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Dendritic Integration in Mammalian Neurons, a Century after Cajal

Review

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Introduction

The role of dendrites in neuronal signal processing has been a topic of research for more than a century. Early work started with Cajal's original postulate that dendrites constitute the input side of the neuron and culminated in the idea that dendrites are passive cables. Later studies, however, showed that dendrites could produce action potentials.

Here, we review within a historical perspective recent experimental work on the function of mammalian dendrites that has used novel approaches such as imaging of calcium concentration and dendritic patch recording. We do not intend an exhaustive review of the field of dendritic physiology nor cover appropriately progress in invertebrate preparations (Borst and Egelhaaf, 1994), but instead focus on a few experimental studies from pyramidal and Purkinje neurons.

These new findings have provided direct evidence for active conductances in dendrites and chemical compartmentalization in spines. Although the logic of dendritic processing is still unclear, new results show that mammalian dendrites have a rich repertoire of electrical and chemical dynamics, suggesting that individual neurons are capable of sophisticated information processing. Combining these novel technologies with studies in behaving animals will greatly help in understanding dendritic integration.

> *In any case, contemplating the form of the cells was one of my most beloved pleasures. Because even from an aesthetic point of view the nervous tissue has fascinating beauty. Are there in our parks any more elegant and lush trees than the Purkinje neuron in the cerebellum or the so-called psychical cell, that is, the famous cortical pyramidal neuron?* (Ramón y Cajal, 1923)

Brief History of Dendritic Research

In the Beginning, There Was Cajal

Deiters is credited as the first to realize that neurons had two morphologically different types of neuronal processes (Deiters, 1865): a long, thin, and unbranched process, named axon after the Greek word for axle (Kölliker, 1889), and the "protoplasmic processes," multiple and branched, and named dendrites after the Greek word for tree, dendron (His, 1893). These anatomical descriptions led to the question of the propagation of the nervous impulse. As Ramón y Cajal (1923) put it, "Does the nervous impulse propagate in all directions, like sound or light, or does it constantly flow in one direction, like water running in a water-mill?"

In 1889, Cajal noticed that in both retina and olfactory bulb dendrites are always oriented toward the external world, while axons are always oriented toward more central neural centers. Based on this observation, he proposed that dendrites conduct current toward the cell body (i.e., centripetally), while axons conduct current away from the cell body and toward other nervous centers (Ramón y Cajal, 1889). Nevertheless, to his dismay, he realized that centripetal current conduction in dendrites could not constitute a general rule of operation in the nervous system because of two contradictory pieces of evidence from his own work: the first one in the optic tectum, where neuronal fields were composed exclusively of dendrites, and the second in sensory ganglia, where axonal-looking processes were oriented toward the periphery. These contradictions caused him to abandon his hypothesis (Ramón y Cajal, 1923).

However, Cajal reexamined this issue 2 years later in response to a severe criticism of his centripetal theory (Van Gehuchten, 1891). Fortunately for him, his brother Pedro had just finished, in his doctoral thesis, a more complete study of the optic tectum, finding that the regions previously considered by Cajal to be composed only of dendrites also had rich axonal terminations (Ramón, 1890). Cajal also then realized that the processes in sensory ganglion neurons that appeared to be axons were, in fact, dendrites (Ramón y Cajal, 1923). Therefore, the two major obstacles to the theory were removed and he proposed the "law of functional polarization:"

> The transmission of the nervous movement always occurs from the protoplasmic branches (dendrites) and cell body towards the axon or functional expansion. Every neuron, then, has a receptive apparatus, which is the soma and protoplasmic prolongations (dendrites), an emitting apparatus, the axon, and a distributing apparatus, the terminal axonal arbors. (Ramón y Cajal, 1891a)

This law, however, did not explain some instances in which the axon originates directly from the dendrite, so he coined a new, final, law in 1897, the so-called "axipetal polarization law:"

> The soma and dendrites have axipetal conduction, i.e., they transmit the nervous waves towards the axon. Inversely, the axon has somatofugal or dendrofugal conduction, propagating the impulses received by the soma or dendrites towards the terminal arborizations. (Ramón y Cajal, 1897)

Thus, dendrites constituted the input side of the neuron, while the axon constituted its output side. It is a tribute to Cajal's foresight that his law basically still stands, over a hundred years from its first proposal. Nevertheless, it is now apparent that there are several important exceptions to his rule, in cases where information is conveyed from the soma or axon back to the dendritic tree and where dendrites also serve as the output side of the neuron (see below).

Passive Dendrites: Motoneurons and Cable Equations

After this initial progress, dendritic research remained in the background of neurobiological studies until the middle of this century, when a golden age for ideas of passive dendrites flourished. This renaissance was fueled by two technical advances: intracellular recording (Hyde, 1921; Ling and Gerard, 1949) and cable theory (Hermann, 1905; Hodgkin and Rushton, 1946; Rall, 1995).

Intracellular recordings with glass microelectrodes enabled investigators for the first time to look into the internal electrophysiology of the neuron. This approach was systematically developed in studies of spinal cord motoneurons (Brock et al., 1952). Two key findings were the existence of excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs) (Coombs et al., 1955a, 1955b) and the generation of the action potential at the axon initial segment (IS) (Fuortes et al., 1957). An integrative model was proposed: dendrites passively summated the net current resulting from EPSPs and IPSPs and electrotonically conveyed it to the IS, where it would trigger an action potential that would then travel down the axon (Fatt, 1957; Coombs et al., 1957). Although investigators did not negate that dendrites also had active properties and in fact proposed that the IS spike secondarily triggered a somatic–dendritic (SD) spike (Eccles, 1964), the passive model dominated dendritic physiology and still today is taught in textbooks.

The behavior of passive dendritic trees was set on a firm theoretical foundation by the application of cable theory to dendrites by Rall (1959) (for a compilation of Rall's work, see Rall, 1995). He derived and, in some cases, analytically solved the equations describing the flow of electric currents in model dendritic trees receiving different spatiotemporal patterns of synaptic input. Rall introduced the concept of electrotonic structure of dendritic trees and defined the basic cable parameters: R_m, membrane resistance; R_i, internal resistance; C_m, membrane capacitance; λ, cable length; ρ, dendritic-to-soma conductance ratio. His results characterized the attenuation of inputs produced by dendrites, illustrating the asymmetric electrical behavior of the dendritic tree produced by the lower somatic impedance. Rall's explorations produced a quantitative picture of dendritic physiology that would influence experimental and theoretical dendritic research to this date.

Decremental Conduction: Dendritic Boosting

In this golden age of passive dendrites, Lorente de Nó and Coundouris (1959) proposed that dendrites could actively amplify synaptic inputs. In their influential paper, they reexamined the theory of decremental conduction in nerve fibers, which stated that nerve fibers conducted impulses of various magnitudes and that impulses decrease (or increase) gradually as they spread throughout the axons. They suggested that dendrites also showed decremental conduction and that their nerve impulses differed from those in axons only in their slower speed. Motivated by previous results from chromatolyzed motoneurons showing spike-like partial responses (Eccles et al., 1958) and spread of axonal impulses increased by excitatory synaptic impulses (Renshaw, 1942), they suggested two mechanisms for enhancing EPSPs: boosting of synaptic impulses produced by previous synaptic excitation and summation of synaptic currents taking place at dendritic branch points. Thus, the dendritic branching pattern and precise location of the inputs could make neurons particularly tuned to specific spatiotemporal patterns of excitation. In spite of this boosting, they argued against dendritic action potentials by pointing out that all-or-none events impoverish dendritic physiology by annihilating subtle temporal summations by subthreshold events.

Active Dendrites: Prepotentials and Dendritic Spikes

The time of active dendrites had arrived. Influential work came from experiments in chromatolyzed motoneurons (Eccles et al., 1958), Purkinje neurons (Llinás and Nicholson, 1971; Llinás and Hess, 1976), and pyramidal neurons (Spencer and Kandel, 1961; Andersen et al., 1966; Wong et al., 1979). These results introduced the idea of dendritic action potentials into the mainstream of dendritic research.

In an intracellular study of hippocampal neurons, Spencer and Kandel (1961) described fast prepotentials (FPPs), which were small potential steps immediately preceding full-blown spikes. They concluded that FPPs were spikes because of their all-or-none character and because their repolarization was faster than the membrane time constant. In their discussion, Spencer and Kandel proposed that FPPs were distant dendritic spikes produced in a "trigger zone," presumably associated with a bifurcation of the apical dendrite.

Although influential conceptually, prepotentials were not unambiguous experimental evidence for active dendrites (see below). Nevertheless, in a series of seminal papers, Llinás and collaborators ushered in a new era in dendritic physiology by recording intracellularly from dendrites of Purkinje neurons and demonstrating directly the existence of dendritic spikes (Llinás and Nicholson, 1971; Llinás and Hess, 1976; Llinás and Sugimori, 1980). Their main findings can be summarized in a picture of the Purkinje neuron in which dendrites produce plateau potentials and calcium spikes while the somatic region produces sodium spikes. Purkinje neurons would then have two distinct functional areas, the soma and the dendritic tree, with different active electrophysiological properties that completely dominate the passive cable parameters. In addition, to explain the different amplitudes of dendritic spikes, they suggested that multiple spike generation zones ("hot spots") existed in the dendritic tree, thus conferring functional independence to individual dendritic branches. Finally, this work introduced to the field of dendritic research the new technology of brain slices, making possible high quality intracellular recordings and thorough pharmacological manipulations (Yamamoto, 1972).

In later work, intradendritic recordings were also achieved in hippocampal pyramidal neurons (Wong et al., 1979). In response to current injection or spontaneous synaptic stimulation, a rich dendritic physiology of sodium and calcium spikes was found. These results were confirmed in surgically isolated dendrites (Bernardo et al., 1982).

Novel Imaging and Electrophysiological Techniques: A New Era for Dendritic Research

In the last decade, several new techniques have revolutionized dendritic research by offering more direct ways of probing dendritic function and answering questions about the spatial distribution of chemical or electrical activity. The first breakthrough was the synthesis of sensitive optical indicators of calcium concentration (reviewed by Tsien, 1989). This technology enabled measurements of the intracellular concentration of free calcium ion ($[Ca^{2+}]_i$) in dendrites and spines. These indicators would not have been so successful without new imaging technologies. Although some initial efforts were carried out with photodiode arrays (Ross et al., 1986; Ross and Werman, 1987), it was the advent of digital imaging using cooled charge-coupled device cameras (cCCD) that finally allowed systematic quantitative measurements of $[Ca^{2+}]_i$ dynamics in neurons (Connor, 1986; Tank et al., 1988; Jaffe et al., 1992).

Another crucial development has been the combination in brain slices of patch-clamp recording (Sakmann and Neher, 1983; Blanton et al., 1989; Edwards et al., 1989) with infrared video microscopy (Dodt and Zieglgänsberger, 1990; Figures 1 and 2). Even though dendritic recordings (Llinás and Hess, 1976), and even simultaneous dendritic and somatic recordings (Sugimori and Llinás, 1984, Soc. Neurosci., abstract; Wong and Steward, 1992), can be carried out with microelectrodes, infrared video microscopy makes it possible to patch and record systematically from identified cells or parts of a cell in slices (Stuart et al., 1993).

Finally, two new forms of microscopy have enabled high resolution imaging of dendrites in brain slices. The first one, confocal microscopy (Minski, 1961; Wilson and Sheppard, 1984; Fine et al., 1988), uses pinholes to exclude out of focus light, while the second one, two-photon microscopy (see Figure 4) (Denk et al., 1990), takes advantage of the restricted spatial profile of two-photon absorption (Goeppert-Mayer, 1931) to excite only fluorophores located at the focal point (Denk et al., 1994).

We will now review the contribution of these new techniques to central questions of dendritic function. Again, we will focus specifically on experimental research on Purkinje and pyramidal neurons.

Purkinje Cells Have Active Dendrites

Recent results have demonstrated the existence of active conductances in dendrites from Purkinje and pyramidal neurons, confirming proposals from pharmacological (Wu et al., 1986) and immunocytochemical localization studies (Westenbroek et al., 1990, 1992; Hillman et al., 1991; Angelides, 1994, Soc. Neurosci., abstract).

