Dendritic Signal Integration

N Spruston, Northwestern University, Evanston, IL, USA

Overview: Questions

Most neurons have elaborately branching dendritic trees that receive thousands of synaptic inputs (Figure 1). A majority of dendritic synapses are excitatory, but inhibitory synapses also contact dendrites. A number of simple questions can be asked about dendritic integration:

- How many excitatory synapses need to be activated before an action potential will occur in the axon?
- To what degree does this number depend on the location of the synapses on the dendritic tree?
- How does the spatial relationship between excitatory synapses affect dendritic integration?
- How does inhibition affect the integration of excitatory synaptic inputs?
- How does dendritic inhibition differ from somatic or axonal inhibition?
- How does the spatial relationship between excitatory and inhibitory synapses affect dendritic integration?
- How does the presence of voltage-gated channels in dendrites affect dendritic integration?
- Can spikes be initiated in dendrites and/or propagate along them?
- How do dendritic spines affect synaptic integration?

The answers to these questions depend on several important factors, such as dendritic structure and excitability, as well as the pattern of synaptic activation and the modulatory state of the neural network. Dendritic integration clearly depends on dendritic structure and ion channel expression, so the dramatic variations between cell types (Figure 1) will certainly lead to cell-specific differences in dendritic integration. One goal of dendritic physiologists is to determine common principles that apply to all cell types, while another goal is to determine cell-specific specializations of dendritic integration. Similarly, dendritic integration of fast excitatory and inhibitory synapses is influenced by the modulatory state of the network, which is determined by slower, neuromodulatory transmitters acting on G-protein-coupled receptors, in turn affecting both synaptic function and voltage-gated channels. Another goal of dendritic physiologists is to determine how dendritic integration is affected by these modulatory neurotransmitters.

Approaches

The study of dendritic integration draws on several approaches. Basic anatomical methods define the architecture of dendritic trees, while electron microscopic analysis provides detailed information about the fine structure of dendrites, spines, and synapses, as well as organelles that influence the function of dendrites. Antibodies against ion channels, receptors, and other proteins can provide important information about the molecular composition and organization of dendrites. Immunolocalization of these molecules can be visualized at the light level, but electron microscopy provides the best way of determining which molecules are expressed in dendrites, as opposed to the presynaptic and glial structures that are closely associated with dendrites.

Dendritic physiology has primarily been studied *in vitro* using sharp-microelectrode or patch-clamp recording from neurons in brain slices. The ability to use several variants of the patch-clamp method to record from dendrites in slices has been particularly helpful for investigating dendritic function. Imaging neurons with calcium or voltage-sensitive fluorescent probes has also provided valuable information about dendritic integration, especially in regions of the dendrites that are currently inaccessible to patch-clamp recording. The development of multiphoton imaging and uncaging has improved the resolution and expanded the scope of optical approaches to studying dendritic integration. Although slice physiology has dominated the study of dendritic function because of technical advantages, *in vivo* studies have also been important, because they allow dendrites to be studied in a more natural state. Dendritic recordings have been obtained *in vivo*, and have been complemented by studies using multiphoton imaging. Finally, computational methods have been used extensively in the study of dendritic integration. Computer models of realistic or abstracted dendritic trees allow data from the variety of experimental approaches to be brought together in a quantitative way. Such models are powerful tools for developing theories of dendritic function and for making experimentally testable predictions that lead to new insights.

