendrite was carefully chosen, it is apparent that getting an accurate spine count would be difficult by light microscopy. Only one of the branched spines (b) can be observed from this viewpoint. Scale: 1 μm.

with spine densities reaching as much as 15 spines/μm (Harris and Stevens 1988). There are so many spines on spiny neurons that they contribute substantially to the cell's surface area. In the case of the CA1 pyramidal cell, spines contribute nearly half of the dendritic surface area (Bannister and Larkman 1995b).

Occasionally, two or more simple spines share a common stalk. These are called *branched spines* (Table 1.3). The individual branches exhibit the same range of morphologies as simple spines (Fig. 1.8) and rarely synapse with the same bouton (Harris and Stevens 1988; Sorra et al. 1998; Trommald and Hullenberg 1997). Branched spines occur infrequently on spiny neurons, being only 2% of all dendritic protrusions on CA1 pyramidal cells (Harris et al. 1992) or dentate granule cells (Trommald and Hullenburg 1997). Apparently, branched spines are formed by accidental proximity of spine origins. This is a rare event because spine origins exhibit a non-random tendency to separate (Trommald et al. 1995; Ward et al. 1995). Branched spines are more frequent on dendrites with higher spine densities, such as Purkinje cell dendrites where approximately 6% of spines are branched (Harris and Stevens 1988). Likewise, higher spine densities lead to larger numbers of branches per occurrence. Up to 5 branches have been found on cerebellar Purkinje cells (Harris and Stevens, 1988), while CA1 branched spines rarely have more than 2 branches (Sorra et al. 1998).

When large axon terminals interact with dendrites, they often do so in synaptic complexes called glomeruli. Dendrites extend complex, multilobed protrusions into these glomeruli to make large areas of synaptic contact, thereby strengthening the efficacy of the connection between the neurons. A simple example is the *claw endings* of the dendrites of granule cells of cerebellar cortex, which make several synapses with a mossy fiber axon terminal (Eccles et al. 1967). Another type of specialized dendritic ending associated with some cerebellar glomeruli is the brush endings of unipolar brush cells (Table 1.3). These multilobed protrusions have a unique appearance which may be related to the fact that they are presynaptic to the claw endings of cerebellar granule cells as well as postsynaptic to mossy fiber rosettes (Mugnaini et al. 1994).

In hippocampus, another type of mossy fiber with large boutons makes contact on the *thorny excrescences* of CA3 pyramidal cells. CA3 pyramidal cells have large numbers of simple spines, but 90% of the dendritic protrusions on the proximal apical dendrite of pyramidal cells are thorny excrescences (Chicurel and Harris 1992). The complexity of these thorny excrescences varies, with some having many lobes and others having just a few. Three-dimensional reconstructions have been obtained of excrescences with as many as 16 lobes, all of which synapse with a single giant mossy fiber bouton. The density of lobes in thorny excrescences often gives them the appearance of a bunch of grapes (Hama et al. 1994). A more sparsely lobed appearance characterizes the *racemose appendages* seen in inferior olive (Ruigrok et al. 1990) and lateral reticular nucleus (Hrycyshyn and Flumerfelt 1981).

A final example, that by no means exhausts the kinds of synaptic specializations of dendrites, is the *coralline excrescences* found on dendrites of the small neurons of the cerebellar and vestibular nuclei. These complex varicosities exhibit numerous synaptic protrusions (Chan-Palay 1977), and sometimes thin tendrils similar in appearance to filopodia (Morest 1969; Sotelo and Angaut 1973). The appearance of filopodia, in adult animals, has lead to the suggestion that these coralline excrescences represent growth processes of dendrites.

Like the dendrites themselves, dendritic surface specializations are not static structures (Chapter 13). In cases where they have been studied by time-lapse microscopy (Dailey and Smith 1996; Dunaevsky et al. 1998; Fischer et al. 1998), they appear to be highly motile structures. The heads of simple pedunculated spines appear to be in constant motion, continually changing shape, and swaying on their necks. Recent data supports the idea that spines extend and retract under the influence of changes in activity (Kirov and Harris 1998), possibly with a time-course of just a few minutes (Halpain et al. 1998).