In Purkinje neurons, intracellular recordings with sharp microelectrodes showed dendritic calcium spikes and somatic sodium spikes (Llinás and Sugimori, 1980). This strongly suggests that calcium channels are present in dendrites, while sodium channels may be restricted to the soma. Calcium imaging results have confirmed that voltage-sensitive calcium channels (VSCCs) are indeed present in the dendrite, as well as in the soma (Ross and Werman, 1987; Tank et al., 1988). In these studies, calcium accumulations appeared throughout the dendrites whenever calcium spikes or plateau potentials took place. The fact that dendritic calcium accumulations occur immediately after calcium

Figure 1. Infrared Video Microscopy Imaging of a Pyramidal Neuron in a Neocortical Slice

Reprinted with permission from Dodt and Zieglgänsberger (1994). The photomicrograph shows a layer 5 pyramidal neuron in a 400 μm thick slice of rat visual cortex. The apical dendrite is clearly visible for approximately 250 μm. A patch pipette is used to record from the soma in whole-cell configuration. Picture taken with infrared gradient contrast imaging.

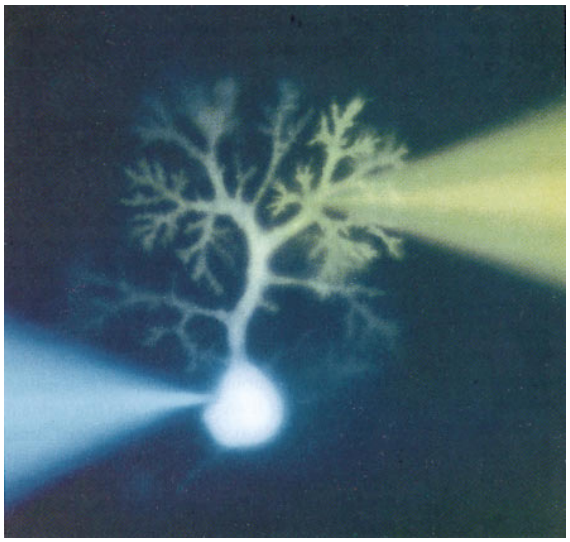

Figure 2. Photomicrograph of a Purkinje Neuron in Cerebellar Slice Filled during Simultaneous Somatic and Dendritic Recording with Two Patch Pipettes in Whole-Cell Configuration

Reprinted with permission from Stuart and Häusser, (1994). Each pipette has a different fluorescent dye, Cascade blue in the somatic one and Lucifer yellow in the dendritic one, which mix in the dendrite of the Purkinje cell.

spikes are triggered, together with the slow diffusion of calcium intracellularly (Hodgkin and Keynes, 1957; Allbritton et al., 1992), indicates that the calcium channels responsible for the spikes must be dendritic (Ross and Werman, 1987; Tank et al., 1988).

Are there sodium channels in dendrites of Purkinje cells? In the original recordings of Llinás and Sugimori (1980), small sodium spikelets were present in dendrites, and outside-out patches from dendrites have directly revealed dendritic sodium channels, although at much smaller densities than the soma (Stuart and Häusser, 1994). From the persistence of sodium spikes after somatic voltage clamp, it has been further argued that dendritic sodium channels can generate full-blown action potentials (Regehr et al., 1992). Nevertheless, combined intra- and extracellular recordings from the same neuron suggest that sodium and calcium spikes are generated by different compartments of the cell (Llinás and Sugimori, 1992). Finally, when the intracellular sodium concentration was imaged during synaptic stimulation, a small sodium influx was detected in dendrites, but was attributed to residual sodium influx through glutamate receptors (Callaway et al., submitted). Taken together, these results suggest that there are indeed dendritic sodium channels in Purkinje cells, but that their usual mode of operation may not be regenerative, although a persistent type of dendritic sodium channel may still significantly contribute to synaptic boosting (Llinás and Sugimori, 1980).

Pyramidal Neurons Have Active Dendrites

In hippocampus and neocortex, dendrites from pyramidal neurons have been shown to have both sodium and calcium channels by electrophysiological and imaging experiments.

Since the Spencer and Kandel experiments, somatic recordings of cortical pyramidal neurons have confirmed the existence of fast prepotentials in vivo after synaptic or sensory stimulation (Purpura and Shofer, 1964; Deschenes, 1981; Hirsch et al., 1995). These prepotentials are resistant to the sodium channel blocker QX-314, suggesting that they are calcium action potentials (Núñez et al., 1993; Hirsch et al., 1995). Although prepotentials may reflect neuronal coupling (MacVicar and Dudek, 1981; Núñez et al., 1990), intradendritic recordings from hippocampal and neocortical neurons have indeed demonstrated full-blown sodium and calcium spikes both in vitro (Schwartzkroin and Slawsky, 1977; Wong et al., 1979; Amitai et al., 1993; Kim and Connors, 1993; Stuart and Sakmann, 1994; Spruston et al., 1995) and in vivo (Houchin, 1973; Pockberger, 1991).

Confirmation of the existence of dendritic calcium channels by cCCD imaging has come in CA1 neurons (Regehr et al., 1989; Jaffe et al., 1992) and layer 5 cells (Yuste et al., 1994). This conclusion rests upon the same argument as the one developed above for cerebellar cells, i.e., the absence of delay between calcium accumulations and electrophysiological responses. Using confocal and two-photon imaging, calcium channels have even been specifically localized to dendritic shafts (Markram and Sakmann, 1994) and spine heads (Yuste and Denk, 1995). Therefore, it appears that the entire dendritic tree of pyramidal neurons is covered with calcium channels. Because a sodium spike is necessary to open those channels antidromically (Jaffe et al., 1992; Regehr and Tank, 1992; Spruston et al., 1995; Yuste and Denk, 1995), sodium channels must also be distributed throughout the dendritic tree, although it is unclear if they are present in spines (Angelides et al., 1995, IBRO, abstract). Finally, direct evidence comes from experiments demonstrating sodium and calcium channels in membrane patches from apical dendrites (Huguenard et al., 1989; Magee and Johnston, 1995a, 1995b). Thus, dendrites from the two populations of pyramidal neurons examined so far have sodium and calcium channels. In contrast with Purkinje cells, in pyramidal neurons both populations of channels appear to produce regenerative spikes in the dendrites.

What Are the Cable Properties of Dendrites?

Although Purkinje and pyramidal neurons have active dendrites, the passive cable properties of dendrites, determined by the three basic cable parameters (C_m, R_m, and R_i), are still necessary to understand dendritic function, since in the subthreshold regime dendrites could behave passively and since in the suprathreshold regime R_i and C_m and the dendritic geometry can affect the spatiotemporal properties of the spikes. Unfortunately, measurements of C_m and R_i in dendrites are difficult and present estimates are based on values that best fit numerical simulations of experimental data. Even R_m, which can be determined experimentally by fitting curves to the decays of hyperpolarizing current pulses (Rall, 1959), is influenced by conductances that are active at rest (Spruston et al., 1994) and may not even be constant throughout the cell (Shelton, 1985; Rapp et al., 1994).

Nevertheless, progress toward the estimation of the passive properties of the neuron has been made on

many fronts. First, whole-cell recordings suggest that the neuronal time constant may be much larger (and thus, the R_m much higher) than previously assumed from microelectrode recordings (Spruston et al., 1994; Major et al., 1994). This discrepancy is attributed to the shunt introduced by the somatic leak induced by the microelectrode impalement. Second, another significant result has been the study of cable models of branched dendritic trees that cannot be approximated by equivalent cylinder models (Stratford et al., 1989; Major et al., 1993; Major, 1993). This work has confirmed the importance of the shunt created by the electrode and has suggested the impossibility of good voltage-clamp control of dendrites from the soma. Finally, two new approaches have been used to estimate the length constant of the main dendrites: the measurement of voltage attenuation between dendritic and somatic electrodes for injected DC pulses of current (Sugimori and Llinás, 1984, Soc. Neurosci., abstract; Stuart and Häusser, 1994) and the use of the voltage ratio between somatic and dendritic calcium plateaus, as recorded at the soma (Reuveni et al., 1993; Yuste et al., 1994).

In spite of this, the basic cable properties of dendrites are unknown, and it is even possible that they may not be constant throughout the dendritic tree. Still, the past few years have seen an explosion of modeling studies of neurons, triggered by the availability of computer programs that implement cable equations in multicompartmental models (reviewed by De Schutter, 1992). Results from different modeling approaches based on careful fitting of experimental data converge on similar values for C_m (0.7–2 μF/cm), R_m (50–200 kΩcm^2), and R_i (200–400 Ωcm), suggesting that these values may be close to the real ones (e.g., Stratford et al., 1989; Spruston et al., 1994; Rapp et al., 1994; Major et al., 1994).

Where Is the Spike Initiation Zone?

In the classical work from the fifties, it was concluded that motoneurons had two thresholds for spike initiation, a lower one ($\sim$10 mV) in the axonal initial segment (IS) and a higher one ($\sim$30 mV) in the soma–dendrites (Coombs et al., 1957). This conclusion was reexamined in CA1 pyramidal neurons in vitro with a combination of extracellular, intrasomatic, and intradendritic microelectrode recordings. In response to synaptic stimulation at threshold, the site of spike initiation was located at or near the soma (Richardson et al., 1987), but shifted to the proximal dendrites when synaptic strength is increased (Turner et al., 1991). Therefore, the spike initiation zone for CA1 neurons is dependent on the stimulation paradigm.

Experiments with patch electrodes have recently addressed this question in neocortical pyramidal neurons. Under somatic voltage clamp, Regehr et al. (1993) found unclamped sodium spikes triggered by synaptic stimulation and suggested that the spike initiation zone was dendritic (Regehr et al., 1993). In contrast, Stuart and Sakmann (1994) used dual recordings from soma and proximal apical dendrites to show that, after synaptic stimulation, dendritic sodium spikes were always backpropagated from the soma (Figure 3). The authors then patched the axon and showed that, in response to somatic current injections, the axon always fired ahead of the soma. They proposed that in neocortical pyramidal neurons the axon is the spike initiation zone and suggested that a major function of dendritic sodium action potentials is to convey information about the state of the soma to the dendrites. This centrifugal, antidromic, or backpropagating role for the action potential has also been proposed in olfactory bulb neurons (Rall and Shepherd, 1968), Purkinje neurons (Llinás and Nicholson, 1971), and CA1 pyramidal neurons (Richardson et al., 1987) and constitutes a blatant contradiction to Cajal's axofugal law.

Similar experiments with dual somatic and dendritic patch recordings have been carried out in other neuron types. While results from Purkinje cells indicate a somatic initiation zone for sodium action potentials (Stuart and Häusser, 1994), in CA1 pyramidal cells the spike initiation was somatic but shifted to proximal dendrites with increased synaptic stimulation (Spruston et al., 1995). Finally, many neurons in substantia nigra had dendritic initiation; interestingly, this was shown to be due to the axon emerging from the dendrite (Häusser et al., 1995).

Taken together, these studies lend support to the idea that in pyramidal and Purkinje cells the spike initiation zone is primarily axonal/somatic. However, several important caveats preclude a definite answer. First, like in CA1 neurons, the location may depend on the intensity of the stimulation. Second, these recent studies do not address the role of calcium spikes in this process, due perhaps to the young age of the cells and the experimental conditions at which experiments were performed. Because calcium spikes are prominent in recordings from mature animals, both in vivo (Pockberger, 1991; Hirsch et al., 1995) or in vitro (Amitai et al., 1993; Sakmann, 1995, Soc. Neurosci., abstract), their existence may change the balance of excitation between dendrites and soma. Third, dendrites in vivo may sustain their own spike-generating zones, isolated from the soma, because of the electrical shunt produced in dendrites by their constant bombardment with excitatory or inhibitory synaptic inputs (Bernarder et al., 1991; see below) and because significant changes in the length constant could be produced by intrinsic electrophysiological states of the neuron (see below). In fact, stimulus-evoked calcium spikes in vivo are more frequent during epochs of strong synaptic barrages (Hirsch et al., 1995).

Inhibition Can Regulate Dendritic Function

Approximately 20% of the synaptic contacts in the brain are inhibitory (Peters et al., 1991); moreover, electron microscopic studies indicate that the location of inhibitory inputs in dendrites can be very specific (Peters et al., 1991; Buhl et al., 1994). The influence of those inhibitory inputs on the physiology of dendrites was demonstrated by the inhibition of dendritic spikes in Purkinje cell by stimulation of inhibitory interneurons (Llinás et al., 1968).

