Diversity and Dynamics of Dendritic Signaling

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Communication between neurons in the brain occurs primarily through synapses made onto elaborate treelike structures called dendrites. New electrical and optical recording techniques have led to tremendous advances in our understanding of how dendrites contribute to neuronal computation in the mammalian brain. The varied morphology and electrical and chemical properties of dendrites enable a spectrum of local and long-range signaling, defining the input-output relationship of neurons and the rules for induction of synaptic plasticity. In this way, diversity in dendritic signaling allows individual neurons to carry out specialized functions within their respective networks.

Dendrites, the delicate processes emerging from the soma of most neurons, are among the most beautiful structures found in the natural world. They come in an extraordinary variety of shapes and sizes, are present in all species with a nervous system, and continue to develop after birth in concert with the establishment of neuronal circuitry. Generating and maintaining these elaborate structures, which occupy a large proportion of our brains (*1*), is energetically costly (*2*), implying that their presence is worth this cost. Historically, the structural role of dendrites in the formation and segregation of synaptic connections has been emphasized, but their role in defining the relationship between synaptic input and neuronal output is receiving increasing attention. Indeed, there is now a growing consensus that understanding how dendrites process the thousands of synaptic inputs they receive is essential if we are to understand how single neurons contribute to information processing in the brain.

A Renaissance in Dendrite Research

Our understanding of signal processing in dendrites has been shaped by experimental and theoretical work spanning more than a century, beginning with Cajal and his ideas on the direction of information flow in neurons (synapse → dendrite → soma → axon → synapse). The theoretical work of Rall during the 1950s and 1960s demonstrated that the structural and electrical properties of dendrites play an important role in the way a neuron processes its synaptic inputs. Although much of this work focused on the passive properties of dendrites, it was also believed that dendrites had active properties—a view that has recently received considerable attention because of its consequences for synaptic plasticity and neuronal computation. Subsequently, dendritic recordings from cerebellar Purkinje and hippocampal pyramidal neurons using sharp microelectrodes provided direct evidence that active responses could be generated in dendrites by voltage-gated ion channels (*3–8*). These early experiments suggested a rich repertoire of dendritic excitability.

More quantitative investigation of dendritic properties and function has recently become possible thanks to two technical breakthroughs that have emerged in the last 10 years. First, the ability to make patch-clamp recordings from dendrites of neurons in brain slices under visual control (*9*) has made it possible to record electrical signals from specific dendritic regions of identified neurons, map dendritic channel densities, and investigate the spread of electrical signals within dendrites by recording from two or more locations on the same neuron. Second, the development of new imaging technologies (*10–12*) has allowed chemical signaling in dendrites to be observed with unprecedented spatial and temporal resolution, permitting the study of dendritic signaling in vivo, as well as in tiny branches and spines currently inaccessible to patch-clamp recording.

Together with the development of powerful numerical simulation programs (*13, 14*), these techniques have revolutionized the study of dendritic function and have led to a remarkable resurgence of interest in these complex structures. Here, we focus on new insights into electrical and chemical signaling in mammalian dendrites that have emerged as a result of these approaches. Invertebrate preparations have also provided key insights and have been reviewed elsewhere (*15, 16*). Our aim is to show how the newly revealed richness in dendritic function contributes to synaptic integration and plasticity and thereby enhances neuronal computation.

Diversity in the Expression of Dendritic Voltage-Gated Ion Channels

Early microelectrode studies demonstrated the existence of large, transient depolarizations (spikes) in dendrites, reflecting the opening of voltage-gated Na^+ and Ca^{2+} channels. These channels open in response to membrane depolarization and in turn cause further depolarization, which is responsible for their regenerative nature. The systematic application of the patch-clamp technique to studying dendritic properties in brain slices has now confirmed the presence of a great variety of voltage-gated ion channels in the dendritic membrane. Together with antibody studies (*17*), this has led to quantitative "maps" of the distribution of voltage-gated ion channels in several neuronal types (*18*).