Shapes of simple spines

The diversity of structure in synaptic specializations of dendrites is most effectively studied with serial EM. This methodology has been used most extensively to study simple spines on spiny neurons. In the mature brain simple spines vary greatly in size, with volumes ranging from less than 0.01 μm^3 to more than 1.5 μm^3 (Table 1.4). Simple spines of different sizes and shapes can be neighbors on the same parent dendrite (Harris and Kater 1994), and occasionally form synapses with the same presynaptic bouton (Sorra and Harris 1993). These observations suggest that dendritic synaptic specializations are unique units that are not determined uniformly by cell type or presynaptic partner.

In pyramidal cells, two principal types of simple spines can be distinguished: *sessile* and *pedunculated* (Jones and Powell 1969). Sessile spines do not exhibit a substantial neck constriction (Fig. 1.8). Sessile spines are often called *stubby* spines (Peters and Kaiserman-Abramof 1970), especially when the length of the spine is less than or equal to its width (Harris et al. 1992). The bulbous head of pedunculated spines attaches to the dendrite through a thin stalk or neck. Among pedunculated spines, two varieties are commonly distinguished. *Thin* spines are those with a small head (Fig. 1.8). Large-headed spines, those with a spine head diameter > 0.6 μm, are called *mushroom* spines (Fig. 1.8).

Not all spiny neurons show the same distribution of spine shapes as pyramidal cells (Fig. 1.9). For example, spines on the tertiary dendrites of cerebellar Purkinje cells constitute a single morphological class with head diameters similar to thin spines on pyramidal cells and neck diameters similar to those of mushroom spines (Spacek and Hartmann 1983). In other spiny neurons there is a continuum of spine shapes, with clear stubby, thin, and mushroom varieties but many spines intermediate between these shapes. For instance, some mushroom spines have very long necks, while some thin spines have rather large heads. This makes distinct shape classes difficult to distinguish (Trommald and Hullenberg 1997; Wilson et al. 1983). Still, the majority of simple spines have a thin shape (Graveland et al. 1985; Harris et al. 1992; Peters and Kaiserman-Abramof 1970).

Additional types of simple spines are found on specific neurons. One example is the bent sessile spines in cerebellar dentate nucleus called *crook thorns* (Chan-Palay 1977). The granule cells of the olfactory bulb have particularly large pedunculated spines sometimes referred to as *gemmules*. These spines may be 5 μm long, with heads 1-2 μm in diameter (Cameron et al. 1991).

Table 1.4 Dimensions of simple spines on spiny neurons

Neuron	Total length (μm)	Neck diameter (μm)	Neck length (μm)	Total volume (μm^3)	Total surface area (μm^2)	PSD area (μm^2)	PSD:head area ratio
Cerebellar Purkinje cell	0.7-3.0	0.1-0.3	0.1-2	0.06-0.2	0.7-2	0.04-0.4	0.17 ± 0.09
CA1 pyramidal cell	0.2-2	0.04-0.5	0.1-2	0.004-0.6	0.1-4	0.01-0.5	0.12 ± 0.06
Visual cortex pyramidal cell	0.5-3	0.07-0.5	—	0.02-0.8	0.5-5	0.02-0.7	0.10 ± 0.04
Neostriatal spiny neuron	—	0.1-0.3	0.6-2	0.04-0.3	0.6-3	0.02-0.3	0.125
Dentate gryus granule cell	0.2-2	0.05-0.5	0.03-0.9	0.003-0.2	0.1-3	0.003-0.2	—

Sources: Harris and Stevens (1988); Harris and Stevens (1989); Spacek and Hartman (1983); Wilson et al. (1983); Trommald and Hullenburg (1997)

