CHAPTER

17

Information Processing in Complex Dendrites

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One of the hallmarks of neurons is the variety of their dendrites. The branching patterns are dazzling and the range of size is astounding, from the large trees of cortical pyramidal neurons to the tiny retinal bipolar cell, which would fit comfortably within the cell body of a pyramidal neuron (see Fig. 17.1)! The

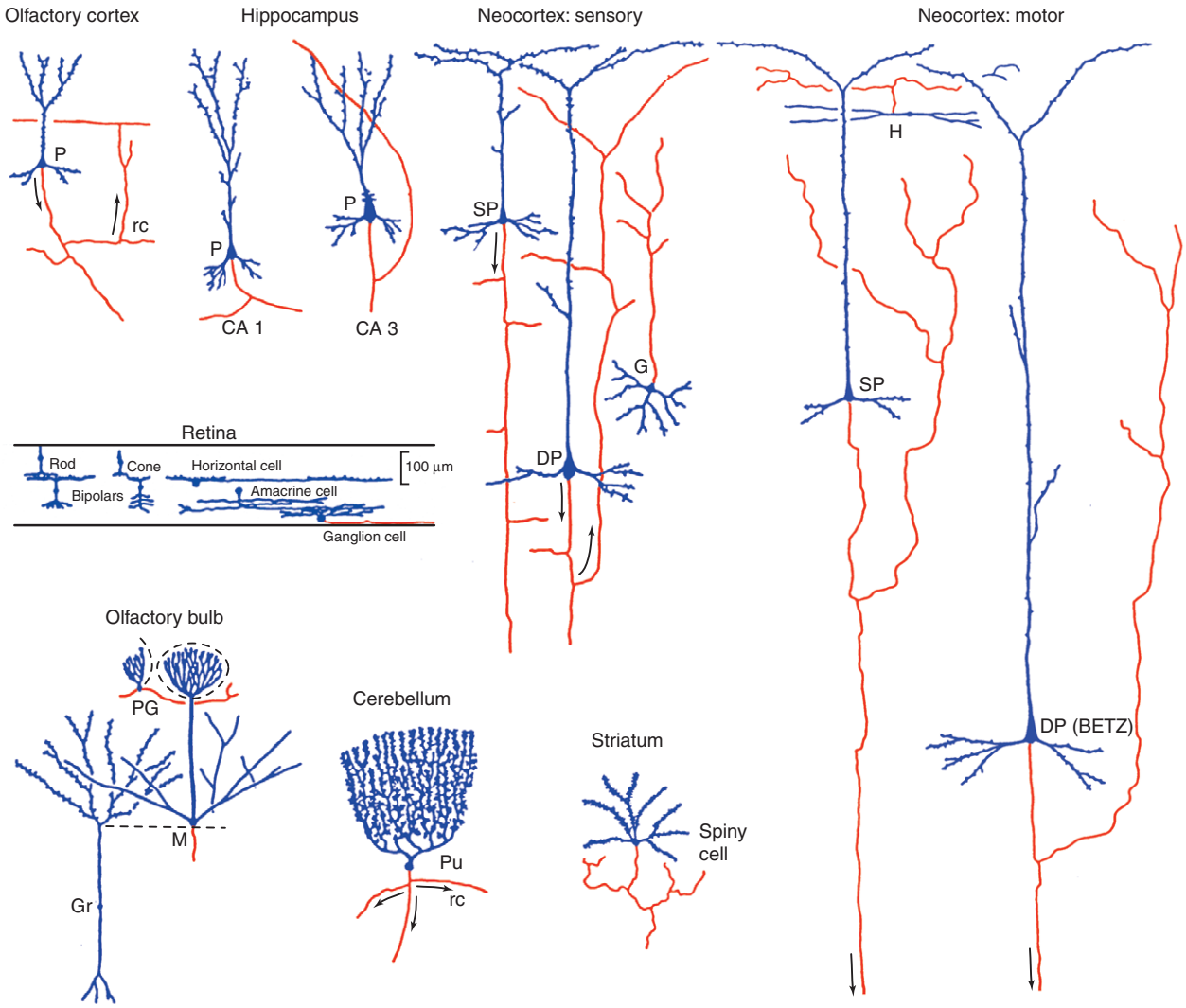

FIGURE 17.1 Varieties of neurons and dendritic trees. Abbreviations: CA1, CA3, hippocampal regions; P, pyramidal cell; rc, recurrent collateral; SP, superficial pyramidal cell; DP, deep pyramidal cell; G, granule (stellate) cell; PG, periglomerular cell; M, mitral cell; Gr, granule cell (olfactory); Pu, Purkinje cell. From Shepherd (1991).

functions of these dendritic trees have drawn increasing interest in recent years (Segev *et al*., 1995; Yuste and Tank, 1996; Wilson, 1998; Stuart *et al*., 1999; Segev and London, 2000; Matus and Shepherd, 2000; Stern and Marx, 2000). The fundamental questions asked in this chapter include: What are the principles of information processing in complex dendritic trees, and how are they adapted for the specific operational tasks of a particular type of dendrite?

STRATEGIES FOR STUDYING COMPLEX DENDRITES

As was discussed in Chapter 4, the neuron processes information through five basic types of activity: intrinsic, reception, integration, encoding, and output. As also discussed in Chapter 4, understanding the ways in which these activities are integrated within the neuron starts with the rules of passive current spread. We now ask how active, voltage-gated channels are involved in *complex information processing*, particularly within branching dendritic trees.

Many of the principles were first worked out in the dendrites of neurons that lack axons or the ability to generate action potentials. There are many examples in invertebrate ganglia. In vertebrates, they include the retinal amacrine cell and the olfactory granule cell. Studies of these neurons are covered in Shepherd (1991). In summary, a dendritic tree by itself is capable of performing many of the basic functions required for information processing, such as generation of intrinsic activity, input–output functions for feature extraction, parallel processing, signal-to-noise enhancement, and oscillatory activity. These cells demonstrate that there is no one thing that dendrites do; they do whatever is required to process information within their particular neuron or neuronal circuit.

Information in dendrites can take many forms. There are actions of neuropeptides on membrane receptors and internal cytoplasmic or nuclear receptors, actions of second and third messengers within the neuron, movement of substances within the dendrites by diffusion or by active transport, and changes occurring during development. All of these types of cellular traffic and information flow in dendrites are coming under direct study (Stuart *et al*., 1999; Matus and Shepherd, 2000). The student should review these subjects in earlier chapters. Here, we focus on information processing involving electrical signaling mechanisms by synapses and voltage-gated channels, and consider how this takes place in neurons with axons.

Among cells with axons, long-axon (output) cells tend to be larger than short-axon (local) cells and have therefore been more accessible to experimental analysis. Indeed, virtually everything that we know about the functional relationships between dendrites and axons has been obtained from studies of long-axon cells. Much of what we think we understand about those relationships in short-axon cells is only by inference.

As in the analysis of the passive properties of neurons, there are a number of sites on the web that support the computational analysis of complex neurons and their active dendrites. They are included in the list in Box 4.2 of Chapter 4 (see also Chapter 7).

An Axon Places Constraints on Dendritic Processing

We immediately recognize that the presence of an axon places critical constraints on dendritic processing (Fig. 17.2).