Synaptic Integration in a Simple Neuron: Cerebellar Granule Cells

A good starting point for understanding synaptic integration is the cerebellar granule cell (Figure 1(e)). These cells are the most numerous types of neurons in
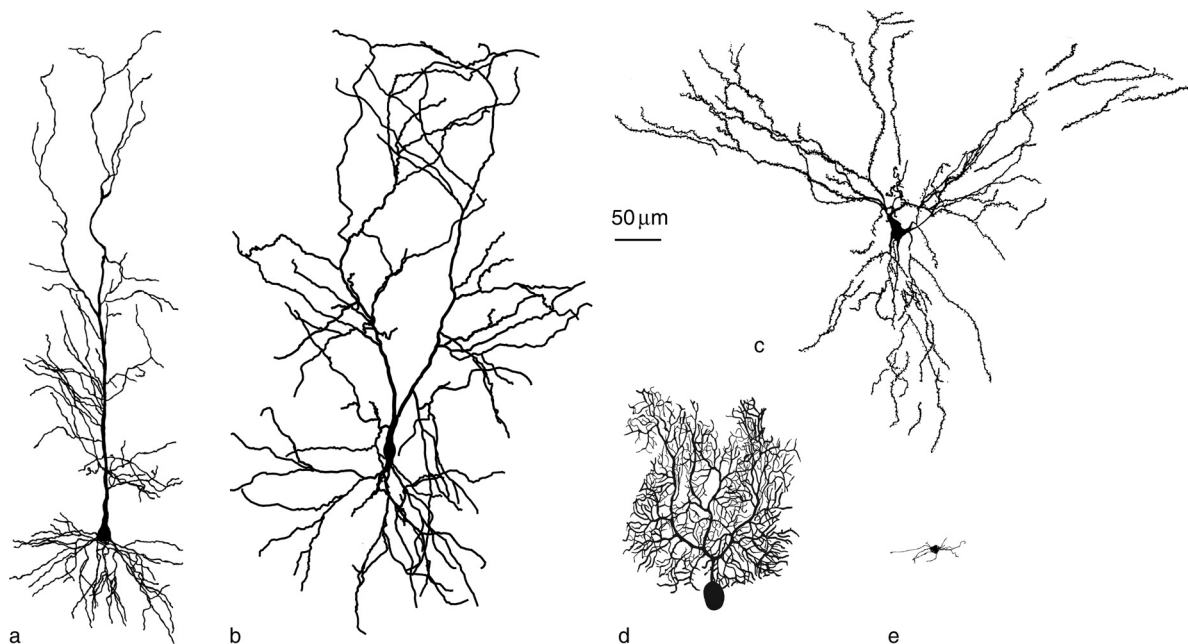
Figure 1 Neurons exhibit variable dendritic structure. (a) A hippocampal CA1 pyramidal neuron. (b) An interneuron from stratum radiatum of CA1. (c) A stellate cell from layer II of the rat entorhinal cortex. (d) A cerebellar Purkinje cell. (e) A cerebellar granule cell. Neurons in all panels are from the rat; axons have been truncated or removed. The scale bar applies to all panels. (a) Adapted from Golding NL, Jung H, Mickus T, et al. (1999) Dendritic calcium spike initiation and repolarization are controlled by distinct potassium channel subtypes in CA1 pyramidal neurons. *Journal of Neuroscience* 19: 8789–8798; (b) from http://www.northwestern.edu/neurobiology/faculty/spruston/sk_models; (c) adapted from Klink R and Alonso A (1997) Morphological characteristics of layer II projection neurons in the rat medial entorhinal cortex. *Hippocampus* 7: 571–583; (d) adapted from Roth A and Häusser M (2001) Compartmental models of rat cerebellar Purkinje cells based on simultaneous somatic and dendritic patch-clamp recordings. *Journal of Physiology* 535: 445–472; (e) adapted from Cathala L, Brickley S, Cull-Candy S, et al. (2003) Maturation of EPSCs and intrinsic membrane properties enhances precision at a cerebellar synapse. *Journal of Neuroscience* 23: 6074–6085.

the brain, and they are also arguably the simplest. Each granule cell receives on average only four excitatory inputs, each made onto a very short dendrite. Because the dendrites are so short, their influence on synaptic integration is minimal. This also offers technical advantages for studying synaptic physiology with patch-clamp recordings from the cell body.

Studies of these and other glutamatergic synapses have revealed that each activated synapse results in an excitatory postsynaptic current (EPSC), which reaches a peak in a fraction of a millisecond and decays in about 1 ms. This unitary EPSC (i.e., one synapse) results in an excitatory postsynaptic potential (EPSP) of a few millivolts. The EPSP, however, decays more slowly than does the EPSC. When current flows though glutamate-gated channels, the charge is stored on the membrane due to its capacitance, thus producing an EPSP. The EPSP continues to grow as long as the synaptic current exceeds the leak current, so the peak of the EPSP corresponds roughly with the end of the EPSC (**Figure 2(a)**). The amplitude of the EPSP depends on both the amplitude and duration of the synaptic current. When the synaptic current has decayed, the charge leaves the cell through leak

channels, resulting in approximately exponential decay of the EPSP. The time constant of this decay is governed by the membrane time constant (τ_m) of the cell, which is determined by the product of the membrane capacitance C and membrane resistance R ($\tau_m = RC$). The leakier the cell (lower R) and the less its ability to store charge (lower C), the lower the time constant, and hence the faster the decay of the EPSP. Thus, resting membrane properties affect synaptic integration as much as do the properties of the synapses. In cerebellar granule cells, the EPSC decays with a time constant of about 1 ms (a property of the synapse), while the EPSP decays with a time constant of about 5 ms (a property of the cell membrane).