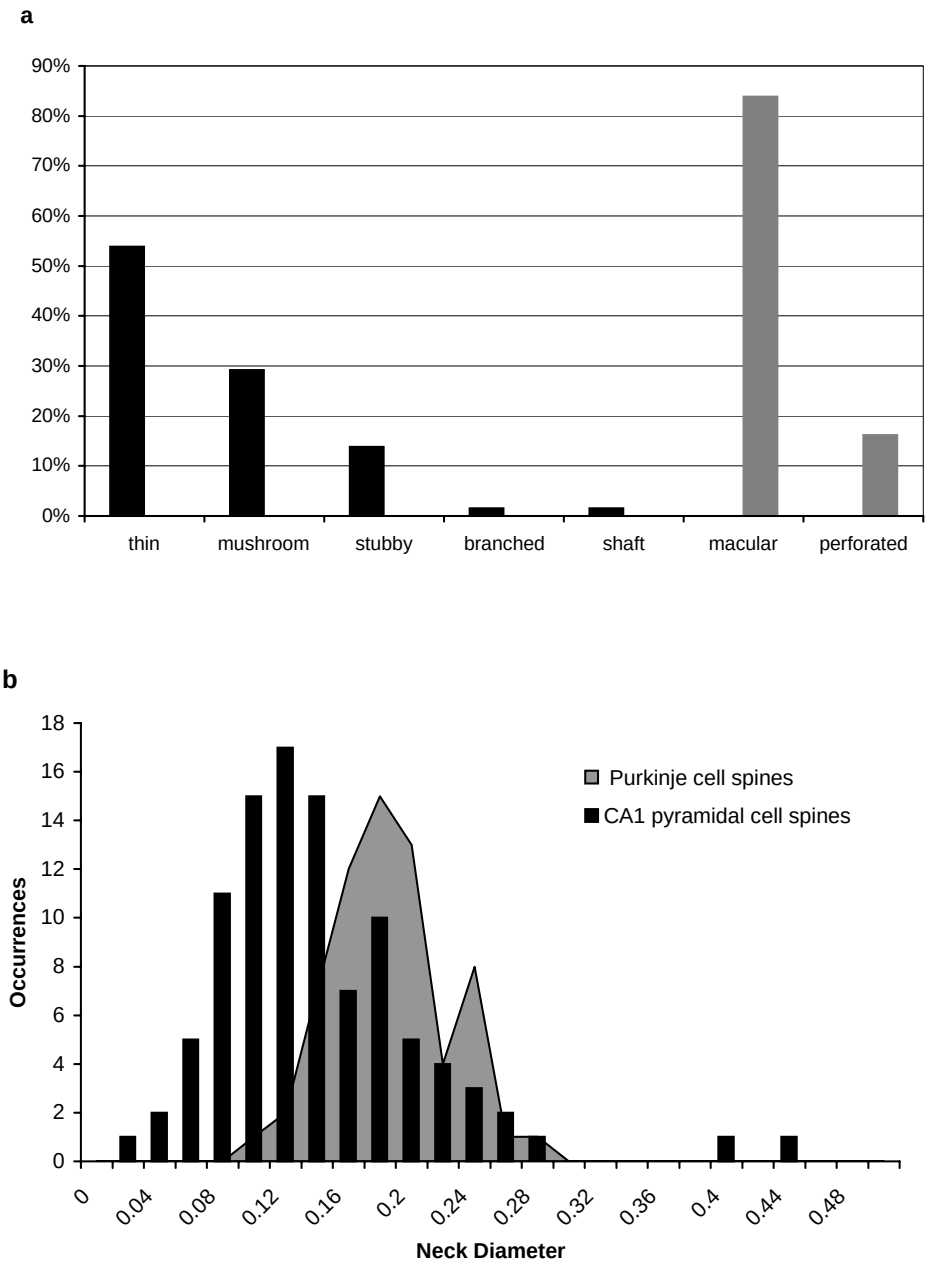


Fig. 1.9 The distribution of simple spine shapes as determined by three-dimensional reconstruction. a. Spines with a thin shape are most frequent in stratum radiatum of area CA1. These spines tend to have macular synapses (see text), the most common synapse shape. b. Measured neck diameters show a skewed distribution, with CA1 pyramidal cell spine necks tending to be thinner than those of spines from cerebellar Purkinje cell tertiary dendrites.

The separation of simple spines into thin-necked and thick-necked varieties may be functionally relevant since the presence of a neck constriction can serve to isolate the spine head compartment from the dendrite (Holmes 1990; Koch and Zador 1993; Svoboda et al. 1996). The distribution of spine neck diameters on most spiny neurons does not follow a normal distribution (Fig. 1.9b). Rather, the distribution is skewed toward larger neck sizes (Trommald and Hullenberg 1997; Wilson et al. 1983). This, and the fact that cerebellar spines have spine neck dimensions similar to thick-necked spines on pyramidal cells (Spacek and Hartmann 1983), suggest the possibility of a functionally distinct thick-necked spine class.

