

Phylogeny and Evolution of Dendrites

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SUMMARY. Dendrites, the neuronal processes that receive synaptic inputs, are found in all nervous systems. The great diversity of dendrites, both within individual species and across phylogeny, reflects their adaptation to particular functional roles. In the present article we use this diversity to consider dendrites from an evolutionary perspective. We first describe some principles seen in the diversity of dendritic forms. We then seek to explain this diversity in terms of tradeoffs among functional optimization constraints; mechanistic limits set by the available molecular toolkit; and developmental mechanisms, the targets upon which selection has acted. Finally, based on these perspectives, we identify areas ripe for future investigation.

0. INTRODUCTION

Dendrites arising from various neurons share basic features at the level of molecules, cell biology, and biophysics. Yet they also show a remarkable diversity in form, molecular composition, integrative properties, and the ability to conduct action potentials. This diversity, which is found both among neuron types and in the same type of neuron across species, suggests the possibility that dendrites have adapted evolutionarily to fill a wide range of functional roles.

Although evolutionary changes in dendrites have not been observed directly, inferences about their history and relatedness can be made by comparative studies of living animals. Neurons in different species or brain regions may play similar roles. Evidence for such homology can be found by examining (a) structure or composition, (b) position in neural

circuitry, (c) developmental history, (d) information-processing capabilities, and (e) functional role. Because our ultimate goal is to understand function rather than evolution *per se*, we intend the last two senses of homology listed here to go beyond the strict evolutionary definition, which requires common descent, to include other types of similarity that may have arisen convergently.

Dendrite evolution must be considered in terms of the function of the entire system, the level at which selection directly occurs. Thus dendrites may change as a direct result of selection pressure to optimize a specific function subject to constraints at the cellular or network level, as a byproduct of optimizing another system, or simply as a result of genetic drift. We will review dendrite evolution in terms of observed variation in morphology, biophysics and molecular composition. We describe possible evolutionary constraints influencing dendrites including biophysical, energetic and metabolic constraints, and the functional needs of the organism. Finally, we discuss how this diversity may have arisen, considering not only genetic events, but also the role of developmental programs and homeostatic mechanisms on shaping the form and function of dendrites. Overall, this framework provides a means for understanding how and why dendrites vary.

1. COMPARATIVE ANATOMY: SCALING OF DENDRITIC ARBORS WITH BRAIN SIZE

Broadly, neurons can be categorized according to whether or not they increase in complexity in animals with larger brains or bodies. This fundamental observation was first framed by Santiago Ramón y Cajal in 1897: “From the appearance of the very first vertebrates, some individual neurons or groups of neurons have been modified more or less continuously before reaching their current state of refinement. In contrast, some neurons remain unchanged over long periods of time, seemingly impervious to all progress.” (Ramón y Cajal, 1995, p. 87)

After more than 100 years of comparative studies, Cajal's original factual observation of diversity remains intact. However, greater structural complexity is found in neurons from large brains in general, and not just "refined" ones. Thus dendritic size and structural complexity scale predominantly not with advancedness of the brain, but rather with absolute brain (and body) size (Purves, 1988). This implies that dendritic form may be shaped largely by global tradeoffs common to all animals of a class.

The nervous system is special in this regard. Most organs scale with body size by increasing the total number of some constant cell type. The relative invariance of cell size across species is typical of a wide variety of cell types, including liver cells, thyroid epithelial cells, renal epithelial cells, pancreatic acinar cells, and red blood cells (Purves, 1988). Invariance is perhaps unsurprising since many cellular functions would be expected to scale up directly with cell number; for instance, doubling the number of red blood cells would double the amount of oxygen carried. In contrast, the brain constitutes an interconnected network, and its information processing capabilities depend not only on the number of neural elements, but also the connections formed by it. The fact that most neurons and their dendrites become larger and more complex as overall brain or body size increases suggests that convergence (the number of synapses received by a neuron) and divergence (the number of neurons contacted by a neuron) contribute integrally to the overall information processing capability of the brain. Changes in convergence are reflected at least to some degree by the overall size of the dendrite. Understanding the principles governing which types of dendrites do not scale with brain size, and which dendrites do scale, may aid in understanding their different roles in information processing.

Insert near here: Figure 1. Comparison of vertebrate dendrites across phylogeny.

A. Cerebellar granule cells. Thornback ray from (Nicholson et al., 1969); dogfish from (Schaper, 1898); zebra finch, rat and cat from our own laboratory. B. Cerebellar Purkinje neurons (Nieuwenhuys, 1967). Neurons in A and B are scaled to fit page. C. Sympathetic neurons (Purves, 1988) D. Neocortical pyramidal neurons (Barasa, 1960). Neurons in C and D are scaled to reflect their true size relative to one another. Where appropriate, axons are indicated with asterisks (*).

Neurons that stay the same. Some types of neurons vary relatively little in size or structural complexity among vertebrates. In these cases the dominant optimization principle may occur at a single-cell level, such as a requirement for a fixed number of synaptic inputs or for temporal precision.

A prominent example of neuronal constancy is the cerebellar granule cell. Granule cells are a canonical element of the cerebellum, a major division of nearly all vertebrate brains (Eccles, 1969; Llinás, 1969; Nieuwenhuys et al., 1998). Cerebellar granule cells have a small cell diameter and extrude four or five short, clawed dendrites, which receive input from mossy fibers (Palay and Chan-Palay, 1974). This overall structure is found universally in all cerebella, including that of one of the most primitive vertebrates, the dogfish (Alvarez and Anadon, 1987). The most salient change in cerebellar granule cell evolution is the appearance of a T-junction in the granule cell axon to form two axonal branches per parallel fiber. The constancy of dendritic structure suggests that the number of mossy fiber inputs per granule cell is central to its role in information processing. This constancy of granule cell structure contrasts with the fact that their main postsynaptic targets, Purkinje cell dendrites, vary considerably across phylogeny. This

scaling of Purkinje cell dendrites may be developmentally driven by the amount of trophic support provided by increasing numbers of granule cells in larger brains, a topic to which we will return.