The pattern of expression of particular channels is remarkably diverse. In many types of neurons, voltage-gated Na^+ channels are distributed uniformly across the somatodendritic axis (*19–23*), albeit at a lower density than in the axon, whereas in other neurons Na^+ channels are present at the soma but largely absent from the dendrites (*24*). Cell-specific and often nonuniform dendritic distributions also have been observed for voltage-gated K^+ channels (*20, 23, 25–28*), different types of voltage-gated Ca^{2+} channels (*19, 23*), and the hyperpolarization-activated cation channel I_h (*29, 30*). The properties of the same type of voltage-gated channel can also be different in somatic and dendritic membranes (*22, 23, 28, 31, 32*), and there can be substantial variability in channel density at similar dendritic locations (perhaps indicating the existence of channel clusters or "hot spots"). So far, there appear to be no general rules determining the distribution of voltage-gated channels in dendrites. Rather, it seems that each neuronal type has a specialized and highly regulated set of dendritic voltage-gated channels, which change during development (*33–36*) and can be modulated by neurotransmitters (*37*).

Multiple Forms of Dendritic Excitability

The final output signal of the neuron is the action potential, which is transmitted to synapses by the axon. There is considerable evidence that the lowest-threshold site for action potential initiation in neurons is in the axon itself (*38*). Yet dendrites are capable of

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a variety of active responses, including active backpropagation of axonal action potentials into the dendritic tree, as well as dendritically generated spikes mediated by voltage-gated Na^+ and/or Ca^{2+} channels (Fig. 1). In addition, dendritic spikes mediated primarily by glutamate-activated *N*-methyl-D-aspartate (NMDA) channels have recently been described (*39*). Most of our knowledge currently comes from in vitro data, but many of these forms of dendritic excitability are now being investigated in vivo, with both electrophysiological and imaging studies providing evidence for action potential backpropagation and dendritically initiated Na^+ and Ca^{2+} spikes in anesthetized and awake animals (*40–47*). As we discuss below, these multiple forms of dendritic excitability influence the way neurons integrate synaptic inputs in complex ways.

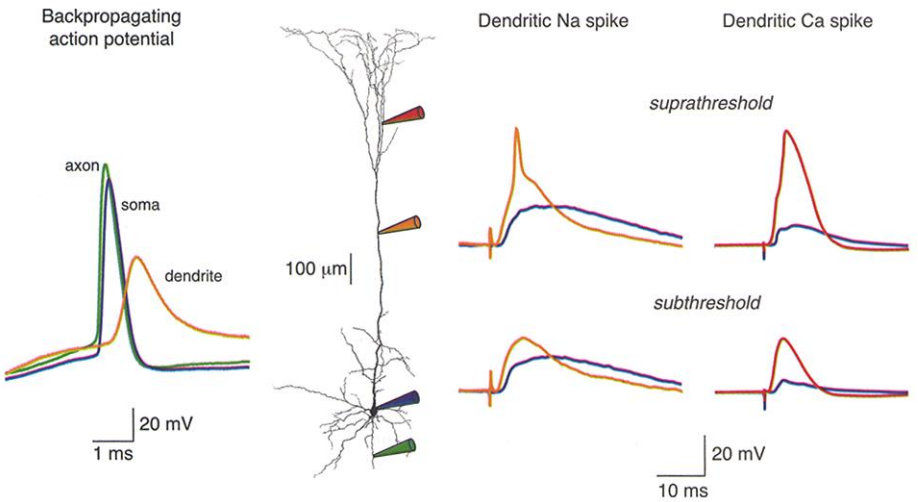

Fig. 1. Diversity in dendritic excitability. All recordings are from different neocortical layer 5 pyramidal neurons, with the recording locations indicated schematically on a typical morphology. (**Left**) Action potential evoked by distal synaptic stimulation recorded simultaneously in the axon (green trace), soma (blue trace), and apical dendrite 300 μm from the soma (orange trace). The action potential is initiated in the axon and backpropagates into the soma and dendritic tree [modified from (*63*)]. (**Right**) Initiation of dendritic Na^+ and Ca^{2+} spikes. In each case, recordings were made simultaneously from the soma and distal dendrites (400 μm from the soma for the Na^+ spike, orange trace; 920 μm from the soma for the Ca^{2+} spike, red trace), and both a subthreshold and a suprathreshold response to distal synaptic activation are shown [adapted from (*63*, *73*)].

