REVIEW

Dendrites

Yuh-Nung Jan¹ and Lily Yeh Jan

Howard Hughes Medical Institute, Departments of Physiology, Biochemistry, and Biophysics, University of California, San Francisco, San Francisco, California 94143-0725, USA

Synapse formation involves two partners, axons and dendrites. The axon of a presynaptic neuron needs to be properly guided to make synapses with the correct targets, which are usually the dendrites of the postsynaptic neurons. Dendrites are not just passive participants in this process. Most likely, synapse formation involves two-way communications between the presynaptic cell and the postsynaptic cell. It is worth noting that not all dendrites receive synaptic input. For example, the dendrites of many sensory neurons are sensory endings that transduce signals from the external environment, such as mechanical or chemical stimuli. These sensory stimuli induce receptor potentials in the dendrite, analogous to the synaptic potentials generated at the synapse (Hille 2001). Regardless of whether they receive sensory or synaptic input, the dendrites are the antennae of the neurons. The dendritic branching pattern varies to a great extent with the neuronal type, and is an important determinant of the synaptic or sensory input received by a neuron (Stuart et al. 2000). In this review, we will first consider the functional implications of dendritic branching patterns and then discuss dendrite formation and possible commonality between dendrite development and synaptic plasticity.

Questions about dendrites for developmental biologists, cell biologists, and neuroscientists

Dendrites pose some extremely interesting problems from several different perspectives. From the developmental biological point of view, the dendritic branching pattern is a hallmark of neuronal type. Even neighboring neurons may exhibit strikingly different dendritic branching patterns (Fig. 1). For example, on the basis of the dendritic branching pattern alone, the amacrine cells (one class of interneurons) in the rabbit retina can be subdivided into at least 20 different subtypes (MacNeil and Masland 1998). By extrapolation, using solely dendrite morphology as a criterion, one could easily define hundreds or thousands of different types of neurons in the mammalian CNS (Stevens 1998). To appreciate the

genesis of neuronal diversity, one has to understand how the dendritic branching pattern of individual neurons is controlled.

From the cell biological point of view, the elaborate and stereotyped dendritic branching of a neuron is a striking example of pattern formation and morphogenesis. For example, a Purkinje cell in the cerebellum can elaborate remarkably complex yet stereotyped dendrites. The cellular mechanisms controlling the formation of these elaborate cellular structures are likely to have some unique features and differ substantially from those regulating the formation of other highly branched structures such as trachea or blood vessels, for those tubular structures are formed by the collaboration of multiple cells, each with simpler morphology (for review, see Hogan 1999). The problem of dendritic morphogenesis goes beyond the branching pattern, because on any given branch there are distinct subregions such as dendritic spines and signaling molecules such as transmitter receptors and ion channels localized to distinct domains. Further, dendritic morphology and the distribution of signaling molecules in dendrites are highly plastic. They can undergo rapid changes within minutes in response to physiological stimuli (Mantyh et al. 1995; Fischer et al. 1998; Engert and Bonhoeffer 1999; Maletic-Savatic et al. 1999; Lüscher et al. 2000; Segal and Andersen 2000; Cline 2001; Shi et al. 2001). This ability to change with experience is believed to be part of the cellular basis for learning and memory (for review, see Bailey and Kandel 1993; Malenka and Nicoll 1999; Malinow et al. 2000).

From the neuronal signaling point of view, it has become increasingly clear that dendrites can perform quite sophisticated information processing. The extent and pattern of dendritic branching determines the range and scope of synaptic inputs a neuron can process intelligently; the size and complexity of the dendrite appear to vary according to the task of the neuron (Elston 2000; Poirazi and Mel 2001). For example, compared with cortical neurons involved in relatively simple sensory processing tasks, much more elaborate dendrites are associated with pyramidal neurons in the prefrontal cortex responsible for associating sensory, motor, and affective variables in learning and memory (Elston and Rosa 1998; Elston et al. 1999; Elston 2000; Poirazi and Mel 2001). The history of synaptic inputs further exerts dynamic influence over the extent to which individual dendritic

¹Corresponding author.

E-MAIL ynjan@itsa.ucsf.edu; FAX (415) 476-5774.

Article and publication are at <http://www.genesdev.org/cgi/doi/10.1101/gad.916501>.

Figure 1. Diverse dendritic branching pattern of ganglion cells in the retina of the spotted lizard from (Ramón y Cajal 1911).

branches process information in isolation or in consultation with the rest of the neuron (Eilers and Konnerth 1997; Hausser et al. 2000; Koch and Segev 2000; Segal et al. 2000). As will be described below, the geometry of dendritic branches as well as the distribution of synapses and signaling molecules play critical roles in determining how the dendrite integrates signals that impinge upon a neuron.

Despite the obvious interests of neurobiologists in dendrites—one can open any one of the classics by Ramón y Cajal and will not fail to notice that the majority of his beautiful drawings feature dendrites of various types of neurons—very little is known about the molecular basis of dendrite development and plasticity. The reason is mainly technical. Until relatively recently, the available tools were simply inadequate to tackle such a daunting task; these limitations have been overcome largely by a number of technical advances over the past decade (for review, see Scott and Luo 2001). The possibility of high-resolution imaging of living neurons with various GFP-tagged reporters along with calcium imaging and electrophysiological recording allows simultaneous real-time monitoring of morphological and electrophysiological changes of the dendrite in response to physiological stimuli. The ability to introduce genes of interest into a subgroup of neurons by biobalistics, viral infection, or by using transgenic animals has been improved continuously. Such tools, in combination with the use of primary neuronal culture and brain slices, allow studies of the potential function of a candidate gene in dendrite development at the single-cell level. More recently, forward genetics, which has played such a pivotal role in unraveling complex biological processes such as the patterning of the embryonic body plan (Nüsslein-Volhard and Wieschaus 1980), has begun to be applied to the problem of dendrite development (Gao et al. 1999; Lee and Luo 1999) as well. Before discussing the function and development of dendrites, we will first provide some background information concerning the structural features of dendrites.

The form and content of dendrites in comparison with axons

Dendrites and axons are both neuronal processes but differ in many aspects. Compared with axons, dendrites usually are shorter and less uniform in cross section; they are thicker near their origin at the cell body and then taper off the farther away they are from the soma. Unlike the axon that tends to branch only distally near its target area, dendrites often branch at semi-regular intervals. Axons and dendrites differ further in the polarity of the microtubules they contain. In axons, the microtubules are uniformly oriented with the plus end pointed distally, whereas in dendrites, the orientation of microtubules is mixed (for reviews, see Craig and Banker 1994; Winckler and Mellman 1999). This has important implications in the microtubule-based intracellular transport of molecules and organelles.

Dendrites and axons differ substantially in their molecular composition (for reviews, see Craig and Banker 1994; Scott and Luo 2001). Various cytoskeletal proteins, motor proteins, transmitter receptors, and ion channels are found exclusively or preferentially in axons or dendrites. Dendrites contain mRNA and essentially all of the organelles that have been found in the soma, including ribosomes, endoplasmic reticulum (ER) and Golgi (Gao 1998; Gardiol et al. 1999; Wells et al. 2000; Baillat et al. 2001; Pierce et al. 2001; Steward and Schuman 2001). Thus, dendrites are capable of local protein synthesis (Kang and Schuman 1996; Weiler et al. 1997; Huber et al. 2000). In contrast, mRNA and ribosomes are scarce, if not absent, in the axon. It is therefore generally thought that there is no protein synthesis in the axon (however, see discussion below).

Both axons and dendrites have structures specialized for synaptic contacts. The axon terminals have the machinery for transmitter release. The dendrites of many, but not all, mammalian neurons have numerous small protrusions called dendritic spines, which are distributed with semi-regular spacing along the dendrites. Spines are

shaped like mushrooms, each with a more or less spherical head, which is connected to the dendritic shaft by a cylindrical neck. Spines are the sites of >90% of the excitatory synapses in the mammalian central nervous system (CNS) (for review, see Harris 1999). The dendritic spine is actin rich and contains the postsynaptic density (PSD), a postsynaptic signaling complex, as well as membrane compartments for protein synthesis or processing (Pierce et al. 2001). The size and shape of dendritic spines varies considerably.

It is worth noting that different neurons vary significantly in their dendrite mass relative to axon mass (Craig and Banker 1994). For example, it has been estimated that >90% of the cell membrane of a spinal motor neuron (which has a very long axon) is axonal membrane. In contrast, >80% of the cell membrane of a dentate granule cell (which has a short axon) is dendritic membrane. Thus, these different types of neurons may face rather different demands of their biosynthetic capacity.

Dendritic integration

How might the dendritic branching pattern affect a neuron's ability to integrate and process impinging signals?

A neuron receives and processes many different synaptic inputs; once the integrated signal brings the membrane potential beyond the threshold, an action potential is initiated at the axon hillock near the soma and propagates down the axon toward the nerve terminals, thereby causing transmitter release (Fig. 2). A synaptic potential produced at a single synapse is usually too small to generate an action potential, even if the synapse is located near the soma. Thus, summation of multiple synaptic potentials generated within a short time interval is often necessary to bring the neuron to the point of firing an action potential. As discussed later, whether an action

potential is generated by these synaptic inputs may be further influenced by the past history of neuronal excitability and synaptic inputs (Eilers and Konnerth 1997; Hausser et al. 2000; Koch and Segev 2000; Segev and London 2000; Stuart and Hausser 2001).

To compound the problem of processing and integrating multiple synaptic inputs impinging onto a neuron, the majority of synapses are located on the dendrite. For example, the excitatory synapses of a pyramidal neuron are found predominantly on the thin, terminal branches of its basal dendrites (Elston and Rosa 1997). The location of synapses on the dendrite matters, because a dendritic branch resembles a leaky cable at first approximation; synaptic potentials moving along this cable are expected to get progressively smaller due to current leakage. Synaptic potentials generated on a dendritic branch may be further attenuated at the branch point due to the abrupt increase in membrane surface area. In reality, a dendrite is more sophisticated than a leaky cable because the many different dendritic ion channels are not uniformly distributed along the dendrite and their activities may vary with neuronal activities. The ability of a synaptic potential to move along the dendrite and reach the cell soma, therefore, depends on the ion channel composition on the dendritic membrane as well as the dendritic branching pattern.