Simple spines occasionally have even smaller protrusions that extend from them into the interior of surrounding structures such as boutons or glia. These *spinules* are surrounded by invaginations of apposed membrane often with a clathrin-like coat visible on the cytoplasmic side at the tip of the invagination (Fig. 1.10). Spinules in the hippocampus originate from all parts of the spine surface, often at the edges of synapses (Sorra et al. 1998; Tarrant and Routtenberg 1977; Westrum and Blackstad 1962). The function of spinules is not known, however it may involve bulk membrane recycling since spinules are increased following intense stimulation (Applegate and Landfield 1988). Similar structures are found on other types of synaptic specializations, such as on the claw endings of cerebellar granule cells (Eccles et al. 1967) and on the lobes of thorny excrescences (Chicurel and Harris 1992).

Intracellular structure of synaptic specializations

The diversity of shapes of synaptic specializations is accompanied by a diversity in intracellular composition. The size of a synaptic specialization seems to be a factor in its composition. Small dendritic protrusions such as simple spines rarely contain

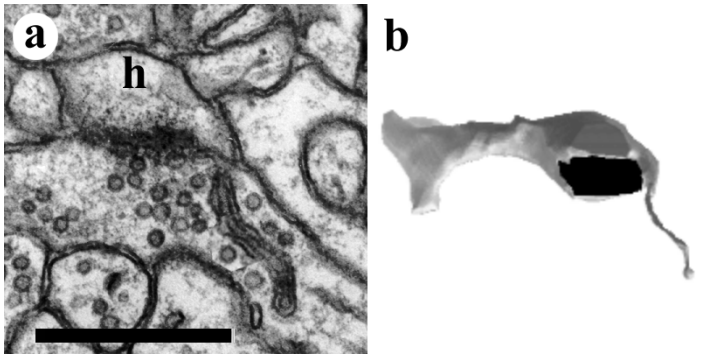


Fig. 1.10 A thin spine from stratum radiatum with a long spinule extending from the edge of the synapse. a. The spinule extends from the head of the spine (h) into the presynaptic bouton. Scale: 0.5 μm. b. Three dimensional reconstruction of the entire spine with the area of synaptic contact shown in black.

microtubules. Simple spines have actin-based cytoskeletons that may facilitate rapid, calcium-induced changes in spine structure (Fifkova 1985; Fischer et al. 1998) or spine loss (Halpain et al. 1998). Similarly, microtubules are absent from filopodia even though they are present in the dendrites from which they arise. Occasionally, microtubules contribute to the cytoskeletons of larger synaptic specializations such as thorny excrescences (Chicurel and Harris 1992; Ebner and Colonnier 1975).

Another major difference between large and small synaptic specializations is the presence of mitochondria. Filopodia and simple spines rarely contain mitochondria. An exception is the large spines of olfactory bulb granule cells that often have mitochondria in the head. Since these spines make reciprocal synapses on mitral cell dendrites, it has been suggested that the presence of mitochondria may be related to presynaptic function (Cameron et al. 1991). Other specializations with presynaptic functions such as the varicosities of AI amacrine cells and the brush endings of unipolar brush cells likewise contain numerous mitochondria. However, thorny excrescences and claw endings are not presynaptic and they also may contain a mitochondrion in the head of a protrusion. The larger synaptic specializations of the relay cells of lateral geniculate nucleus also contain many mitochondria without having a presynaptic function (Wilson et al. 1984).

Most synaptic specializations also contain SER (Fig. 1.5, 1.11). These cisternae are continuous with the reticulum in the dendrite. Thin spines and filopodia contain relatively little SER. In claw endings of cerebellar granule cells, each mitochondrion is surrounded by a single cistern of SER. Larger spines contain larger amounts of SER that often becomes laminated into a characteristic appearance (Fig. 1.11), called the *spine apparatus* (Gray 1959). Mushroom spines and gemmules frequently contain spine apparati, as do the thorny excrescences of area CA3.

Smooth and coated vesicles, endosomes, and polyribosomes also occur in synaptic specializations (Fig. 1.11; see also Spacek and Harris, 1997). However the complement of organelles in each instance is unique, suggesting local regulation of subcellular functions, possibly in response to different levels of neuronal activity. In dentate granule cells, as many as 80% of polyribosome clusters in dendrites may lie within or at the base of spines, while only 12% of spines exhibit these polyribosome clusters (Steward et al. 1996). In hippocampal area CA1, serial EM analyses reveal that more than 50% of spines have some polyribosomes (Harris and Spacek 1995). A similarly high frequency was found in the lobes of thorny excrescences using serial EM (Chicurel and Harris 1992), suggesting that polyribosomes are more common in synaptic specializations than is obvious through single section analysis.