Receptor cells are also unchanging across species. For instance, in the retina, rod outer segments from diurnal mammals are of fairly uniform length and diameter (Sterling, 2003), and these dimensions are similar even in other warm-blooded animals such as nocturnal mammals (Sterling, 2003) and birds (Braekevelt, 1998; Rojas et al., 2004). Rods in these animals are uniformly narrow, 1 to 2 μm in diameter, ensuring a rapid response time and concomitant with the fact that mammals and birds move fast. Temporal performance requirements may thus impose a general cell-level constraint across species (Sterling, 2003). In contrast, cold-blooded vertebrates, which move more slowly, have considerably larger rods (for instance, 5-fold wider in sluggish amphibians) with correspondingly slower response times (Sterling, 1997). Thus optimization of rod structure appears to respond to organismal selection expressed directly on single-cell functional properties, without regard to network size.

Neurons that change as brains get larger. In contrast to granule cells, most other neuronal types vary in their dendritic complexity across species. In these cases the general form of the dendrite remains recognizable across species, although the addition and loss of dendritic elements can occur (Dryer and Graziadei, 1994). Typically, cell body diameter and dendritic arbor size both increase as a function of body size (and therefore of brain size) (Bok, 1959; Purves and Lichtman, 1985; Snider, 1987; Kötter and Feizelmeier, 1998). Scaling of dendritic size occurs throughout the peripheral and central nervous system. Examples include sympathetic ganglion cells (Ebbesson, 1968a, 1968b; Purves and Lichtman, 1985), olfactory mitral cells

(Dryer and Graziadei, 1994), thalamocortical neurons (Ohara and Havton, 1994), cerebellar Purkinje neurons (Smolyaninov, 1971; Harvey and Napper, 1991), substantia nigra neurons (Yelnik et al., 1987; Tepper et al., 1994; Kötter and Feizelmeier, 1998), hippocampal mossy cells (Buckmaster and Amaral, 2001), and pyramidal neurons of the hippocampus (Bekkers and Stevens, 1990; Buckmaster and Amaral, 2001), entorhinal cortex (Buckmaster et al., 2004), and neocortex (Barasa, 1960; Ramón y Cajal, 1995).

Although dendrites are often larger and more branching in large animals, their general forms are preserved across species. In somatosensory thalamocortical projection neurons Ohara and Havton (Ohara and Havton, 1994) found in rat, cat, and macaque that total dendritic length per neuron varied, but branching parameters such as degree of bifurcation and terminal branch order were conserved. Similar conservation of dendritic branching form has been found among several neuron types of the substantia nigra in rat, macaque and human (Yelnik et al., 1987; Tepper et al., 1994; Kötter and Feizelmeier, 1998) and in frog, rat and cat motoneurons (Dityatev et al., 2001). This conservation of branch patterning suggests that dendrites grow according to shared developmental mechanisms.

A case study: sympathetic neurons. A particularly well-studied case of dendritic diversity is that of autonomic ganglion cells. These neurons are unusual in that they have only one axonal input per dendrite. Scaling principles in these neurons have been investigated extensively (Ebbesson, 1968a, 1968b; Forehand, 1985; Purves and Lichtman, 1985; Purves et al., 1986; Snider, 1987; Ivanov and Purves, 1989).

Purves and colleagues made a number of correlative measurements in five mammals ranging in body size (and target size, in this case the eyeball) from mouse to rabbit. They found

that the number of sympathetic neurons increased with body size, but did not maintain proportionality. However, they also found that sympathetic neurons from larger-sized animals have more dendrites (Purves and Lichtman, 1985) and larger cell bodies (Snider, 1987). Increases in dendrite number are matched one-to-one by increases in the number of innervating axons: a neuron with no dendrites or one dendrite typically has one input, one with two dendrites two inputs, and so on (Lichtman and Purves, 1980; Lichtman et al., 1980; Purves and Hume, 1981; Hume and Purves, 1983; Forehand, 1985; Purves and Lichtman, 1985).

They suggested that in the sympathetic periphery, the number of dendrites, by modulating competition among the axons innervating the same neuron, determines the number of inputs. Thus cell number and dendritic complexity may both provide ways to match target size with the total amount of central drive (Purves, 1988). The fact that scaling occurs at these different stages of processing suggests that adaptations that match a neural system to target size can be distributed over multiple steps of the neural pathway.

2. COMPARATIVE ANATOMY: SCALING AND BIOPHYSICS OF DENDRITE DIAMETER

Dendrites vary not only in form but also in diameter along their length. Variations in dendritic diameter are important determinants of both electrical signaling properties and transport properties (Hillman, 1979). These functions may therefore play a critical role in optimizing the shape of dendrites.

As dendrites become larger and more branched, voltage signals traverse a longer distance before reaching the cell body and therefore may be affected more by the filtering properties of the dendritic membrane. These properties are determined by the diameter of the dendrite. In

wider dendrites, passive signals are attenuated less, and both passive spread and active propagation are faster (Rall, 1977). Because of this relationship between diameter and signaling properties, the form of a dendrite might be shaped in part by its signal integration requirements (Purves and Lichtman, 1985; Bekkers and Stevens, 1990; Olsen et al., 1996).