Molecular heterogeneity compounds the morphological complexity of dendrites

Several recent studies show that dendrites are not just leaky cables. First, if the membrane properties were uniform along the dendrite, synaptic potentials generated at the distal tip of the dendrite should produce potential changes in the soma that are much smaller and longer lasting, as compared with those generated in proximal dendrites near the soma. Interestingly, this prediction is not borne out in recordings from pyramidal neurons in

Figure 2. Action potential initiation in the axon hillock and back propagation into dendrites. (A) Camera-lucida drawing of rat neocortical layer 5 pyramidal neuron. (B) Somatic and dendritic action potential due to synaptic activities that just reached threshold. (C) Somatic and axonal action potential due to threshold synaptic stimulation in a different cell. From Stuart et al. (1997).

the hippocampus and cortex (Magee and Cook 2000; Williams and Stuart 2000b). Rather, it appears that the synapses are calibrated according to their locations; larger synaptic potentials are generated at more distal dendrites so that they achieve similar sizes as they reach the soma. Moreover, both the density and the open probability of ion channels appear to form gradients along the dendrite. For example, there is a higher density of active hyperpolarization-activated cation channels at the more distal dendrite (Magee 1998). As a consequence of this gradient of leak conductance, synaptic potentials generated at either distal or proximal dendrites display a similar time course once they arrive at the soma of these neurons. On the other hand, gradients of other ion channels, such as the voltage-gated A-type potassium channels discussed below, have been found to bias synaptic inputs according to their site of generation. It is an intriguing, but unanswered, question just how the density of various ion channels is adjusted according to their distance from the soma on the dendrite.

Second, not only do the channel densities vary along dendrites, but their properties also may change according to neuronal activity. For example, inwardly rectifying potassium (Kir) channels maintain the resting membrane potential of striatal spiny neurons at the hyperpolarized down state and prevent synaptic potentials generated infrequently on the dendrites from significantly altering the membrane potential in the soma. These channels may be inactivated by membrane depolarization due to increased excitatory synaptic inputs (Wilson and Kawaguchi 1996), causing the resting potential to shift by >20 mV to the up state. The dendrites also become less leaky as these channels no longer allow ion passage, so that the synaptic potentials can spread farther and summate with one another better—the entire character of the neuron changes as a result.

Active conductances in dendrites expand the dynamic range for signal processing

Voltage-gated sodium and calcium channels have also been found on dendritic membranes (Stuart and Hausser 1994; Magee and Johnston 1995; Martina et al. 2000; Williams and Stuart 2000a)—these channels may be activated by excitatory synaptic potentials (Golding and Spruston 1998; Golding et al. 1999) or action potentials initiated near the soma (Johnston et al. 1999), causing action potentials to propagate along the dendrites. Thus, the processing and integration of synaptic inputs may be further influenced by prior neuronal activities via the dynamic changes of dendritic membrane properties as well as the calcium influx induced by dendritic action potentials (Magee and Johnston 1997; Markram et al. 1997).

Action potentials generated near the soma can back propagate into dendrites (Hausser et al. 2000), providing one mechanism for a neuron to take into account its past activities and process its synaptic inputs accordingly. For example, the NMDA receptors function as coincidence

detectors; their activation requires both binding of the excitatory transmitter glutamate and membrane depolarization (Hille 2001). NMDA receptor activation and the resultant calcium entry may ensue when glutamate released at the excitatory synapse and back propagating action potentials converge on the dendrite, causing long-term potentiation (Magee and Johnston 1997).

For various central neurons examined thus far, back propagation of action potentials involves voltage-gated sodium channels in the dendrite. Just how far action potentials propagate back up the dendrite depends on the neuronal type, the frequency of action potentials, the density and modulation of various ion channels on the dendrite, and past experience (Colbert et al. 1997; Stuart et al. 1997; Helmchen et al. 1999; Margrie et al. 2001). When several action potentials back propagate in rapid succession, the later ones attenuate much more than the first, because the dendritic sodium channels inactivate shortly after they open and take a long time to recover from inactivation. The extent of back propagation into the dendrite may also be limited by spatial gradients; the amount of dendritic sodium channel inactivation in hippocampal CA1 pyramidal neurons increases as a function of distance from the soma (Mickus et al. 1999), and the density of A-type potassium channels forms a gradient such that distal dendrites have more channels (Hoffman et al. 1997). Beside diminishing the likelihood of action potential invasion into dendrites, these potassium channels reduce excitatory synaptic potentials. When these channels become inactivated, due to increased excitatory synaptic activities as the animal gains familiarity with its environment, back propagation is enhanced and cellular responsiveness is heightened (Quirk et al. 2001). These studies underscore the physiological importance of integrating back-propagating action potentials with synaptic inputs.

Voltage-gated calcium channels are present within the spine, the smallest unit of neuronal integration; whereas synaptic activities may activate calcium channels within a spine, causing calcium increases confined to a single spine; action potential back propagation may invade spines as well as dendritic shafts and cause widespread calcium influx in dendrites and spines (Denk et al. 1995; Yuste and Denk 1995; Sabatini and Svoboda 2000). As another example of the intriguing molecular heterogeneity, activation of the G protein-coupled GABA_B receptors reduces the probability of calcium channel activation in apical spines but not in neighboring dendritic shafts or basal spines of the CA1 hippocampal pyramidal neurons (Sabatini and Svoboda 2000).

Stronger interactions between synapses that are closer together

In general, synapses in physical proximity are expected to interact more strongly with one another for several reasons. First, because synaptic potentials attenuate in size as they travel away from their site of generation, stronger interaction is expected between synaptic potentials generated at nearby synapses on the same dendritic

branch (Poirazi and Mel 2001). In particular, activities of neighboring glutamatergic synapses are more likely to summate to the extent of activating NMDA receptors and allow calcium entry. Second, whether synaptic potentials from one dendritic branch can reach the soma depends not only on the dimension and electrical properties of the dendritic branches at the junction, but also on the timing of other synaptic potentials generated on convergent dendritic branches (Segev and London 2000).

Dendritic voltage-gated ion channels may further influence interactions between adjacent synapses. First, because action potentials attenuate in size as they back propagate into the dendrites (Colbert et al. 1997; Stuart et al. 1997; Helmchen et al. 1999; Margrie et al. 2001), coincidence detection of back-propagating action potentials and synaptic inputs is more likely to take place at proximal dendrites. Second, whereas action potentials are normally generated near the soma, strong depolarization resulting from simultaneously occurring synaptic inputs could activate voltage-gated calcium channels at distal dendrites, triggering calcium influx and sometimes even the generation of action potentials locally in the dendrite (Hausser et al. 2000; Martina et al. 2000). These scenarios, along with the likelihood of back-propagating action potentials to fail at the dendritic branch point (Spruston et al. 1995; Williams and Stuart 2000a), indicate that individual dendritic branches may sometimes operate, more or less, on their own. Thus, there is a richness of possibilities concerning the integration of signals impinging onto one dendritic branch with or without consideration of prior action potential activities in the soma. Several types of neurons in the retina and olfactory bulb are known to have different synaptic inputs segregated to different dendritic compartments (Nelson et al. 1975; Young and Rubel 1986; Agmon-Snir et al. 1998; Yoshihara et al. 2001).

Taking all the factors discussed above into consideration, one may expect synaptic inputs at the distal dendrites to be processed differently from those on proximal dendrites. It would also appear likely that proximity of synapses matters in terms of the likelihood that their synchrony will have an impact (Poirazi and Mel 2001). Synapses onto separate branches could potentially form individual functional groups, given that synapses on the same dendritic branch are likely to be isolated to the same extent, depending on the relative timing of synaptic activities of adjacent branches. Finally, the size and number of dendritic branches obviously will determine not only the scope of synaptic inputs received, but also the complexity of the computation a neuron is capable of executing.

Initiation and orientation of dendrite outgrowth

A mature neuron is a highly polarized cell. Dendrites and axons differ greatly in microtubule polarity, molecular composition, and function. When does a neuron first become polarized? How are the sites for dendrite and axon

outgrowth selected? What controls the direction of the initial axon and dendrite outgrowth?

To address these issues, one of the most extensively studied systems is the primary cell culture of pyramidal neurons from the rat embryonic hippocampus. These cultured neurons exhibit many of the properties of neurons *in situ*, including the asymmetric distribution of axonal and somatodendritic proteins (for review, see Craig and Banker 1994). However, it should be noted that not all of the properties of neurons *in situ* are preserved in the culture system (Shi et al. 2001). Dotti et al (1988) characterized the development of those neurons in culture and identified five developmental stages. Stage 1 occurs shortly after the plating of the cells, after the neurons attach themselves to the substrate, and is characterized by the formation of lamellipodia around the cell soma. At stage 2, the cultured neuron sends out four to five short neurites, which are indistinguishable from one another in appearance and have not yet shown any obvious characteristics of axons or dendrites. At stage 3, one of the neurites is singled out to become an axon; this neurite begins to elongate rapidly and starts to acquire the properties of an axon. At stage 4, the other neurites begin to exhibit features of dendrites. At stage 5, those processes continue to adopt mature features of axons and dendrites and proceed with synaptogenesis, dendritic branching, and the formation of dendritic spines (Dotti et al. 1988; Craig and Banker 1994).

How is one of several apparently equivalent neurites singled out to become an axon leaving the others to become dendrites? Experiments with the cell culture system suggest that this is a random process (for review, see Craig and Banker 1994). No evidence has been obtained to indicate an intrinsic positional cue for the site of origin of the axon. Further, at stage 3, if the neurite that is already singled out to become axon is transected near the cell body, then one of the remaining neurites will emerge as the new axon (Dotti and Banker 1987). Those observations led to the following hypothesis (Goslin and Banker 1989; Bradke and Dotti 2000): "Each of the neurites of the stage 2 cells sends growth-discouraging signals to the other neurites, whereas each neurite has a self-promoting growth activity . . . a stochastic process marks one neurite to become axon. The 'chosen' neurite then sends stronger growth-discouraging signals to the other neurites while it promotes its own growth. The minor neurites, weakened by the inhibitory signal from the axon, send fewer inhibitory signals to the other neurites including the chosen neurite; the result is that only one neurite becomes the axon." Those hypothetical signals have not yet been identified. Interestingly, Bradke and Dotti (1999) found that local perfusion of cytochalasin D onto a growth cone induces it to grow as an axon. They suggest that the polarized actin-filament instability determines the initial neuronal polarization. The actin cytoskeleton of the future axonal growth cone is highly dynamic and less restrictive for microtubule protrusion and may allow the polarized growth of the future axon (Bradke and Dotti 2000). According to this model, the hypothetical sig-

nals presumably regulate the actin dynamics directly or indirectly.