The difference between the resting potential and action potential threshold in granule cells is about 15 mV, so more than one excitatory synapse needs to be activated simultaneously in order for an action potential to occur in the axon. This is referred to as 'spatial summation' of EPSPs (**Figure 2(b)**), because the synapses are spatially distinct (even though granule cells are very small). Alternatively, one or more synapses may be activated repeatedly, leading to 'temporal summation' of EPSPs (**Figure 2(c)**). In order for
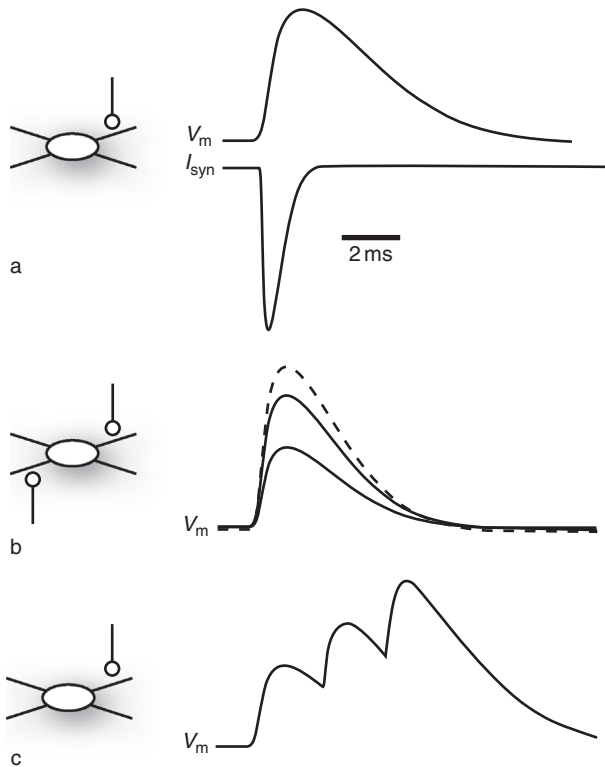
Figure 2 Integration of EPSPs. (a) Activation of a single synaptic input (as shown schematically for a synapse on a cerebellar granule cell) results in a fast inward current (I_{syn}) that produces a change in membrane potential (V_m). The magnitude of the EPSP (V_m) depends on the amplitude and duration of the EPSC (I_{syn}); the EPSP peaks approximately when the EPSC decays to zero. The magnitude of the EPSP also depends on the postsynaptic capacitance and input resistance, as does the final decay rate of the EPSP. See text for details. (b) Simultaneous activation of two synapses results in spatial summation, which is slightly less than the linear sum of the two inputs alone (dashed line). (c) Repeated activation of a synapse results in temporal summation (also sublinear), provided that the activation interval is shorter than the EPSP decay time. All traces are schematic (additional details are provided in the text).

this to occur, the frequency of this repeated activation must be high enough for each EPSP to occur before the preceding EPSP decays.

A complication of spatial or temporal summation in these neurons is that the EPSP generated by one synapse reduces the current flow at other synapses; thus, EPSP summation is slightly sublinear. This sublinear summation is caused by the effect of membrane potential on current flow at the synapse, which is governed by the driving force for synaptic current. Driving force is the difference between the membrane potential (e.g., at rest, $V_m = -70$ mV) and the synaptic reversal potential, which is determined by the ionic permeability of the channels activated at the synapse. For glutamate-gated channels, which are roughly equally permeable to Na^+ and K^+, the synaptic reversal

potential (E_{rev}) is 0 mV, so the driving force ($V_m - E_{rev}$) is 70 mV. When one EPSP has depolarized the membrane, the driving force is accordingly reduced, thus reducing the charge that enters at the synapse. For example, a 7 mV EPSP would reduce the driving force by 10%.