The first principle is: *if a neuron has an axon, it has only one*. This near-universal single-axon rule is remarkable and still little understood. It results from developmental mechanisms that provide for differentiation of a single axon from among early undifferentiated processes; these mechanisms are currently being analyzed in neuronal cultures (Craig and Banker, 1994). The principle, which can be regarded virtually as a law for neurons, means that for dendritic integration to lead to output from the neuron to distant targets, all of the activity within the dendrites must eventually be funneled into the origin of the axon in the single axon hillock. Therefore, in these cells the flow of information in dendrites has an overall orientation, just as surmised by the classic neuroanatomists. We thus have a principle of *global output*:

> To transfer information between regions, the information distributed at different sites within a dendritic tree of an output neuron must be encoded for global output at a single site at the origin of the axon.

A related principle, and virtually another universal rule, is that the main function of the axon in long-axon cells is to support the generation of action potentials in the axon hillock–initial segment region. By definition, action potentials have thresholds for generation; thus, the principle of *frequency encoding of global output* in an axonal neuron is:

> The results of dendritic integration affect the output through the axon only by initiating or modulating action potential generation in the axon hillock–initial segment. Global output from

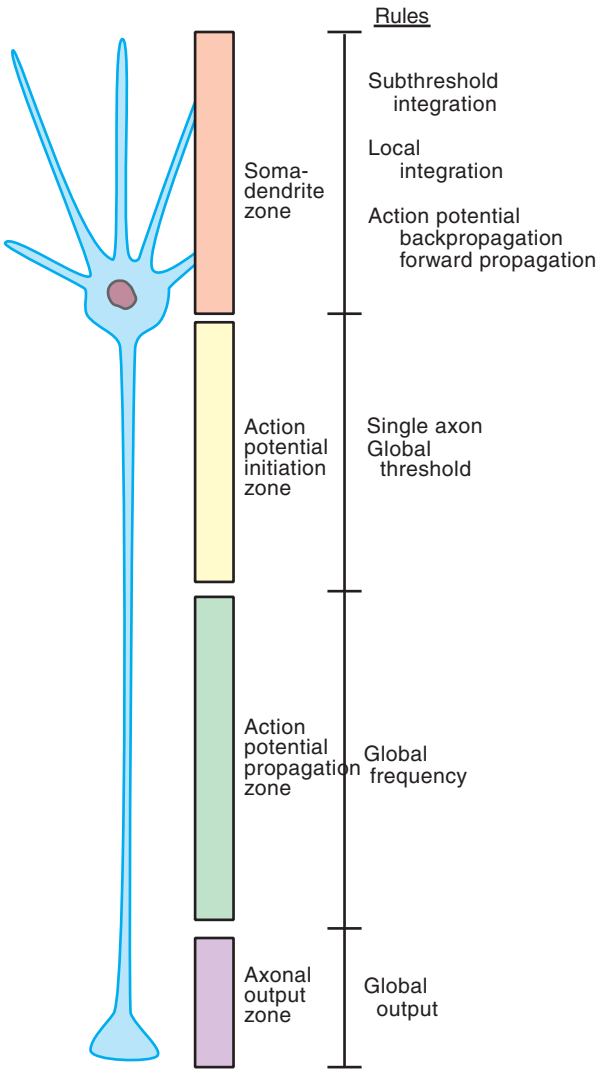

FIGURE 17.2 The presence of a single axon forces several organizational rules onto a neuron. See text for details.

dendritic integration is therefore encoded in impulse frequency in a single axon.

A further consequence of the spatial separation of dendrites and axon is the presence of *subthreshold dendritic activity*:

> A considerable amount of subthreshold activity, including local active potentials, can affect the integrative states of the dendrites and their local outputs but not necessarily directly or immediately affect the global output of the neuron.

We turn now to the functional properties that allow dendritic trees to process information within these constraints.

Dendrodendritic Interactions between Axonal Cells

First recognize that with axonal cells, as with anaxonal cells, output can be through the dendrites (see principle of subthreshold dendritic activity above). This is against the common wisdom, which assumes that if a neuron has an axon, all the output goes through the axon. There are many examples in invertebrates.

Neurite–Neurite Synapses in the Lobster Stomatogastric Ganglion

One of the first examples in invertebrates was in the stomatogastric ganglion of the lobster (Selverston *et al.*, 1976). Neurons were recorded intracellularly and stained with Procion yellow. Serial electron micrographic reconstructions showed the synaptic relationships between stained varicosities in the processes and their neighbors (the processes are equivalent to dendrites, but are often referred to as neurites in the invertebrate literature). In many cases, a varicosity could be seen to be not only presynaptic to a neighboring varicosity, but also postsynaptic to that same process. It was concluded that synaptic inputs and outputs are distributed over the entire neuritic arborization. Polarization was not from one part of the tree to another. The "bifunctional" varicosities appeared to act as local input–output units, similar to the manner in which granule cell spines appear to operate (see below). Similar organization has been found in other types of stomatogastric neurons (Fig. 17.3A).

Sets of these local input–output units, distributed throughout the neuritic tree, participate in the generation and coordination of oscillatory activity involved in controlling the rhythmic movements of the stomach. In a current model of this oscillatory circuit these interactions are mutually inhibitory (see Fig. 17.3B).

Summary

A cell with an axon can have local outputs through its dendrites as well as its axon, which may be involved in specific functions such as oscillatory circuits.

Passive Dendritic Trees Can Perform Complex Computations

Another principle that carries over from axonless nonspiking cells is the ability of axonal cells to carry out complex computations in dendritic trees with passive properties. This is exemplified by neurons that are motion detectors.

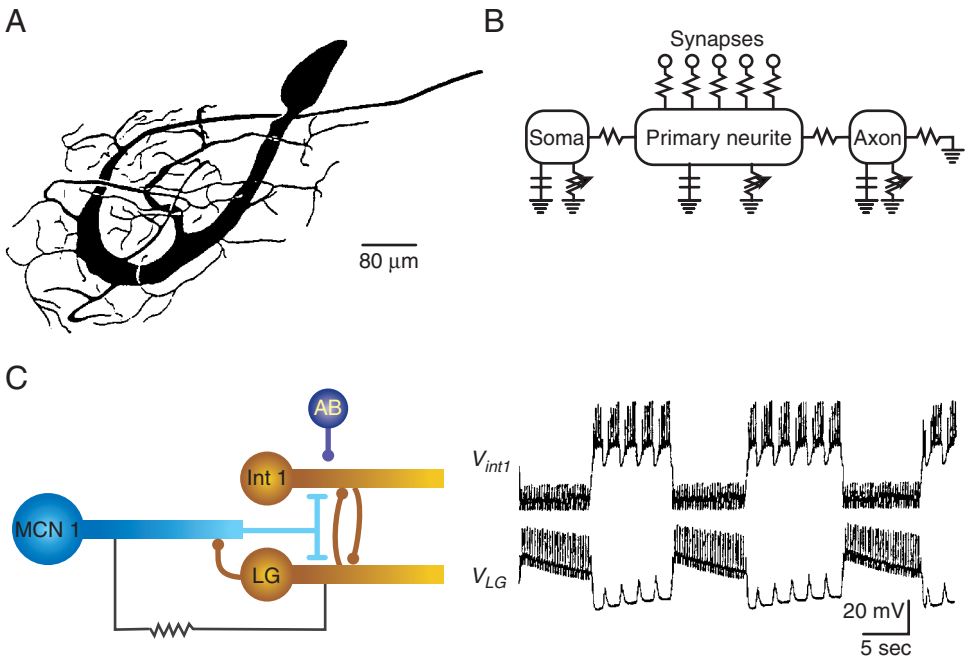

FIGURE 17.3 Local synaptic input–output sites are widely found within the neuropil of invertebrate ganglia. (A) Neurite–neurite interactons in the gastric mill ganglion of the lobster. (B) Compartment model of stomatogastric neuron. (C) Model of rhythm generating circuit of the gastric mill of the lobster, involving neurite-neurite interactions. (A) and (B) from Golowasch and Marder (1992). (C) from Manor *et al*. (1999).