This model for singling out an axon from an equivalent group of neurites by a stochastic process involving both positive and negative feedback is conceptually similar to the lateral specification model of singling out a neural precursor from an equivalent group of ectodermal cells. It is known that Notch signaling provides the feedback to mediate the singling out of neural precursor (for review, see Ghysen et al. 1993). One wonders whether Notch signaling also plays a role in the singling out of axons considering the multiplicity of developmental processes that involve Notch signaling, including the process of neurite outgrowth (Giniger 1998; Sestan et al. 1999; Redmond et al. 2000).

Although the selection of individual neurites to form axon or dendrite appears to be a stochastic process in the cultured hippocampal neurons, this has not been demonstrated *in situ*. In contrast, live imaging of zebrafish motoneuron (Myers et al. 1986; Westerfield et al. 1986) and *Drosophila* embryonic sensory neurons (Gao et al. 1999) revealed that each of those neurons initially put out only a single process, which forms an axon, and dendrites develop later. Further, as polarity information and asymmetry can be altered by interfering with cell–cell contacts (Lu et al. 2001), one has to be very cautious in extrapolating cell culture studies to *in situ* situations.

One of the systems in which the initial axon and dendrite outgrowth has been analyzed relative to tissue polarity *in situ* is the *Drosophila* peripheral nervous system. In that system, the sensory neurons are derived from sensory organ precursors (SOP) through stereotyped lineages. For example, a simple SOP generates a neuron and four accessory cells through four rounds of asymmetric cell divisions (Gho et al. 1999). The orientation of each division is fixed relative to the body axis and the newly formed neuron is already polarized as evident from the asymmetric localization of cell polarity markers such as Bazooka, a PDZ domain containing protein (Bellaiche et al. 2001; Orgogozo et al. 2001; Rogiers et al. 2001). In these sensory neurons, the orientation of the outgrowth of axon and dendrite is not random. For example, each of the embryonic sensory neurons in the dorsal clusters of the abdominal segments sends a single axon ventrally toward the CNS. This is followed by the subsequent dendrite outgrowth in the opposite direction.

What controls the sites and the orientation of the initial axon and dendrite outgrowth? Intrinsic polarity information, such as asymmetrically localized Bazooka in the newborn neuron, certainly has the potential of providing cues for orienting the initial outgrowth of axon and dendrites. Alternatively, this could be coordinated by extrinsic dorsal-ventral positional information. It is also possible that a combination of intrinsic and extrinsic mechanisms determine the sites and directions of initial axon and dendrite outgrowth. Mutations affecting axon and/or dendrite outgrowth have been and continue to be isolated from genetic screens (e.g.,

Vactor et al. 1993; Kolodziej et al. 1995; Gao et al. 1999) and they should provide insight into the underlying mechanisms.

Molecules implicated as regulators of dendrite outgrowth and orientation

Several diffusible factors that affect dendrite outgrowth or orientation have been found in vertebrates. One such factor is osteogenic protein-1 (OP-1), also known as bone morphogenetic protein-7 (BMP-7), a member of the transforming growth factor β (TGF β) superfamily (Lein et al. 1995). *In situ*, rat sympathetic neurons have an axon and dendrites. However, sympathetic neurons from rat pups extend an axon but no dendrites when maintained in culture in the absence of glia and serum. Exposure of OP-1 induces the formation of dendrites in these cultured neurons. Because many sympathetic neurons of newborn rats already have rudimentary dendrites, which are likely severed during culturing procedure, the observed effect of OP-1 on dendrite growth could conceivably be on dendrite regeneration. However, OP-1 can also induce dendrite growth from naïve neurons derived from 14.5-day embryos, suggesting that OP-1 is capable of promoting *de novo* formation of dendrites as opposed to merely promoting dendritic regeneration. The action of OP-1 is likely specific for dendrites as it has no obvious effect on axon numbers. This effect on dendrite outgrowth is specific for OP-1 and some of its close relatives in the BMP family as many other members of the TGF β family of growth factors, neurotrophins, and basic fibroblast growth factors were tested and found to have no such effect (Lein et al. 1995).

Semaphorins (also known as collapsins) were originally identified by their ability to collapse or repel axon growth cones (Luo et al. 1993; Messersmith et al. 1995). Interestingly, *Sema 3A* functions as an attractant for cortical apical dendrite, an effect opposite to its chemorepulsive action on cortical axons (Polleux et al. 2000). Pyramidal neurons from the cerebral cortex normally have their apical dendrites extending toward the pial surface. By using cultured brain slice preparations, Polleux et al. (2000) showed that there is a diffusible factor that can orient apical dendrites toward the pial surface. This diffusible factor is probably *Sema 3A*, because an ectopically placed *Sema 3A* source is sufficient to attract apical dendrites. Furthermore, in the *Sema 3A* null mice, many of the cortical pyramidal neurons have an abnormal morphology. Polleux et al. (2000) propose that the difference in the effects of *Sema 3A* on axons and dendrites is due to the asymmetric localization of soluble guanylate cyclase (SGC) in axons and dendrites; apical dendrites express high levels of SGC and cGMP signaling appears to be necessary for the pial-directed orientation of dendritic growth. Thus, the differential effect of *Sema 3A* on axons and dendrites, possibly mediated by asymmetric localization of intracellular signal molecules such as SGC, can contribute to the orientation of axon and dendrite outgrowth.

Once axon and dendrite outgrowth have occurred, how

does a neuron maintain the axon/dendrite differences? Recent experiments by Yu et al. (2000) suggest that the microtubule-associated motor protein CHO1/MKLP1 has a significant role. They reduced the level of CHO1/MKLP1 in cultured rat sympathetic neurons by using antisense oligonucleotides and observed a rapid redistribution within the dendrites such that minus-end-distal microtubules are moved back to the cell body, whereas the plus-end-distal microtubules are redistributed outward. The dendrites grow significantly longer and thinner, lose their taper, and acquire a progressively more axon-like organelle composition. Those observations are consistent with a model that CHO1/MKLP1 is essential for the appearance of minus-end-distal microtubules within developing neurites and their differentiation into dendrites (Baas 1999; Yu et al. 2000).

How is dendritic field specified?

The dendrite branching patterns are hallmarks of neuronal type. The area covered by the dendrites of a given neuron is known as its dendritic field. How does a neuron decide to branch or not to branch? How does it know when to stop its dendrite branching? How do cell intrinsic factors and dendritic branch interactions such as avoidance and repulsion shape a neuron's dendritic field?

Before discussing how dendritic fields are specified, it is useful to consider whether dendritic field formation is cell autonomous. Neurons such as Purkinje cells kept in primary culture do form dendritic arbors with characteristic and recognizable branching pattern. Thus, for those neurons, intrinsic developmental programs appear to play a role in shaping their dendritic fields. It is also clear that such cultured neurons lack certain characteristics and complexity of the neurons in vivo, presumably because they lack many of the cell-cell interaction and environmental cues necessary for its normal dendrite development. When Purkinje cells are co-cultured with granule cells, their dendritic arbors resemble more closely those in vivo (Baptista et al. 1994). Thus, it is reasonable to expect that, like most complex biological processes, dendrite development would require both cell intrinsic programs and extrinsic influence.

Control of dendritic branching via regulators of the cytoskeleton

What controls dendritic branching? There is good evidence that RhoA, Rac, and Cdc42, members of the Rho family of small GTPases, play important roles in regulating neuronal morphogenesis including dendrite outgrowth, branching, and spine formation. Because there are excellent recent reviews on the function of Rho family GTPases in dendritic morphogenesis (Luo 2000; Redmond and Ghosh 2001), we will not cover this subject extensively. Briefly, different members of the Rho family appear to regulate different aspects of dendritic morphogenesis. RhoA affects dendrite growth primarily. Rac is important for dendritic branching stability and morpho-

genesis of dendritic spines. Cdc 42 is also important for the regulation of dendritic branching and remodeling. Given that small GTPases of the Rho family are regulators of actin cytoskeletal elements, the essential structural components of the dendrite, they and their associated signaling pathways are excellent candidates as sites of convergence of extrinsic and intrinsic regulators of dendritic morphogenesis.

Together with the Rho family of small GTPases, other regulators of the cytoskeleton are implicated in the control of dendritic branching, including the *Drosophila* gene *kakapo* (Gao et al. 1999). The *kakapo* (also known as *short stop*) mutants are defective in dendritic branching of both sensory neurons (Gao et al. 1999) and motor neurons (Prokop et al. 1998). Kakapo is a member of the Plakin family (Gregory and Brown 1998; Strumpf and Volk 1998) of very large (200–700 kD) proteins. Plakin can anchor cytoskeletal networks (e.g., actin and microtubule networks) to each other and/or to cellular structures such as adhesive junctions in both vertebrates and invertebrates (Fuchs and Karakesisoglou 2001). The *Drosophila kakapo* mutant embryos do exhibit defects in microtubule attachment to adhesive junctions in epidermal cells, supporting the potential role of Kakapo as a cytoskeletal linker protein (Prokop et al. 1998). The reduced dendritic branching phenotype of *kakapo* mutants suggests that linking actin with microtubule network or adhesive junctions is important for stabilizing dendritic branches.

Factors that regulate dendrite patterning

As mentioned earlier, several diffusible factors such as OP-1 and Sema 3A have been found to affect dendrite outgrowth or orientation. Additional diffusible or membrane-anchored factors including neurotrophins and CPG15 have been found to affect dendrite growth, branching, or spine formation in vertebrates. *cpg15* was identified as a neuronal activity-regulated gene. It encodes a small secreted protein that is associated with the membrane via a glycosylphosphatidylinositol (GPI) linkage. In the developing *Xenopus* optic tectum, CPG15 increases dendritic growth and complexity in projection neurons but not in interneurons (Nedivi et al. 1998).