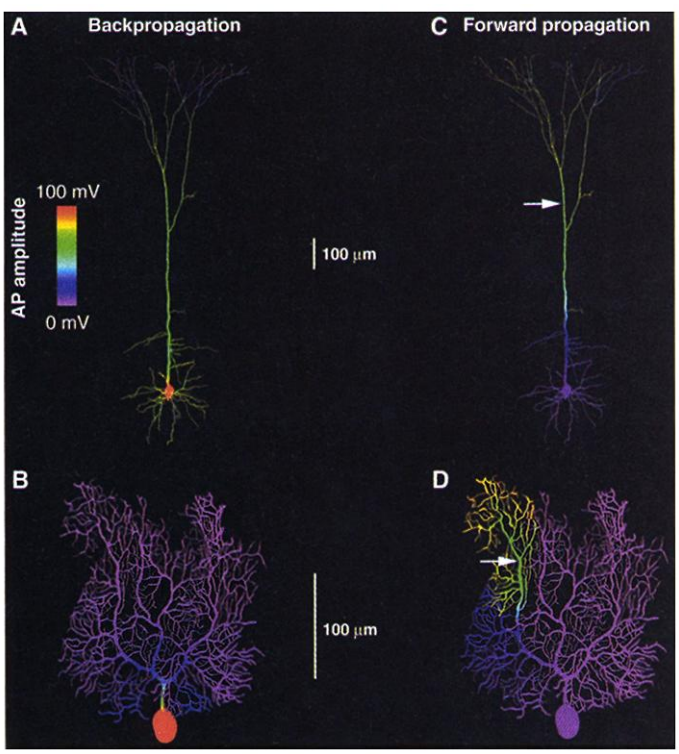

Fig. 2. Diversity of compartmentalization in dendrites caused by cell-specific differences in dendritic morphology. Action potential backpropagation and forward propagation of a dendritic spike was simulated in a neocortical layer 5 neocortical pyramidal neuron (**A** and **C**) and a cerebellar Purkinje cell (**B** and **D**). Both morphologies were provided with the same uniform dendritic density of voltage-gated Na^+ and K^+ channels [35 and 30 pS/μm^2, respectively; channel models from (*129*)] to isolate the effect of dendritic morphology. The local amplitude of the backpropagating action potential (AP) or dendritic spike is coded by color in each cell type [modified from (*71*)].

Modulation of Synaptic Potentials by Voltage-Gated Ion Channels

Synaptic potentials are filtered by the cable structure of the dendritic tree. The size and shape of synaptic potentials reaching the site of action potential initiation thus depend in part on the location of the synaptic input (*48, 49*). This location dependence may provide a form of dendritic computation (*50, 51*), or alternatively can be viewed as a complication that must be overcome. There is now evidence that in some neurons, synaptic and active properties of dendrites may act to equalize the efficacy of inputs distributed along the dendritic tree. Early work in motoneurons (*52, 53*) and more recent studies in hippocampal neurons (*54, 55*) suggest that synaptic conductance increases with distance from the soma, thereby mitigating the effect of dendritic filtering. Numerous studies have also shown that the time course and amplitude of synaptic potentials can be affected by voltage-gated ion channels, with dendritic patch-clamp recordings and imaging studies providing direct evidence for interaction of dendritic voltage-gated channels with excitatory postsynaptic potentials (EPSPs) (*56*). Although some of these studies indicate that dendritic voltage-gated channels can amplify distal synaptic inputs, other studies show that amplification of synaptic potentials is greatest near the soma (*57, 58*), or that activation of inward dendritic conductances can be balanced by outward conductances such as dendritic K^+ channels (*28, 59, 60*). It therefore seems likely that the role of dendritic voltage-gated channels may be more complex than simply increasing the influence of distal synapses on action potential initiation, although this may occur under some conditions. Instead, the way in which dendritic conductances influence synaptic integration will depend on the cell-specific distribution of dendritic voltage-gated channels and the location, amplitude, and time course of synaptic input, thus providing a rich repertoire of excitability.