Motion detection is a fundamental operation carried out by the nervous systems of most species; it is essential for detecting prey and predator alike. In invertebrates, motion detection has been studied especially in the brain of the blowfly. In the lobula plate of the third optic neuropil are tangential cells (LPTCs) that respond to preferential direction (PD) of motion with increased depolarization due to sequential responses across their dendritic fields. This response has been modeled by Reichardt and his colleagues by a series of elementary motion detectors (EMDs) in the dendrites. A compartmental model (Single and Borst, 1998) reproduces the experimental results and theoretical predictions by showing how local modulations at each EMD are smoothed by integration in the dendritic tree to give a smoothed high-fidelity global output at the axon (see Fig. 17.4A). In the model, spatial integration is largely independent of specific electrotonic properties but depends critically on the geometry and orientation of the dendritic tree.

In the vertebrates, motion detection is built into the visual pathway at various stages in different species, principally the retina, midbrain (optic tectum), and cerebral cortex. Recent studies in the optic tectum have revealed cells with splayed uniplanar dendritic trees and specialized distal appendages that appear highly homologous across reptiles, birds, and mammals (Fig. 17.4B) (Luksch *et al*., 1998). These are presumed to mediate motion detection. Physiological studies are needed to test the hypothesis that these cells perform operations through their dendritic fields similar to those of the LPTC cells in the insect. To the extent that this is borne out, it will support a principle of *motion detection through spatially distributed dendritic computations* that is conserved across vertebrates and invertebrates. This kind of directional selectivity of dendritic processing was predicted by Rall (1964) from his studies of dendritic electrotonus (see Chapter 4).

Distal Dendrites Can Be Closely Linked to Axonal Output

An obvious problem for a neuron with an axon is that the distal branches of dendritic trees are a long distance from site of axon origin at or near the cell body. As mentioned earlier, the common perception is that these distal dendrites are too distant from the site of axonal origin and impulse generation to have more than a slow and weak background modulation of impulse output.

This perception is disproved by many kinds of neurons in which specific inputs are located preferentially on their distal dendrites. Such is true of the mitral and tufted cells in the olfactory bulb, where the

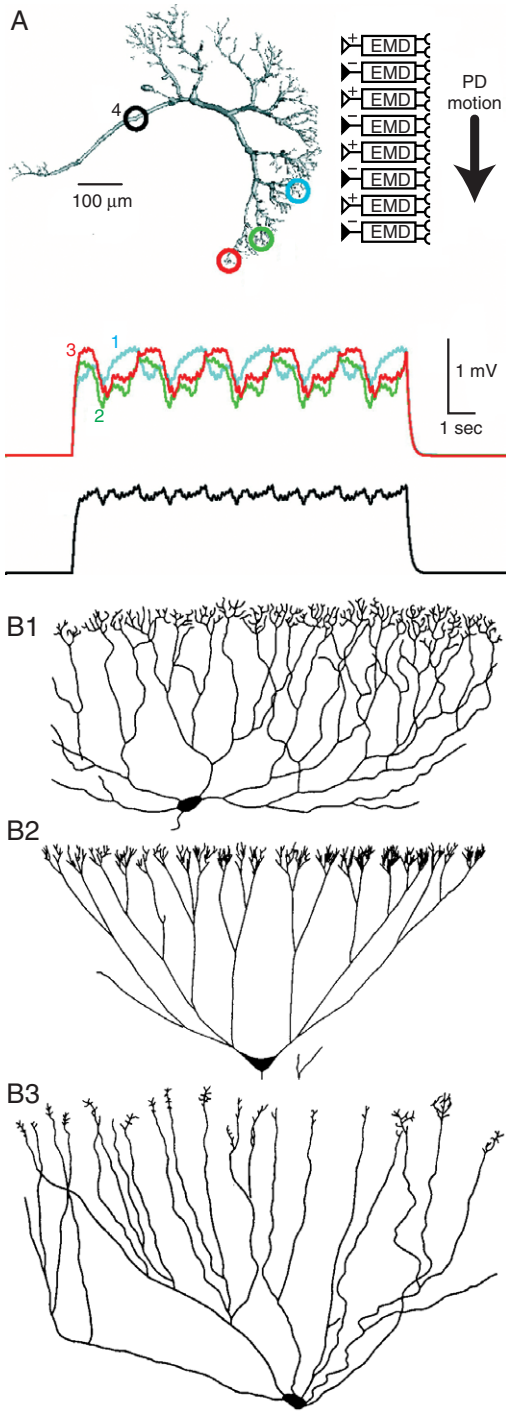

FIGURE 17.4 Dendritic systems as motion detectors. (A) A computational model of a motion detector neuron in the visual system of the fly, consisting of elementary motion detector (EMD) units in its dendritic tree activated by the preferential direction (PD) of motion. The local modulations of the individual EMDs (1–3) are integrated in the dendritic tree to give the smooth global output in the axon (bottom trace) (Single and Borst, 1998). (B) The dendritic trees of neurons in the optic tectum of lizard (B1), chick (B2), and gray squirrel (B3). The architecture of the dendritic branching patterns and distal specialization for reception of retinal inputs is highly homologous. (References in Luksch *et al.*, 1998.)

input from the olfactory nerves ends on the most distal dendritic branches in the glomeruli; in rat mitral cells this may be 400–500 μm or more from the cell body, in turtle, 600–700 μm. The same applies to their targets, the pyramidal neurons of the olfactory cortex, where the input terminates on the spines of the most distal dendrites in layer I. In many other neurons, a given type of input terminates over much or all of the dendritic tree; such is the case, for example, for climbing fiber and parallel fiber inputs to the cerebellar Purkinje cells. The relative significance of the more distal inputs in these cells is not so apparent. All of these examples are shown in Fig. 17.1.

How do distal dendrites effectively control axonal output? We consider several important properties.

Large Synaptic Conductances

Of key importance is the amplitude of the conductance generated by the synapse itself (Fig. 17.5A). In motor neurons, the conductances of the most distal excitatory synapses may be many times the amplitude of proximal synapses (Redman and Walmsley, 1983). This would account for the fact that the peak unitary synaptic response recorded at the soma varies in time course according to synaptic location but has a constant amplitude of approximately 100 μV (Fig. 17.5A). Recent studies have provided evidence for a similar increase in synaptic conductance in the distal dendrites of cortical pyramidal neurons (Magee, 2000).