In the vertebrate neocortex, neurotrophins regulate dendrite growth of developing pyramidal neurons. Application of each of the four neurotrophins (NGF, BDNF, NT-3, and NT-4) to organotypic slices of the developing ferret visual cortex increases the length and complexity of the dendrites of cortical neurons. Interestingly, neurons in each cortical layer respond to the neurotrophins with a distinct pattern of changes of their basal and apical dendrites (McAllister et al. 1995). Those results suggest that neurotrophins are not just promoters of dendrite growth; they have instructive roles in shaping particular patterns of dendritic arborization in different neurons.

The experiments mentioned above are gain-of-function type of manipulations. They show what the neurotrophins are capable of doing. To find out the actual in

vivo function of neurotrophins, loss-of-function experiments are needed. One approach is to use the Trk receptor bodies, which are fusion proteins containing the ligand-binding domains of each Trk receptor type (Trk receptors are the receptors for neurotrophins) and the Fc domains of IgG. Application of Trk receptor bodies, which can bind and neutralize endogenous neurotrophins, did affect the dendritic pattern of the developing cortex and thus support an endogenous role of neurotrophins in shaping dendritic branching patterns (McAllister et al. 1997). Experiments with various knock out mice lacking neurotrophins, Trk receptors, and the associated signal transduction pathways should provide further insight to the role of neurotrophins in dendrite development.

A particularly interesting aspect of neurotrophins' action on dendrite morphogenesis is the potential links neurotrophins provide between neuronal activity and the sculpting of dendritic morphology (McAllister et al. 1996). For example, application of BDNF to pyramidal neurons in cultured slices of developing ferret visual cortex elicits dramatic sprouting of basal dendrites and a regression of dendritic spines. Those newly formed dendrites and spines are less stable than the control. Such structural instability of dendrites and spines induced by BDNF might be restricted to subregions of a dendritic arbor and provides a potential mechanism for electrical activity to modulate the morphology of part of the dendritic arbor (Horch et al. 1999).

Are there gene regulation programs that control dendrite morphogenesis?

It is not yet clear how factors such as CPG15 or neurotrophins regulate dendrite morphogenesis, whether they act directly on the cytoskeletal elements or whether they act at the level of gene regulation by turning on cell intrinsic programs for dendrite morphogenesis. It is not even known whether the neurons have gene regulation programs designed to control dendrite morphogenesis. Studies with forward genetics in *Drosophila* suggest that such a program exists.

One of the genes that was identified in a mutant screen for dendrite patterning defect is *sequoia* (Gao et al. 1999). In *sequoia* loss-of-function mutants, the axon and dendrite morphology of most—possibly all—neurons are abnormal, but many other aspects of neuronal differentiation appear to be normal. Sequoia encodes a Zn finger protein expressed in all neurons and is likely to function as a transcriptional regulator. Thus, Sequoia appears to be a pan-neuronal regulator that functions to carry out a subroutine for controlling dendrite and axon morphogenesis in fly (J. Brenman, F.B. Gao, L.Y. Jan, and Y.N. Jan, in prep.). Genes of this type have the potential of providing a nodal point in which different signals regulating neuronal morphogenesis converge.

Tiling

To elaborate its dendrite field, a neuron needs to decide whether to branch, when and where to branch, how of-

ten to branch, and just as importantly, when to stop dendritic growth and branching. Beside the cell intrinsic capacity of branching as controlled by the cell's genetic program and other factors such as cell size (it is unlikely that a tiny neuron can support a dendritic arbor of a Purkinje cell), cell-cell interaction is likely to have a major role in shaping dendritic field as evident from the phenomenon known as tiling (Wassle et al. 1981; Stevens 1998). An excellent example of tiling is illustrated in the vertebrate retina (Devries and Baylor 1997; MacNeil and Masland 1998). By use of photochemical methods, a large number of amacrine cells in the rabbit retina can be filled randomly with fluorescent dye. On the basis of dendritic branching pattern, those neurons can be divided into at least 20 different subtypes. In most cases, the dendritic fields of neurons of a given subtype cover the retina once, and only once, with very little overlap between these dendrites, like tiles covering a floor. On the other hand, the dendrites of neighboring neurons of different subtypes can have extensive overlap. This arrangement seems to make functional sense, as each subtype of neurons presumably serves a particular function. Tiling would ensure that every area of the retina, and hence, every part of the visual field, would be covered (usually once) by the dendrites of each subtype of neurons (MacNeil and Masland 1998). Tiling suggests that neurons of the same type can recognize each other. Perhaps there is a like-repels-like mechanism at work so that the dendrites of the same type of neurons tend not to overlap.

Tiling phenomenon is also found in *Drosophila*. In *Drosophila* embryos and larvae, the body wall is covered with the dendrites of the MD sensory neurons. There are several different types of MD neurons and the dendritic fields of each type tile the body wall once (W. Grueber, L.Y. Jan, and Y.N. Jan, in prep.). A gene called *flamingo* may give insights into the molecular mechanisms of tiling. In *flamingo* mutants, dendrites of homologous neurons of the same type fail to repel each other when they meet at the dorsal midline of the larva (Gao et al. 2000). *flamingo* encodes a seven-pass transmembrane protein that resembles G protein-coupled receptors (Usui et al. 1999). Thus, Flamingo might function as a receptor that mediates the repulsion between dendrites of the homologous neurons either through direct contact or by indirect means (Gao et al. 2000). Flamingo belongs to the protocadherin subclass of the cadherin superfamily; its extracellular domain contains cadherin repeats (Usui et al. 1999). In human, there is a large number of protocadherin genes. The role of Flamingo in *Drosophila* MD sensory neuron tiling raises the interesting possibility of protocadherins functioning in tiling of different type of neurons (Ghosh 2000).

How might neuronal activity shape dendritic field and spines?

Dendrite development is concurrent with synapse formation and maturation of neuronal excitability. Mechanisms that underlie structural and functional changes of

neurons during development may also operate in the adult nervous system, in which synaptic plasticity involves not only alterations of functional components at the synapse but also structural changes (Bailey and Kan-del 1993; Mantyh et al. 1995).

Sequential appearance of different glutamate receptors

The sequence of appearance of different ionotropic glutamate receptors during development is recapitulated in synaptic plasticity of adult central neurons. In the developing glutamatergic synapse, NMDA receptors appear first, before AMPA receptors; the activity of these NMDA receptors regulates dendrite growth rate and branching dynamics (Cline 2001). A striking parallel is found in synaptic plasticity of adult neurons, which poses silent synapses with only NMDA receptors; long-term potentiation of such synapses involves the insertion of AMPA receptors (Lüscher et al. 2000; Malinow et al. 2000).

Also common to neural development and plasticity of the adult nervous system is the dynamic regulation of glutamate receptor composition. For example, AMPA receptors contain the GluR2 subunit in adult, but not immature, hippocampal neurons (Zhu et al. 2000; Shi et al. 2001). These glutamate-gated cation channels are impermeable to calcium due to RNA editing of GluR2. In contrast, AMPA receptors that lack GluR2 allow calcium influx. Interestingly, adult cerebellar stellate neurons express GluR2-lacking receptors in an activity-dependent manner; calcium influx due to strong activation of these receptors causes rapid insertion of GluR2-containing receptors, thereby reducing calcium entry upon extensive neuronal activities (Liu and Cull-Candy 2000).

A similar scenario plays out for the NMDA glutamate receptor. The NMDA receptors in adult, but not immature, neurons contain the NR2A subunit, which reduces the duration of receptor activation, presumably reducing the likelihood of excitotoxicity as neuronal activities increase with maturation. This switch of receptor subtype depends on experience; it takes place remarkably rapidly in the visual cortex, after young animals reared in total darkness are exposed to light (Quinlan et al. 1999).

Role of calcium signaling in development and synaptic plasticity

For both AMPA and NMDA receptor subtype switching, the common theme appears to be a restriction of calcium entry and downstream signaling as the neuronal activity increases during development or in adult life. Consequently, in mature cortical and hippocampal neurons, NMDA but not AMPA receptors are permeable to calcium ions. As coincidence detectors, NMDA receptors then mediate calcium entry and strengthen the adult synapse by activating calcium/calmodulin activated kinases (CAMK) and downstream pathways such as the MAP kinase pathway. The basis for synapse strengthen-

ing could involve insertion of AMPA receptors (Chen et al. 2000; Shi et al. 2001), potentiation of existing signaling pathways (Malenka and Nicoll 1999), and stimulation of filopodial extension from dendrites and spines (Wu et al. 2001).

Not only does heightened neuronal activity trigger glutamate receptor subtype switching, calcium activation of kinases also signals neuronal maturation and halts dendrite outgrowth. Thus, the appearance of CAMKII during development coincides with slowing of dendritic arbor growth in *Xenopus* optic tectal neurons; manipulation of CAMKII activities alters dendritic growth accordingly (for review, see Cline 2001).

Plasticity of spines

Spines may be isolated functional entities at times; calcium influx from NMDA receptors or calcium channels activated by weak synaptic inputs may cause an increase in calcium concentration within the spine (Denk et al. 1995; Petrozzino et al. 1995; Yuste and Denk 1995; Yuste et al. 1999; Miyata et al. 2000; Sabatini and Svoboda 2000). This may lead to the activation of signaling cascades other than membrane potential changes. For instance, the length and shape of the spine neck, which determines how well the synaptic potentials that are generated within a spine will spread to the dendritic shaft, could conceivably vary with cytoskeletal rearrangements that are dependent on this calcium influx (Matus 2000). It has been proposed that a moderate increase of cytoplasmic calcium concentration causes elongation of spines, whereas a very large increase of calcium concentration causes shrinkage and collapse of spines (Segal et al. 2000).