Backpropagating Action Potentials

Action potentials initiated in the axon subsequently invade the soma and dendrites (Fig. 1, left), providing a retrograde signal informing synapses in the dendritic tree that the neuron has generated an output. The efficacy of this backpropagation spans a wide range in different neuronal types (Fig. 2, A and B). At one extreme, action potentials invade the dendrites of some neurons with little or no amplitude decrement (*20, 22, 61, 62*). In contrast, cerebellar Purkinje neurons show very poor action potential backpropagation (*8, 24*), whereas other neuronal types (*21, 23, 63–67*) exhibit varying degrees of amplitude decrement. The efficacy of backpropagation can

also vary in different dendrites of the same neuron (*67, 68*). This diversity is due in part to the differential expression of dendritic voltage-gated Na^+ and K^+ channels in different neuronal types (*18*), or in different branches of the same neuron. Diversity in structure of the dendritic tree (*69*) is another key determinant of backpropagation efficacy (*66, 70*), with a recent modeling study showing that the same complement of voltage-gated channels in different dendritic morphologies can reproduce the range of backpropagation efficacies observed experimentally (*71*). It will be important to relate this diversity in backpropagation to function. Given that one of the roles of backpropagation is to trigger dendritic release of neurotransmitter, it is interesting to note that in two neuronal types where this occurs—dopamine neurons of the substantia nigra and mitral cells of the olfactory bulb—action potential backpropagation is very effective (*20, 61, 62*).

Dendritic Spikes

Dendritic spikes arise as a result of regenerative Na^+ and/or Ca^{2+} channel activation that begins in the dendrites (Fig. 1, right). Because the local voltage threshold for generation of these dendritic events is higher than for action potential initiation in the axon, dendritic spike initiation usually requires relatively strong synchronous synaptic activation (*72*) and thus may represent a form of local coincidence detection. Backpropagating action potentials and dendritic Na^+ and Ca^{2+} spikes are therefore likely to be generated by different patterns of synaptic activity. Dendritically generated spikes exhibit a range of propagation efficacies as they spread in the forward direction toward the soma (Fig. 2, C and D). In some neurons, forward propagation of dendritic spikes is quite robust, exhibiting little amplitude decrement (*22, 61, 62*). In others, dendritic spikes can remain largely isolated to the dendrites (*63, 73–75*). A consequence of this heterogeneity is that dendritic spikes are variable triggers of action potential initiation, dependent on prior axonal action potential firing (*74*) as well as the level of somatic excitation and inhibition (*62*) (Fig. 3A). Both the distribution of dendritic voltage-gated ion channels and the dendritic morphology will contribute to this diversity, with dendritic branch points increasing attenuation of forward-propagating dendritic spikes relative to backpropagating action potentials (Fig. 2).

Electrical Compartmentalization of Dendrites

The incomplete propagation of these multiple forms of dendritic excitability results in compartmentalization of the dendritic tree. This compartmentalization is determined by the dendritic morphology and voltage-gated ion channel distributions of each neuronal type, as well as by the spatiotemporal pattern of synaptic activation. The ability to modulate voltage-gated ion channels implies that the extent to which the dendritic tree will be compartmentalized can be dynamically regulated by the state of the network. The functional consequence of this dendritic compartmentalization is that there can be multiple sites for integration of synaptic inputs, theoretically leading to a significant enhancement of the computational power of single neurons (*76*).

These electrical compartments are not fixed, as both backpropagation and forward propagation can be dynamically regulated. Slow recovery from inactivation of dendritic Na^+ channels causes an activity-induced decline in action potential backpropagation (*31, 32, 66, 77*) (Fig. 3B), whereas high-frequency bursts of action potentials can lead to activity-dependent increases in backpropagation (*23, 63, 78–80*). Moreover, backpropagating action potentials can be amplified by EPSPs (*81, 82*) or dendritic oscillations (Fig. 3C) and can be blocked by inhibition (*83, 84*). Modulation of dendritic Na^+ and K^+ channels by neurotransmitters can also regulate action potential backpropagation (*37*). Because the density of these channels is likely to change during development (*33–35*) together with changes in dendritic morphology, the extent of forward and backpropagation—and thus the degree of compartmentalization—will depend on the developmental and behavioral state of the network.