High Specific Membrane Resistance

A second key property is the specific membrane resistance (R_m) of the dendritic membrane. Traditionally, the argument was that if R_m is relatively low, the characteristic length of the dendrites will be relatively short, the electrotonic length will be correspondingly long, and synaptic potentials will therefore decrement sharply in spreading toward the axon hillock. However, as discussed in Chapter 4, intracellular recordings indicated that R_m is sufficiently high that the electrotonic lengths of most dendrites are in the range of 1–2 (Johnston and Wu, 1995) and recent patch recordings suggest much higher R_m values, indicating electrotonic lengths less than 1. Thus, a relatively high R_m seems adequate for close electrotonic linkage, at least in the steady state (Fig. 17.5B).

Low K^+ Conductances

An important factor controlling the effective membrane resistance is K^+ conductances. Chapter 4 discussed how a K^+ channel, I_h, can affect the summation of EPSPs in striatal spiny cells. There is increasing evidence for control of dendritic input conductance by

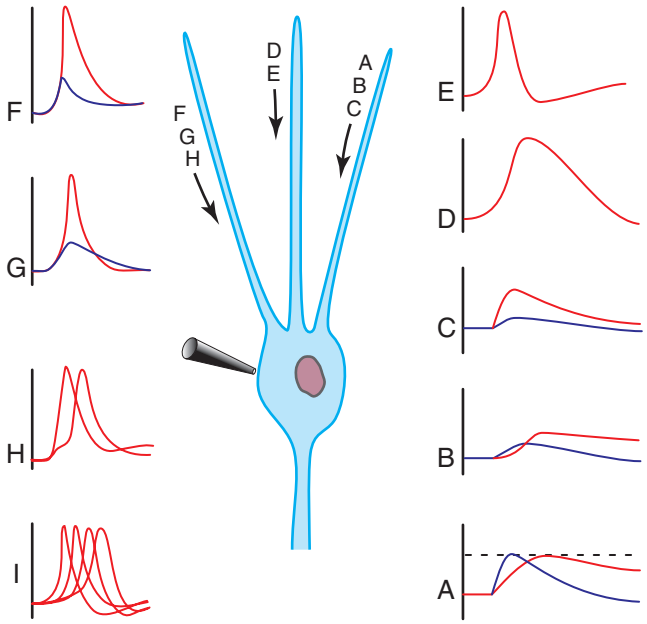

FIGURE 17.5 Mechanisms by which the synaptic responses in distal dendrites can have an enhanced effect in controlling impulse output from the axon hillock–initial segment region. Schematized neuron with patch electrode on the soma. Blue traces show responses with passive dendritic membrane; red traces show responses with dendritic boosting mechanisms. (A) Larger distal synaptic conductances (the response is of the same amplitude but slower compared with a soma synaptic conductance because of the electrotonic delay in the intervening dendrites). Spine stem diameter = 0.1 μm. (B) Higher membrane resistance (the response is slowed compared with the response to a soma input by the larger time constant). Voltage-gated channels (VGCs) may increase an EPSP amplitude as seen at the soma (C). Within the dendrites, VGCs can give rise to slow action potentials (D) or to forwardpropagating full action potentials (E). Dendritic VGCs can set up fast prepotentials as recorded at the soma (F); they can also function as coincidence detectors (G) which give rise to "pseudosaltatory conduction" toward the soma through individual sites (H) or clusters (I). (see text).

different types of K^+ currents (Midtgaard *et al.*, 1993; Magee, 1999). When dendritic K^+ conductances are turned off, R_m increases and dendritic coupling to the soma is enhanced. These conductances also control backpropagating action potentials, as we discuss below.

Voltage-Gated Depolarizing Conductances

For transient responses, the electrotonic linkage becomes weaker because of the filtering effect of the capacitance of the membrane, and it is made worse by a higher R_m, which increases the membrane time constant and thereby slows the spread of a passive potential (see Chapter 4). This disadvantage can be overcome by depolarizing voltage-gated conductances, either Na^+ or Ca^{2+}, or both. Box 17.1 discusses the variety of mechanisms by which these voltage-gated conductances can operate.

Summary

These examples illustrate an important principle of *distal dendritic processing*:

> Distal dendrites can mediate relatively rapid, specific information processing, even at the weakest levels of detection, in addition to slower modulation of overall neuronal activity. Spread of potentials to the site of global output from the axon is enhanced by multiple passive and active mechanisms.

Depolarizing and Hyperpolarizing Dendritic Conductances Interact Dynamically

We see that depolarizing conductances increase the excitability of the distal dendrites and the effectiveness of distal synapses, whereas K^+ conductances reduce the excitability and control the temporal characteristics of the dendritic activity. This balance is thus crucial to the functions of dendrites. Figure 17.7 summarizes recent data, showing how these conductances vary along the extents of the dendrites of mitral cells, hippocampal and neocortical pyramidal neurons, and Purkinje cells.

The significance of a particular density of channel needs to be judged in relation to the electrotonic properties discussed in Chapter 4. For instance, a given conductance has more effect on membrane potential in smaller distal branches because of the higher input resistance (see Fig. 4.9). We discuss the significance of these conductance interactions for the firing properties of these different cell types below. Dendritic conductances can be crucial in setting the intrinsic excitability state of the neuron. In the motor neuron, for example, the neuron can alternate between bistable states dependent on activation of dendritic metabotropic glutamate receptors (Svirskie *et al.*, 2001).

Summary

The combination of conductances at different levels of the dendritic tree involves a delicate balance between depolarizing and hyperpolarizing actions acting over different time periods. The combination of conductances at different levels of the dendritic tree is characteristic for different morphological types of neurons.

The Axon Hillock–Initial Segment Encodes Global Output

In cells with long axons, activity in the dendrites eventually leads to activation and modulation of

BOX 17.1

VOLTAGE-GATED COMPUTATIONS IN DENDRITES

Active sites within branches or spines may act as *coincidence detectors* of simultaneous synaptic responses. Through such mechanisms, simple logic gates are set up, which can perform the basic logic operations of AND (e.g., Fig. 17.6), OR, and AND-NOT. Other types of computation in dendrites include linearization of synaptic interactions and basic types of arithmetic processing: addition, subtraction, multiplication, and division (Koch, 1999).

There may be a sequence of coincidence detection as an active response spreads from site to site through the branching tree. This means that *the effectiveness of a distal EPSP may depend not on spreading all the way to the soma, but rather on spreading to the nearest site containing voltage-gated Na^+ or Ca^{2+} channels, for coincidence detection and conduction to the next local site*, and so on. Sequential spread of local active potentials from site to site provides for *pseudosaltatory conduction* through the dendritic tree (Fig. 17.5H). This may occur between individual sites or multiple sites forming clusters (Fig. 17.5I). There is experimental and/or theoretical evidence for all of these mechanisms, some of which is considered below.

How does forwardpropagation of active responses in dendrites fit with the classic model of action potential initiation at the axonal initial segment? We see that there are cells in which the initiation site actually shifts between initial segment and distal dendrite depending on the strengths and locations of synaptic excitation and inhibition. *The site of action potential initiation thus can vary depending on the dynamic state of the neuron*. It is also important to recognize that, because of the filtering effect of the dendritic cable properties, dendritic action potentials that spread to the soma may be indistinguishable at the soma from EPSPs (Fig. 17.6B; see Chapter 4). Thus, dendritic EPSPs that trigger the action potential at the initial segment, as in the classic model, may actually include significant contributions from active dendritic depolarization.