In addition to structural changes, the type and number of transmitter receptors on the spine also vary with synaptic plasticity as well as development (Lüscher et al. 2000; Malinow et al. 2000; Cline 2001). These structural and molecular changes may depend on signaling via second messengers as well as biosynthesis. The dendritic spines contain membranous compartments for the synthesis and processing of secretory and membrane proteins, providing the potential for rapid, dynamic changes of the dendritic spines (Pierce et al. 2001). Moreover, abnormal spine formation is induced by mutations of anchor proteins for protein phosphatase 1, or the fragile X mental-retardation protein required for dendritic protein synthesis in response to stimulation (Comery et al. 1997; Feng et al. 2000).

Different alterations of spine morphology may take place following neuronal activity, ranging from spine formation, bifurcation of spine head, alteration of spine dimension, to spine elimination (for reviews, see Matus 2000; Segal and Andersen 2000). Formation of new spines and enhanced growth of filopodial-like protrusion from dendrites may be induced by synaptic activity, a form of structural plasticity that appears within an hour of the initiation of long-term potentiation in the hippocampus (Engert and Bonhoeffer 1999; Maletic-Savatic et

al. 1999). In the cerebellum, removing the climbing fiber input or silencing neuronal activity by blocking voltage-gated sodium channels with TTX causes cerebellar Purkinje neurons to increase the number of their spines. On the other hand, hibernation causes reduction of spines and dendrites, which is then fully restored within 2 h of arousal of the ground squirrel (Popov et al. 1992). In the developing rat barrel cortex involved in processing sensory information from the whiskers, spines and filopodia form, disappear, and change shape over tens of minutes. Moreover, whisker trimming during a critical period between postnatal day 11 and 13 reduces this motility without altering the overall density, length, or shape of the spines and filopodia. These findings indicate that the structural plasticity in dendrites underlie the ability of neural circuit reorganization due to sensory deprivation (Lendval 2000). Unraveling the molecular basis for these dynamic changes will most likely advance our understanding of both dendrite development and synaptic plasticity of the adult nervous system.

Local protein synthesis as a mechanism for synaptic plasticity

Structural and molecular differences between dendrites and axons are essential for their functional differentiation and require specific transport and targeting mechanisms (Sheetz et al. 1998; Foletti et al. 1999; Kirsch 1999; Winckler and Mellman 1999; Kennedy 2000; Penzes et al. 2001). The density and distribution of transmitter receptors and other ion channels may further vary with experience, leading to synaptic plasticity (Lüscher et al. 2000; Cline 2001; Shi et al. 2001). Given that a neuron may possess many synapses, only a small fraction of which may be active at any one time, how might this plasticity be achieved specifically for those particularly active synapses?

Polarity issues

Before discussing synapse-specific changes, we need to first consider how molecules are differentially targeted to the axon or the dendrite. One possibility is that neurons, as cells derived from the ectoderm, rely on the same polarity cues used by epithelial cells. Consistent with this idea, viral proteins known to be targeted to either the apical (the influenza HA protein) or the basolateral (the VSV G protein) surface of epithelial cells are targeted to the axon and dendrites of cultured hippocampal neurons, respectively (Dotti and Simons 1990). However, whether the axon of a neuron corresponds to the apical compartment of an epithelial cell remains an open question (Colman 1999; for review, see Winckler and Mellman 1999). Given the physiological significance of the precise arrangement of molecules on the neuronal membrane much like a fine mosaic, it will be an important challenge to learn about the specialized targeting and anchoring machinery for the exquisite compartmentalization of molecules in dendrites and axons.

Protein synthesis in dendrites

Given the large number of synapses impinging on a single neuron, it is appealing to consider local protein synthesis in the dendrite as a mechanism for individual synapses to adjust their membrane excitability according to their own synaptic activity (Huang 1999; Kiebler and DesGroseillers 2000; Steward and Schuman 2001). Dendrites appear to possess the capacity for protein synthesis. They contain messenger RNA, proteins for RNA transport or polyadenylation, and protein synthetic machinery (Weiler et al. 1997; Gao 1998; Gardiol et al. 1999; Kiebler et al. 1999; Wells et al. 2000; Baillat et al. 2001; Steward and Schuman 2001). Several dendritically localized mRNAs contain internal initiation sites for translation, which tend to be utilized when the supply of the protein synthetic machinery is limited (Pinkstaff et al. 2001). Some mRNA actually moves to dendritic locations with active synaptic inputs (Steward et al. 1998; Steward and Worley 2001), whereas others, such as the mRNA for the α subunit of CAMKII, are chronically localized to the dendrites due to targeting signals in the 3' UTR (Mayford et al. 1996; Mori et al. 2000).

Is local protein synthesis important for synaptic plasticity? Protein synthesis in dendrites is required for long-term depression induced by stimulation of metabotropic glutamate receptors in hippocampal neurons (Huber et al. 2000). Similarly, the neurotrophin BDNF is capable of stimulating protein synthesis in dendrites of cultured hippocampal neurons (Aakalu et al. 2001), and synaptic strengthening by neurotrophins in hippocampal slice preparations appears to require local protein synthesis (Kang and Schuman 1996). To substantiate the involvement of local protein synthesis in synaptic plasticity, it would be important to identify those proteins that are synthesized in dendrites or spines to mediate synaptic plasticity. Interestingly, for heteromultimeric protein complexes such as calcium/calmodulin-dependent protein kinase II (CAMKII) and the glycine receptor, mRNA for one subunit (the α subunits in these examples) is transported to the dendrite, whereas mRNA for the other subunit appears restricted to the cell soma (for reviews, see Steward 1997; Gao 1998). Could it be that the neuron synthesizes and transports all but those subunits critical for adjusting the functional protein levels at specific synapses, perhaps to optimize the rate of response following synaptic activity?

Protein synthesis in axons?

Not only does a neuron receive multiple synaptic inputs, its axon may also form multiple synaptic contacts with different post-synaptic neurons. Thus, the same issues concerning synapse-specific changes are likely to apply to both axons and dendrites. Axonal targeting of specific mRNAs has been shown for both vertebrate and invertebrate neurons (Mohr 1999; Martin et al. 2000). In invertebrate axons, protein synthetic machinery is readily detectable and local protein synthesis has been shown (Koenig and Giuditta 1999; Alvarez et al. 2000; Koenig et

al. 2000; Martin et al. 2000). Long-term facilitation induced by serotonin application specifically to the synapse between an *Aplysia* sensory neuron and one of its two postsynaptic motoneurons in culture requires protein synthesis within the sensory axon (Casadio et al. 1999). Thus, local protein synthesis in axons provides one mechanism for synapse-specific changes of the pre-synaptic neuron. However, this possibility runs counter to the doctrine that protein synthesis takes place in the soma but not in the axon, and it has been suggested that the restriction of synapses to the neuropils in invertebrates somehow blurs the distinction between axons and dendrites (Martin et al. 2000).

For vertebrate axons, the dogma holds that there is no local protein synthesis because ribosomes are not found in axons. How secure might be the argument, not seeing is disbelieving, in this case? Whole-mount staining of axoplasms extruded from goldfish or mammalian myelinated axons reveals periaxoplasmic plaques that contain RNA, ribosomal P protein, the signal recognition particle (SRP) protein SRP 54 as well as 7S RNA, a structural RNA of the SRP. These periaxoplasmic plaques are dispersed along the axon in the cortical region of the axoplasm, in the vicinity of the axonal cell membrane (Koenig et al. 2000). Given that these plaques are sparsely, although semi-regularly, distributed along the axon, it is perhaps not surprising that ribosomes are difficult to find in thin sections of the nerve with electron microscopy (Pannese and Ledda 1991). Moreover, local protein synthesis in the axon has been detected for cytoskeletal proteins (Eng et al. 1999; Koenig et al. 2000). This provides an attractive alternative to slow axonal transport, especially for axons that extend over great distances. Given that a neuron may form synapses with multiple target neurons, and considering the possibility that synaptic plasticity may involve presynaptic as well as postsynaptic changes that are specific to the synapse, it would be prudent to not totally disregard the possibility of protein synthesis in vertebrate axons.

Perspective

It should be clear from this review that relatively little is really known about the control of dendrite development and plasticity. For most of the questions, we have either no answer or at best some tentative answers. We think some of the most central issues to be addressed are as follows. (1) It is reasonably certain that the dendritic arbor of any given neuron is shaped by extrinsic factors (either diffusible or contact mediated), intrinsic genetic programs, as well as local regulators of cytoskeletal elements. Only a few of those molecular components are known. Identification of the rest of those molecules is an important first step. The challenge is then to know how the functions of those different sets of molecules are linked together to shape dendritic arbor, and whether they also contribute to the dynamic changes that underlie synaptic plasticity. (2) One of the most intriguing questions is how the dendritic field of each neuron is specified. We think a good place to start is to try to un-

derstand the molecular basis of tiling, that is, why the dendrites of neuron of the same type tend not to overlap, whereas dendrites of different types of neurons can overlap extensively. (3) It is important to appreciate that dendrites are extremely heterogeneous and have dynamic structure. Many dendrites have specialized structures such as dendritic spines. Further, ion channels, receptors, and other signaling molecules are distributed unevenly, forming a fine mosaic of microdomains in dendrites. It will be very important to understand how those signaling molecules are synthesized, transported, and targeted to various dendritic microdomains during development and as a result of experience. Eventually, the challenge is to use this information to understand the dendrite's computational ability. With the new techniques developed in the last few years (for review, see Scott and Luo 2001), researchers may now have the tools equal to the task. The first decade of the new millennium promises to be an interesting period for the study of dendrite.

Acknowledgments

We thank Liqun Luo, Wes Grueber, Mike Rothenberg, Gaia Tavosanis, Frank Bradke, Dan Cox, Patrick Haddick, and Kimberly Raab-Graham for very helpful comments on this review. Because of space limitation, we often had to cite reviews rather than the original papers. We apologize to the authors. The dendrite work in our laboratory is supported by National Institutes of Health Grant R01NS40929. We are both Investigators of the Howard Hughes Medical Institute.