Indeed, dendrites do show great variability in diameter scaling. At one extreme is no scaling, in which dendrites are of similar diameter regardless of length. This trend would be sufficient to support signaling in short dendrites, where passive losses are minimal; or in active dendrites, assuming negligible conduction delays. At the other extreme are dendrites whose thickness increases as the square of total dendrite length. This scaling would tend to conserve the amount of passive attenuation along the length of the dendrite. These forms of dendritic scaling, as well as intermediate cases, have been observed across species and are discussed below. The type of scaling that occurs plays a key role in the properties of signal integration by the dendrite as a whole.

Non-scaling dendrites. Non-scaling (constant diameter across species) dendrites have been observed in neurons of the pars reticulata and pars lateralis of the substantia nigra (Yelnik et al., 1987); reviewed by (Kötter and Feizelmeier, 1998). In these neurons, soma diameter and dendritic length are larger in humans than in macaques, but dendrite thickness is about the same. Such a lack of scaling suggests that in these neurons, input location does not influence integration by postsynaptic summation mechanisms (Bekkers and Stevens, 1990). This would occur if, for instance, information processing in these neurons were dominated by regenerative events in dendrites or the cell body.

Constant-diameter dendrites would also be expected in neurons that receive input from only one axon per dendrite, such as cerebellar granule cells. In these neurons, summation occurs at the cell body, and a single input may be sufficient to cause the cell to fire. In this situation small dendrites might be favored as a means of reducing capacitance and therefore the energy cost of changes in membrane voltage. This comparative measurement has not been done (though note the apparent similarity of traced dendritic thickness across species in another cell type with one input per dendrite, superior cervical ganglion cells (Purves and Lichtman, 1985)).

Another case in which dendritic diameter is approximately constant is hippocampal dentate gyrus granule cells (Bekkers and Stevens, 1990). In a comparison of human and cat, principal dendritic shafts measured at the midpoint of the arbor were of similar diameter. More detailed measurements in macaque and rat show that dentate gyrus granule cells (St. John et al., 1997) have similar total dendritic length, somatic area, and passive electrical properties, but somewhat different action potential widths. A modest increase in the vertical extent of dendrites occurs in larger animals (St. John et al., 1997).

Isoelectrotonic scaling. At the other extreme of scaling, Bekkers and Stevens reported that dendrites might vary in an electrotonically conservative fashion across species (cat vs. human) in the apical dendritic shafts of CA1 pyramidal neurons. These main shafts were substantially thicker in human than in cat. They proposed that dendritic diameter scaled up as the square of dendrite length in order to preserve the electrotonic distance from the cell body to the ends of the dendrites. This would be consistent with a more passive summation process in apical dendrites. Thickening of dendrites also argues against active processes, since active

amplification in a thicker process would add to the energy cost without contributing to signal integration properties.

The measurements of Bekkers and Stevens were made at a single site halfway up the apical dendrite. However, the scaling of apical dendrites would not necessarily be true of basal dendrites, which in rat can generate local regenerative voltage events (Polsky et al., 2004). Even within the apical dendrite, regenerative spike-like events can be induced in distal dendrites (Golding et al., 2002) and plateau potentials can be induced in both distal and oblique dendrites (Cai et al., 2004). Dendritic action potentials may serve multiple functions, including the propagation of signals to guide associative plasticity (Hebb, 1949; Brown et al., 1988; Raymond et al., 1996; Malenka and Nicoll, 1999), reset excitability (Hausser et al., 2001), and even drive secretory events (Lledo et al., 1998). These possibilities suggest the need for measurements of dendritic diameter at multiple sites, and correlation with physiological observations.

Scaling of dendrite diameter with length has also been studied over the lifetime of an individual as it grows (Huxley, 1932). Isoelectrotonic growth has been observed in the medial giant interneuron of the cricket, in which passive membrane integrative properties are preserved even as the organism increases sevenfold in length and the dendrite increases 2.6-fold in length (Hill et al., 1994). Isoelectrotonic scaling is also observed in some retinal ganglion cells in the rainbow trout (Picones et al., 2003). In both of these examples, the relative efficacies of synapses on different locations of the arbor are preserved independent of the size or pattern of their dendritic arbor.

Intermediate scaling. Intermediate cases of scaling of dendritic diameter have also been observed. In type I neurons of the substantia nigra pars compacta, the maximal dendrite length is

progressively larger from rat to macaque to human (Yelnik et al., 1987; Tepper et al., 1994; Kötter and Feizelmeier, 1998). However, diameters scale up only linearly (isometrically) with dendrite length, insufficient to preserve electrotonic properties (Kötter and Feizelmeier, 1998). In these cases conservation of electrotonic function would require additional scaling of channel density and the balance and distribution of channels (Kötter and Feizelmeier, 1998). Isometric scaling of dendrites has also been observed during growth of the lateral giant interneuron of crayfish (Edwards et al., 1994; Hill et al., 1994) and in some retinal ganglion cells in the rainbow trout (Picones et al., 2003). Isometric scaling may represent a case in which the exact integrative properties of dendrites are not critical to the neuron's function.

Other biophysical constraints. Preservation of electrotonic properties is not the only possible explanation for the scaling of dendritic diameters. Dendrites are also conduits for the transport of materials along their length. As a result they may be under pressure to move material efficiently. Evidence for this comes from the observation that when a dendrite branches, the daughter branches are smaller in diameter than the parent branch (Lux et al., 1970; Barrett and Crill, 1974a, 1974b; Hillman, 1979). Daughter branches d_1 , d_2 and the parent diameter D approximately observe the relationship $d_1^N + d_2^N = D^N$, where N ranges from 1.5 to 2. An exponent of $N=2$ indicates preservation of cross-sectional area before and after a branch point, a condition that would preserve per-area rates of transport; this has been seen in pyramidal and Purkinje cells (Hillman, 1979). An exponent of $N=1.5$ is consistent with preservation of charge and has been approximately observed in motoneurons (Lux et al., 1970; Barrett and Crill, 1974a, 1974b; Hillman, 1979). In any case, this range of exponents corresponds to a fairly narrow range of branching ratios; for symmetric bifurcations, exponents between 1.5 and 2 correspond to a daughter branch being 0.63-0.71 times as wide as its parent.