The role of inhibition in controlling dendritic excitation has been recently explored in pyramidal and Purkinje neurons with calcium imaging and dendritic recordings (Callaway et al., 1995; Kim et al., 1995). Callaway et al. (1995) have studied the effect of inhibition on calcium accumulations of Purkinje neurons and find that IPSPs reduce the dendritic depolarizations and calcium accumulations produced by climbing fiber activation. This

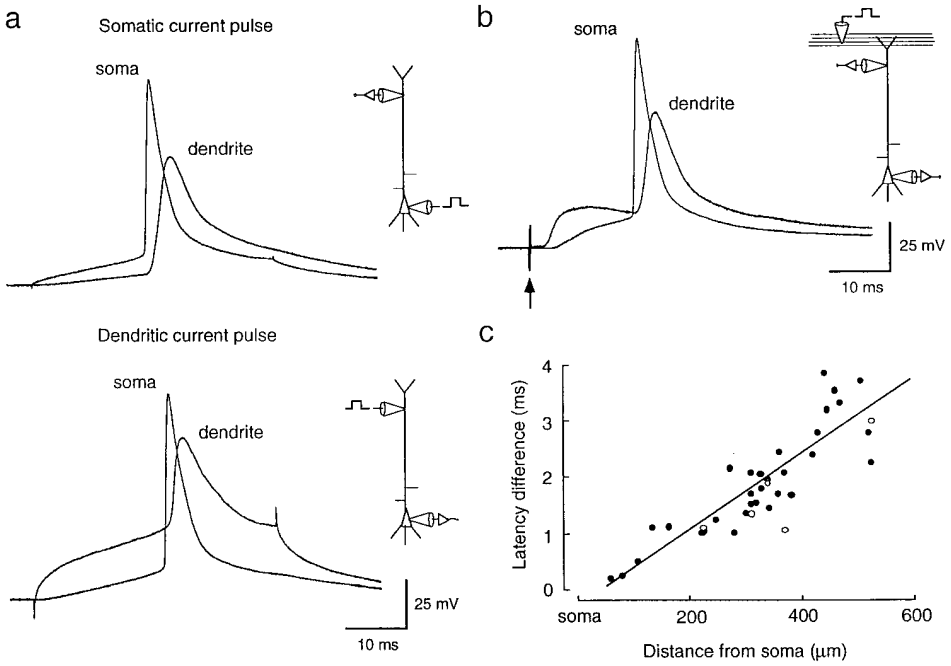

Figure 3. Somatic Spike Initiation Zone in Pyramidal Neurons

Reprinted with permission from Stuart and Sakmann (1994).

(a) Simultaneous recording from the soma and apical dendrite of the same layer 5 pyramidal neuron. An action potential is evoked in response to a depolarizing current pulse injected in the soma (top) or the apical dendrite (bottom). In both cases, the soma fires ahead of the dendrite.

(b) In response to synaptic stimulation in layer 1, the action potential occurs first in the soma.

(c) Latency distribution of the action potential in the apical dendrite as a function of the distance from the soma, in response to somatic current pulses (closed circles) or distal synaptic stimulation (open circles). Note the linear relation between the time of onset of the dendritic action potential and the distance from the soma, indicating that the action potential originates in the soma and propagates back into the apical dendrite.

effect is graded and can be restricted to individual dendritic branches. In intradendritic recordings from neocortical pyramidal neurons, Kim et al. (1995) have shown that IPSPs can reduce, and eventually block, the dendritic sodium and calcium spikes generated by current injections. They also report that the IPSP timing controls the timing of dendritic spiking, producing phase-advance or phase-delay effects. These two studies demonstrate that inhibition can play a fundamental role in the control of dendritic spiking. Besides its traditional role of blocking excitatory inputs, inhibition may also control temporal aspects of the dendritic response.

The mechanisms by which inhibitory inputs produce these effects are likely to be multiple. The increases in chloride permeability produced by γ-aminobutyric acid (GABA) could lead to a hyperpolarization of the neuron or to a shunt of depolarizing current produced by the concomitant decrease in R_{in}. Also, an inhibition of the calcium current by GABA independent from changes in chloride permeability has been described (Dunlap and Fischbach, 1978; Sugimori and Llinás, 1985, Soc. Neurosci., abstract) and could be mediated by cisternal organelles (Benedeczky et al., 1994).

Dendrites Can Be Turned off by Spikes

One noteworthy recent result has been the discovery that dendritic function can be intrinsically modulated by activity-dependent mechanisms.

The first evidence came from imaging experiments in CA1 neurons (Jaffe et al., 1992), where, in response to a train of spikes generated at the soma by an intracellular current injection, the authors detected a difference in calcium and sodium dynamics between proximal and distal dendrites. While calcium and sodium accumulated in proximal dendrites during the entire spike train, the accumulations in distal dendrites were limited to the first few spikes, indicating that the sodium and calcium channels responsible for the distal accumulations had turned off. Hence, sustained firing of the cell produced higher calcium accumulations in proximal dendrites (Regehr et al., 1989). A similar result was found in neocortical intrinsically bursting neurons, where a train of antidromic spikes generated a dissociation in the calcium dynamics of the proximal versus distal apical dendrite (Yuste et al., 1994). Again, while calcium accumulated in the proximal compartment of the cell during the entire train, the distal apical dendrite only increased its calcium at the beginning of the train. It was hypothesized that calcium-activated hyperpolarizing conductances mediated the switching off of the distal dendrite.

More direct evidence for an activity-dependent switching off of CA1 dendrites was obtained recently with intradendritic recordings (Spruston et al., 1995; Callaway and Ross, 1995). In both studies, the first spike of an antidromic spike train propagated throughout the entire dendritic tree, while subsequent spikes were filtered to different degrees. In most distal dendrites, a

gradual decrement in the amplitude of the action potentials during the train was observed. This activity-dependent filtering was triggered by action potentials and had a slow time course that produced frequency dependency, i.e., faster firing rates resulted in more attenuation (Callaway and Ross, 1995). Interestingly, all-or-none filtering was seen at some branch points, producing spike invasion failures (Spruston et al., 1995). Finally, the recovery from this activity-dependent inactivation of a dendrite was accelerated by hyperpolarization (Spruston et al., 1995).

Thus, although the mechanisms responsible are still unknown, the intrinsic properties of neurons can turn off certain dendrites in an activity-dependent fashion. This produces a situation where the specific location of the inputs matters, as opposed to a dendritic tree where, like a computer network, the physical location of the connection is irrelevant. For instance, synapses located in distal dendrites may only be sensitive to the first few spikes from a train of action potentials produced by the soma, while those located more proximally may be sensitive to every action potential. This filtering would make distal synapses sensitive only to changes in the rate of output of the cell, a mechanism that might be used to implement synaptic algorithms gated by the derivative of postsynaptic activity, similar to the delta learning rules explored in artificial neural networks.

What Is the Minimal Functional Compartment of the Dendrite?

A central question in dendritic integration is whether the dendritic tree works as one unit, or whether it has different functional compartments. We can define a functional compartment as the morphological unit of the cell that carries out a determined functional role. Functional compartments do not necessarily have to be electrical units, since chemical compartmentalization may be of fundamental importance to the function of the neuron. Moreover, certain computations may be implemented chemically, rather than electrically (Sobel and Tank, 1994).

In 1891, Cajal first described the existence of dendritic spines (Ramón y Cajal, 1891b) and speculated that their function was to increase the receptive surface of the dendrites and enable intimate contacts between axons and dendrites (Ramón y Cajal, 1904). The idea that spines were sites of synaptic contacts was confirmed with electron microscopy (DeRobertis and Bennett, 1955; Palay, 1956). Hence, anatomically, spines are a basic subunit of the dendrite. Still, no functional information existed about dendritic spines until the advent of calcium imaging techniques. Initial experiments in hippocampal pyramidal neurons showed that individual spines could have different calcium dynamics than their parent dendrites, behaving as independent calcium compartments (Müller and Connor, 1991; Guthrie et al., 1991). In contrast, experiments imaging spines in cultured hippocampal neurons and Purkinje cells in slices suggested that spines did not become activated independently, but rather as part of a branchlet, composed of a small segment of a dendrite with all its spines (Murphy et al., 1994; Eilers et al., 1995). The branchlet then would constitute the minimal compartment of the dendrite. Recently, this issue has been reexamined with two-photon microscopy (Denk et al., 1990), which enables imaging of spines in brain slices for extended periods of time (Figure 4). New results in CA1 and Purkinje neurons show that individual spines are activated under subthreshold synaptic stimulation, but that once the cell fires an action potential, every spine in the cell becomes activated (Yuste and Denk, 1995; Denk et al., 1995). These findings therefore show that spines behave as chemical compartments that could constitute the minimal functional compartment of the dendrite.

What function might spines serve? The restriction of calcium accumulations during subthreshold synaptic stimulation to a single spine indicates that spines compartmentalize biochemical changes (Gamble and Koch, 1987; Wickens, 1988; Koch and Zador, 1993). This compartmentalization could segregate plastic changes in synaptic transmission (Rall, 1974; Lisman, 1989). In fact, electrophysiological experiments in vivo have implied that individual spines may be specifically potentiated because granule cell spines contacted by the contralateral perforant pathway, but interspersed among spines contacted by the ipsilateral pathway, are not potentiated together with the rest of the spines (Levy and Steward, 1979; Levy and Desmond, 1985). In agreement with this, supralinear calcium accumulations occurred in hippocampal spines when synaptic and spike activation occurred simultaneously, indicating that spines may be able to function as coincidence detectors (Yuste and Denk, 1995). An implication from this argument is that smooth neurons, with few or no spines, cannot compartmentalize plastic changes in synaptic transmission like spiny neurons (Wickens, 1988), if plasticity is not produced by highly localized, submembrane calcium concentrations. In preliminary experiments from CA1 stellate cells, changes of synaptic efficacy in one input do influence a second distant input, suggesting that spines are necessary to compartmentalize plasticity (S. J. Redman, personal communication).

Interaction among Dendritic Compartments

Even if spines are the smallest functional compartment of a dendrite, a more pertinent question is what the typical functional compartments are under the conditions in which dendrites are integrating inputs. In fact, there is clear evidence that dendritic compartments of a larger scale than a dendritic spine may be functional units. Whereas anatomical evidence suggests that several functional areas exist in dendrites, physiological data show that different dendritic compartments can interact to generate intrinsic functional dynamics in the neuron.

While studying the development of synaptic connections in cilliary ganglion cells, Purves and Hume found that developing neurons were innervated by a similar number of axons, but in adult neurons the number of innervating axons precisely matched the number of primary dendrites (Purves and Hume, 1981; Hume and Purves, 1981). They concluded that cilliary ganglion cells had a number of separate spatial dendritic domains, each one receiving input from a single axon. This implied that dendrites could serve to isolate inputs from one another and suggested that a single axon would only innervate one dendrite. Nevertheless, in a follow-up study with electron microscopy, single dendrites were

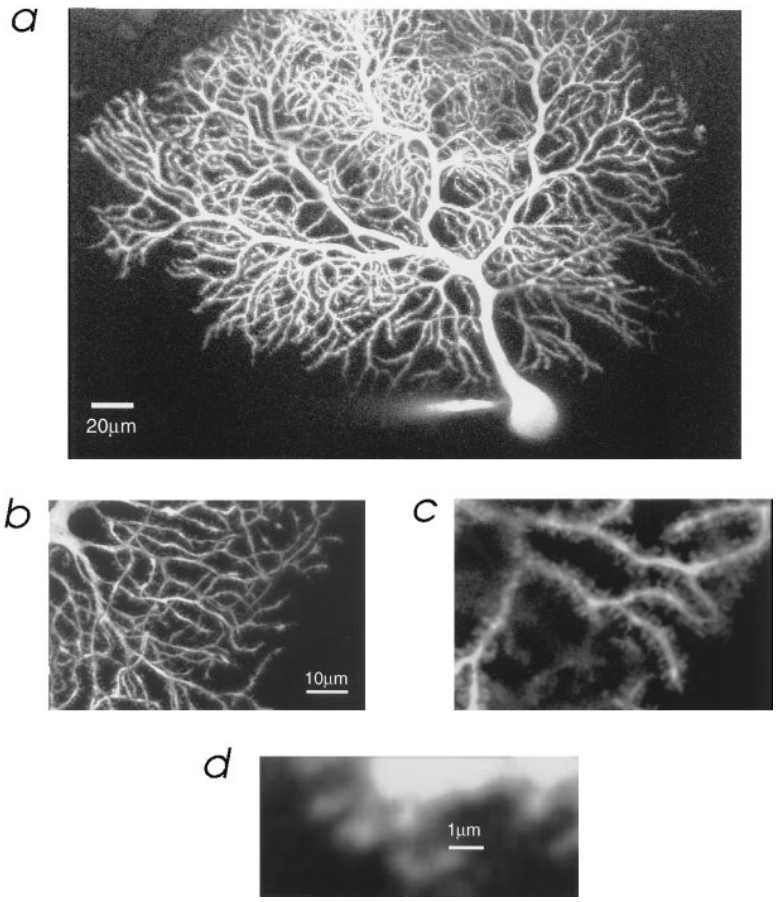

Figure 4. Two-Photon Imaging of Dendritic Spines in Purkinje Neurons

Reprinted with permission from Denk et al. (1995). The top panel (a) shows the complete dendritic tree of a Purkinje neuron in a 400 μm guinea-pig cerebellar slice, filled with the calcium indicator Calcium Green. In the lower panels (b–d), progressively higher magnification images from the dendritic tree of a different neuron are shown. Dendritic spines are clearly visible. Image taken with a custom-made laser scanning microscope using two-photon excitation.

shown to be innervated by multiple axons, although a spatial segregation of competing inputs was still present (Forehand and Purves, 1984). Altogether, these results suggested the existence of different dendritic compartments dominated by different inputs. A similar relationship between dendritic domains and functional compartments was suggested by reconstructions of neurons from the tecta of three-eyed frogs (Katz and Constantine-Paton, 1988). In these animals, the tectum is divided into interdigitating stripes, alternatively innervated by each eye. In some tectal neurons individual dendritic branches were confined to the stripe of a single eye, although the entire dendritic tree occupied more than one stripe. This result suggested that dendritic branches were functional units, because they received only one type of input.