Interactions Between Electrical Compartments

Electrical compartments in dendrites do not operate in isolation, but are sensitive to and can influence activity in other regions of the dendritic tree. Pairing action potentials with EPSPs can cause a substantial amplification of backpropagating action potentials in the distal dendrites (*81, 82*) and can trigger dendritic Ca^{2+} spikes (*85*) (Fig. 3D). A similar amplification of backpropagating action potentials is seen in vivo during sharp waves in the distal dendrites of hippocampal neurons (*43*). Dendritic Ca^{2+} spikes can in turn trigger burst firing at the soma and axon (*73, 85–88*). Dendritic spike initiation zones can thus shape the final output of the neuron. Conversely, activation of proximal dendritic K^+ channels during action potential firing restricts Ca^{2+} spike initiation to the dendrites and may limit the propagation of Ca^{2+} spikes toward the soma (*86*). Synaptic inhibition can also uncouple dendritic compartments by limiting the spread of both backpropagating action potentials (*83, 84*) and forward-propagating dendritic spikes (*62*).

Axonal action potentials can also affect synaptic integration in other neuronal compartments. The axonal conductances activated during the action potential can shunt synaptic potentials, electrically isolating dendritic compartments from the soma (*89*). Because the backpropagating action potential activates a lower density of conductances than in the axon and often does not effective-

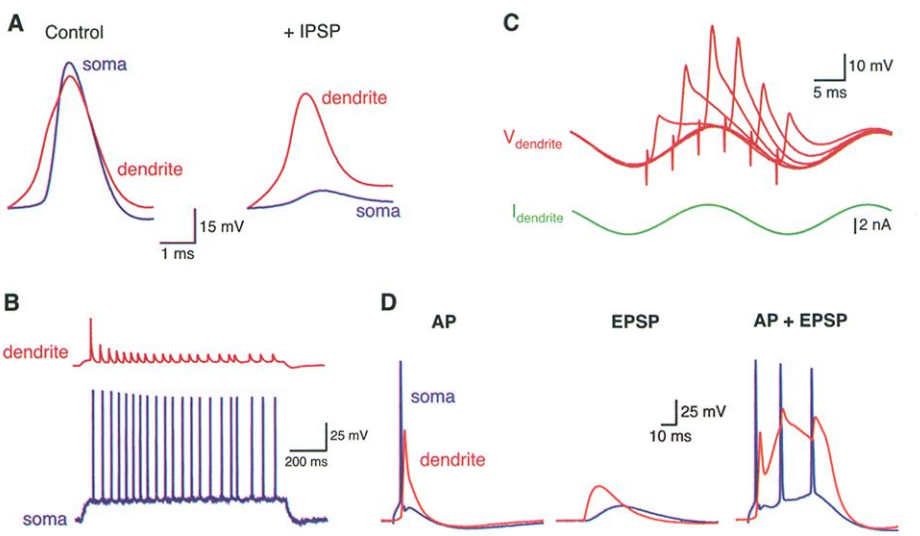

Fig. 3. Modulation of dendritic excitability and interactions between electrical compartments. **(A)** Dynamic compartmentalization of dendrites by inhibition in an olfactory bulb mitral cell. Activation of an inhibitory postsynaptic potential (IPSP) prevents forward propagation of a dendritic spike to the soma [from (*62*)]. **(B)** Activity-dependent backpropagation of action potentials in a hippocampal CA1 pyramidal neuron. Action potentials evoked by a somatic current pulse decline progressively in the distal dendrites [from (*66*)]. **(C)** Modulation of action potential backpropagation by subthreshold oscillations in dendritic membrane potential in a neocortical layer 5 pyramidal neuron [modified from (*82*)]. **(D)** Pairing a backpropagating action potential (AP) with distal EPSPs (simulated by dendritic current injection) in a neocortical layer 5 pyramidal neuron leads to a distal Ca^{2+} spike and a somatic burst [modified from (*85*)].

ly backpropagate into all dendrites, the dendritic tree is thus functionally compartmentalized, allowing integration in distal dendritic regions to continue uninterrupted by axonal output (*89*).