This branching may contribute to observations of diameter scaling. If in CA1 pyramidal neurons the branching depth (number of branch points between soma and dendritic tips) depends on the arbor diameter and the terminal tip diameter is constant, then the diameter at the midpoint of the arbor would have to be larger in human pyramidal neurons, which are more elaborate and have more branches than their counterparts in smaller-brained mammals.

Thus, dendritic diameter scales in two ways: (a) across species, at a defined location, diameter is either constant or scales up as a function of arbor size, and (b) within an individual arbor, with successive branching, diameter decreases. Taken together, these phenomena suggest that scaling of dendrite diameter is related to dendrite-specific mechanisms for establishing a branched architecture. If the size of the smallest dendritic structures is conserved, variations in diameter may regulate the total size of the arbor and thus the degree of synaptic convergence (Purves, 1988; Chklovskii, 2000). Dendrite diameter also affects cable and electrical signaling properties (Purves, 1988; Bekkers and Stevens, 1990) and may be optimized for efficient transport of materials (West et al., 1997; Banavar et al., 1999). The fact that a dendrite must carry out all of these functions suggests that scaling of dendritic diameter may result from the competing influence of these needs.

A constant underlying unit: the single synapse? Even when dendrites vary, their components might still remain constant if function is optimized locally. Examples of local function include chemical signals such as synaptic transmission and second messenger signaling, and cell biological phenomena such as vesicle trafficking and secretion. One neuronal structure at which all of these functions occur is the synapse. In the mammalian neocortex, the total density of synapses per unit volume is remarkably constant both among functional areas and

species (Schüz and Demianenko, 1995; reviewed in Harrison et al., 2002). Thus, on average, the amount of volume available to a bouton-plus-spine may be relatively constant across species. This raises the possibility of *synaptic constancy*: single presynaptic and postsynaptic terminals of a given type may be similar in size across species, and be optimized in a way that is independent of overall brain size. This question has not been fully investigated.

3. COMPARATIVE PHYSIOLOGY: EXPRESSION PATTERNS OF DENDRITIC MOLECULES

In addition to physical form, another feature distinguishing dendrites of different neuronal types is the expression pattern of various molecules important for dendrite function. In vertebrates, reception and processing of signals on dendrites begins primarily at chemical synapses. The subsequent processing of inputs is determined by both the composition and the spatial distribution of passive and active ion channels in the arbor and the complement of neurotransmitters, neuromodulators, postsynaptic receptors, and signal transduction machinery. The manner in which neuronal inputs are processed can change over time through synaptic plasticity, which depends on many signaling molecules, including the NMDA receptor, metabotropic glutamate receptors, IP₃ and ryanodine receptors, calcium buffer proteins, and downstream kinases and phosphatases.

These molecular building blocks are found across the vertebrates, and some in a wider variety of organisms. However, even among neurons their expression can vary considerably. For example, excitatory pyramidal neurons of neocortical areas and the hippocampus have apical dendrites in which action potentials can backpropagate at least part way, which when paired with presynaptic activation can induce synaptic plasticity (Magee and Johnston, 1997; Markram et al., 1997). The large tree-like Purkinje cell dendrites, on the other hand, do not support action

potential backpropagation at all, but instead generate calcium channel-based action potentials (Llinás and Sugimori, 1980). However, like pyramidal neuron action potentials, these calcium-based action potentials can also drive synaptic plasticity (Raymond et al., 1996). Neurons also differ greatly in their firing properties. These properties are set in part by patterns of channel expression on the soma and dendritic arbor. Additional differences exist at the level of cell biology, neurochemistry, receptor type, and plasticity transduction machinery. This great diversity suggests that different cell types have evolved either to perform different computations or under different sets of constraints. Contrasts of dendrites among neuron classes are discussed in detail elsewhere in this text (see chapters 1, 7, 8, and 9).

Unfortunately, these differences are all studied principally within single species, usually rats; comparative molecular and physiological information from multiple species is scarce. Although it is true that in recent years a large body of comparative DNA and protein sequence information has accumulated, functional comparative information, for instance about channel kinetics and distribution, firing properties, or signaling properties, has not been gathered. This is a major area of ignorance in the study of the evolution of dendrites, and of neurons in general.

A handful of studies illustrate the potential of comparative studies to yield insights into neuronal function. In the cerebellum, Llinás and co-workers have found that the climbing fiber input triggers a characteristic, dendritically-generated complex spike that takes on a similar multiphasic waveform in the Purkinje neurons of mammals, alligator, frog, and an elasmobranch fish (Llinás, 1969). These spikes have been suggested to provide an instructive signal to guide plasticity (Raymond et al., 1996); whatever their function, their role is likely to be as old as the vertebrates. In an example of dissimilarity across species, resting firing rates of sympathetic

neurons increase with body size (Ivanov and Purves, 1989); both subthreshold and suprathreshold activity rates are higher in larger mammals. This variation may be driven by progressively larger amounts of converging synaptic drive, in line with anatomical findings (see Section 2), and provide an example in which firing rates are not conserved across phylogeny. Finally, at the level of channels, gating parameters may be adapted across species. In a variety of mollusks, sodium channel gating parameters are correlated with locomotory speed (Gilly et al., 1997); animals with faster rates of movement have faster neuronal sodium channel gating.