The first demonstration of a functional interaction by separate compartments in a neuron came from work in inferior olive cells (Llinás and Yarom, 1981). From the mismatch in the sign of the spikes between intra- and extracellular recordings, the authors deduced that sodium and low threshold calcium conductances were located in the soma, while high threshold calcium conductances were dendritic. The spatial separation of the conductances into somatic and dendritic compartments generated an intrinsic oscillatory dynamics of these neurons, following this sequence of events: a somatic sodium spike (1) triggers a dendritic high threshold calcium spike (2), which activates a calcium-dependent potassium current (3) that deinactivates a somatic low threshold calcium spike (4), which finally triggers again a somatic sodium spike (1).

A second case in which the interaction between dendritic and somatic compartments produces intrinsic electrophysiological responses is the generation of spike bursting by CA3 neurons. There is evidence that high threshold calcium conductances, present in dendrites from CA3 pyramidal neurons, are necessary for burst responses (Wong and Prince, 1978). While single compartment models of CA3 pyramidal neurons have been unable to reproduce adequately the electrophysiology, the nonuniform distribution of calcium and sodium channels into at least two compartments can generate burst responses (Traub et al., 1991; Pinsky and Rinzel, 1994; Rhodes and Gray, 1994). Consistent with this, imaging of CA3 neurons during bursts and single spike firing shows that normalized calcium accumulations are larger in dendrites than in the soma during bursting (Strowbridge and Tank, 1994, Soc. Neurosci., abstract). Thus, the sequence of events during a burst would be as follows: somatic sodium spike (1) that triggers a dendritic calcium spike (2) that depolarizes the soma producing the envelope of the burst and triggering additional somatic sodium spikes (3). Finally, a recent simulation study has extended these ideas by suggesting that even the detailed dendritic morphology of neocortical pyramidal neurons could influence many of

their intrinsic electrophysiological properties (T. J. Sejnowski, personal communication).

Dendrites Can Serve as the Output Side of the Neuron

Dendrites in many invertebrate nervous systems serve as both input and output side of the neuron (Bullock, 1977; Watson and Burrows, 1988), and this motivated the use of the term "neurite" instead of dendrite to express the lack of specialization among the processes. Since Cajal, however, dendrites in vertebrate systems have been considered the input side of the neuron. Nevertheless, the existence of dendrodendritic synaptic interaction and dendrodendritic gap junctions are clear contradictions of Cajal's law and may constitute general forms of neuronal communications present throughout the vertebrate central nervous system.

Dendrodendritic synapses have been clearly documented in mammalian olfactory bulb and retina. In the bulb, the antidromic excitation of mitral cells is followed by a long-lasting inhibition (Phillips et al., 1963). In a computational and electrophysiological study, it was proposed that secondary dendrites of mitral cells excited granule cells, which would then mediate the inhibition of mitral cells (Rall and Shepherd, 1968). Because granule cells lack axons, their output had to be dendritic. Finally, reciprocal dendrodendritic synapses between mitral and granule cells were found with electron microscopy (Rall et al., 1966). The circuitry of the retina also provides, in the amacrine cell, one clear example of a neuron in which dendritic spines and axonal terminals are not morphologically segregated to different processes (Dowling, 1968; Dubin, 1970). Finally, a different form of dendrodendritic synaptic interactions is the dendritic release of neurotransmitters by substantia nigra neurons (Cheramy et al., 1981; Llinás and Greenfield, 1987). This release is calcium sensitive and may require exocytosis from subcisternal systems.

An issue that has reemerged in the last decade is whether mammalian neurons are coupled via dendritic gap junctions, as was first established in olivary neurons (Sotelo et al., 1974; Llinás et al., 1974). The existence of dendrodendritic gap junctions was suggested to explain dye coupling in neocortical and hippocampal slices (Gutnick and Prince, 1981; MacVicar and Dudek, 1981). This coupling is particularly dramatic in developing cortex (Connors et al., 1983; Lo Turco and Kriegstein, 1991; Peinado et al., 1993), where it can lead to coactivation of large groups of neurons (Yuste et al., 1992, 1995). These functional results indicate that in development dendrites can serve as the output side of the neuron. In the adult brain, the extent of dendritic gap-junctional coupling remains a matter of controversy. While inferior olive neurons (Sotelo et al., 1974), granule cells in the olfactory bulb (Reyher et al., 1991), and many neuronal types in the retina (Vaney, 1991) have dendrodendritic gap junctions, in adult pyramidal neurons dye neuronal coupling practically disappears (Connors et al., 1983; Peinado et al., 1993; cf. Michelson and Wong, 1994). Evidence for gap junctions in adult cortex and hippocampus from electron microscopy is scant (Sloper, 1972; Powell, 1981; Kosaka, 1983) and could be due to the difficulty of detecting them. Nevertheless, recent studies suggest that there are, in fact, dendritic gap junctions in adult neocortex (Parnavelas et al., 1994, 1995, Soc. Neurosci., abstracts) and nonpyramidal neurons in hippocampus (Gulyás et al., submitted; Acsady et al., submitted). Finally, dendritic gap junctions among interneurons may be necessary to generate hippocampal oscillations in the presence of synaptic blockers (Michelson and Wong, 1994; Traub, 1996).

Future Issues: The Time of Dendritic Computation

In this last section, we review experimental and theoretical findings that address more speculative issues of dendritic integration. A review covering many theoretical results has been recently published (Mel, 1994).

Direct Measurements of Cable Parameters

Simultaneous somatic and dendritic recordings can be used to measure the cable attenuation produced in test voltage pulses (Stuart and Häusser, 1994; Stuart and Sakmann, 1994; Sugimori and Llinás, 1984, Soc. Neurosci., abstract). This approach could be used to estimate R_i for the dendritic segment between the two electrodes and establish the basic cable parameters of the main dendritic shafts. The difficulty in obtaining whole-cell recordings from small dendritic branches, however, makes this strategy less optimal when trying to estimate the values of cable parameters in secondary and tertiary dendrites, which are target regions for the majority of the inputs (Larkman, 1991).

As an alternative approach, voltage-sensitive dyes (VSDs) have been used to measure voltage transients in small processes from cultured invertebrate neurons (Grinvald et al., 1981). In a recent study, cable equations were fitted to measured spatiotemporal voltage patterns, and tentative values for R_m ($\sim$22 kΩcm^2) and R_i ($\sim$250 Ωcm) were concluded (Fromherz and Müller, 1994). These values, incidentally, are not that different from those found in numerical simulation studies (see above).

It should be possible to apply optical recording with VSDs to cultured mammalian neurons, or even to neurons in a slice, and estimate R_i and R_m more directly. Efforts in that direction have already started, using traditional dyes (Borst et al., 1995, Soc. Neurosci., abstract) or injectable VSDs that may obviate poor signal-to-background ratio when recording optically from dendrites in a slice (Antic and Zecevic, 1995; Kogan et al., 1996). Also, ratio imaging may enable accurate quantitative measurements of dendritic voltages (Montana et al., 1989; González and Tsien, 1995). Optical approaches seem ideally suited to investigate questions such as whether cable parameters are constant in the dendritic tree, or what the behavior of branch points is during the propagation of voltage signals.

What Is the Role of the Active Conductances in Dendrites?

Although it is clear that there are active conductances throughout the dendritic trees of both pyramidal and Purkinje cells, the role of these conductances remains a mystery. Because they are voltage sensitive, they could amplify synaptic inputs and help relay distal EPSPs to the soma (Lorente de Nó and Coundouris, 1959; Shepherd et al., 1985). In fact, many recent studies demonstrate that synaptic inputs are indeed amplified by the

dendritic tree. For example, in neocortical neurons, depolarization of the soma increases the amplitude and duration of EPSPs (Stafstrom et al., 1985; Thompson et al., 1988; Sutor and Hablitz, 1989; Hirsch and Gilbert, 1991; Cauller and Connors, 1994). This subthreshold amplification is gradual and has been attributed to either sodium, calcium, or NMDA receptor conductances. A recent report has suggested that it may preferentially occur near the soma (Stuart et al., 1995, Soc. Neurosci., abstract). In addition, EPSPs can become amplified into the suprathreshold regime, evoking dendritic spikes. In fact, in Purkinje cells, climbing fiber input triggers dendritic spikes (Llinás and Nicholson, 1971), and a similar situation occurs in neocortex with strong layer 1 inputs to apical dendrites (Cauller and Connors, 1992). Active conductances in dendrites may act regeneratively under some conditions and in a subthreshold regime under others, thus providing dendrites with two different modes of operation.

Another possible function for active conductances is the "linearization" of synaptic inputs, i.e, the progressive changes in electrical properties induced to avoid saturation by synchronous inputs (Bernarder et al., 1994). This idea builds upon research proposing that active conductances control the gain of synaptic inputs (Laurent and Burrows, 1989). Finally, as explained above, dendritic voltage-activated conductances may also regulate the intrinsic temporal dynamics of neurons (Llinás, 1988).

What Is the Role of Antidromic Spikes?

In many neurons, action potentials originating at the soma can invade the dendritic tree (see above) and, in CA1 neurons, it even reaches every spine in the cell (Yuste and Denk, 1995). What functional significance could this antidromic or backpropagating spike have? The temporal coincidence of synaptic inputs with postsynaptic spikes (i.e., the output of the neuron) could trigger a change in synaptic efficacy, analogous to the Hebb rule (Hebb, 1949). Thus, the spike might be the temporal signal used for coincidence detection by the spines. This idea has been corroborated in experiments showing that action potential blockade by local perfusion of TTX blocks long-term potentiation (LTP) (Scharfman and Sarvey, 1985), although LTP persists under sodium (but not calcium) action potential blockade with intracellular QX-314 (Gustafsson et al., 1987). Furthermore, recent results show that the temporal coincidence of synaptic inputs and spikes produces cooperative calcium accumulations in dendritic spines (Yuste and Denk, 1995). Studies of LTP in identified connections could help resolve this issue (Markram and Sakmann, 1995, IBRO, abstract).

Do Different Dendritic Compartment Carry out Different Computations?

Anatomical results suggest the possibility of a relationship between dendritic morphology and functional compartments (see above). In agreement with this, Purkinje cells have clear functional differences in the action of climbing and parallel fibers (Llinás and Sugimori, 1992), inputs that impinge onto different areas of the dendritic tree (Ramón y Cajal, 1904), although the exact location of the parallel fiber input may not matter (De Schutter and Bower, 1994). Therefore, it is possible to speak of two functional compartments in the dendritic tree of Purkinje cells, which might be specialized for different computations. For instance, timing information (when) could be provided by climbing fibers and preserved in the complex spike, while other types of information (what) might be conveyed by parallel fibers and plateau potentials (Llinás and Sugimori, 1992).