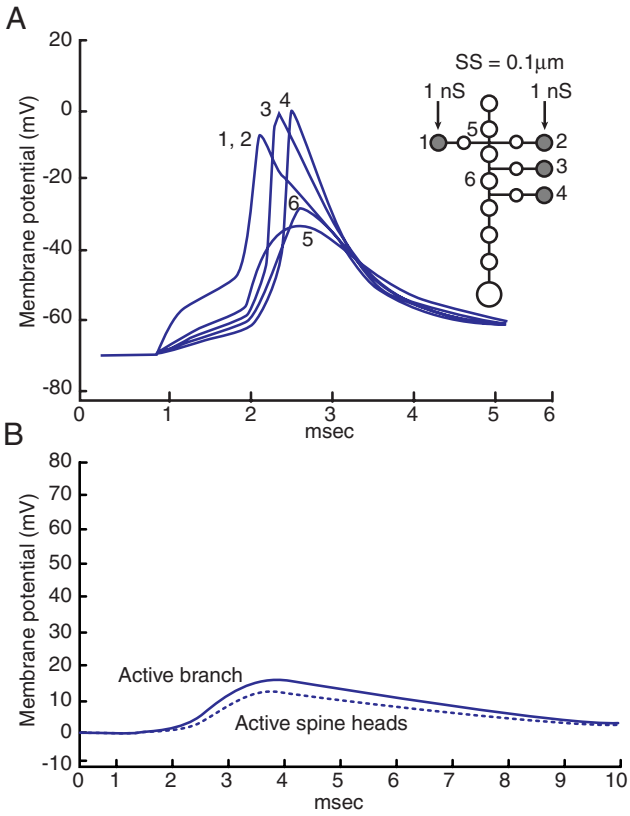

FIGURE 17.6 Logic operations are inherent in coincidence detection by active dendritic sites. The example is an AND operation performed by two dendritic spines with Hodgkin–Huxley–type active kinetics, with intervening passive dendritic membrane. (A) Simultaneous synaptic input of 1-nS conductance to spines 1 AND 2 gives rise to action potentials within both spines, which spread passively to activate action potentials in spines 3 and 4. Decreasing the synaptic conductance or increasing the spine stem diameter causes the coincidence mechanism to fail. Sequential coincidence detection by active spines can thus bring boosted synaptic responses close to the soma. (B) Recording of the boosted spine responses at the soma shows their similarity to the slow time course of classic EPSPs, due to the electrotonic properties of the intervening dendritic membrane. See text. (A) from Shepherd and Brayton (1979). (B) from Woolf *et al.* (1991).

action potential output in the axon. A key question is the precise site of origin of this action potential. This question was one of the first to be addressed in the rise of modern neuroscience; the historical background is summarized in Box 17.2.

These studies established the classic model: the lowest threshold site for action potential generation is in the *axonal initial segment*.

Further testing had to await the development of methods for recording directly from dendrites in tissue slices. In CA1 hippocampal pyramidal neurons, weak synaptic potentials elicited action potentials near the cell body (Richardson *et al.*, 1987), but this site shifted to the proximal dendrites with stronger synaptic excitation (Turner *et al.*, 1991). This confirmed the suggestion of Fuortes and his col-

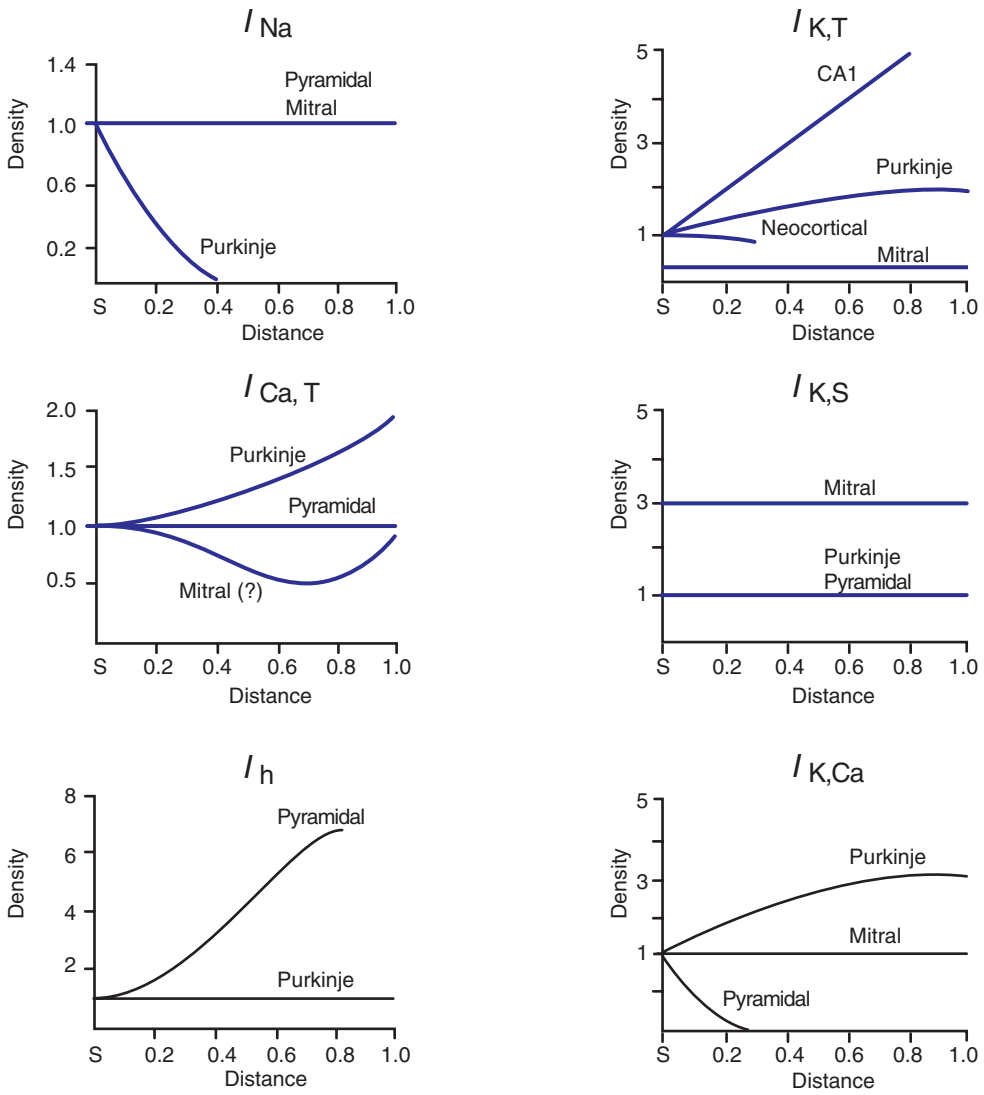

FIGURE 17.7 Graphs of the distribution of different types of conductances at different levels of the dendritic trees in different types of neurons. S: normalized extent of dendritic tree. From Magee (1999, p. 149).

leagues that the site can shift under different stimulus conditions, and was consistent with the stretch receptor, where larger receptor potentials shift the initiation site closer to the cell body.