The synapses on synaptic specializations have also been extensively examined with EM. The majority of synapses in the brain are chemical synapses, and these are the principal type of synapses found on the synaptic specializations of dendrites. A chemical synapse consists of apposed membranes separated by a gap called the *synaptic cleft* (Fig. 1.12). Neurotransmitters released from synaptic vesicles on the presynaptic side of the cleft diffuse across the cleft to activate receptors in the postsynaptic membrane. The presynaptic element is usually a varicosity or end bulb of an axon, called a *bouton*.

In aldehyde-fixed tissue, several different types of chemical synapses can be distinguished based on the size and shape of the presynaptic vesicles and the form of the perisynaptic structures (Peters and Palay 1996). Two principal types are

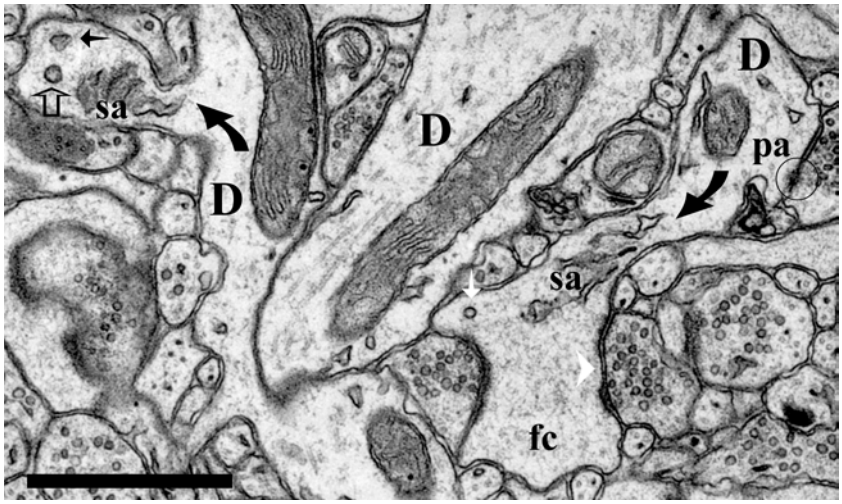


Fig. 1.11 Simple spines contain a unique complement of organelles. Dendrites (D) from stratum radiatum give rise to large spines (large arrows). The spines contain mainly a darker, floccular cytoplasm (fc) consistent with a denser actin matrix. The spines contain a specialization of SER called the spine apparatus (sa). A further extension of SER can be seen in one spine (small arrow). This spine also contains a spherical vesicle (open arrow). The other large spine contains a smaller clear profile (white arrow) that can be seen to be a tubule, perhaps endosomal, in cross-section by examining adjacent serial sections. The bouton presynaptic to this spine wraps around the spine head so that the synapse appears on both sides in this section. The postsynaptic density has a gap, or perforation, on one side (white arrow head). Also visible in this section is a puncta adhaerens junction (pa; see text) next to a symmetric synapse. Scale: 1 μm.

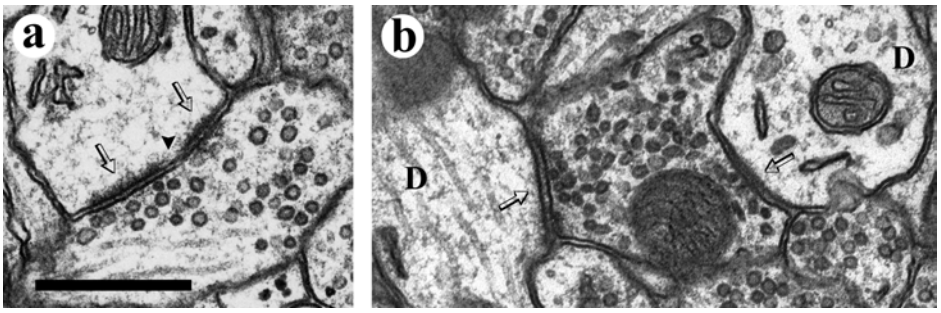


Fig. 1.12 The two most common types of synapses seen in the brain are asymmetrical and symmetrical types with small vesicles. a. The asymmetrical synapse is characterized by a thick postsynaptic density (arrows) and small, round vesicles presynaptically. This synapse, located on stubby protrusion, exhibits a perforation (arrow head). b. The symmetrical synapse is characterized by equal densities pre- and postsynaptically, and small, flattened vesicles presynaptically. This bouton makes two symmetrical synapses (arrows) on the shafts of two different dendrites (D). Scale: 0.5 μm.