Pyramidal neurons also have segregated dendritic fields for specific inputs. In hippocampus, CA3 pyramidal neurons are contacted by mossy fiber terminals selectively at the base of apical dendrites (Claiborne et al., 1986), while different populations of interneurons contact specific areas of dendritic trees of pyramidal neurons (Buhl et al., 1994). In neocortex, feedback axonal projections make specific contacts with the tips of apical dendrites, located in layer 1 (Rockland and Virga, 1989), while stellate cells can project specifically to the base of the apical dendrite (Kisvarday et al., 1987). In fact, the laminar structure of the cortex is a direct reflection of specific input/output relations, and particular layers can be thought of as having a functional identity (Gilbert and Wiesel, 1979; Zeki, 1993), which could be preserved in the dendritic tree. Nevertheless, it is still unknown whether neurons can distinguish between inputs coming from different layers. Also, the reason behind the morphological differences between apical and basal dendritic trees is still mysterious. Electrophysiological and imaging data indicates that distal apical dendrites are a separate functional compartment from the rest of the cell (Yuste et al., 1994), and data from awake behaving monkeys suggests that they could mediate specific behavioral responses (Cauller and Kulics, 1991).

Do Dendrites Translate Spatial Patterns of Inputs?

The use of the spatial properties of the dendritic tree to filter directional differences in input was proposed by Rall (1964). In his model with a passive dendritic tree, excitatory inputs located in a line would preferentially excite the soma if they were activated in an ordered sequence, with distal inputs excited ahead of proximal ones. This resulted from the time delays associated with the transmission of EPSPs to the soma and suggested that dendrites could serve to detect spatiotemporal patterns of inputs. A similar idea, incorporating inhibitory inputs, was used to explain direction selectivity by the retina (Koch et al., 1983). In this model, the topographic map of visual inputs into a dendritic tree produced a direction-selective response if excitatory inputs were distal to inhibitory ones. Although recent results suggest that the extent of the dendritic tree is the same as the extent of the receptive field of rabbit ganglion cells (Yang and Masland, 1992), the location of excitatory and inhibitory inputs into ganglion cell dendrites does not seem to follow any spatial rule (T. Famiglietti, personal communication).

Do Dendrites Read Temporal Codes?

A closely related issue is whether dendrites are built to detect temporal input patterns. This issue is actively debated because of the increased awareness that precise timing may be used by the nervous system to code information (Abeles et al., 1993; Softky and Koch, 1992; Hopfield, 1995). In cerebellum, recent results show that submillisecond timing differences from the olive are preserved by the olivocerebellar projection by subtle adjustments in the conduction velocity of climbing fiber

axons (Sugihara et al., 1993). This striking finding suggests that precise timing is essential for cerebellar computations. In neocortex, however, it is controversial whether precise timing is utilized (Schadlen and Newsome, 1994). On the one hand, repeated temporal firing patterns can be detected in cortical neurons in vivo (Abeles et al., 1993), and millisecond temporal synchrony has been proposed to underlie the solution of the binding problem by primary visual cortex (Gray et al., 1989). In addition, the firing of neocortical neurons in vitro appears surprisingly reliable in response to injections of noisy current waveforms (Mainen and Sejnowski, 1995). On the other hand, the behavior of awake monkeys performing perceptual tasks can be predicted from the average firing rate of MT neurons (Zohary et al., 1994; Schadlen and Newsome, 1994). In addition, the time constants of many of the biophysical events in neocortical neurons appear too slow for implementation of millisecond timing detection, while, for example, neurons from the cochlear nucleus, specialized in temporal detection, have dendritic morphologies and receptors that enable fast transmission (Rubel and Parks, 1988; Raman and Trussell, 1992).

Experimental evidence of temporal selectivity by dendritic trees is scarce. An intriguing study of neurons in the torus semicircularis in the electric fish has recently shown two populations of neurons with differential frequency sensitivity to sensory stimulation (Rose and Call, 1993). The cell type that responds better to lower frequencies has dendritic spines, while the type that responds better to higher frequencies lacks them. The authors have suggested that spines serve as frequency filters.

Do Dendrites Implement Logical Elements?

Imaginative proposals have suggested that dendrites are small logical elements (Koch et al., 1983; Shepherd and Brayton, 1987; Rall and Segev, 1987). The basic idea is that summation or shunting occurs when excitatory and inhibitory inputs interact in a dendritic tree. If there is a nonlinear threshold mechanism afterward, such as an action potential, these interactions can be translated into a binary decision. For example, an AND gate would result if two excitatory inputs are simultaneously active, an OR gate would result if there is saturation by either one, and an AND/NOT gate would result if there is a response to an excitatory input, provided that a shunting inhibitory one is not active. Although intriguing, there is at present no experimental evidence to support or contradict these ideas.

Studying Dendrites during Behavior: A Lesson from Invertebrate Work

Perhaps the major obstacle in the study of the function of mammalian dendrites is our lack of understanding of the particular computational tasks that these cells are solving. This problem has been tackled in invertebrate systems, where dendrites can be recorded optically or electrically during behavioral tasks (Borst and Egelhaaf, 1994). Although conclusions reached from invertebrate work on dendrites may not be applicable to understand mammalian neurons, the general approach of identifying the dendritic computation by studying the dendrites during the performance of a behavior may be key toward revealing the logic behind the design of dendrites.

An example of this behavioral approach is the study of the optomotor response in the fly (Borst and Egelhaaf, 1992). Using calcium imaging, the visual field was shown to map topographically into the dendritic field of the neuron. This topographic arrangement of inputs could enable local amplification among inputs coming from the same area of the visual space. A different strategy appears to be employed by dendrites from auditory interneurons in the female cricket (Sobel and Tank, 1994; Figure 5). With in vivo intracellular recording and calcium imaging from identified neurons, it was demonstrated that the dendrite becomes progressively inhibited in response to loud chirps. This inhibition is mediated by a calcium-activated hyperpolarizing current and could contribute to the forward masking of auditory stimuli (Pollack, 1988). An additional example comes from the recent study of collision-sensitive neurons in the visual system of the locus (Hatsopoulos et al., 1995). In this system, the dendritic tree of a single neuron is thought to carry out the multiplication of two independent input signals that enable the neuron to calculate the time of collision of an approaching object. Finally, the role of active conductances have been investigated in visual interneurons in the fly, by comparing the responses of a type of neuron with dendritic sodium action potentials with another type that lacks them (Haag and Borst, 1996). In this study, a correlation was found between synaptic responses to higher temporal frequencies and active dendrites, suggesting that dendritic action potentials might be used for amplification of transient inputs.

A similar research program studying dendrites from vertebrate neurons in vivo is feasible. Intracellular recordings from mammalian dendrites can be carried out in anesthetized animals (Llinás and Nicholson, 1971; Houchin, 1973; Pockberger, 1991; B. W. Connors, personal communication), while intracellular recordings from awake behaving monkeys have been achieved (Matsumura et al., 1988; Glenn et al., 1988). In addition, two-photon microscopy can be used to image individual neurons in anesthetized rats (Denk et al., 1994). Moreover, the study of nonmammalian vertebrate systems in which the basic cellular machinery may be highly homologous to that of mammalian neurons, but in which experimental access to behaving preparations is easier, should speed up these investigations (Connors and Kriegstein, 1986; Heiligenberg, 1991; Fetcho and O'Malley, 1995). It appears to us that the combination of the new generation of electrophysiological and imaging techniques with the biological relevance of studies in behaving animals holds many fruitful experimental avenues for those who wonder, like Cajal did a century ago, what are the functions hidden behind the intriguing morphologies of the dendrites.

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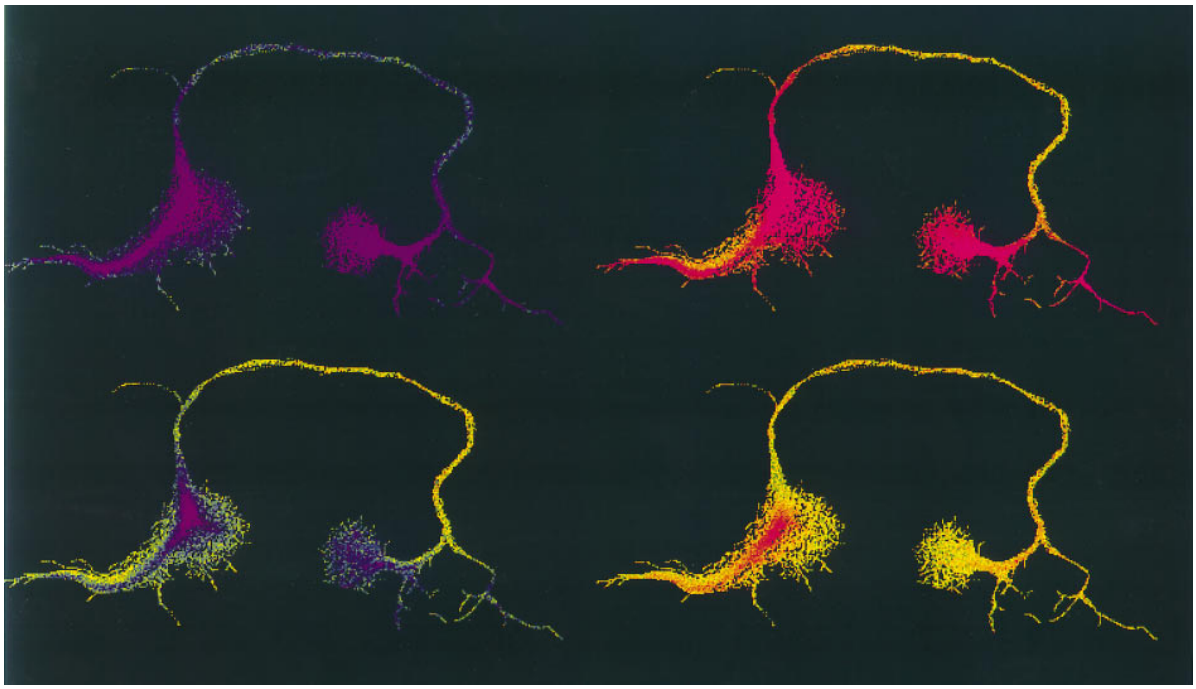

Figure 5. In Vivo Calcium Imaging from a Cricket Auditory Interneuron during a Behavioral Response

Courtesy of E. Sobel, Harvard University. Pseudocolor fluorescence images depicting increases in $[Ca^{2+}]_i$ in an omega neuron from a live female cricket, in response to a simulated male song. The neurites that receive input from auditory fibers are located in the lower left quadrant of the cell. The cell was filled with the calcium indicator fura-2 using intracellular iontophoretic injection. Violet/blue corresponds to resting $[Ca^{2+}]_i$, while red corresponds to high $[Ca^{2+}]_i$. The four images were taken with a cooled CCD camera over a period of 20 s, and they are displayed in the following order: top left, bottom left, top right, bottom right. Scale bar is 50 μm.

References

Abeles, M., Bergman, H., Margalit, E., and Vaadia, E. (1993). Spatiotemporal firing patterns in the frontal cortex of behaving monkeys. J. Neurophysiol. *70*, 1629–1638.

Allbritton, N.L., Meyer, T., and Stryer, L. (1992). Range of messenger action of calcium ion and inositol 1,4,5-trisphosphate. Science *258*, 1812–1815.

Amitai, Y., Friedman, A., Connors, B.W., and Gutnick, M.J. (1993). Regenerative activity in apical dendrites of pyramidal cells in neocortex. Cerebral Cortex *3*, 26–38.

Andersen, P., Holmquist, B., and Voorhoeve, P.E. (1966). Excitatory synapses on hippocampal apical dendrites activated by entorhinal stimulation. Acta Physiol. Scand. *66*, 461–472.

Antic, S., and Zecevic, D. (1995). Optical signals from neurons with internally applied voltage-sensitive dyes. J. Neurosci. *15*, 1392–1405.

Benedeczky, I., Molnár, E., and Somogyi, P. (1994). The cisternal organelle as a Ca^{2+}-storing compartment associated with GABAergic synapses in the axon initial segment of hippocampal pyramidal neurones. Exp. Brain Res. *101*, 216–230.

Bernarder, O., Douglas, R.D., Martin, K.A., and Koch, C. (1991). Synaptic background activity influences spatiotemporal integration in single pyramidal cells. Proc. Natl. Acad. Sci. USA *88*, 11569–11573.