This is the basis for sublinear EPSP summation in a passive system. Most neurons, however, also contain voltage-activated channels that are activated in the voltage range between rest and the action potential threshold. The effects of these channels depend on their ionic permeability. For example, subthreshold activation of K^+ channels tends to increase the sublinearity of EPSP summation, while subthreshold Na^+ or Ca^{2+} channel activation can reduce sublinearity or even lead to supralinear EPSP summation. As these channels are voltage sensitive, their effects are dependent on the size of the EPSP. Similarly, the N-methyl-D-aspartate (NMDA) type of glutamate receptor has voltage-dependent properties that can amplify EPSPs.

Basic Effects of Dendrites on Synaptic Integration

Because granule cell dendrites are so short, they have a minimal effect on synaptic integration. Most neurons, however, have considerably longer and elaborately branching dendritic trees, which introduces further complexities to the process of dendritic integration. The simplest of these effects is that EPSPs are attenuated as current flows from the dendrites (where most excitatory synapses are located) toward the soma. This attenuation is a significant consideration, because the action potential is initiated in the axon, which typically emanates from the soma. Thus, the soma and axon are often considered to be the final site of synaptic integration.

When charge enters a dendrite through synaptically activated ion channels, much of the charge is deposited onto the membrane locally, due to its capacitance, thus producing a local depolarization. All of the charge eventually flows away from the vicinity of the synapse, however, causing the local membrane potential to decay. Some of this charge leaves the cell via the leak channels that are open at rest in the membrane. Most of the charge, however, first flows along the dendrites, with only some of it flowing toward the soma. Furthermore, as charge flows toward the soma, some of it continues to leak out of the cell through the resting leak channels. As a result, the charge that reaches the soma is just a fraction of the original synaptic charge that entered the dendrite. Accordingly, the synaptic potential is smaller in the soma than it is in the dendrite (**Figure 3**).
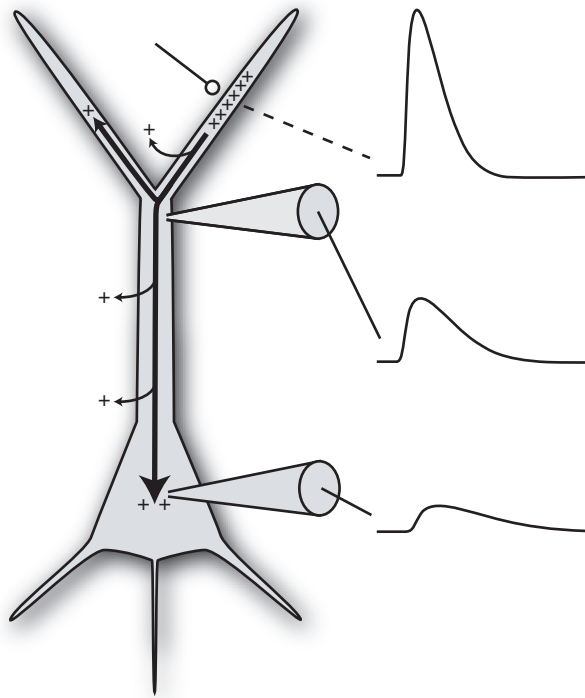
Figure 3 Dendritic attenuation and filtering of an excitatory postsynaptic potential (EPSP). A schematic diagram of a pyramidal neuron is shown, containing a pyramidal soma, apical dendrites (from soma apex), basal dendrites (corners of soma base), and an axon (from center of soma base). Activation of a synapse on an apical dendrite produces a local EPSP (top) that is larger and faster than the EPSP recorded at more proximal locations (as indicated by recording electrodes). EPSP attenuation is caused by loss of charge between the synapse and other locations, as well as changes in local input impedance. See text for details.

The attenuation of EPSPs between the synapse and the soma raises the important question of whether synapses that are far from the soma compensate in some way for this distance-dependent disadvantage. Although there is evidence that some synapses, in some neurons, may have larger conductances at more distal locations, different results have been obtained in other types of neurons, so the issue remains unresolved and somewhat controversial.

Another factor increases the difference between the local synaptic EPSP and the somatic EPSP. Because dendrites are small, they have a high input impedance (high resistance); thus, the current flowing at the synapse produces a large voltage change. By contrast, the soma is much larger and therefore has a much lower impedance; the voltage change resulting from an equivalent current is therefore smaller than in the dendrite. Thus, two factors result in EPSP attenuation between the dendritic synapse and the soma: charge attenuation and impedance differences. Both of these factors become more pronounced for synapses located

at greater distances from the soma, but the magnitude of the effects depends on many factors, including dendritic structure (diameter, length, and branching) and membrane properties, as well as the kinetics of the EPSP (faster EPSPs attenuate more).