Definitive analysis was achieved by Stuart and Sakmann (1994) using dual patch recordings from cortical pyramidal neurons under infrared differential contrast microscopy. As shown in Fig. 17.10, with depolarization of the distal dendrites by injected current or excitatory synaptic inputs, a large amplitude depolarization is produced in the dendrites which spreads to the soma. Despite its lower amplitude, the soma depolarization is the first to initiate the action potential. Subsequent studies with triple patch electrodes have shown that the action potential actually arises first in the initial segment and first node (as we saw in Chapter 4, Fig. 4.15) This approach has provided the breakthrough for subsequent analyses of dendritic properties and their coupling to the axon, as is discussed below.

Retrograde Impulse Spread into Dendrites Can Have Several Functions

In addition to identifying the preferential site for action potential initiation in the axonal initial segment, the experiments of Stuart and Sackmann (1994) showed clearly that the action potential does not merely spread passively back into the dendrites but actively backpropagates. Note that we distinguish between passive "spread" and active "propagation" of the action potential.

BOX 17.2

CLASSIC STUDIES OF THE ACTION POTENTIAL INITIATION SITE

Fuortes and colleagues (1957) were the first to deduce, redundant that the EPSP spreads from the dendrites through the soma to initiate the action potential in the region of the axon hillock and the initial axon segment. They suggested that the action potential has two components: (1) an A component that is normally associated with the axon hillock and initial segment, and (2) a B component that is normally associated with retrograde invasion of the cell body. The site of action potential initiation can shift under different membrane potentials, so they preferred the noncommittal terms "A" and "B" for the two components as recorded from the cell body. In contrast, Eccles (1957) referred to the initial component as the initial segment (IS) component and to the second component as the soma dendritic (SD) component (Fig. 17.8).

Apart from the motor neuron, the best early model for intracellular analysis of neuronal mechanisms was the crayfish stretch receptor, described by Eyzaguirre and Kuffler (1955). Intracellular recordings from the cell body showed that stretch causes a depolarizing receptor potential equivalent to an EPSP, which spreads through the cell to initiate an action potential. It was first assumed that this action potential arose at or near the cell body.

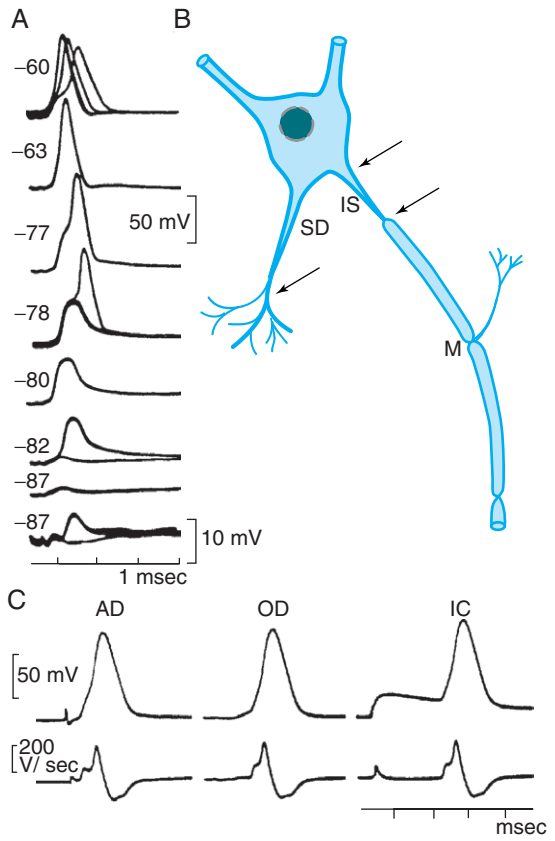

FIGURE 17.8 Classic evidence for the site of action potential initiation. Intracellular recordings were from the cell body of the motor neuron of an anesthetized cat. (A) Differential blockade of an antidromic impulse by adjusting the membrane potential by holding currents. The recordings reveal the sequence of impulse invasion in the myelinated axon (recordings at –87 mV, two amplifications), initial segment of the axon (first component of the impulse beginning at –82 mV), and soma–dendritic region (large component beginning at –78 mV). (B) Sites of the three regions of impulse generation (M, myelinated axon; IS, initial segment; SD, soma and dendrites); arrows show probable sites of impulse blockade in (A). (C) Comparison of intracellular recordings of impulses generated antidromically (AD), synaptically (orthodromically, OD), and by direct current injection (IC). Lower traces indicate electrical differentiation of these recordings, showing the separation of the impulse into the same two components and indicating that sequence of impulse generation from the initial segment into the soma–dendritic region is the same in all cases. From Eccles (1957).

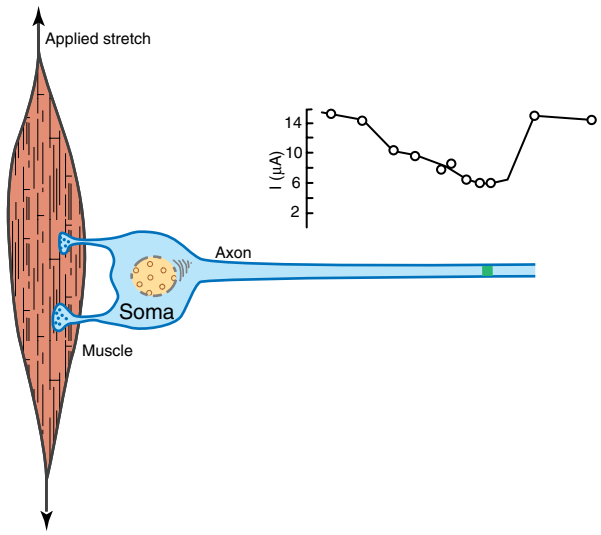

FIGURE 17.9 Classic demonstration of the site of impulse initiation in the stretch receptor cell of the crayfish. Moderate stretch of the receptor muscle generated a receptor potential that spread from the dendrites across the cell body to initiate the action potential in the axon. The excitability curve (shown above the axon) was obtained by passing current between extracellular electrodes along the axon and finding the current (*I*) intensity needed to evoke an action potential response; this shows the trigger zone (site with lowest threshold) to be several hundred micrometers out on the axon (green region in axon). From Ringham (1971).

BOX 17.2 (continued)

Edwards and Ottoson (1958), working in Kuffler's laboratory, tested this postulate by recording the local extracellular current to locate precisely the site of inward current associated with action potential initiation. Surprisingly, this site turned out to be far out on the axon, some 200 μm from the cell body (Fig. 17.9). This result showed that potentials generated in the distal dendrites can spread all the way through the dendrites and soma well out into the initial segment of the axon to initiate impulses. It further showed that the action potential recorded at the cell body is the backward spreading impulse from the initiation site. Edwards and Ottoson's study was important in establishing the basic model of impulse initiation in the axonal initial segment.