4. NETWORK-LEVEL CONSTRAINTS INFLUENCING DENDRITIC FORM

While several clear trends are seen in how dendrites scale with brain or body size, clear statements as to *why* any trend is seen at the dendritic level are difficult to make with any certainty. The fitness of a neural phenotype is likely to reflect a combination of information processing needs in single dendrites, network-level functional requirements and global energetic constraints. Along these lines a number of functional principles have been suggested.

Metabolic/energetic cost and wire length minimization. Neural tissue is energetically costly to operate; this creates pressure to minimize metabolic energy costs from neuronal activity (Attwell and Laughlin, 2001). As a result, developmental mechanisms would be expected to drive dendrites to take forms that minimize volume and/or length (Cherniak, 1994; Van Essen, 1997; Chklovskii and Stevens, 2000; Zhang and Sejnowski, 2000; Changizi, 2001). For instance, in layered structures a particular width of dendritic arbor can minimize and equalize the total volumes of axons and dendrites; the arbor width may therefore be closely related to synaptic convergence and divergence ratios (Chklovskii, 2000), and the branching patterns of arbors may have the smallest possible length to achieve a given interconnectivity (Chklovskii, 2004).

Input convergence and network architecture. Central neurons may also be constrained by the need to communicate with one another within the brain. This may drive the need for dendritic arbors to receive input from more neurons. This is subject to constraints of the connectivity that is possible within a large network. For instance, connecting to a constant fraction of the neurons within a neural structure cannot be scaled up because the total number of synaptic elements would then need to scale up as the square of the number of neurons. This would lead to runaway increases in volume (Ringo, 1991; Changizi, 2001). However, a functional network architecture may not require the number of synapses per dendritic arbor to scale proportionally with brain size. Instead, in a recurrently connected network a parameter of great functional interest is the typical number of degrees of separation between any two nodes. Maintaining this network diameter at a given value N requires only the number of connections per node (*i.e.* synapses per neuron) to scale proportionally to the N th root of the number of neurons in the network (Changizi, 2001).

In particular, principal neurons, which are sites of great synaptic convergence and divergence, may need to scale up with network size. For example, in larger brains, neocortical pyramidal neuron dendritic arbors increase in size (Bok, 1959; Barasa, 1960; Purves, 1988; Ramón y Cajal, 1995) and in the number of synapses per neuron (O'Kusky and Colonnier, 1982; Elston et al., 2001; reviewed in DeFelipe et al., 2002; Harrison et al., 2002). From monkey to human, the increase in number of synapses per neuron has been suggested to support cognitive complexity (Elston et al., 2001). However, this increase may well be simply a general scaling consequence of the large absolute size of human brains. It will be of interest to ascertain whether the neocortex maintains a constant network diameter across a wide range of mammals.

In nonrecurrent networks such as the cerebellar cortex, which has a multilayered architecture (Marr, 1969; Albus, 1971), the optimal design of a network may require some of its elements to scale up with overall network size. As described earlier, cerebellar granule cells do not scale with cerebellum size. However, Purkinje cell arbors, which predominantly receive parallel fiber synapses from granule cells, may become larger with brain size both among taxa (Nieuwenhuys, 1967; Eccles, 1969; Smolyaninov, 1971). In a comparison of rat and cat (Harvey and Napper, 1991) the number of spines per Purkinje cell increased from 150,000-175,000 in rat to 300,000-360,000 in cat. This and some structural data from other species (Smolyaninov, 1971; Harvey and Napper, 1991) indicate that processing in large cerebella is made most efficient by scaling up the amount of parallel fiber convergence on each Purkinje cell. This reason for this is not known.

Network degeneracy. Neural computations are performed at the network level. As a result, neurons are adapted to the wider context of the network in which they reside. For example, in the central pattern generator controlling aerial respiration in the slug *Lymnaea stagnalis* (McComb et al., 2003), the respiration frequency is higher in adults than in juveniles. However, the neuron initiating rhythmogenesis, RPeD1, scales isometrically over the animal's lifetime, showing a decrease in membrane resistance and an increase in membrane time constant. This modification alone would correspond with decreased excitability in the adult; instead a compensatory increase in synaptic connectivity works to increase rhythmic activity of the pattern generator. More complex tradeoffs can occur as well at a whole-network level. For example, in the lobster stomatogastric system, very different combinations of neuronal parameters can lead to nearly indistinguishable output patterns (Bucher et al., 2005). Thus, even in a simple network the

large number of degrees of freedom in the system can adapt in many ways to produce a limited range of output patterns.

Brain architecture and species-specific adaptations. The finding that dendritic form scales largely as a function of brain and body size suggests that the differing capabilities of brains in different species would be more likely to be generated not by varying dendritic and other aspects of neuronal form, but rather by varying the size of a brain or brain region (Kaas, 2000). If this is the case then individual neuronal design may be imposed by a neural architecture's overall layout and absolute size, and added functionality may come about in large part from adding more neurons or modules of neurons. Prominent examples of enhanced function associated with larger region size include the correspondence between cognitive complexity and telencephalic size in mammals (Dunbar, 1992; Clark et al., 2001) and birds (Lefebvre et al., 2002; Burish et al., 2004); electrolocation/echolocation and cerebellar volume in mormyrid fishes, bats, and whales (Meek, 1992; Clark et al., 2001); and song repertoire and volume of song system nuclei in passeriform birds (DeVoogd et al., 1993).

In some cases, however, variation in dendritic form may be species-specific. Such specializations might be evident as a departure from the expected scaling relationship. These departures are of particular interest from evolutionary or ethological perspectives. Perhaps as a result, the best evidence for exceptional dendrites has been found in animals with unusual behavioral specializations.