Bernarder, O., Koch, C., and Douglas, R.J. (1994). Amplification and linearization of distal synaptic input to cortical pyramidal cells. J. Neurophysiol. *72*, 2743–2753.

Bernardo, L.S., Masukawa, L.M., and Prince, D.A. (1982). Electrophysiology of isolated hippocampal pyramidal dendrites. J. Neurosci. *2*, 1614–1622.

Blanton, M.G., Lo Turco, J.J., and Kriegstein, A.R. (1989). Whole-cell recording from neurons in slices of reptilian and mammalian cerebral cortex. J. Neurosci. Meth. *30*, 203–210.

Borst, A., and Egelhaaf, M. (1992). *In vivo* imaging of calcium accumulation in fly interneurons as elicited by visual motion stimulation. Proc. Natl. Acad. Sci. USA *89*, 4139–4143.

Borst, A., and Egelhaaf, M. (1994). Dendritic processing of synaptic information by sensory interneurons. Trends Neurosci. *17*, 257–273.

Brock, L.G., Coombs, J.S., and Eccles, J.C. (1952). The recording of potentials from motoneurones with an intracellular electrode. J. Physiol. *117*, 431–460.

Buhl, E.H., Halasy, K., and Somogyi, P. (1994). Diverse sources of hippocampal unitary inhibitory postynaptic potentials and the number of synaptic release sites. Nature *368*, 823–828.

Bullock, T.H. (1977). Introduction to Nervous Systems (San Francisco: Freeman).

Callaway, J.C., and Ross, W.N. (1995). Frequency-dependent propagation of sodium action potentials in dendrites of hippocampal CA1 pyramidal neurons. J. Neurophysiol. *74*, 1–9.

Callaway, J.C., Lasser-Ross, N., and Ross, W.N. (1995). IPSPs strongly inhibit climbing fiber–activated $[Ca^{2+}]$ in the dendrites of cerebellar Purkinje neurons. J. Neurosci. *15*, 2777–2787.

Cauller, L.J., and Connors, B.W. (1992). Functions of very distal dendrites: experimental and computational studies of layer I synapses on neocortical pyramidal cells. In Single Neuron Computation, T. McKenna, ed. (San Diego: Academic Press), pp. 199–229.

Cauller, L.J., and Connors, B.W. (1994). Synaptic physiology of horizontal afferents to layer 1 in slices of rat S1 neocortex. J. Neurosci. *14*, 751–762.

Cauller, L.J., and Kulics, A.T. (1991). The neural basis of the behaviourally relevant N1 component of the somatosensory-evoked potentials of S1 cortex of awake monkeys: evidence that backward cortical projection signals conscious touch sensation. Exp. Brain Res. *84*, 607–619.

Cheramy, A., Leviel, V., and Glowinski, J. (1981). Dendritic release of dopamine in the substantia nigra. Nature *289*, 537–542.

Claiborne, B.J., Amaral, D.G., and Cowan, W.M. (1986). A light and electron microscopic analysis of the mossy fibers of the rat dentate gyrus. J. Comp. Neurol. *246*, 435–458.

Connor, J.A. (1986). Digital imaging of free calcium changes and of spatial gradients in growing processes in single, mammalian central nervous system cells. Proc. Natl. Acad. Sci. USA *83*, 6179–6183.

Connors, B.W., and Kriegstein, A.R. (1986). Cellular physiology of the turtle visual cortex: distinctive properties of pyramidal and stellate neurons. J. Neurosci. *6*, 164–177.

Connors, B.W., Bernardo, L.S., and Prince, D.A. (1983). Coupling between neurons of the developing rat neocortex. J. Neurosci. *3*, 773–782.

Coombs, S.J., Eccles, J.C., and Fatt, P. (1955a). Excitatory synaptic actions in motoneurons. J. Physiol. *130*, 374–395.

Coombs, S.J., Eccles, J.C., and Fatt, P. (1955b). The specific ionic conductances and the ionic movements across the motoneuronal membrane that produce the inhibitory post-synaptic potential. J. Physiol. *130*, 396–413.

Coombs, S.J., Curtis, D.R., and Eccles, J.C. (1957). The interpretation of spike potentials of motorneurones. J. Physiol. *139*, 198–231.

Deiters, O. (1865). Untersuchungen über Gehirn und Rückenmark des Menschen und der Säugethiere. (Braunschweig).

Denk, W., Strickler, J.H., and Webb, W.W. (1990). Two-photon laser scanning fluorescence microscopy. Science *248*, 73–76.

Denk, W., Delaney, K.R., Gelperin, A., Kleinfeld, D., Strowbridge, B.W., Tank, D.W., and Yuste, R. (1994). Anatomical and functional imaging of neurons using 2-photon laser scanning microscopy. J. Neurosci. Meth. *54*, 151–162.

Denk, W., Sugimori, M., and Llinás, R. (1995). Two types of calcium response limited to single spines in cerebellar Purkinje cells. Proc. Natl. Acad. Sci. USA *92*, 8279–8282.

DeRobertis, E.D.P., and Bennett, H.S. (1955). Some features of the submicroscopic morphology of synapses in frog and earthworm. J. Biophys. Biochem. Cytol. *1*, 47–58.

Deschenes, M. (1981). Dendritic spikes induced in fast pyramidal tract neurons by thalamic stimulation. Exp. Brain Res. *43*, 304–308.

De Schutter, E. (1992). A consumer guide to neuronal modeling software. Trends. Neurosci. *15*, 462–464.

De Schutter, E., and Bower, J.M. (1994). Simulated responses of cerebellar Purkinje cells are independent of the dendritic location of granule cell synaptic inputs. Proc. Natl. Acad. Sci. USA *91*, 4736–4740.

Dodt, H.-U., and Zieglgänsberger, W. (1990). Visualizing unstained neurons in living brain slices by infrared DIC. Brain Res. *537*, 333–336.

Dodt, H.-U., and Zieglgänsberger, W. (1994). Infrared videomicroscopy: a new look at neuronal structure and function. Trends Neurosci. *17*, 453–458.

Dowling, J.E. (1968). Synaptic organization of the frog retina: an electron microscopic analysis comparing the retinas of frogs and primates. Proc. R. Soc. Lond. (B) *170*, 205–228.

Dubin, M.W. (1970). The inner plexiform layer of the vertebrate retina: a quantitative and comparative electron microscope analysis. J. Comp. Neurol. *140*, 479–506.

Dunlap, K., and Fischbach, G.D. (1978). Neurotransmitters decrease the calcium component of sensory neuron action potentials. Nature *276*, 837–838.

Eccles, J.C. (1964). The Physiology of Synapses (Berlin: Springer), pg. 104.

Eccles, J.C., Libet, B., and Young, R.R. (1958). The behavior of chromatolysed motoneurons studied by intracellular recording. J. Physiol. (Lond.) *143*, 11–40.

Edwards, F.A., Konnerth, A., Sakmann, B., and Takahashi, T. (1989). A thin slice preparation for patch recordings from neurones of mammalian central nervous system. Pflügers Arch. *414*, 600–612.

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

Fatt, P. (1957). Sequence of events in synaptic activation of a motoneurone. J. Neurophysiol. *20*, 61–80.

Fetcho, J.R., and O'Malley, D.M. (1995). Visualization of active neural circuitry in the spinal chord of intact zebrafish. J. Neurophys. *73*, 399–406.

Fine, A., Amos, W.B., Durbin, R.M., and McNaughton, P.A. (1988). Confocal microscopy: applications in neurobiology. Trends Neurosci. *11*, 345–351.

Forehand, C.J., and Purves, D. (1984). Regional innervation of rabbit ciliary ganglion cells by the terminals of preganglionic axons. J. Neurosci. *4*, 1–12.

Fromherz, P., and Müller, C.O. (1994). Cable properties of a straight neurite of a leech neuron probed by a voltage-sensitive dye. Proc. Natl. Acad. Sci. USA *91*, 4604–4608.

Fuortes, M.G.F., Frank, K., and Becker, M.C. (1957). Steps in the production of the motoneuron spikes. J. Gen. Physiol. *40*, 735–752.

Gamble, E., and Koch, C. (1987). The dynamics of free calcium in dendritic spines in response to repetitive input. Science *236*, 1311–1315.

Gilbert, C., and Wiesel, T.N. (1979). Morphology and intracortical projections of functionally characterised neurons in the cat visual cortex. Nature *280*, 120–125.

Glenn, L.L., Whitney, J.F., Rewitzer, J.S., Salamone, J.A., and Mariash, S.A. (1988). Method for stable intracellular recordings of spinal α-motoneurons during treadmill walking in awake, intact cats. Brain Res. *439*, 396–401.

Goeppert-Mayer, M. (1931). Ueber Elementareakte mit zwei Quantensprungen. Ann. Physik *9*, 273–283.

González, J.E., and Tsien, R.Y. (1995). Voltage sensing by fluorescence resonacne energy transfer in single cells. Biophys. J. *69*, 1272–1280.

Gray, C.M., Konig, P., Engel, A.K., and Singer, W. (1989). Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. Nature *338*, 334–337.

Grinvald, A., Ross, W.N., and Farber, I. (1981). Simultaneous optical measurements of electrical activity from mutiple sites on processes of cultured neurons. Proc. Natl. Acad. Sci. USA *78*, 3145–3249.

Gustafsson, B., Wigstrom, H., Abraham, W.C., and Huang Y.-Y. (1987). Long-term potentiation in the hippocampus using depolarizing current pulses as the conditioning stimulus to single volley synaptic potentials. J. Neurosci. *7*, 774–780.

Guthrie, P.B., Segal, M., and Kater, S.B. (1991). Independent regulation of calcium revealed by imaging dendritic spines. Nature *354*, 76–80.

Gutnick, M.J., and Prince, D.A. (1981). Dye coupling and possible electrotonic coupling in the guinea pig neocortical slice. Science *211*, 67–70.

Haag, J., and Borst, A. (1996). Amplification of high-frequency synaptic inputs by active dendritic membrane processes. Nature *379*, 639–641.

Hatsopoulos, N., Gabbiani, F., and Laurent, G. (1995). Elementary computation of object approach by a wide-field visual neuron. Science *270*, 1000–1003.

Häusser, M., Stuart, G., Racca, C., and Sakmann, B. (1995). Axonal initiation and active dendritic propagation of action potentials in substantia nigra neurons. Neuron *15*, 637–647.

Hebb, D.O. (1949). The Organization of Behaviour (New York: Wiley).

Heiligenberg, W. (1991). Neural Nets in Electric Fish: Computational Neuroscience Series (Cambridge, Massachusetts: MIT Press).

Hermann, L. (1905). Beiträge zur Physiologie und Physiks des Nerven. Pflügers Arch. *109*, 95–120.

Hillman, D., Chen, S., Aung, T.T., Cherksey, B., Sugimori, M., and Llinás, R.R. (1991). Localization of P-type calcium channels in the central nervous system. Proc. Natl. Acad. Sci. USA *88*, 7076–7080.

Hirsch, J.A., and Gilbert, C.D. (1991). Synaptic physiology of horizontal connections in the cat's visual cortex. J. Neurosci. *11*, 1800–1809.

Hirsch, J.A., Alonso, J.-M., and Reid, R.C. (1995). Visually evoked calcium action potentials in cat striate cortex. Nature *378*, 612–616.

His, W. (1893). Über den Aufbau unseres Nervensystems. Berl. Klin. Wochenschr. *40*, 41.

Hodgkin, A.L., and Keynes, R.D. (1957). Movements of labelled calcium in squid giant axons. J. Physiol. *138*, 253–281.

Hodgkin, A.L., and Rushton, W.A.H. (1946). The electrical constants of a crustacean nerve fiber. Proc. R. Soc. Lond. (B) *133*, 444–479.

Hopfield, J.J. (1995). Pattern recognition computation using action potential timing for stimulus representation. Nature *376*, 33–36.

Houchin, J. (1973). Procion Yellow electrodes for intracellular recording and staining of neurons in the somatosensory cortex of the rat. J. Physiol. *232*, 67–69.

Huguenard, J.R., Hamill, O.P., and Prince, D.A. (1989). Sodium channels in dendrites of rat cortical pyramidal neurons. Proc. Natl. Acad. Sci. USA *86*, 2473–2477.

Hume, R.I., and Purves, D. (1981). Geometry of neonatal neurons and the regulation of synaptic elimination. Nature *293*, 469–471.