commonly referred to as *asymmetric* and *symmetric* synapses. Asymmetric synapses are characterized by round presynaptic vesicles ~30-50 nm in diameter and a *postsynaptic density* (Fig. 1.12a). The postsynaptic density (PSD) is a densely stained structure that contains numerous receptors, structural proteins, and signaling molecules that are important for synaptic transmission and plasticity (Kennedy 1997). Symmetric synapses have a much thinner postsynaptic density, matched by an equal density on the presynaptic side (Fig. 1.12b). In addition, many of the presynaptic vesicles at symmetric synapses appear flattened rather than round. Asymmetric synapses are usually excitatory and contain the neurotransmitter glutamate. In contrast, symmetric synapses usually contain the inhibitory neurotransmitters GABA or glycine, and often neuromodulatory peptides.

In visual cortex, 84% of synapses are asymmetric, while 16% are symmetric (Beaulieu and Colonnier 1985). Most of the asymmetric synapses (79%) occur on dendritic spines, while 21% occur on dendrite shafts, and very few (0.1%) are found on cell bodies. The inhibitory synapses show a different pattern. Most are found on dendrite shafts (62%), while 31% occur on dendritic spines, and 7% occur on cell bodies. Thus, symmetric synapses are only 7% of all dendritic spine synapses, but 93% of all soma synapses in this brain region.

Simple spines typically have a single asymmetric synapse located on the spine head. Occasionally spines have a second synapse, usually on the spine neck (Spacek and Hartmann 1983). The second synapse can be either symmetric or asymmetric (Jones and Powell 1969). In neostriatum, approximately 8% of spines receive a second symmetric synapse (Wilson et al. 1983). The striatal neurons that make reciprocal connections with substantia nigra have an additional 39% of their spines contacted by a different (probably dopaminergic) type of symmetric synapse containing large, pleomorphic vesicles (Freund et al. 1984).

Glomeruli often contain inhibitory axons in addition to the primary excitatory terminals. Thus it is common for synaptic specializations that project into glomeruli to receive multiple types of synaptic contacts. For example, the racemose appendages of inferior olivary neurons receive both excitatory and inhibitory synapses (De Zeeuw et al. 1990).

When viewed in three dimensions, synapses can be seen to exhibit size-dependent variations in morphology (Spacek and Hartmann 1983). Small synapses, like those on the heads of thin spines, are typically *macular* (Fig. 1.9), consisting of a single round region without holes (Fig. 1.13). Larger synaptic junctions often exhibit interior regions devoid of pre- and postsynaptic density. These synapses can be U-shaped, annular, or exhibit multiple holes, and are often called *perforated* synapses. In some cases, a contact between a single bouton and a dendrite is composed of two or more disjoint synaptic regions. This type of perforated synapse is sometimes referred to as a *segmented*, or multifocal, synapse (Geinisman et al. 1987).

Macular and perforated synapses can all be found on simple spines as well as on the shafts of dendrites. When located on spines, the synaptic area occupies approximately 10% of the surface area of the spine head (Spacek and Hartmann 1983). This relationship between synapse and spine area is consistent over different spine morphologies and neuron types. This relationship appears to hold for more complicated synaptic specializations as well, such as the thorny excrescences of CA3 (Chicurel and Harris 1992). Spine surface area, spine volume, SER volume, bouton