One such type of specialization encompasses acoustic localization, echolocation and electroreception. In all of these functions localization of acoustic and electrical stimuli requires calculation of phase differences among signals from multiple sources. Structural adaptations in

dendrites may aid in this process biophysically by making the timing of membrane electrical signals particularly precise or fast. In barn owls, which use interaural time and phase differences to locate prey by their sounds, nucleus magnocellularis neurons are more numerous than in other birds (Carr and Boudreau, 1993). In addition, magnocellularis and laminaris neurons that are sensitive to higher frequencies have few and short dendrites and thick axons. These differences have been suggested to have the effect of reducing capacitance and increasing the speed of responses. This could be useful in detecting fine differences in the timing of acoustic signals. As another example, mormyrid fish are capable of electroreception. In their exceptionally large “gigantocerebella” the palisade patterns of Purkinje cell dendrites may be adapted in some way for signal processing via parallel fiber pathways (Meek and Nieuwenhuys, 1991). Echolocation, an ability found in cetaceans and insectivorous bats, is accompanied by exceptionally large cerebella (Clark et al., 2001); dendrites of cerebellar neurons in these species have not been examined systematically.

Another place in which unusual dendritic specializations may occur is the neocortex of great apes, which show unusual social and cognitive complexity. These animals have several types of giant neocortical neurons, including Betz cells (Sherwood et al., 2003), Meynert cells (Sherwood et al., 2003), and spindle cells (Nimchinsky et al., 1999). These giant cells may have arisen in great apes as extreme adaptations of pyramidal neurons. Among primates their somata show distinct scaling relationships relative to brain and body size. Like other neocortical pyramidal neurons (Elston et al., 2001), they may vary in dendritic extent and synapse number across species as well. At present, however, little is known about their dendrites.

5. GENETIC AND DEVELOPMENTAL CONSTRAINTS INFLUENCING DENDRITIC FORM

Although in animal evolution the unit of natural selection is the individual organism, the target upon which selection acts is development. Thus, to better understand the origins of diversity in dendritic structure and to get a feel for what types of changes might occur, we need to consider how changes at the level of DNA can lead to changes in the molecular mechanisms that shape dendrite structure. The evolution of single proteins is a well-known concept. Here we will emphasize a few additional points to guide thinking about how morphological changes can arise.

Gene regulatory networks are organized, at least in part, in a hierarchical manner. Genes at the top of such hierarchies may act as “master control genes” for large-scale developmental programs (Keynes and Krumlauf, 1994; Halder et al., 1995). For example, the cerebellum and several cerebellar-like structures, including the medial octavolateral nucleus, dorsal octavolateral nucleus, electrosensory lobe, and dorsal cochlear nucleus show striking similarities at both the cellular and network level and originate from one region of the alar plate (Devor, 2000; Bell, 2002), suggesting that these structures arise from a shared developmental program (Bell, 2002). Indeed, small, ectopic cerebellum-like structures can be induced in the forebrain or midbrain simply by placing beads coated with fibroblast growth factor 8 into developing embryos (Martinez et al., 1999). Hierarchical regulation may also regulate modular structures: new neocortical areas have been suggested to arise from the duplication of an existing area by changing a discrete developmental step (Krubitzer, 1995; Kaas, 2000). Thus, mutations of important developmental genes represent one means of achieving large-scale modifications in brain structure.

Another means of effecting changes in macroscopic and cellular form is mutation that regulates growth rates during development. These mutations could affect multiple cell types, but not necessarily so; for example, mutations in *cis*-regulatory DNA elements can have fairly specific effects and have been suggested to be a major source of organ-level morphological evolution (Stern, 2000). Application of these concepts at the level of dendritic structure suggests that depending on the specificity of effect, mutations might be able to affect the scaling of one neuron type or many neuron types at once.

In the case of dendritic form and size, the targets of selection would be mechanisms regulating the growth and maturation of arbors. These mechanisms are studied in several key model systems, including cultured mammalian cells (Craig and Banker, 1994; McAllister, 2000; Scott and Luo, 2001; Whitford et al., 2002) and *in vivo* studies of identified neurons from the fruitfly *Drosophila melanogaster* (Gao et al., 1999; Gao and Bogert, 2003; Grueber and Jan, 2004). Thorough reviews of the literature can be found both in this text (see Chapter 3) and elsewhere (Scott and Luo, 2001; Cline, 2003).

Dendrite development can be broken down into four stages: initial dendrite outgrowth, branching, stopping, and pruning and refinement. Here we offer a brief overview of intrinsic and extrinsic mechanisms regulating dendrite shape and size. This overview provides a means for thinking about how developmental mechanisms, shaped by natural selection, might influence dendritic form.

Dendrite outgrowth and branching. The first stage of dendrite growth is the polarization of neurons to generate distinct axonal and dendritic processes. Neurons develop axon-somato-dendritic polarity even in cell culture (for review see (Craig and Banker, 1994).

Even at this early developmental stage, initial process outgrowth can be greatly influenced by extrinsic factors such as growth factors and extracellular matrix proteins (Chamak and Prochiantz, 1989; Lein and Higgins, 1989; Lein et al., 1992; Osterhout et al., 1992). As development proceeds, dendrites begin to branch. Diversity of branching structures has been generated by modeling different growth rules (van Pelt et al., 1997; Cannon et al., 1999), suggesting these rules as a target for selection. Branching patterns can be described in terms of branching probability as a function of distance from the soma, a parameter that can capture differences between complex pyramidal cells and cells of simpler dendritic structure such as various classes of motoneurons and dentate granule cells (van Pelt et al., 1997). Two different types of branching events have been observed: splitting of growth cones to generate two new branches, and interstitial branching, the emergence of a new branch from an established dendritic shaft (Bray, 1973; Dailey and Smith, 1996; Scott and Luo, 2001). The first step in interstitial branch formation is the extension of a filopodium from a shaft, which can extend, retract, or become a spine or new branch (Dailey and Smith, 1996). In this way a combination of growth and retraction results in an elaborated arbor of branches and spines.