References

- Aakalu, G., Smith, W.B., Nguyen, N., Jiang, C., and Schuman, E.M. 2001. Dynamic visualization of local protein synthesis in hippocampal neurons. *Neuron* **30**: 489–502.
- Agmon-Snir, H., Carr, C.E., and Rinzel, J. 1998. The role of dendrites in auditory coincidence detection. *Nature* **393**: 268–272.
- Alvarez, J., Giuditta, A., and Koenig, E. 2000. Protein synthesis in axons and terminals: Significance for maintenance, plasticity and regulation of phenotype. With a critique of slow transport theory. *Prog. Neurobiol.* **62**: 1–62.
- Baas, P.W. 1999. Microtubules and neuronal polarity: Lessons from mitosis. *Neuron* **22**: 23–31.
- Bailey, C.H. and Kandel, E.R. 1993. Structural changes accompanying memory storage. *Annu. Rev. Physiol.* **55**: 397–426.
- Baillat, G., Moqrich, A., Castets, F., Baude, A., Bailly, Y., Benmerah, A., and Monneron, A. 2001. Molecular cloning and characterization of phocein, a protein found from the golgi complex to dendritic spines. *Mol. Biol. Cell* **12**: 663–673.
- Baptista, C.A., Hatten, M.E., Blazeski, R., and Mason, C.A. 1994. Cell-cell interactions influence survival and differentiation of purified Purkinje cells in vitro. *Neuron* **12**: 243–260.
- Bellaiche, Y., Ghoo, M., Kaltschmidt, J.A., Brand, A.H., and Schweisguth, F. 2001. Frizzled regulates localization of cell-fate determinants and mitotic spindle rotation during asymmetric cell division. *Nat. Cell. Biol.* **3**: 50–57.
- Bradke, F. and Dotti, C.G. 1999. The role of local actin stability in axon formation. *Science* **283**: 1931–1934.

- Bradke, F. and Dotti, C.G. 2000. Establishment of neuronal polarity: Lessons from cultured hippocampal neurons. *Curr. Opin. Neurobiol.* **10**: 574–581.
- Casadio, A., Martin, K.C., Giustetto, M., Zhu, H., Chen, M., Bartsch, D., Bailey, C.H., and Kandel, E.R. 1999. A transient, neuron-wide form of CREB-mediated long-term facilitation can be stabilized at specific synapses by local protein synthesis. *Cell* **99**: 221–237.
- Chen, L., Chetkovich, D.M., Petralia, R.S., Sweeney, N.T., Kawasaki, Y., Wenthold, R.J., Brecht, D.S., and Nicoll, R.A. 2000. Stargazing regulates synaptic targeting of AMPA receptors by two distinct mechanisms. *Nature* **408**: 936–943.
- Cline, H.T. 2001. Dendritic arbor development and synaptogenesis. *Curr. Opin. Neurobiol.* **11**: 118–126.
- Colbert, C.M., Magee, J.C., Hoffman, D.A., and Johnston, D. 1997. Slow recovery from inactivation of Na⁺ channels underlies the activity-dependent attenuation of dendritic action potentials in hippocampal CA1 pyramidal neurons. *J. Neurosci.* **17**: 6512–6521.
- Colman, D.R. 1999. Neuronal polarity and the epithelial metaphor. *Neuron* **23**: 649–651.
- Comery, T.A., Harris, J.B., Willems, P.J., Oostra, B.A., Irwin, S.A., Weiler, J.J., and Greenough, W.T. 1997. Abnormal dendritic spines in fragile X knockout mice: Maturation and pruning deficits. *Proc. Natl. Acad. Sci.* **94**: 5401–5404.
- Craig, A.M. and Banker, G. 1994. Neuronal polarity. *Annu. Rev. Neurosci.* **17**: 267–310.
- Denk, W., Sugimori, M., and Llinas, R. 1995. Two types of calcium response limited to single spines in cerebellar Purkinje cells. *Proc. Natl. Acad. Sci.* **92**: 8279–8282.
- Devries, S.H. and Baylor, D.A. 1997. Mosaic arrangement of ganglion cell receptive fields in rabbit retina. *J. Neurophysiol.* **78**: 2048–2060.
- Dotti, C.G. and Banker, G.A. 1987. Experimentally induced alteration in the polarity of developing neurons. *Nature* **330**: 254–256.
- Dotti, C.G. and Simons, K. 1990. Polarized sorting of viral glycoproteins to the axon and dendrites of hippocampal neurons in culture. *Cell* **62**: 63–72.
- Dotti, C.G., Sullivan, C.A., and Banker, G.A. 1988. The establishment of polarity by hippocampal neurons in culture. *J. Neurosci.* **8**: 1454–1468.
- Eilers, J. and Konnerth, A. 1997. Dendritic signal integration. *Curr. Opin. Neurobiol.* **7**: 385–390.
- Elston, G.N. 2000. Pyramidal cells of the frontal lobe: All the more spinous to think with. *J. Neurosci.* **20**: RC95.
- Elston, G.N. and Rosa, M.G. 1997. The occipitoparietal pathway of the macaque monkey: Comparison of pyramidal cell morphology in layer III of functionally related cortical visual areas. *Cereb. Cortex* **7**: 432–452.
- . 1998. Morphological variation of layer III pyramidal neurons in the occipitotemporal pathway of the macaque monkey visual cortex. *Cereb. Cortex* **8**: 278–294.
- Elston, G.N., Tweedale, R., and Rosa, M.G.P. 1999. Cortical integration in the visual system of the macaque monkey: Large scale morphological differences of pyramidal neurons in the occipital, parietal and temporal lobes. *Proc. Roy. Soc. London B* **266**: 1367–1374.
- Eng, H., Lund, K., and Campenot, R.B. 1999. Synthesis of β -tubulin, actin, and other proteins in axons of sympathetic neurons in compartmented cultures. *J. Neurosci.* **19**: 1–9.
- Engert, F. and Bonhoeffer, T. 1999. Dendritic spine changes associated with hippocampal long-term synaptic plasticity. *Nature* **399**: 66–70.
- Feng, J., Yan, Z., Ferreira, A., Tomizawa, K., Liauw, J.A., Zhuo, M., Allen, P.B., Ouimet, C.C., and Greengard, P. 2000. Synphilin regulates the formation and function of dendritic spines. *Proc. Natl. Acad. Sci.* **97**: 9287–9292.
- Fischer, M., Kaech, S., Knutti, D., and Matus, A. 1998. Rapid actin-based plasticity in dendritic spines. *Neuron* **20**: 847–854.
- Foletti, D.L., Prekeris, R., and Scheller, R.H. 1999. Generation and maintenance of neuronal polarity: Mechanisms of transport and targeting. *Neuron* **23**: 641–644.
- Fuchs, E. and Karakesisoglou, I. 2001. Bridging cytoskeletal intersections. *Genes & Dev.* **15**: 1–14.
- Gao, F.B. 1998. Messenger RNAs in dendrites: Localization, stability, and implications for neuronal function. *BioEssays* **20**: 70–78.
- Gao, F.B., Brenman, J.E., Jan, L.Y., and Jan, Y.N. 1999. Genes regulating dendritic outgrowth, branching, and routing in *Drosophila*. *Genes & Dev.* **13**: 2549–2561.
- Gao, F.B., Kohwi, M., Brenman, J.E., Jan, L.Y., and Jan, Y.N. 2000. Control of dendritic field formation in *Drosophila*: The roles of flamingo and competition between homologous neurons. *Neuron* **28**: 91–101.
- Gardioli, A., Racca, C., and Triller, A. 1999. Dendritic and post-synaptic protein synthetic machinery. *J. Neurosci.* **19**: 168–179.
- Gho, M., Bellaiche, Y., and Schweisguth, F. 1999. Revisiting the *Drosophila* microchaete lineage: A novel intrinsically asymmetric cell division generates a glial cell. *Development* **126**: 3573–3584.
- Ghosh, A. 2000. Dendritic growth: Don't go says flamingo. *Neuron* **28**: 3–4.
- Ghysen, A., Dambly-Chaudière, C., Jan, L.Y., and Jan, Y.N. 1993. Cell interactions and gene interactions in peripheral neurogenesis. *Genes & Dev.* **7**: 723–733.
- GINIGER, E. 1998. A role for Abl in Notch signaling. *Neuron* **20**: 667–681.
- Golding, N.L. and Spruston, N. 1998. Dendritic sodium spikes are variable triggers of axonal action potentials in hippocampal CA1 pyramidal neurons. *Neuron* **21**: 1189–1200.
- Golding, N.L., Jung, H.Y., Mickus, T., and Spruston, N. 1999. Dendritic calcium spike initiation and repolarization are controlled by distinct potassium channel subtypes in CA1 pyramidal neurons. *J. Neurosci.* **19**: 8789–8798.
- Goslin, K. and Banker, G. 1989. Experimental observations on the development of polarity by hippocampal neurons in culture. *J. Cell. Biol.* **108**: 1507–1516.
- Gregory, S.L. and Brown, N.H. 1998. *kakapo*, a gene required for adhesion between and within cell layers in *Drosophila*, encodes a large cytoskeletal linker protein related to plectin and dystrophin. *J. Cell. Biol.* **143**: 1271–1282.
- Harris, K.M. 1999. Structure, development, and plasticity of dendritic spines. *Curr. Opin. Neurobiol.* **9**: 343–348.
- Hausser, M., Spruston, N., and Stuart, G.J. 2000. Diversity and dynamics of dendritic signaling. *Science* **290**: 739–744.
- Helmchen, F., Svoboda, K., Denk, W., and Tank, D.W. 1999. In vivo dendritic calcium dynamics in deep-layer cortical pyramidal neurons. *Nat. Neurosci.* **2**: 989–996.
- Hille, B. 2001. *Ionic channels of excitable membranes*. Sinauer Associates, Sunderland, MA.
- Hoffman, D.A., Magee, J.C., Colbert, C.M., and Johnston, D. 1997. K⁺ channel regulation of signal propagation in dendrites of hippocampal pyramidal neurons. *Nature* **387**: 869–875.
- Hogan, B.L. 1999. Morphogenesis. *Cell* **96**: 225–233.
- Horch, H.W., Kruttgen, A., Portbury, S.D., and Katz, L.C. 1999. Destabilization of cortical dendrites and spines by BDNF. *Neuron* **23**: 353–364.
- Huang, E.P. 1999. Synaptic plasticity: Regulated translation in