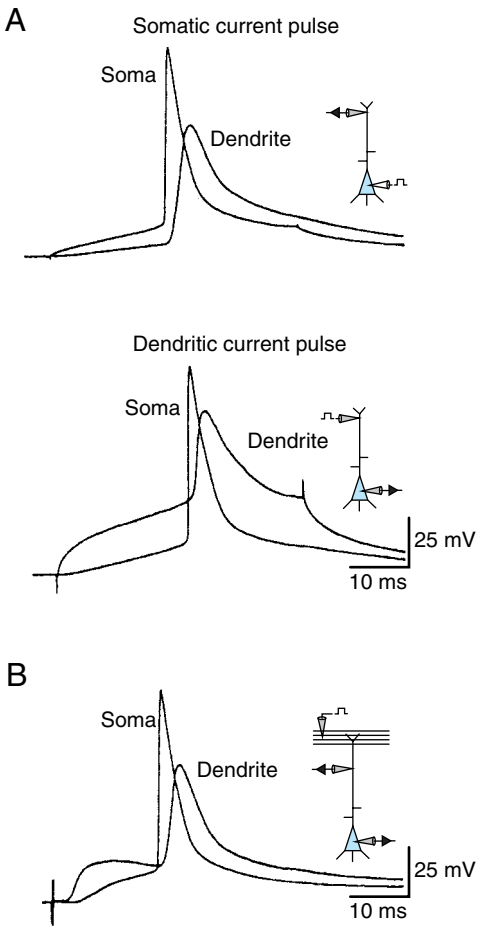

FIGURE 17.10 Direct demonstration of impulse initiation zone and backpropagation into dendrites, using dual patch recordings from soma and dendrites of a layer V pyramidal neuron in a slice preparation of the rat neocortex. (A) Depolarizing current injection in either the soma or the dendrites elicits an impulse first in the soma. (B) The same result is obtained with synaptic activation of layer I input to distal dendrites. Note the close similarity of these results to the earlier findings in the motor neuron (Fig. 17.8). From Stuart and Sakmann (1994).

What is the function of the backpropagating action potential? Experimental evidence shows that it can have a variety of functions.

Dendrodendritic Inhibition

A clear function for a backpropagating action potential was first suggested for the olfactory mitral cell, where the mitral-to-granule dendrodendritic synapses are triggered by the action potential spreading from the soma into the secondary dendrites (Fig. 17.11). Because of the delay in activating the reciprocal inhibitory synapses from the granule cells, self-inhibition of the mitral cell occurs in the wake of the passing impulse; the two do not collide. The mechanism functions similarly with both active backpropagation and passive electrotonic spread into the dendrites, as tested in computer simulations (Rall and Shepherd, 1968). The functions of the dendrodendritic inhibition include center–surround antagonism mediating the abstraction of molecular determinants underlying the discrimination of different odor molecules, storing of olfactory memories at the reciprocal synapses, and generation of oscillating activity in mitral and granule cell populations.

Boosting Synaptic Responses

In several types of pyramidal neurons, active dendritic properties appear to boost action potential invasion, so that summation with EPSPs occurs that makes them effective in spreading to the soma.

Resetting the Membrane Potential

A possible function is that the Na^+ and K^+ conductance increases associated with active propagation wipe out the existing membrane potential, resetting the membrane potential for new inputs.

Synaptic Plasticity

The action potential in the dendritic branches presumably depolarizes the spines (because of the

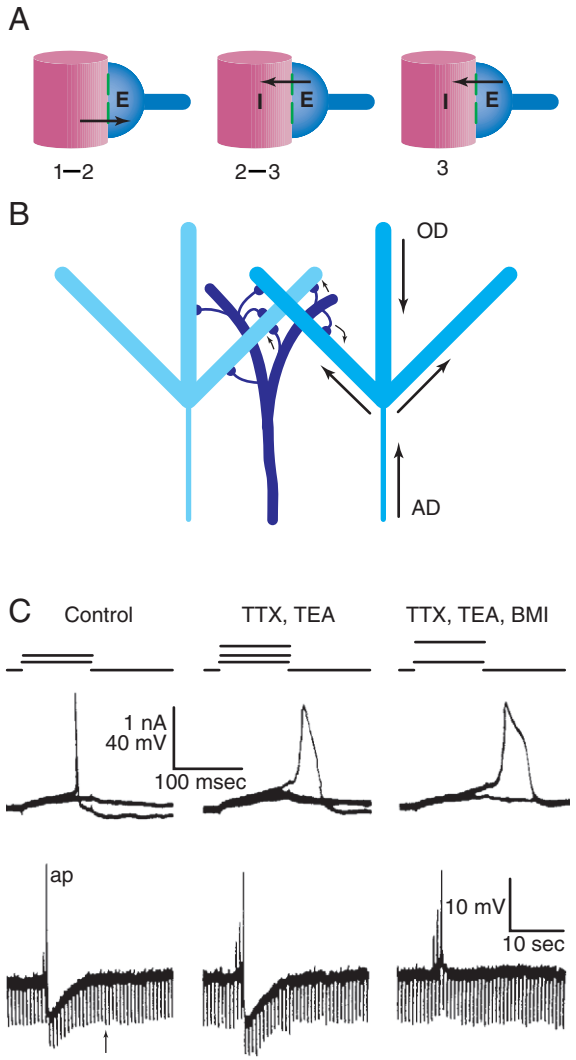

FIGURE 17.11 Dendrodendritic interactions in the olfactory bulb. (A) Depolarization by an action potential in period 1–2 activates excitatory output from mitral cell dendrite, setting up an EPSP (E) in a granule cell spine. During period 2–3, the granule spine EPSP activates a reciprocal inhibitory synapse, setting up an IPSP (I) in the mitral cell dendrite which lasts into period 3. (B) Either orthodromic (OD) or antidromic (AD) activation of the mitral cell sets up a backspreading/backpropagating impulse into the secondary dendrites, activating both feedback and lateral inhibition of the mitral cells through the dendrodendritic pathway. (C) Experimental demonstration of the dendrodendritic pathway. (Left) In an intracellular recording from a mitral cell in an isolated turtle olfactory bulb, injected depolarizing current elicits an action potential [fast trace and action potential (AP) in slow trace below] followed by a long-lasting hyperpolarizing IPSP; transient downward deflections used to measure input resistance are reduced during the IPSP, indicating an increase in membrane conductance during the IPSP. (Middle) Depolarizing current elicits a lower-amplitude and slower action potential when the preparation is bathed in TTX (which blocks the Na^+ component of the impulse) and TEA (which blocks K^+ conductances that would shunt the remaining Ca^{2+} component). The IPSP persists (bottom trace), activated by the Ca^{2+}-dependent action potential. (Right) Addition of bicuculline (BMI) to the bath blocks the IPSP (bottom trace), presumably by blocking the granule-to-mitral reciprocal synapse. (A) and (B) from Rall and Shepherd (1968). (C) adapted from Jahr and Nicoll (1982).

favorable impedance matching, as discussed in Chapter 4), which means that the impulse depolarization would summate with the synaptic depolarization of the spines. This process would enable the spines to function as coincidence detectors and implement Hebb-like changes in synaptic plasticity (as discussed in detail in Chapter 18). This postulate has been tested by electrophysiological recordings (Spruston *et al.*, 1995) and Ca^{2+} imaging (Yuste *et al.*, 1994 and 1995). Activity-dependent changes in dendritic synaptic potency are not seen with passive retrograde depolarization but appear to require actively propagating retrograde impulses (Spruston *et al.*, 1995).

Frequency Dependence

Trains of action potentials generated at the soma–axon hillock can invade the dendrites to varying extents. The proximal dendrites appear to be invaded throughout a high-frequency burst, whereas the distal dendrites appear to be invaded mainly by the early action potentials (Spruston *et al.*, 1995; Yuste *et al.*, 1994; Regehr *et al.*, 1989; Callaway and Ross, 1995). Activation of Ca^{2+} -activated K^+ conductances by the early impulses may effectively switch off the distal dendritic compartment.