Chemical Compartmentalization of Dendrites

Synaptic and regenerative activity in dendrites is often associated with an increase in intracellular Ca^{2+}, linking electrical events to a variety of cytosolic signal transduction systems. The magnitude and spatial extent of these dendritic Ca^{2+} signals depends on several factors, the most important being the source of the Ca^{2+} signal. When the source is primarily synaptic, the Ca^{2+} signal will depend on the strength and pattern of synaptic input and the types of transmitter channels activated. When the source is a regenerative event, the Ca^{2+} signal will be defined in part by the extent to which this event propagates in the dendritic tree. Other factors that will influence the size of chemical compartments include intracellular Ca^{2+} buffering, uptake, extrusion, and dendritic geometry (*90*). Because synaptic input can interact with regenerative events in complex ways, and because calcium signals can themselves be enhanced by Ca^{2+}-induced Ca^{2+} release (*91–93*), the extent of chemical compartmentalization will be highly dynamic.

Localized Ca^{2+} influx has been observed during synaptic stimulation below the threshold for axonal action potential initiation in a variety of cell types (*90, 94*). Dendritic Ca^{2+} signals can be highly localized, restricted to single spines (*95–97*), or can spread to larger dendritic regions during stronger synaptic stimulation, particularly when associated with dendritic spikes (*73, 98, 99*). Backpropagating action potentials produce an increase in dendritic Ca^{2+} that largely reflects backpropagation efficacy in each cell type, with pyramidal neurons showing relatively widespread dendritic Ca^{2+} signals [(*80, 95, 100–102*), but compare (*41, 46*)], whereas Purkinje cells essentially lack dendritic Ca^{2+} signals in response to action potentials (*103*).

Chemical compartmentalization is not limited to Ca; it is likely to apply to a variety of cytosolic substances, particularly within spines, the smallest chemical compartments (*104, 105*). 1,4,5-Inositol trisphosphate (IP_3)–induced Ca^{2+} release is highly restricted in the dendrites of Purkinje neurons (Fig. 4A) (*106–108*) and hippocampal neurons (*93*), which suggests that IP_3 itself can be compartmentalized in dendrites. The cooperative activation of IP_3 receptors by IP_3 and Ca^{2+} provides a mechanism by which Ca^{2+} influx can trigger supralinear Ca^{2+} signals in dendritic compartments where IP_3 has been generated by synaptic activation (*93, 109*). This indicates that separate chemical and electrical compartments can interact in a highly nonlinear manner (*110*).

Dendritic Properties Influence the Induction and Expression of Synaptic Plasticity

The electrical and chemical compartmentalization of dendrites provides mechanisms for defining the rules governing the induction of synaptic plasticity. The induction of both long-term potentiation and long-term depression (LTP and LTD) during pairing of EPSPs with postsynaptic action potentials requires that they occur within a narrow time window (*111*). This suggests that backpropagating action potentials may act as a retrograde signal important for the induction of synaptic plasticity. Direct evidence that this is the case comes from the finding that at least some forms of LTP require active action potential backpropagation (*81*), indicating that modulation of backpropagation can have important