- dendrites. *Curr. Biol.* **9**: R168–R170.
- Huber, K.M., Kayser, M.S., and Bear, M.F. 2000. Role for rapid dendritic protein synthesis in hippocampal mGluR-dependent long-term depression. *Science* **288**: 1254–1257.
- Johnston, D., Hoffman, D.A., Colbert, C.M., and Magee, J.C. 1999. Regulation of back-propagating action potentials in hippocampal neurons. *Curr. Opin. Neurobiol.* **9**: 288–292.
- Kang, H. and Schuman, E.M. 1996. A requirement for local protein synthesis in neurotrophin-induced hippocampal synaptic plasticity. *Science* **273**: 1402–1406.
- Kennedy, M.B. 2000. Signal-processing machines at the post-synaptic density. *Science* **290**: 750–754.
- Kiebler, M.A. and DesGroseillers, L. 2000. Molecular insights into mRNA transport and local translation in the mammalian nervous system. *Neuron* **25**: 19–28.
- Kiebler, M.A., Hemraj, I., Verkade, P., Kohrmann, M., Fortes, P., Marion, R.M., Ortin, J., and Dotti, C.G. 1999. The mammalian stau protein localizes to the somatodendritic domain of cultured hippocampal neurons: Implications for its involvement in mRNA transport. *J. Neurosci.* **19**: 288–297.
- Kirsch, J. 1999. Assembly of signaling machinery at the post-synaptic membrane. *Curr. Opin. Neurobiol.* **9**: 329–335.
- Koch, C. and Segev, I. 2000. The role of single neurons in information processing. *Nat. Neurosci.* **3 Suppl**: 1171–1177.
- Koenig, E. and Giuditta, A. 1999. Protein-synthesizing machinery in the axon compartment. *Neuroscience* **89**: 5–15.
- Koenig, E., Martin, R., Titmus, M., and Sotelo-Silveira, J.R. 2000. Cryptic peripheral ribosomal domains distributed intermittently along mammalian myelinated axons. *J. Neurosci.* **20**: 8390–8400.
- Kolodziej, P.A., Jan, L.Y., and Jan, Y.N. 1995. Mutations that affect the length, fasciculation, or ventral orientation of specific sensory axons in the *Drosophila* embryo. *Neuron* **15**: 273–286.
- Lee, T. and Luo, L. 1999. Mosaic analysis with a repressible neurotechnique cell marker for studies of gene function in neuronal morphogenesis. *Neuron* **22**: 451–461.
- Lein, P., Johnson, M., Guo, X., Rueger, D., and Higgins, D. 1995. Osteogenic protein-1 induces dendritic growth in rat sympathetic neurons. *Neuron* **15**: 597–605.
- Lendvai, B., Stern, E.A., Dhen, B., and Svoboda, K. 2000. Experience-dependent plasticity of dendritic spines in the developing rat barrel cortex in vivo. *Nature* **404**: 876–881.
- Liu, S.Q. and Cull-Candy, S.G. 2000. Synaptic activity at calcium-permeable AMPA receptors induces a switch in receptor subtype. *Nature* **405**: 454–458.
- Lu, B., Roegiers, F., Jan, L.Y., and Jan, Y.N. 2001. Adherens junctions inhibit asymmetric division in the *Drosophila* epithelium. *Nature* **409**: 522–525.
- Luo, L. 2000. Rho GTPases in neuronal morphogenesis. *Nat. Rev. Neurosci.* **1**: 173–180.
- Luo, Y., Raible, D., and Raper, J.A. 1993. Collapsin: A protein in brain that induces the collapse and paralysis of neuronal growth cones. *Cell* **75**: 217–227.
- Lüscher, C., Nicoll, R.A., Malenka, R.C., and Muller, D. 2000. Synaptic plasticity and dynamic modulation of the postsynaptic membrane. *Nat. Neurosci.* **3**: 545–550.
- MacNeil, M.A. and Masland, R.H. 1998. Extreme diversity among amacrine cells: Implications for function. *Neuron* **20**: 971–982.
- Magee, J.C. 1998. Dendritic hyperpolarization-activated currents modify the integrative properties of hippocampal CA1 pyramidal neurons. *J. Neurosci.* **18**: 7613–7624.
- Magee, J.C. and Cook, E.P. 2000. Somatic EPSP amplitude is independent of synapse location in hippocampal pyramidal neurons. *Nat. Neurosci.* **3**: 895–903.
- Magee, J.C. and Johnston, D. 1995. Characterization of single voltage-gated Na⁺ and Ca²⁺ channels in apical dendrites of rat CA1 pyramidal neurons. *J. Physiol.* **487**: 67–90.
- . 1997. A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. *Science* **275**: 209–213.
- Malenka, R.C. and Nicoll, R.A. 1999. Long-term potentiation — a decade of progress? *Science* **285**: 1870–1874.
- Maletic-Savatic, M., Malinow, R., and Svoboda, K. 1999. Rapid dendritic morphogenesis in CA1 hippocampal dendrites induced by synaptic activity. *Science* **283**: 1923–1927.
- Malinow, R., Mainen, Z.F., and Hayashi, Y. 2000. LTP mechanisms: From silence to four-lane traffic. *Curr. Opin. Neurobiol.* **10**: 352–357.
- Mantyh, P.W., DeMaster, E., Malhotra, A., Ghilardi, J.R., Rogers, S.D., Mantyh, C.R., Liu, H., Basbaum, A.I., Vigna, S.R., Maggio, J.E., et al. 1995. Receptor endocytosis and dendrite reshaping in spinal neurons after somatosensory stimulation. *Science* **268**: 1629–1632.
- Margrie, T.W., Sakmann, B., and Urban, N.N. 2001. Action potential propagation in mitral cell lateral dendrites is decremental and controls recurrent and lateral inhibition in the mammalian olfactory bulb. *Proc. Natl. Acad. Sci.* **98**: 319–324.
- Markram, H., Lubke, J., Frotscher, M., and Sakmann, B. 1997. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* **275**: 213–215.
- Martin, K.C., Barad, M., and Kandel, E.R. 2000. Local protein synthesis and its role in synapse-specific plasticity. *Curr. Opin. Neurobiol.* **10**: 587–592.
- Martina, M., Vida, I., and Jonas, P. 2000. Distal initiation and active propagation of action potentials in interneuron dendrites. *Science* **287**: 295–300.
- Matus, A. 2000. Actin-based plasticity in dendritic spines. *Science* **290**: 754–758.
- Mayford, M., Baranes, D., Podsypanina, K., and Kandel, E.R. 1996. The 3′-untranslated region of CaMKII α is a cis-acting signal for the localization and translation of mRNA in dendrites. *Proc. Natl. Acad. Sci.* **93**: 13250–13255.
- McAllister, A.K., Lo, D.C., and Katz, L.C. 1995. Neurotrophins regulate dendritic growth in developing visual cortex. *Neuron* **15**: 791–803.
- McAllister, A.K., Katz, L.C., and Lo, D.C. 1996. Neurotrophin regulation of cortical dendritic growth requires activity. *Neuron* **17**: 1057–1064.
- . 1997. Opposing roles for endogenous BDNF and NT-3 in regulating cortical dendritic growth. *Neuron* **18**: 767–778.
- Messersmith, E.K., Leonardo, E.D., Shatz, C.J., Tessier-Lavigne, M., Goodman, C.S., and Kolodkin, A.L. 1995. Semaphorin III can function as a selective chemorepellent to pattern sensory projections in the spinal cord. *Neuron* **14**: 949–959.
- Mickus, T., Jung, H., and Spruston, N. 1999. Properties of slow, cumulative sodium channel inactivation in rat hippocampal CA1 pyramidal neurons. *Biophys. J.* **76**: 846–860.
- Miyata, M., Finch, E.A., Khiroug, L., Hashimoto, K., Hayasaka, S., Oda, S.I., Inouye, M., Takagishi, Y., Augustine, G.J., and Kano, M. 2000. Local calcium release in dendritic spines required for long-term synaptic depression. *Neuron* **28**: 233–244.
- Mohr, E. 1999. Subcellular RNA compartmentalization. *Prog. Neurobiol.* **57**: 507–525.
- Mori, Y., Imaizumi, K., Katayama, T., Yoneda, T., and Tohyama, M. 2000. Two cis-acting elements in the 3′ untranslated region of α -CaMKII regulate its dendritic targeting. *Nat. Neurosci.* **3**: 1079–1084.
- Myers, P.Z., Eisen, J.S., and Westerfield, M. 1986. Development