Hyde, I.H. (1921). A micro-electrode and unicellular stimulation. Biol. Bull. *40*, 130–133.

Jaffe, D.B., Johnston, D., Lasser-Ross, N., Lisman, J.E., Miyakawa, H., and Ross, W.N. (1992). The spread of Na spikes determines the pattern of dendritic Ca entry into hippocampal neurons. Nature *357*, 244–246.

Katz, L.C., and Constantine-Paton, M. (1988). Relationships between segregated afferents and postsynaptic neurons in the optic tectum of three-eyed frogs. J. Neurosci. *8*, 3160–3180.

Kim, H.G., and Connors, B.W. (1993). Apical dendrites of the neocortex: correlation between sodium- and calcium-dependent spiking and pyramidal cell morphology. J. Neurosci. *13*, 5301–5311.

Kim, H.G., Beierlein, M., and Connors, B.W. (1995). Inhibitory control of excitable dendrites in neocortex. J. Neurophysiol. *74*, 1810–1815.

Kisvarday, Z.F., Martin, K.A.C., Friedlander, M.J., and Somogyi, P. (1987). Evidence for interlaminar inhibitory circuits in the striate cortex of the cat. J. Comp. Neurol. *260*, 1–19.

Koch, C., and Zador, A. (1993). The function of dendritic spines: devices subserving biochemical rather than electrical compartmentalization. J. Neurosci. *13*, 413–422.

Koch, C., Poggio, T., and Torre, V. (1983). Nonlinear interactions in a dendritic tree: localization, timing, and role in information processing. Proc. Natl. Acad. Sci. USA *80*, 2799–2802.

Kogan, A., Ross, W.N., Zecevic, D., and Lasser-Ross, N. (1996). Optical recording from cerebellar Purkinje cells using intracellularly injected voltage-sensitive dyes. Brain Res., in press.

Kölliker A. (1889). Handbuch der Gewebelehre (Leipzig).

Kosaka, T. (1983). Neuronal gap junctions in the polymorph layer of the rat dentate gyrus. Brain Res. *277*, 347–351.

Larkman, A.U. (1991). Dendritic morphology of pyramidal neurons of the visual cortex of the rat. III. Spine distributions. J. Comp. Neurol. *306*, 332–343.

Laurent, G., and Burrows, M. (1989). Intersegmental interneurons can control the gain of reflexes in adjacent segments of the locust by their action on nonspiking local interneurons. J. Neurosci. *9*, 3030–3039.

Levy, W.B., and Desmond, N.L. (1985). Associative potentiation/depression in the hippocampal dentate gyrus. In Electrical Activity of the Archicortex, G. Buzsáki and C.H. Vanderwolf, eds. (Budapest: Akademiai Kiado), pp. 359–373.

Levy, W.B., and Steward, O. (1979). Synapses as associative memory elements in the hippocampal formation. Brain Res. *175*, 233–245.

Ling, G., and Gerard, R.W. (1949). The normal membrane potential of frog sartorius fibers. J. Cell Comp. Physiol. *34*, 383–396.

Lisman, J. (1989). A mechanism for the Hebb and anti-Hebb processes underlying learning and memory. Proc. Natl. Acad. Sci. USA *86*, 9574–9578.

Llinás, R. (1988). The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function. Science *242*, 1654–1664.

Llinás, R., and Greenfield, S.A. (1987). On-line visualization of dendritic release of acetylcholinesterase from mammalian substantia nigra neurons. Proc. Natl. Acad. Sci. USA *84*, 3047–3050.

Llinás, R., and Hess, R. (1976). Tetrodotoxin-resistant dendritic spikes in avian Purkinje cells. Proc. Natl. Acad. Sci. USA *73*, 2520–2523.

Llinás, R., and Nicholson, C. (1971). Electroresponsive properties of dendrites and somata in alligator Purkinje cells. J. Neurophysiol. *34*, 532–551.

Llinás, R., and Sugimori, M. (1980). Electrophysiological properties of *in vitro* Purkinje cell dendrites in mammalian cerebellar slices. J. Physiol. *305*, 197–213.

Llinás, R., and Sugimori, M. (1992). The electrophysiology of the cerebellar Purkinje cells revisited. In The Cerebellum Revisited, R. Llinás and C. Sotelo, eds. (New York: Springer-Verlag), pp. 167–181.

Llinás, R., and Yarom, Y. (1981). Properties and distribution of ionic conductances generating electroresponsiveness of mammalian inferior olivary neurones *in vitro*. J. Physiol. (Lond.) *315*, 569–584.

Llinás, R., Nicholson, C., Freeman, J.A., and Hillman, D.E. (1968). Dendritic spikes and their inhibition in alligator Purkinje cells. Science *160*, 1132–1135.

Llinás, R., Baker, R., and Sotelo, C. (1974). Electrotonic coupling between neurons in cat inferior olive. J. Neurophysiol. *37*, 560–571.

Lorente de Nó, R., and Coundouris, G.A. (1959). Decremental conduction in peripheral nerve integration of stimuli in the neuron. Proc. Natl. Acad. Sci. USA *45*, 592–617.

Lo Turco, J.J., and Kriegstein, A.R. (1991). Clusters of coupled neuroblasts in embryonic neocortex. Science *252*, 563–566.

MacVicar, B.A., and Dudek, F.E. (1981). Electrotonic coupling between pyramidal cells: a direct demonstration in rat hippocampal slices. Science *213*, 782–785.

Magee, J.C., and Johnston, D. (1995a). Characterization of single voltage-gated Na^+ and Ca^{2+} channels in apical dendrites of rat CA1 pyramidal neurons. J. Physiol. *487*, 67–90.

Magee, J.C., and Johnston, D. (1995b). Synaptic activation of voltage-gated channels in the dendrites of hippocampal pyramidal neurons. Science *268*, 301–304.

Mainen, Z.F., and Sejnowski, T.J. (1995). Reliability of spike timing in neocortical neurons. Science *268*, 1503–1506.

Major, G. (1993). Solutions for transients in arbitrarily branching cables. III. Voltage clamp problems. Biophys. J. *65*, 469–491.

Major, G., Evans, J.D., and Jack, J.B. (1993). Solutions for transients in arbitrary branching cables: I. Voltage recording with a somatic shunt. Biophys. J. *65*, 423–449.

Major, G., Larkman, A.U., Jonas, P., Sakmann, B., and Jack, J.J. (1994). Detailed passive cable models of whole-cell recorded CA3 pyramidal neurons in rat hippocampal slices. J. Neurosci. *14*, 4613–4638.

Markram, H., and Sakmann, B. (1994). Calcium transients in apical dendrites evoked by single sub-threshold excitatory post-synaptic potentials via low voltage-activated calcium channels. Proc. Natl. Acad. Sci. USA *91*, 5207–5211.

Matsumura, M., Cope, T., and Fetz, E.E. (1988). Sustained excitatory synaptic input to motor cortex neurons in awake animals revealed by intracellular recording of membrane potentials. Exp. Brain Res. *70*, 463–469.

Mel, B.W. (1994). Information processing in dendritic trees. Neural Comp. *6*, 1031–1085.

Michelson, H.B., and Wong, R.K.S. (1994). Synchronization of inhibitory neurons in the guinea pig hippocampus *in vitro*. J. Physiol. *477*, 35–45.

Minski, M. (1961). Microscopy apparatus. US Patent *1961*, 3013467.

Montana, V., Farkas, D.L., and Loew, L.M. (1989). Dual-wavelength ratiometric fluorescence measurements of membrane potential. Biochemistry *28*, 4536–4539.

Müller, W., and Connor, J.A. (1991). Dendritic spines as individual

neuronal compartments for synaptic Ca^{2+} responses. Nature *354*, 73–76.

Murphy, T.H., Baraban, J.M., Gil Wier, W., and Blatter, L.A. (1994). Visualization of quantal synaptic transmission by dendritic calcium imaging. Nature *263*, 529–532.

Núñez, A., García-Austt, E., and Buño, W. (1990). *In vivo* electrophysiological analysis of Lucifer Yellow–coupled hippocampal pyramids. Exp. Neurol. *108*, 76–82.

Núñez, A., Amzica, F., and Steriade, M. (1993). Electrophysiology of cat association cortical cells *in vivo*: intrinsic properties and synaptic responses. J. Neurophys. *70*, 418–430.

Palay, S.L. (1956). Synapses in the central nervous system. J. Biophys. Biochem. Cytol. *2*, 193–201.

Peinado, A., Yuste, R., and Katz, L.C. (1993). Extensive dye coupling between rat neocortical neurons during the period of circuit formation. Neuron *10*, 103–114.

Peters, A., Palay, S.L., and Webster, H.D. (1991). The Fine Structure of the Nervous System (New York: Oxford University Press).

Phillips, C.G., Powel, T.P.S., and Shepherd, G.M. (1963). Responses of mitral cells to stimulation of the lateral olfactory tract in the rabbit. J. Physiol. *168*, 65–88.

Pinsky, P.F., and Rinzel, J. (1994). Intrinsic and network rhythmogenesis in a reduced Traub model for CA3 neurons. J. Comput. Neurosci. *1*, 39–60.

Pockberger, H. (1991). Electrophysiological and morphological properties of rat motor cortex neurons *in vivo*. Brain Res. *539*, 181–190.

Pollack, G.S. (1988). Selective attention in an insect auditory neuron. J. Neurosci. *8*, 2635–2639.

Powell, T.P.S. (1981). Certain aspects of the intrinsic organization of the cerebral cortex. In Brain Mechanisms and Perceptual Awareness, O. Pompeiano and C. Ajmone Marsan, eds. (New York: Raven Press), pp. 1–19.

Purpura, D.P. (1967). Comparative physiology of dendrites. In The Neurosciences: A Study Program, G.C. Quarton, T. Melnechuk, and F.O. Schmitt, eds. (New York: Rockefeller University Press), pp. 372–875.

Purpura, D.P., and Shofer, R.J. (1964). Cortical intracellular potentials during augmenting and recruiting responses. I. Effects on injected hyperpolarizing currents on evoked membrane potential changes. J. Neurophysiol. *27*, 117–132.

Purves, D., and Hume, R.I. (1981). The relation of postsynaptic geometry to the number of presynaptic axons that innervate autonomic ganglion cells. J. Neurosci. *1*, 441–452.

Rall, W. (1959). Branching dendritic trees and motoneuron membrane resistivity. Exp. Neurol. *1*, 491–527.

Rall, W. (1964). Theoretical significance of dendritic trees for neuronal input-output relations. In Neural Theory and Modeling, R.F. Reiss, ed. (Stanford: Stanford University Press), pp. 73–97.

Rall, W. (1974). Dendritic spines, synaptic potency and neuronal plasticity. In Cellular Mechanisms Subserving Changes in Neuronal Activity, C.D. Woody, K.A. Brown, T.J. Crow, and J.D. Knispel, eds. (Los Angeles: Brain Information Services), pp. 13–21.

Rall, W. (1995). The Theoretical Foundation of Dendritic Function, I. Segev, J. Rinzel, and G.M. Shepherd, eds. (Cambridge, Massachusetts: MIT Press).

Rall, W., and Segev, I. (1987). Functional possibilities for synapses on dendrites and on dendritic spines. In Synaptic Function, G.E. Edelman, W.F. Gall, and W.M. Cowan, eds. (New York: Wiley), pp. 605–637.

Rall, W., and Shepherd, G.M. (1968). Theoretical reconstruction of field potentials and dendro-dendritic synaptic interactions in olfactory bulb. J. Neurophys. *31*, 884–915.

Rall, W., Shepherd, G.M., Reese, T.S., and Brightman, M.W. (1966). Dendrodenritic synaptic pathways for inhibition in the olfactory bulb. Exp. Neurol. *14*, 44–56.

Raman, I.M., and Trussell, L.O. (1992). The kinetics of the response to glutamate and kainate in neurons of the avian cochlear nucleus. Neuron *9*, 173–186.

Ramón, P. (1890). Investigaciones de histología comparada en los centros ópticos de los vertebrados. PhD thesis, University of Madrid.

Ramón y Cajal, S. (1889). Conexión general de los elementos nerviosos. Medicina Práctica.

Ramón y Cajal, S. (1891a). Significación fisiológica de las expansiones protoplásmicas y nerviosas de la sustancia gris. Rev. Ciencias Méd. *22*, 23.

Ramón y Cajal, S. (1891b). Sur la structure de l'ecorce cerebrale de quelques mamiferes. Cellule *7*.