A mathematical theory for analyzing current flow in dendrites and the resultant effects on EPSP attenuation was provided by Wilfrid Rall in the 1950s and 1960s. This theory was called 'cable theory,' because it treated dendrites as conductive cables with leaky membranes immersed in a conductive medium (the extracellular space). The theory drew extensively on insights provided by the analysis of current flow in transatlantic telephone cables. Rall's cable theory now serves as the foundation for modern computer modeling of neurons with dendritic trees. Such models are now being used to provide insight into how charge spreads in elaborately branching dendritic trees containing many different types of ion channels.

Another way that dendrites influence EPSPs is via their effect on spatial summation. If two synapses on the same dendrite are activated together, they will sum sublinearly for the same reasons as described for the simple case of a cerebellar granule cell. If the two synapses are on different dendrites, however, the sublinearity of spatial summation will be reduced, because each synapse has a reduced influence on the other, due to the attenuation from one location to the other. For synapses located on different dendrites this effect can be quite large.

Dendrites also influence EPSPs by affecting temporal summation. Because of the resistance and capacitance of dendrites, EPSP time course is filtered between the dendrites and the soma. At the site of the synapse, the decay of the EPSP is governed primarily by the flow of current along the dendrites, away from the synapse. Because this pathway has a resistance lower than the resistance of the membrane to current flow, most of the local, dendritic EPSP decays more rapidly than the membrane time constant. By the time the EPSP reaches the soma, however, the EPSP decay is governed mostly by the membrane time constant, which is slower. In addition, the intervening dendrites filter the rise time of the somatic EPSP. As a result of this difference in time course, temporal summation is greater in the soma than it would be in the dendrites. Furthermore, synapses located more distally are filtered more, so in a passive system their temporal summation in the soma is greater.

Effects of Inhibition on Dendritic Integration

Some subtypes of inhibitory interneurons specifically target dendrites. Although relatively little is known

about the differences between these dendritic inhibitory synapses and their counterparts on the soma and axon, an understanding of cable theory informs speculation about the possibly specialized role of dendritic inhibition.

Just as EPSPs are attenuated and filtered between the dendrites and the soma, inhibitory postsynaptic potentials (IPSPs) generated in the dendrites will be smaller and slower in the soma. However, the mechanism of action of most inhibitory synapses is activation of Cl^- channels (e.g., $GABA_A$ receptors). In most cells, the reversal potential of synapses using Cl^- channels is very close to the resting potential, so the driving force at rest is very small. Therefore, activation of these synapses may not produce significant IPSPs; instead, a major effect of Cl^- channel activation is 'shunting inhibition.' If the conductance is large, shunting inhibition can be very effective. When positive charge from an activated excitatory synapse arrives at the inhibitory synapse, it attracts Cl^- ions through the activated Cl^- channels, thus reducing the EPSP. Thus, inhibitory synapses can 'shunt' current from excitatory synapses.

The effectiveness of shunting inhibition is particularly dependent on the relative location of the excitatory and inhibitory synapses activated. Inhibitory synapses located on the soma can shunt excitatory current originating anywhere in the dendritic tree. By contrast, dendritic inhibition will shunt excitatory synapses on the same (or nearby) dendrites more effectively than it will those on other (or more distal)

dendrites. Shunting inhibition also has a greater effect on somatic membrane potential (and therefore on action potential initiation in the axon) if it is located on the path between the excitatory synapses and the soma (Figure 4). Inhibitory synapses located off this path are less effective at shunting current as it flows from the synapse to the soma.