- and axonal outgrowth of identified motoneurons in the zebrafish. *J. Neurosci.* **6**: 2278–2289.
- Nedivi, E., Wu, G.Y., and Cline, H.T. 1998. Promotion of dendritic growth by CPG15, an activity-induced signaling molecule. *Science* **281**: 1863–1866.
- Nelson, R., von Litzow, A., Kolb, H., and Gouras, P. 1975. Horizontal cells in cat retina with independent dendritic systems. *Science* **189**: 137–139.
- Nusslein-Volhard, C. and Wieschaus, E. 1980. Mutations affecting segment number and polarity in *Drosophila*. *Nature* **287**: 795–801.
- Orgogozo, V., Schweisguth, F., and Bellaiche, Y. 2001. Lineage, cell polarity and inscuteable function in the peripheral nervous system of the *Drosophila* embryo. *Development* **128**: 631–643.
- Pannese, E. and Ledda, M. 1991. Ribosomes in myelinated axons of the rabbit spinal ganglion neurons. *J. Submicrosc. Cytol. Pathol.* **23**: 33–38.
- Penzes, P., Johnson, R.C., Sattler, R., Zhang, X., Huganir, R.L., Kambampati, V., Mains, R.E., and Eipper, B.A. 2001. The neuronal Rho-GEF Kalirin-7 interacts with PDZ domain-containing proteins and regulates dendritic morphogenesis. *Neuron* **29**: 229–242.
- Petrozzino, J.J., Pozzo Miller, L.D., and Connor, J.A. 1995. Micromolar Ca²⁺ transients in dendritic spines of hippocampal pyramidal neurons in brain slice. *Neuron* **14**: 1223–1231.
- Pierce, J.P., Mayer, T., and McCarthy, J.B. 2001. Evidence for a satellite secretory pathway in neuronal dendritic spines. *Curr. Biol.* **11**: 351–355.
- Pinkstaff, J.K., Chappell, S.A., Mauro, V.P., Edelman, G.M., and Krushel, L.A. 2001. Internal initiation of translation of five dendritically localized neuronal mRNAs. *Proc. Natl. Acad. Sci.* **98**: 2770–2775.
- Poirazi, P. and Mel, B.W. 2001. Impact of active dendrites and structural plasticity on the memory capacity of neural tissue. *Neuron* **29**: 779–796.
- Polleux, F., Morrow, T., and Ghosh, A. 2000. Semaphorin 3A is a chemoattractant for cortical apical dendrites. *Nature* **404**: 567–573.
- Popov, V.I., Bocharova, L.S., and Bragin, A.G. 1992. Repeated changes of dendritic morphology in the hippocampus of ground squirrels in the course of hibernation. *Neuroscience* **48**: 45–51.
- Prokop, A., Uhler, J., Roote, J., and Bate, M. 1998. The kakapo mutation affects terminal arborization and central dendritic sprouting of *Drosophila* motoneurons. *J. Cell. Biol.* **143**: 1283–1294.
- Quinlan, E.M., Philpot, B.D., Huganir, R.L., and Bear, M.F. 1999. Rapid, experience-dependent expression of synaptic NMDA receptors in visual cortex in vivo. *Nat. Neurosci.* **2**: 352–357.
- Quirk, M.C., Blum, K.I., and Wilson, M.A. 2001. Experience-dependent changes in extracellular spike amplitude may reflect regulation of dendritic action potential back-propagation in rat hippocampal pyramidal cells. *J. Neurosci.* **21**: 240–248.
- Ramón y Cajal, S. 1911. *Histology of the nervous system of man and vertebrates*, (1995 translation). Oxford University Press, Oxford, UK.
- Redmond, L. and Ghosh, A. 2001. The role of Notch and Rho GTPase signaling in the control of dendritic development. *Curr. Opin. Neurobiol.* **11**: 111–117.
- Redmond, L., Oh, S.R., Hicks, C., Weinmaster, G., and Ghosh, A. 2000. Nuclear Notch1 signaling and the regulation of dendritic development. *Nat. Neurosci.* **3**: 30–40.
- Roegiers, F., Younger-Shepherd, S., Jan, L.Y., and Jan, Y.N. 2001. Two types of asymmetric divisions in the *Drosophila* sensory organ precursor cell lineage. *Nat. Cell. Biol.* **3**: 58–67.
- Sabatini, B.L. and Svoboda, K. 2000. Analysis of calcium channels in single spines using optical fluctuation analysis. *Nature* **408**: 589–593.
- Scott, E.K. and Luo, L. 2001. How do dendrites take their shape? *Nat. Neurosci.* **4**: 359–365.
- Segal, I., Korkotian, I., and Murphy, D.D. 2000. Dendritic spine formation and pruning: Common cellular mechanisms? *Trends Neurosci.* **23**: 53–57.
- Segal, M. and Andersen, P. 2000. Dendritic spines shaped by synaptic activity. *Curr. Opin. Neurobiol.* **10**: 582–586.
- Segev, I. and London, M. 2000. Untangling dendrites with quantitative models. *Science* **290**: 744–750.
- Sestan, N., Artavanis-Tsakonas, S., and Rakic, P. 1999. Contact-dependent inhibition of cortical neurite growth mediated by notch signaling. *Science* **286**: 741–746.
- Sheetz, M.P., Pfister, K.K., Bulinski, J.C., and Cotman, C.W. 1998. Mechanisms of trafficking in axons and dendrites: Implications for development and neurodegeneration. *Prog. Neurobiol.* **55**: 577–594.
- Shi, S.H., Hayashi, Y., Esteban, J.A., and Malinow, R. 2001. Subunit-specific rules governing AMPA receptor trafficking to synapses in hippocampal pyramidal neurons. *Cell* **105**: 331–343.
- Spruston, N., Schiller, Y., Stuart, G., and Sakmann, B. 1995. Activity-dependent action potential invasion and calcium influx into hippocampal CA1 dendrites. *Science* **268**: 297–300.
- Stevens, C.F. 1998. Neuronal diversity: Too many cell types for comfort? *Curr. Biol.* **8**: R708–R710.
- Steward, O. 1997. mRNA localization in neurons: A multipurpose mechanism? *Neuron* **18**: 9–12.
- Steward, O. and Schuman, E.M. 2001. Protein synthesis at synaptic sites on dendrites. *Annu. Rev. Neurosci.* **24**: 299–325.
- Steward, O. and Worley, P.F. 2001. Selective targeting of newly synthesized arc mRNA to active synapses requires NMDA receptor activation. *Neuron* **30**: 227–240.
- Steward, O., Wallace, C.S., Lyford, G.L., and Worley, P.F. 1998. Synaptic activation causes the mRNA for the IEG Arc to localize selectively near activated postsynaptic sites on dendrites. *Neuron* **21**: 741–751.
- Strumpf, D. and Volk, T. 1998. Kakapo, a novel cytoskeletal-associated protein is essential for the restricted localization of the neuregulin-like factor, vein, at the muscle-tendon junction site. *J. Cell. Biol.* **143**: 1259–1270.
- Stuart, G. and Häusser, M. 1994. Initiation and spread of sodium action potentials in cerebellar Purkinje cells. *Neuron* **13**: 703–712.
- . 2001. Dendritic coincidence detection of EPSPs and action potentials. *Nat. Neurosci.* **4**: 63–71.
- Stuart, G., Spruston, N., Sakmann, B., and Häusser, M. 1997. Action potential initiation and backpropagation in neurons of the mammalian CNS. *Trends Neurosci.* **20**: 125–131.
- Stuart, G., Spruston, N., and Häusser, M. 2000. *Dendrites*. Oxford University Press, Cary, NC.
- Usui, T., Shima, Y., Shimada, Y., Hirano, S., Burgess, R.W., Schwarz, T.L., Takeichi, M., and Uemura, T. 1999. Flamingo, a seven-pass transmembrane cadherin, regulates planar cell polarity under the control of Frizzled. *Cell* **98**: 585–595.
- Vactor, D.V., Sink, H., Fambrough, D., Tsoo, R., and Goodman, C.S. 1993. Genes that control neuromuscular specificity in *Drosophila*. *Cell* **73**: 1137–1153.
- Wassle, H., Peichl, L., and Boycott, B.B. 1981. Dendritic territories of cat retinal ganglion cells. *Nature* **292**: 344–345.
- Weiler, I.J., Irwin, S.A., Klintsova, A.Y., Spencer, C.M., Brazel-

- ton, A.D., Miyashiro, K., Comery, T.A., Patel, B., Eberwine, J., and Greenough, W.T. 1997. Fragile X mental retardation protein is translated near synapses in response to neurotransmitter activation. *Proc. Natl. Acad. Sci.* **94**: 5395–5400.
- Wells, D.G., Richter, J.D., and Fallon, J.R. 2000. Molecular mechanisms for activity-regulated protein synthesis in the synapto-dendritic compartment. *Curr. Opin. Neurobiol.* **10**: 132–137.
- Westerfield, M., McMurray, J.V., and Eisen, J.S. 1986. Identified motoneurons and their innervation of axial muscles in the zebrafish. *J. Neurosci.* **6**: 2267–2277.
- Williams, S.R. and Stuart, G.J. 2000a. Action potential back-propagation and somato-dendritic distribution of ion channels in thalamocortical neurons. *J. Neurosci.* **20**: 1307–1317.
- . 2000b. Site independence of EPSP time course is mediated by dendritic I(h) in neocortical pyramidal neurons. *J. Neurophysiol.* **83**: 3177–3182.
- Wilson, C.J. and Kawaguchi, Y. 1996. The origins of two-state spontaneous membrane potential fluctuations of neostriatal spiny neurons. *J. Neurosci.* **16**: 2397–2410.
- Winckler, B. and Mellman, I. 1999. Neuronal polarity: Controlling the sorting and diffusion of membrane components. *Neuron* **23**: 637–640.
- Wu, G.Y., Deisseroth, K., and Tsien, R.W. 2001. Spaced stimuli stabilize MAPK pathway activation and its effects on dendritic morphology. *Nat. Neurosci.* **4**: 151–158.
- Yoshihara, Y., Nagao, H., and Mori, K. 2001. Neurobiology. Sniffing out odors with multiple dendrites. *Science* **291**: 835–837.
- Young, S.R. and Rubel, E.W. 1986. Embryogenesis of arborization pattern and topography of individual axons in N. laminaris of the chicken brain stem. *J. Comp. Neurol.* **254**: 425–459.
- Yu, W., Cook, C., Sauter, C., Kuriyama, R., Kaplan, P.L., and Baas, P.W. 2000. Depletion of a microtubule-associated motor protein induces the loss of dendritic identity. *J. Neurosci.* **20**: 5782–5791.
- Yuste, R. and Denk, W. 1995. Dendritic spines as basic functional units of neuronal integration. *Nature* **375**: 682–684.
- Yuste, R., Majewska, A., Cash, S.S., and Denk, W. 1999. Mechanisms of calcium influx into hippocampal spines: Heterogeneity among spines, coincidence detection by NMDA receptors, and optical quantal analysis. *J. Neurosci.* **19**: 1976–1987.
- Zhu, J.J., Esteban, J.A., Hayashi, Y., and Malinow, R. 2000. Postnatal synaptic potentiation: Delivery of GluR4-containing AMPA receptors by spontaneous activity. *Nat. Neurosci.* **3**: 1098–1106.

Dendrites

Yuh-Nung Jan and Lily Yeh Jan

Genes Dev. 2001, **15**:

Access the most recent version at doi:[10.1101/gad.916501](https://doi.org/10.1101/gad.916501)

References

This article cites 146 articles, 50 of which can be accessed free at:
<http://genesdev.cshlp.org/content/15/20/2627.full.html#ref-list-1>

License

Email Alerting Service

Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article or [click here](#).