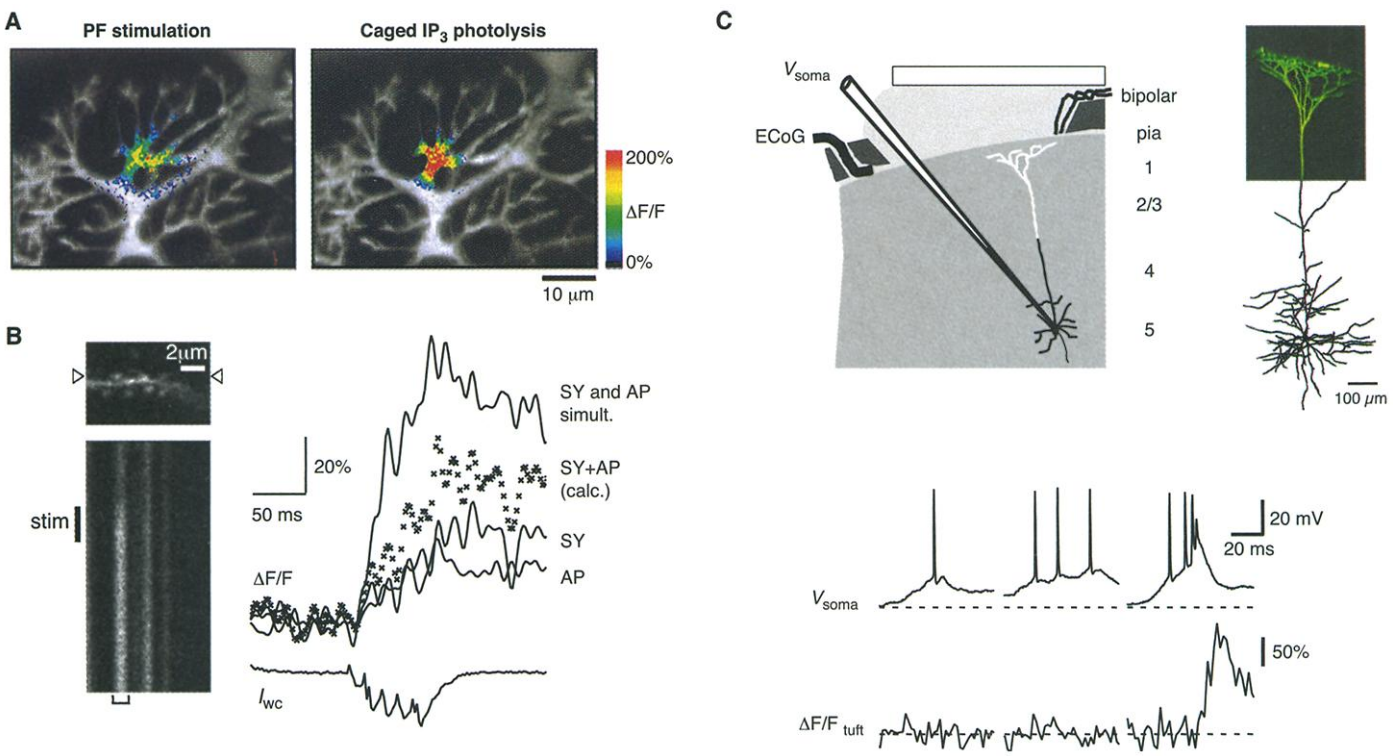

Fig. 4. Chemical computation and compartmentalization in dendrites. (**A**) Chemical compartmentalization in cerebellar Purkinje cell dendrites. Local dendritic Ca^{2+} signals ($\Delta F/F$) in response to synaptic stimulation of parallel fibers (PF, left) or uncaging of IP_3 [modified from (*106*)]. (**B**) Coincidence detection in dendritic spines mediated by supralinear Ca^{2+} signals. Line scan (left) and Ca^{2+} signals ($\Delta F/F$, right) in spines of a hippocampal CA1 pyramidal neuron in response to conjunction of synaptic input (SY) and a train of backpropagating action potentials (AP). The synaptic current in the whole-cell recording (I_{wc}) is shown below [modified from (*95*)]. (**C**) In vivo measurements of dendritic Ca^{2+} dynamics in neocortical layer 5 neocortical pyramidal neurons. Top: Schematic illustration of the recording arrangement, which also allows stimulation of synaptic input (bipolar) and recording of the electrocorticogram (EcoG). Bottom: Fluorescence changes in the apical tuft in response to backpropagating action potentials and Ca^{2+} spikes associated with a somatic action potential burst [adapted from (*46*)].

consequences for synaptic plasticity. The mechanism underlying this association, which generates supralinear Ca^{2+} signals in dendritic spines (*95, 112–114*) (Fig. 4B), appears to be relief of voltage-dependent magnesium block of the NMDA receptor (*112*), which may be enhanced by amplification of backpropagation by EPSPs (*81, 82*). As these forms of coincidence detection only occur at active synapses, this ensures the specificity of the resulting synaptic plasticity.

In neurons that lack effective action potential backpropagation, alternative mechanisms are required to form associations between synaptic inputs. For example, the climbing fiber input in Purkinje neurons appears to play a role analogous to the backpropagating action potential by providing a global Ca^{2+} signal that can trigger synaptic depression at coactive parallel fiber synapses (*115*). Dendritic Ca^{2+} spikes in other neurons may also provide dendritic Ca^{2+} influx leading to the induction of synaptic plasticity. Plasticity induced by these more widespread increases in dendritic Ca^{2+} will display both cooperativity and associativity but may spread to inactive synapses (*116*). These considerations suggest that the dendritic mechanisms recruited during the induction of synaptic plasticity, and the specificity of the resulting plasticity, will depend on the pattern of synaptic activity.