Effects of Voltage-Gated Channels on Dendritic Integration

Most of the foregoing analysis of dendritic integration has been based on passive dendrites (i.e., lacking voltage-gated channels). However, it is well known that dendrites contain voltage-gated conductances, which dramatically influence dendritic function. Dendritic patch-clamp recordings have provided direct evidence for the presence of Na^+, Ca^{2+}, K^+, and other voltage-gated channels in the dendrites of many cells. There is also compelling evidence for differences between the density and properties of these channels in dendrites as compared to the soma of the same cell type. For instance, in hippocampal pyramidal neurons, A-type K^+ channels have a higher density and lower activation threshold at increasingly distal dendritic locations. In the same cells, HCN channels (hyperpolarization-activated Na^+/K^+ channels) have the highest density in the most distal apical dendrites. Although some explanations for the functions of these nonuniform channel distributions have been reported, they remain under investigation. In
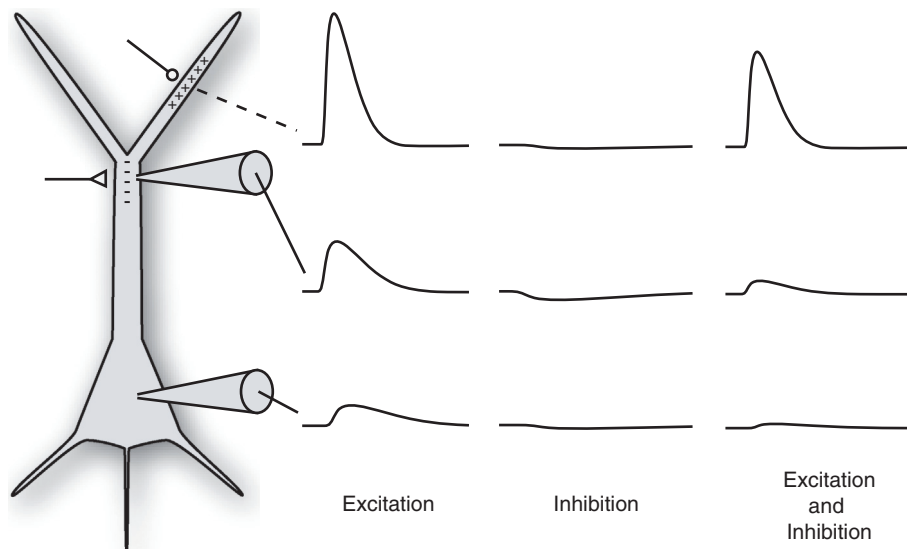

Figure 4 Dendritic inhibition. A single excitatory synapse (circle) on an apical dendrite is shunted by an inhibitory synapse (triangle) on the path between the synapse and the soma. In response to activation of both synapses (right), the somatic excitatory postsynaptic potential (EPSP) is much smaller than the sum of the EPSP on its own (left) and the inhibitory postsynaptic potential on its own (middle). See text for details.

addition to these region-specific differences in channel densities and properties, there are also cell-specific differences. For example, while expression of dendritic voltage-gated Na^+ channels has been observed in most cell types, these channels are virtually absent from the dendrites of cerebellar Purkinje cells.

Voltage-gated channels expressed in the dendrites may support some of the same functions as do channels expressed in the soma or the axon. For example, there is some evidence that subthreshold activation of dendritic Na^+, Ca^{2+}, or K^+ channels can affect EPSP summation. More compelling evidence exists for two functions of dendritic Na^+, Ca^{2+}, and K^+ channels: dendritically initiated spikes and backpropagating action potentials.

Spikes mediated by voltage-gated Na^+ and Ca^{2+} channels can be initiated in dendrites, usually in response to relatively strong excitatory synaptic activation (Figure 5(a)). NMDA receptors can also contribute to the initiation of spikes in dendrites because of their highly nonlinear voltage dependence. Dendritically initiated spikes may serve several functions, including the induction of plasticity and the release of neurotransmitters or growth factors from dendrites. In addition, dendritic spikes are likely to be important for dendritic integration. Synapses located very far from the soma may not be able to exert a significant influence over action potential initiation in the axon unless they trigger dendritic spikes locally. The ability of dendritic spikes to influence axonal action potential initiation, however, depends on their ability to propagate toward the soma. In pyramidal neurons, where dendritic spikes have been studied most extensively, the forward propagation of dendritic spikes is unreliable, often leading to propagation failure (Figure 5(a)).

Given that forward propagation of dendritic spikes is unreliable, there are two possible scenarios for the function of dendritically initiated spikes. One is that they serve a primarily local function, regulating the induction of synaptic plasticity or release of neurotransmitters from dendrites. Another possibility, however, is that forward propagation of spikes can be regulated by other factors, such as synaptic activity or the modulatory state of the neuron. Indeed, these possible functions are not mutually exclusive and there is some evidence for both of these functions.