Ramón y Cajal, S. (1897). Las leyes de la morfología y dinamismo de las células nerviosas. Revista Trim. Microgr. *1*.

Ramón y Cajal, S. (1904). La Textura del Sistema Nerviosa del Hombre y los Vertebrados (Madrid: Moya).

Ramón y Cajal, S. (1923). Recuerdos de mi Vida: Historia de mi Labor Científica (Madrid: Alianza Editorial).

Rapp, M., Segev, I., and Yarom, Y. (1994). Physiology, morphology and detailed passive models of guinea-pig Purkinje cells. J. Physiol. (Lond.) *474*, 101–118.

Regehr, W.G., and Tank, D.W. (1992). Calcium concentration dynamics produced by synaptic activation of CA1 hippocampal pyramidal cells. J. Neurosci. *12*, 4202–4223.

Regehr, W.G., Connor, J.A., and Tank, D.W. (1989). Optical imaging of calcium accumulation in hippocampal pyramidal cells during synaptic activation. Nature *341*, 533–536.

Regehr, W.G., Konnerth, A., and Armstrong, C.M. (1992). Sodium action potentials in the dendrites of cerebellar Purkinje cells. Proc. Natl. Acad. Sci. USA *89*, 5492–5496.

Regehr, W.G., Kehoe, J., Ascher, P., and Armstrong, C. (1993). Synaptically triggered action potentials in dendrites. Neuron *11*, 145–151.

Renshaw, B. (1942). Effects of presynaptic volleys on spread of impulses over the soma of the motoneurons. J. Neurophysiol. *5*, 235–243.

Reuveni, I., Friedman, A., Amitai, Y., and Gutnick, M.J. (1993). Stepwise repolarization from Ca^{2+} plateaus in neocortical pyramidal cells: evidence for nonhomogeneous distribution of HVA Ca^{2+} channels in dendrites. J. Neurosci. *13*, 4609–4621.

Reyher, C.H.K., Lubke, J., Larsen, W.J., Hendrix, G.M., Shipley, M.T., and Baumgarten, H.G. (1991). Olfactory bulb granule cell aggregates: morphological evidence for interperikaryal electrotronic coupling via gap junctions. J. Neurosci. *11*, 1485–1495.

Rhodes, P.A., and Gray, C.M. (1994). Simulations of intrinsically bursting neocortical pyramidal neurons. Neural Comp. *6*, 1086–1110.

Richardson, T.L., Turner, R.W., and Miller, J.J. (1987). Action-potential discharge in hippocampal CA1 pyramidal neurons. J. Neurophys. *58*, 981–996.

Rockland, K.S., and Virga, A. (1989). Terminal arbors of individual "feedback" axons projecting from V2 to V1 in the macaque monkey: a study using immunocytochemistry of anterogradely transported *Phaseolus vulgaris* leucoagglutinin. J. Comp. Neurol. *285*, 54–72.

Rose, G.J., and Call, S.J. (1993). Temporal filtering properties of midbrain neurons in an electric fish: implications for the function of dendritic spines. J. Neurosci. *13*, 1178–1189.

Ross, W.N., and Werman, R. (1987). Mapping calcium transients in the dendrites of Purkinje cells from guinea-pig cerebellum *in vitro*. J. Physiol. *389*, 319–336.

Ross, W.N., Lewenstein Stockbridge, L., and Stockbridge, N.L. (1986). Regional properties of calcium entry in barnacle neurons determined with Arsenazo III and a photodiode array. J. Neurosci. *6*, 1148–1159.

Rubel, E.W., and Parks, T.N. (1988). Organization and development of the avian brain-stem auditory system. In Auditory Function, G.M. Edelman, W.E. Gall, and W.M. Cowan, eds. (New York: John Wiley and Sons), pp. 3–93.

Sakmann, B., and Neher, E. (1983). Single Channel Recording (New York: Plenum).

Schadlen, M.N., and Newsome, W.T. (1994). Noise, neural codes and cortical organization. Curr. Opin. Neurobiol. *4*, 569–579.

Scharfman, H.E., and Sarvey, J.M. (1985). Postsynaptic firing during repetitive stimulation is required for long-term potentiation in hippocampus. Brain Res. *331*, 267–274.

Schwartzkroin, P.A., and Slawsky, M. (1977). Probable calcium spikes in hippocampus neurons. Brain Res. *135*, 157–161.

Shelton, D.P. (1985). Membrane resistivity estimated for the Purkinje neuron by means of a passive computer model. Neuroscience *14*, 111–131.

Shepherd, G.M., and Brayton, R.K. (1987). Logic operations are properties of computer-simulated interactions between excitable dendritic spines. Neuroscience *21*, 151–165.

Shepherd, G.M., Brayton, R.K., Miller, J.P., Segev, I., Rinzel, J., and Rall, W. (1985). Signal enhancement in distal cortical dendrites by means of interactions between active dendritic spines. Proc. Natl. Acad. Sci. USA *82*, 2192–2195.

Sloper, J.J. (1972). Gap junctions between dendrites in the primate neocortex. Brain Res. *44*, 641–646.

Sobel, E.C., and Tank, D. W. (1994). *In vivo* Ca^{2+} dynamics in a cricket auditory neuron: an example of chemical computation. Science *263*, 823–826.

Softky, W.R., and Koch, C. (1992). The highly irregular firing of cortical cells is inconsistent with temporal integration of random EPSPs. J. Neurosci. *13*, 334–350.

Sotelo, C., Llinás, R., and Baker, R. (1974). Structural study of inferior olivary nucleus of the cat: morphological correlates of electrotonic coupling. J. Neurophysiol. *37*, 541–559.

Spencer, W.A., and Kandel, E.R. (1961). Electrophysiology of hippocampal neurons: IV. Fast prepotentials. J. Neurophysiol. *24*, 272–285.

Spruston, N., Jaffe, D.B., and Johnston, D. (1994). Dendritic attenuation of synaptic potentials and currents: the role of passive membrane properties. Trends Neurosci. *17*, 161–166.

Spruston, N., Schiller, Y., Stuart, G., and Sakmann, B. (1995). Activity-dependent action potential invasion and calcium influx into hippocampal CA1 dendrites. Science *286*, 297–300.

Stafstrom, C.E., Schwindt, P.C., Chabb, M.C., and Crill, W.E. (1985). Properties of persistent sodium and calcium conductances of layer 5 neurons from cat sensory motor cortex *in vivo*. J. Neurophysiol. *55*, 153–170.

Stratford, K., Mason, A., Larkman, A., Major, G., and Jack, J.J. (1989). The modelling of pyramidal neurons in the visual cortex. In The Computing Neuron, R. Durbin, C. Miall, and G. Mitchinson, eds. (Workingham, England: Addison-Wesley), pp. 296–322.

Stuart, G.J., and Häusser, M. (1994). Initiation and spread of sodium action potentials in cerebellar Purkinje cells. Neuron *13*, 703–712.

Stuart, G.J., and Sakmann, B. (1994). Active propagation of somatic action potentials into neocortical pyramidal cell dendrites. Nature *367*, 69–72.

Stuart, G.J., Dodt, H.-U., and Sakmann, B. (1993). Patch clamp recording from the soma and dendrites of neurons in brain slices using infrared video microscopy. Pflügers Arch. *423*, 511–518.

Sugihara, I., Lang, E.J., and Llinás, R. (1993). Uniform olivocerebellar conduction time underlies Purkinje cell complex spike synchronicity in the rat cerebellum. J Physiol. (Lond.) *470*, 243–271.

Sutor, B., and Hablitz, J.J. (1989). EPSPs in rat neocortical neurons *in vitro*. II. Involvement of N-methyl-D-aspartate receptors in the generation of EPSPs. J. Neurophysiol. *61*, 621–634.

Tank, D.W., Sugimori, M., Connor, J.A., and Llinás, R.R. (1988). Spatially resolved calcium dynamics of mammalian Purkinje cells in cerebellar slice. Science *242*, 773–777.

Thompson, A.M., Girdlestone, D., and West, D.C. (1988). Voltage-dependent currents prolong single-axon postsynaptic potentials in layer III pyramidal neurons in rat neocortical slices. J. Neurophysiol. *60*, 1896–1907.

Traub, R.D. (1996). Model of sustained population bursts in electrically coupled inerneurons containing active dendritic conductances. J. Comput. Neurosci., in press.

Traub, R.D., Wong, R.K., Miles, R., and Michelson, H. (1991). A model of a CA3 hippocampal pyramidal neuron incorporating voltage-clamp data on intrinsic conductances. J. Neurophysiol. *66*, 635–650.

Tsien, R.Y. (1989). Fluorescent probes of cell signaling. Annu. Rev. Neurosci. *12*, 227–253.

Turner, R.W., Meyers, E.R., Richardson, D.L., and Barker, J.L. (1991). The site for initiation of action potential discharge over the somatosensory axis of rat hippocampal CA1 pyramidal neurons. J. Neurosci. *11*, 2270–2280.

Vaney, D.I. (1991). Many diverse types of retinal neurons show tracer coupling when injected with biocytin or neurobiotin. Neurosci. Lett. *125*, 187–190.

Van Gehuchten, A. (1891). La moelle epiniere et le cervelet. Cellule *7*.

Watson, A.H.D., and Burrows, M. (1988). Distribution and morphology of synapses on nonspiking local interneurons in the thoracic nervous system of the locust. J. Comp. Neurol. *272*, 605–616.

Westenbroek, R.E., Ahlijanian, M.K., and Catterall, W.A. (1990). Clustering of L-type Ca^{2+} channnels at the base of major dendrites in hippocampal pyramidal neurons. Nature *347*, 281–284.

Westenbroek, R.E., Hell, J.W., Warner, C., Dubel, S.J., Snutch, T.P., and Catterall, W.A. (1992). Biochemical properties and subcellular distribution of an N-type calcium channel $\alpha 1$ subunit. Neuron *9*, 1099–1115.

Wickens, J. (1988). Electrically coupled but chemically isolated synapses: dendritic spines and calcium in a rule for synaptic modification. Prog. Neurobiol. *31*, 507–528.

Wilson, T., and Sheppard, C. (1984). Theory and Practice of Scanning Optical Microscopy (New York: Academic Press).

Wong, R.K.S., and Prince, D.A. (1978). Participation of calcium spikes during intrinsic burst firing in hippocampal neurons. Brain Res. *159*, 385–390.

Wong, R.K.S., and Steward, M. (1992). Different firing patterns generated in dendrites and somata of CA1 pyramidal neurones in guinea-pig hippocampus. J. Physiol. *457*, 675–687.

Wong, R.K.S., Prince, D.A., and Basbaum, A.I. (1979). Intradendritic recordings from hippocampal neurons. Proc. Natl. Acad. Sci. USA *76*, 986–990.

Wu, K., Sachs, L., Carlin, R.K., and Siekevitz P. (1986). Characteristics of a Ca^{2+}/calmodulin-dependent binding of the Ca^{2+} channel antagonists nitrendipine, to a postsynaptic density fraction isolated from canine cerebral cortex. Mol. Brain Res. *1*, 176–184.

Yamamoto, C. (1972). Activation of hippocampal neurons by mossy fiber stimulation in thin brain sections *in vitro*. Exp. Brain Res. *14*, 423–435.

Yang, G., and Masland, R.H. (1992). Direct visualization of the dendritic and receptive fields of directionally selective retinal ganglion cells. Science *258*, 1949–1952.

Yuste, R., and Denk, W. (1995). Dendritic spines as basic units of synaptic integration. Nature *375*, 682–684.

Yuste, R., Peinado, A., and Katz, L.C. (1992). Neuronal domains in developing neocortex. Science *257*, 665–669.

Yuste, R., Gutnick, M.J., Saar, D., Delaney, K.D., and Tank, D.W. (1994). Calcium accumulations in dendrites from neocortical neurons: an apical band and evidence for functional compartments. Neuron *13*, 23–43.

Yuste, R., Nelson, D., Rubin, W., and Katz, L.C. (1995). Neuronal domains in developing neocortex: mechanisms of coactivation. Neuron *14*, 7–17.

Zeki, S. (1993). The modularity of the brain. In A Vision of the Brain, S. Zeki, ed. (Oxford: Blackwell), pp. 197–296.

Zohary, E., Shadlen, M.N., and Newsome, W. T. (1994). Correlated neuronal discharge rate and its implications for psychophysical performance. Nature *370*, 140–143.