Dendritic growth and branching is affected by both intrinsic and extrinsic factors. Branching is influenced intrinsically by cytoskeletal-associated proteins, small GTPases, transmembrane proteins, and transcription factors (Threadgill et al., 1997; Ruchhoeft et al., 1999; Lee et al., 2000; Li et al., 2000; Hakeda-Suzuki et al., 2002; Luo, 2002; Whitford et al., 2002; Gao and Bogert, 2003; Emoto et al., 2004; Rosso et al., 2005) Extrinsic factors include a wide range of neurotrophins, which affect both cell survival and dendritic growth in a neurotrophin and cell type-specific manner (Snider, 1988; McAllister et al., 1995; McAllister et al., 1997). The growth of dendrites proceeds through several stages marked by the appearance of morphological

features, and different factors are involved in the regulation of each stage of growth (Scott and Luo, 2001).

However, normal branching patterns cannot be entirely replicated in culture. For instance, although Purkinje neurons cocultured with granule cells or densely plated Purkinje cells or neurotrophins (BDNF or NT-4) develop distinctive Purkinje-like arbors (Baptista et al., 1994; Morrison and Mason, 1998), they do not have the same planar arrangement and appear to branch less frequently. Likewise, cultured pyramidal neurons (Dotti et al., 1988; Collin et al., 1997) fail to form distinct apical and basal dendrites. This suggests that cultures lack other signaling factors or some other aspect of the normal three-dimensional matrix in which neurons grow.

In addition to branching patterns, another key aspect of a neuron's function is the orientation of its dendrites relative to other neural elements. As in the case of axon guidance, this orientation is established at least in part by chemical cues. One well-studied example is the effect of the diffusible ligand semaphorin 3A. Neocortical pyramidal neurons dendrites grow toward and axons grow away from the cortical plate where Sem3A is expressed (Giger et al., 1996; Polleux et al., 1998; Scott and Luo, 2001); a similar effect of Sem3A is seen in slice cultures (Polleux et al., 1998; Polleux et al., 2000). In larger-brained animals, the fact that this gradient should extend over a larger region in space may indirectly result in larger dendrites, as opposed to a direct evolution of a larger dendrite to fulfill some functional objective.

Stopping. Establishment of a dendritic arbor must include a mechanism for stopping growth. One well-studied example is the effect of contact inhibition on halting the growth of neurons of the same type (homotypic). A well-known example of tiling is observed in the retina, where the dendrites of some ganglion cell types appear to tile the retina with minimal overlap of

neighboring dendritic fields (Wässle et al., 1975). Tiling mechanisms are beginning to be investigated in *Drosophila* (Gao et al., 2000; Grueber et al., 2002; Grueber et al., 2003; Emoto et al., 2004) and in *C. elegans* (Gallegos and Bargmann, 2004). In *Drosophila*, the dendrites of larval medial dorsal (MD) neurons grow until their arbors contact one another around the dorsal midline (Gao et al., 2000). Ablation of one MD neuron results in overgrowth of the contralateral surviving neuron. In addition, the dendritic arborization (DA) neurons of the epidermis also exhibit tiling and can be classified into four neuronal subtypes based on their dendritic branching morphologies and tiling rules. Type I and II neurons show homotypic repulsion. Neurons in the third class repel one another only at terminal branches. Neurons of the fourth class show persistent repulsion of all branches (Grueber et al., 2002; Grueber et al., 2003). Stopping mechanisms may provide a means of determining dendritic arbor size by allowing more widely spaced neurons to generate dendrites whose size increases with the distance between neurons. Again, in larger-brained animals, the distance to homologous neurons would be expected to be greater, which should result in dendrites which are larger when their growth is terminated.

Pruning and refinement. Another well-studied type of extrinsic regulation of dendritic form is neural activity (reviewed extensively in Chapter 3). Activity has been shown to influence structural changes including spine addition and retraction (Engert and Bonhoeffer, 1999; Trachtenberg et al., 2002; Holtmaat et al., 2005) as well as larger scale effects on branch addition and elimination (McAllister et al., 1997; Maletic-Savatic et al., 1999). In several brain regions it has been observed that synaptic density decreases with age (Purves and Lichtman, 1980; Rakic et al., 1986; Bourgeois and Rakic, 1993; Rakic et al., 1994), suggesting that overgrowth occurs during the initial development of dendrites in these brain regions. In many cases, the subsequent pruning of synapses over the course of maturation appears to be activity-dependent (Bock and

Braun, 1999; Kakizawa et al., 2000). The effects of neural activity on structure at the synaptic and on dendritic level seems to be exerted by factors such as neurotrophins and/or other molecules involved in synaptic plasticity, such as NMDA receptors (Katz and Shatz, 1996; McAllister et al., 1996, 1997; Bock and Braun, 1999).

These developmental mechanisms provide numerous possibilities for the regulation of dendritic form. The dramatic influence of extrinsic factors on dendrite development suggests that these factors may participate in driving the scaling of dendrites with brain and body size. These factors could act independently or in conjunction with neural activity to regulate growth. The role of extrinsic factors also suggests that in larger-brained animals, gradients of diffusible ligands may extend over larger spatial scales; for example, chemoattractive gradients should extend over larger spatial scales in larger brains and perhaps make dendrites grow longer. Intercellular inhibitory mechanisms will also scale if like neurons are spaced farther apart in larger brains. Finally, dendrite development could proceed in a programmed fashion, so that larger dendrites could be generated simply by allowing growth to proceed for a longer period of time.