The end result of synaptic integration is an action potential in the axon, but these signals can also propagate back into the dendrites. Backpropagating action potentials have been studied in several cell types and in all cases the amplitude of the backpropagating action potential gets smaller as it travels further from the soma (Figure 5(b)). This distance-dependent attenuation of the backpropagating action potential is caused by a relatively low Na^+ channel
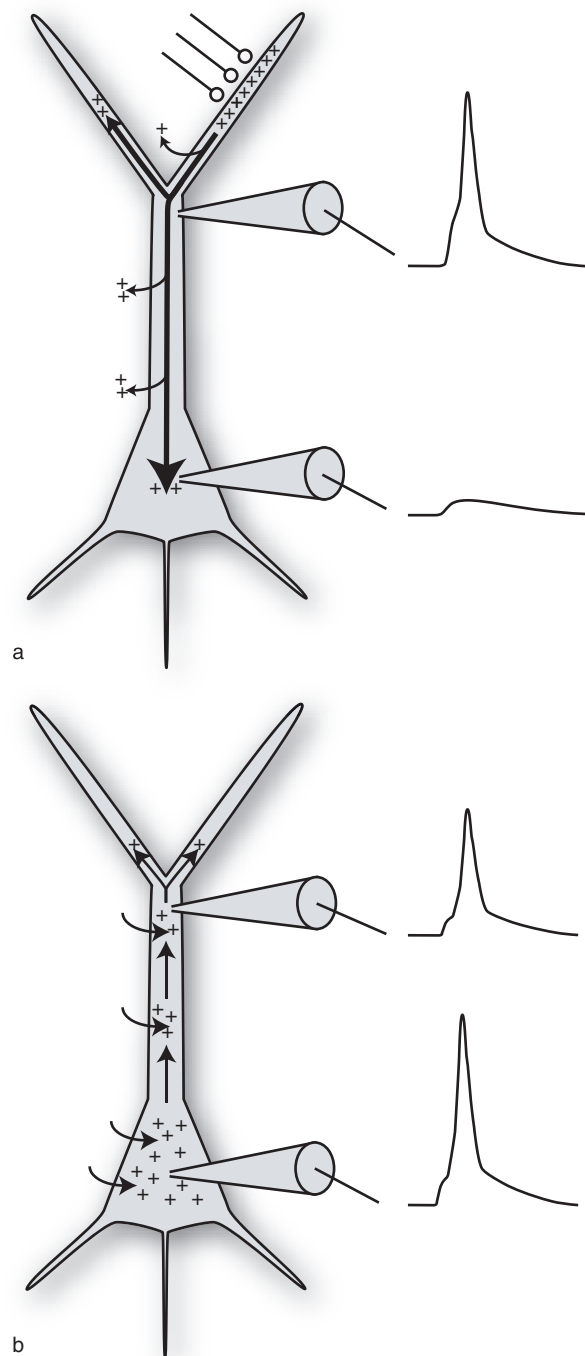

Figure 5 Dendritic excitability. (a) Strong synaptic stimulation can lead to spike initiation in the dendrites. Whether or not the dendritic spike fails (as shown) or propagates successfully to the soma (not shown) depends on several factors (see text for details). (b) An action potential that begins in the axon and soma propagates actively back into the apical dendrites, but with some amplitude attenuation. Backpropagation into basal dendrites may also occur, but is not shown.

density, compared to the axon, where action potential propagation is reliable over long distances. Some dendrites also have high K^+ channel density, especially in distal regions. The attenuation of backpropagating

action potentials also depends on dendritic structure, with dendritic branching tending to reduce backpropagation. Because both channel density and dendritic architecture vary across cell types, the attenuation of the backpropagating action potential is also cell-type specific. At one extreme are cerebellar Purkinje cells, which lack a significant backpropagating action potential because of the absence of Na^+ channels, as well as extensive dendritic branching. At the other extreme are the dopamine cells of substantia nigra, which show almost no attenuation of the backpropagating action potential, because of high Na^+ channel density and very limited dendritic branching. Even within one cell type, however, backpropagating action potentials are influenced by a variety of factors, including modulatory state and synaptic activity.

The functions of backpropagating action potentials are currently being explored, but there is evidence that they may be involved in the induction of synaptic plasticity and the dendritic release of neurotransmitters or growth factors. Voltage-gated Ca^{2+} channels in dendrites are activated by backpropagating action potentials. Although these channels are not essential for backpropagation, their activation is likely to be important for triggering biochemical events crucial for the functions mentioned above.