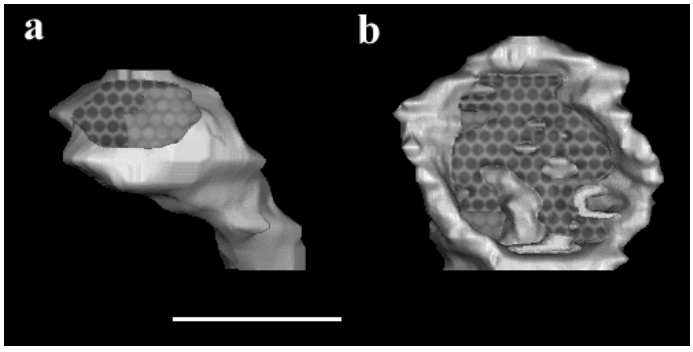


Fig. 1.13 Three-dimensional reconstruction of perforated and macular synapses. a. The region with dark circles (left) indicates the synaptic area of a macular synapse. This is adjacent to a large puncta adhaerens junction (light circles; right) between the spine and the presynaptic bouton. b. A perforated synapse (dark circles) has places in the interior of the synaptic region which are non-synaptic, seen as islands of gray spine head within the synapse. Puncta adhaerentia are also present (light circles; lower and upper left). Scale: 1μm.

volume, and number of synaptic vesicles are all highly correlated with synapse size (Harris and Stevens 1988, 1989; Harris and Sultan 1995). Thus, smaller thin spines have smaller synapses, which tend to be macular. Larger mushroom spines have larger synapses, which tend to be perforated (Harris and Stevens 1989; Harris et al. 1992).

It has been suggested that synapse perforations may be related to synaptic plasticity, representing a state of enhanced efficacy or an intermediate stage in a process of synapse proliferation through splitting (Jones and Harris 1995). Spinous synapses do not appear to split, however (Sorra et al. 1998). Instead, perforations may be related to the excess membrane inserted during synaptic vesicle fusion prior to bulk endocytosis (Shupliakov et al. 1997). Many aspects of the synaptic anatomy, such as the number of synaptic vesicles, the frequency and appearance of membrane recycling components, and the curvature of the synapse, may be related to functional state (Applegate and Landfield 1988; Van Harreveld and Trubatch 1975).

Cell-adhesion junctions, sometimes referred to as *puncta adhaerentia* (Fig. 1.11, 2.13), are occasionally located at the edges of the PSDs of simple spines (Spacek and Harris 1998). These junctions contain a different set of structural and signaling molecules from those in the PSD (Fields and Ito 1997; Fannon and Colman 1996). Puncta may also modulate synaptic efficacy since their disassembly and reassembly may be needed for synaptic plasticity (Luthl et al 1994; Muller et al. 1996; Tang et al 1996).

Finally, synapses differ in the degree to which they are surrounded by glial processes. In cerebellar cortex, nearly all spine synapses are completely ensheathed by the Bergmann astroglial processes (Spacek 1985). In contrast, only 58% of hippocampal synapses have even partial astroglial ensheathment (Ventura and Harris 1998), which is comparable to cortical spine synapses (Spacek 1985). Thus many, but certainly not all synapses have astrocytic processes at their perimeter,

whereby neurotransmitter could be detected and spillover between neighboring synapses limited (Bergles et al. 1997; Diamond et al. 1998; Luscher et al. 1998). An important question is whether the degree of astrocytic ensheathment is regulated by activity, such that astrocytic processes grow to synapses where glutamate is escaping from the synaptic cleft (Cornell-Bell et al. 1990).

Concluding remarks

A hundred years after Ramón y Cajal, the intricacies of the relationship between structure and function in neurons are still being discovered. The pattern of dendritic arborization is clearly related to connectivity, but also appears to contribute to dendritic computation, particularly when the dendrite is endowed with active mechanisms (Shepherd 1998). Similarly, the synaptic specializations extended by dendrites contribute significantly to connectivity. They allow thin dendrites to reach multiple axons such that larger numbers of synapses interdigitate in a relatively small brain volume. However, they probably have additional functions related to neuronal computation and learning (Shepherd 1996). The enormous diversity in the structure, composition, and plasticity of dendrites and their synaptic specializations suggests that the functional contributions of these structures to mind and brain are enormously diverse.

Acknowledgements

Thanks to Marcia Feinberg and Karen Szumowski for assistance with figures. Thanks also to Betsy Velasquez for assistance with the bibliographic material. Contributions to some three-dimensional reconstructions were made by Josef Spacek and Rachel Ventura. This work was supported by NIH grants NS21184, NS33574, Human Brain Project (HBP) grant R01 MH/DA 57351 (KMH) and MR center grant P30-HD18655 (Dr. Joseph Volpe, PI). The HBP research is funded jointly by NIMH, NIDA, and NASA.

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