6. EPILOGUE AND FUTURE DIRECTIONS

In reviewing dendritic variation across species we have identified three major themes. The first theme is that many neurons and dendrites scale up in size and complexity as a function of overall brain or body size. This scaling is not homogeneous: some cell types show strong scaling and others are nearly constant in form. The second theme is the presence of constraints at the level of cellular and network function that have guided dendritic form. The third theme is the fact that this dendritic diversity has been generated by natural selection acting upon

developmental mechanisms. Our review suggests that the study of dendritic optimization and evolution could be advanced by directed work in a number of areas.

1. Comparative investigations of scaling. The bulk of work on comparative dendritic form has focused on branching patterns. Advances during the last twenty years in the study of synaptic physiology and dendritic function establish a framework within which to examine interspecies variability. Parameters that need to be characterized on a comparative basis are morphological, such as dendrite diameter and spine number; biochemical, such as the abundance and kinetics of signaling molecules; and physiological, such as neuronal firing rates and dendritic integrative properties. These investigations would be directed at the questions of how parameters vary systematically across phylogeny, and what neuronal functional principles are invariant. It would be most advantageous to focus on standard cell types that are already well studied in rodents at all these levels. A prominent candidate would be the pyramidal neuron in either hippocampus or neocortex. Other good choices would include Purkinje neurons and cerebellar granule cells, which are found in nearly all vertebrates and furthermore offer a contrast in scaling properties with one another.

2. Linkages to animal behavior. A significantly under-investigated area is the linkage of behavioral specializations with variation at a cellular level. In brain regions and cell types with known involvement in specific behaviors, it should be possible to systematically connect variations in the number of neurons and their anatomical and physiological features with variations in function. One particularly promising target of study is the song system in passeriform birds, in which at a gross level, the diversity of song repertoire has been

demonstrated to be correlated with the size of associated nuclei such as HVC and RA (DeVoogd et al., 1993).

3. Developmental mechanisms. How these variations arose during evolution must ultimately be understood in terms of developmental mechanisms and how they have been selected to generate the diversity of observed forms. The study of dendrite development is an exciting area of research, but at present it is focused on specific model organisms such as *Drosophila* or mouse. Future expansion to consider the variation of developmental mechanisms across species would be greatly illuminating. Of particular interest are the mechanisms that guide the formation of branching patterns such as extension, pruning and stopping.

4. Data sharing through online databases. The acquisition of a solid body of data for comparative studies requires measurements of dendritic morphology, protein expression and physiology across a wide range of species and many different neuronal subtypes. This task is larger than the mission of any one neurobiology laboratory. As more data become available, the need will increase for central repositories for data sharing across laboratories. Not only will this create a larger more cohesive set of data, it will also enable subsequent studies by any scientist on parameters not measured in the original work. Several morphology databases currently exist, sponsored by laboratories at Yale (<http://senselab.med.yale.edu/senselab/NeuronDB>), the Krasnow Institute for Advanced Study at George Mason University (<http://www.krasnow.gmu.edu/L-Neuron/database>), and Duke/Southampton (<http://www.cns.soton.ac.uk/~jchad/cellArchive/cellArchive.html>). One database goes beyond morphology to include protein expression: the Cell Centered Database, sponsored by the National Center for Microscopy and Imaging Research at the University of California San Diego

(<https://ccdb.ucsd.edu/CCDB/index.shtml>). A still more useful step in any of these databases would be the systematic inclusion of physiological or other functional data. Although these databases are currently dominated by rodent neurons, extension to other animals would be of immense value.

The future availability of comparative information will allow a better understanding of how dendrites have evolved in terms of optimization principles, systems neurobiology, and developmental mechanisms. Ultimately, such an integrated approach may reveal universal functions of dendrites that transcend their functions in any one species.

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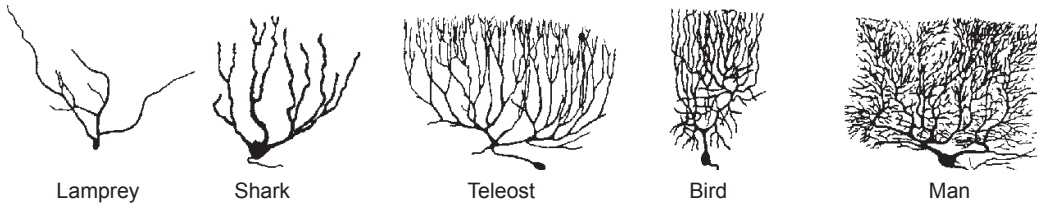
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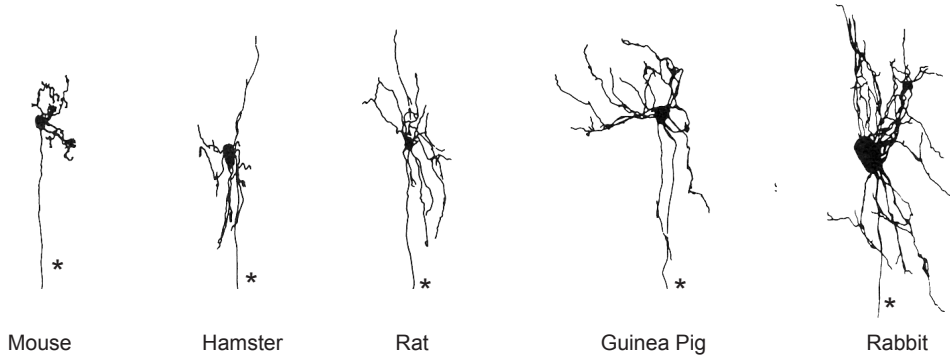
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