Backpropagating action potentials, though attenuated, are always detectable in dendritic recordings. The reverse is not true, however, for dendritically initiated spikes, which sometimes fail to propagate, thus resulting in diminishingly small potentials in the soma. This intriguing difference between backward and forward propagation is actually expected from the branching structure of pyramidal neuron dendrites. When axonal and somatic Na^+ current produces an action potential, a large current is required to support the action potential in the soma, because of its large surface area (and hence low impedance). As this current flows into the dendrites, which are smaller (and have higher impedance), it is relatively easy to depolarize the dendrite to activate the voltage-gated channels required for action potential backpropagation. However, when a spike begins in a dendrite, only a small current is required because of the small size (and high impedance) of the dendrite. As the spike propagates from small dendrites to larger dendrites and eventually into the very large soma, the small current initially generated by the dendritic spike will produce less depolarization of the larger structures (lower impedance). Thus, progressively fewer Na^+ channels may be activated as the spike propagates forward, eventually causing propagation failure.

Although dendritically initiated spikes and backpropagating action potentials are distinct dendritic events, they are not mutually exclusive; a few interesting interactions have been reported. In regions of the dendrites where dendritic spikes are large, Na^+ channels will be inactivated for a period of time following the spike, thus reducing the amplitude of the backpropagating action potential in the same region. The converse situation can also occur, where backpropagating action potentials result in Na^+ channel inactivation and hence a higher threshold for dendritic spike initiation. Another intriguing interaction has been observed in cortical neurons, where backpropagating action potentials – either alone or in combination with synaptic input – can lead to the generation of large dendritic spikes involving sustained activation of voltage-gated Ca^{2+} channels.

Contributions of Dendritic Spines to Dendritic Integration

One of the big mysteries of dendrites is the function of dendritic spines. Aside from relatively simple functions such as increasing dendritic surface area and space for synapses, two functions have been proposed for spines: biochemical and electrical compartmentalization. Biochemical compartmentalization may limit the spread of second messengers and other regulatory factors, thus increasing the specificity of synaptic plasticity. Compartmentalization of Ca^{2+} by the spine has been demonstrated by numerous studies. Electrical compartmentalization is more complicated and has also been more difficult to demonstrate. Membrane potential changes in the dendrite are not likely to attenuate significantly as they spread into spines. This is because the small size (high impedance) of spines makes them very easy to depolarize. On the other hand, EPSPs in spines may attenuate significantly as they spread into the larger (lower impedance) parent dendrite. Such attenuation, if significant, could mean that EPSPs in spines are very large, possibly resulting in activation of voltage-gated channels in spines, such as Ca^{2+} channels known to be present in the spine head. Quantitatively, the magnitude of the electrical compartmentalization imposed by spines depends on the resistance of the spine neck. This parameter is not well known, but imaging studies are beginning to yield important data that will address these and other issues, leading to an improved understanding of the function of dendritic spines.

Concluding Remarks

The basic principles of synaptic integration are well understood, and cable theory provides a solid foundation for using computational models to predict

how dendrites affect synaptic integration in a passive system. However, many questions remain about how excitation and inhibition interact in the dendritic tree and how dendritic integration is influenced by voltage-gated channels. Different types of neurons have different dendritic structure and appear to be equally diverse in the types of voltage-gated channels they contain. In addition, synaptic activity and modulatory neurotransmitters strongly affect how dendritic integration proceeds in any given neuron. Thus, dendritic integration needs to be studied in many different types of neurons and under different conditions. One of the most important issues will be to determine how dendritic integration works in behaving animals. This will require an understanding not only of the structural and functional properties of dendrites, but also knowledge of the patterns of synaptic activation and neuromodulatory background that occurs during various behaviors. Ultimately, this will require refinements, improvements, and extensions of the methods used to study dendrites *in vitro* and *in vivo*.

See also: Action Potential Initiation and Conduction in Axons; Activity-Dependent Remodeling of Presynaptic Boutons; Axonal and Dendritic Identity and Structure: Control of; Dendrite Development, Synapse Formation and Elimination; Dendritic Spine History; Eph Receptor Signaling and Spine Morphology; Ion Channel Localization in Cell Bodies and Dendrites; LIM Kinase and Actin Regulation of Spines; Rho GTPases and Spines; Translational Regulation at the Synapse.

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Relevant Websites

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http://www.northwestern.edu/dendrite – The Spruston Lab (Northwestern University, Department of Neurobiology and Physiology).

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