The expression of synaptic plasticity may also be influenced by dendritic properties. Local translation of dendritic mRNAs and/or addition of somatically synthesized proteins to potentiated synapses may contribute to the maintenance of LTP. This requires the compartmentalization of dendritic mRNAs, or local dendritic mechanisms for synaptic tagging (*117–119*). In addition, synaptic activity can trigger long-term changes in both the expression of voltage-gated ion channels and the firing properties of neurons (*120, 121*). Indeed, the original report on LTP indicated that it is associated not only with an increase in synaptic strength per se, but also with an increase in the probability of spiking in response to an EPSP of the same strength (*122*), now known as EPSP-spike potentiation (*123*).

The locus of these changes in excitability has important consequences for the specificity of plasticity. Changes in the density or properties of dendritic voltage-gated channels at activated synapses would permit local modulation of the postsynaptic response, providing a mechanism for synapse-specific regulation of excitability. More global changes in excitability—such as changes in spike threshold, amplification of EPSPs by somatic or axonal voltage-gated channels, or changes in passive membrane properties—would affect the neuronal response to activity at every synapse. Finally, changes in dendritic excitability are not limited to the long term; short-term memory of recent activity may be represented by storing patterns of synaptic input in the states of dendritic voltage- and Ca-dependent channels (*124*).

Conclusions

Dendritic signaling appears to be remarkably diverse and dynamic. Multiple forms of dendritic excitability have been described that allow dendrites to generate responses that depend on the pattern of synaptic activation. Differential propagation of these various active responses results in electrical and chemical compartmentalization, which defines rules for synaptic plasticity and greatly enriches the computational capacity of dendrites. The diversity of dendritic excitability arises from variations in dendritic morphology and channel distributions, whereas the modulation of synaptic and voltage-gated channels results in dynamic, state-dependent changes in function. Some of these alterations are rapid, whereas others are more long-lasting, with the most permanent changes in dendritic function being mediated by the growth of spines and dendrites (*125*).

The similarity in dendritic structure and function of specific neuronal types across different species suggests that the properties of dendrites are tuned to the functional requirements of each cell type. The challenge for the future is to demonstrate more directly how specific dendritic mechanisms in individual cell types contribute to information processing in their respective neuronal networks (*69, 126*). This will require a variety of approaches. First, we must investigate how diversity in the properties of dendrites leads to diversity of input-output relationships and synaptic plasticity rules in different neurons. This will be greatly aided by molecular and pharmacological tools that allow particular dendritic properties to be modified or eliminated in specific cell types. Second, we must investigate the properties of dendrites in a functional context. Electrical and optical recordings from neurons in awake animals (Fig. 4C) (*127, 128*) are necessary to establish whether specific dendritic computations are associated with and ultimately contribute to behavior. Finally, network models need to incorporate neurons featuring dendrites in order to understand how dendritic mechanisms can enhance their computational power. This convergence of different approaches should help us tease out the secrets of dendritic computation from these remarkable structures.

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REVIEW

Untangling Dendrites with Quantitative Models

Idan Segev and Michael London

Our understanding of the function of dendrites has been greatly enriched by an inspiring dialogue between theory and experiments. Rather than functionally ignoring dendrites, representing neurons as single summing points, we have realized that dendrites are electrically and chemically distributed nonlinear units and that this has important consequences for interpreting experimental data and for the role of neurons in information processing. Here, we examine the route to unraveling some of the enigmas of dendrites and highlight the main insights that have been gained. Future directions are discussed that will enable theory and models to keep shedding light on dendrites, where the most fundamental input-output adaptive processes take place.

It has been known since the beginning of the 20th century that the gray matter in our cortex is composed mostly of dendrites, that communication in cortical networks is made via connections made on dendrites, and that dendrites have exquisite shapes specific to different brain regions. It was thus for the last 100 years, and still is, very natural to wonder "What do dendrites do?"

But alas, dendrites are thin (~1 μm in diameter) and many of them are decorated with thousands of even tinier "leaves"—the dendritic spines. Until very recently, dendrites were therefore inaccessible to direct measurements and most of what we knew about dendrites came from recordings made from the relatively large soma (cell body). Settling at the soma, however, was an unsatisfactory deal between the experimenter and the concealing dendrites. The advantage is that the soma is a stable recording site con-

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