Retrograde Actions at Synapses

The retrograde action potential may contribute to the activation of neurotransmitter release from the dendrites. Dynorphin released by synaptically stimulated dentate granule cells can affect the presynaptic terminals (Simmons *et al.*, 1995). In the cerebral cortex there is evidence that GABAergic interneuronal dendrites act back on axonal terminals of pyramidal cells, and glutamatergic pyramidal cell dendrites act back on axonal terminals of the interneurons (Fig. 17.12). The combined effects of the axonal and dendritic compartments of both neuronal types regulate the normal excitability of pyramidal neurons, and may be a factor in the development of cortical hyperexcitability and epilepsy (Zilberter, 2000).

Conditional Axonal Output

Because of the long distance between distal dendrites and initial axonal segment, we may hypothesize that the coupling between the two is not automatic. Indeed, conditional coupling dependent on synaptic inputs and intrinsic activity states at intervening dendritic sites appears to be fundamental to the relationship between local dendritic inputs and global axonal output (Spruston, 2000).

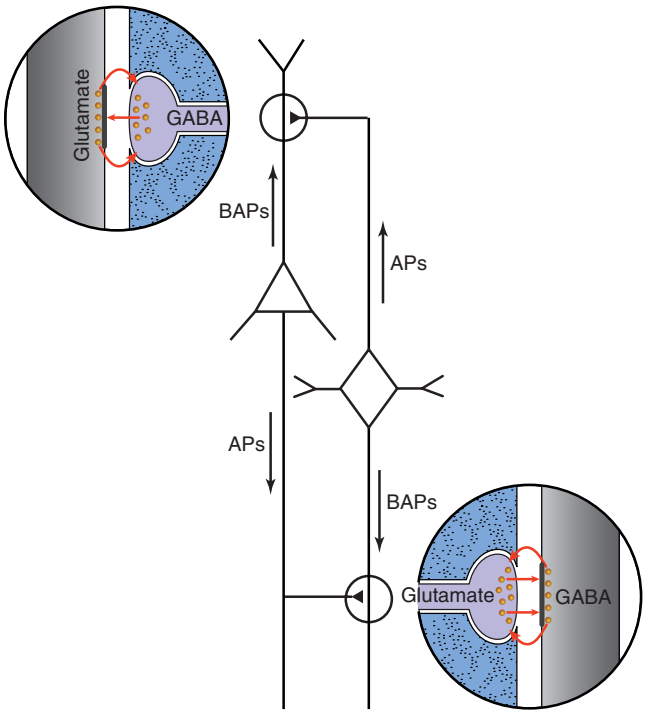

FIGURE 17.12 Pyramidal neurons and interneurons in the cerebral cortex interact through axodendritic and dendroaxonic contacts. APs, action potentials in axons; BAPs, backpropagating action potentials in dendrites. See text. From Zilberter (2000).

Examples of How Voltage-Gated Channels Take Part in Dendritic Integration

It is commonly believed that active dendrites are a modern concept, but in fact this idea is as old as Cajal. Box 17.3 gives a short history of this idea and the experimental evidence that has been obtained over the years.

Detailed analysis of active dendritic properties began with the computational studies of olfactory mitral cells and experimental studies of cerebellar Purkinje cells. Since then studies of active dendritic properties have proliferated, particularly since the introduction of the patch recording method. Several types of neurons have provided important models for the possible functional roles of active dendritic properties.

Purkinje Cells

The cerebellar Purkinje cell has the most elaborate dendritic tree in the nervous system, with more than 100,000 dendritic spines receiving synaptic inputs from parallel fibers and mossy fibers. The basic distribution of active properties in the Purkinje cell was indicated by the pioneering experiments of Llinas and Sugimori (1980) in tissue slices (Fig. 17.14). The action potential in the cell body and axon hillock is due mainly to fast Na^+ and delayed K^+ channels; there is also a Ca^{2+} component. The action potential correspondingly has a large amplitude in the cell body and decreases by electrotonic decay in the dendrites. In contrast, the recordings in the dendrites are dominated by slower "spike" potentials that are Ca^{2+} dependent, owing to a P-type Ca^{2+} conductance (see Fig. 17.14). These spikes are generated from a plateau potential due to a persistent Na_p current (see Chapter 5).

There are two distinct operating modes of the Purkinje cell in relation to its distinctive inputs. Climbing fibers mediate strong depolarizing EPSPs throughout most of the dendrites that appear to give rise to synchronous Ca^{2+} dendritic action potentials throughout the dendritic tree, which then spread to the soma to elicit the bursting "complex spike" in the axon hillock. In contrast, parallel fibers are active in small groups, giving rise to smaller populations of individual EPSPs possibly targeted to particular dendritic regions (compartments). In this mode, *subthreshold amplification* through active dendritic properties may enhance the effect of a particular set of input fibers in controlling or modulating the frequency of Purkinje cell action potential output in the axon hillock. The Purkinje cell is subjected to local inhibitory control by stellate cell synapses targeted to specific dendritic compartments, and *global inhibitory control* of axonal output by basket cell synapses on the axonal initial segment.

Pyramidal Neurons

Active properties of the apical dendrite of hippocampal pyramidal neurons have been amply documented by patch recordings (Magee and Johnston, 1995). In contrast to the Purkinje cell, both fast Na^+ and Ca^{2+} conductances have been shown throughout the dendritic tree of the pyramidal neuron by electrophysiological and dye-imaging methods (see Fig. 17.7). Activation of the low-threshold Na^+ channels is believed to play an important role in triggering the higher-threshold Ca^{2+} channels. Similar results have been obtained in studies of pyramidal neurons of the cerebral cortex.

The output pattern of a neuron depends on its dendritic properties and their interaction with the soma. This is exemplified by the generation of a burst response in a pyramidal neuron. EPSPs spread through the dendrite, activating fast Na^+ and then high-threshold (HT) Ca^{2+} channels that give a subthreshold boost to the EPSP. The enhanced EPSP spreads to the soma–axon hillock, triggering a Na^+ action potential. This propagates into the axon and also backpropagates into the dendrites, eliciting a

BOX 17.3

CLASSIC STUDIES OF ACTIVE DENDRITIC PROPERTIES

The first intracellular recordings of active properties of dendrites were obtained in 1958 by Eccles and collaborators from motor neurons undergoing chromatolytic degeneration after amputation of their axons (Eccles *et al.*, 1958). Small spikes could be seen riding on EPSPs, which were thought to be due to impulse "booster" sites in the dendrites. Similar activity was seen in the first intracellular recordings from hippocampal pyramidal neurons (Spencer and Kandel, 1961). These "fast prepotentials" appeared to intervene between the EPSP in the dendrite and the impulse initiation in the soma–axon hillock region (Fig. 17.13). These active sites were suggested to be at branch points in the apical dendrite, where they would serve to boost the EPSPs generated by more distal dendritic inputs. This boosting property has provided an important model for the possible significance of active dendritic properties. Active properties of dendrites were the subject of increasing study from the 1950s on, with extracellular [see Fatt (1947) and Anderson (1960)] and intracellular recordings. The use of dual patch recordings finally enabled direct recordings from dendrites and comparisons with soma recordings, as discussed in the text.

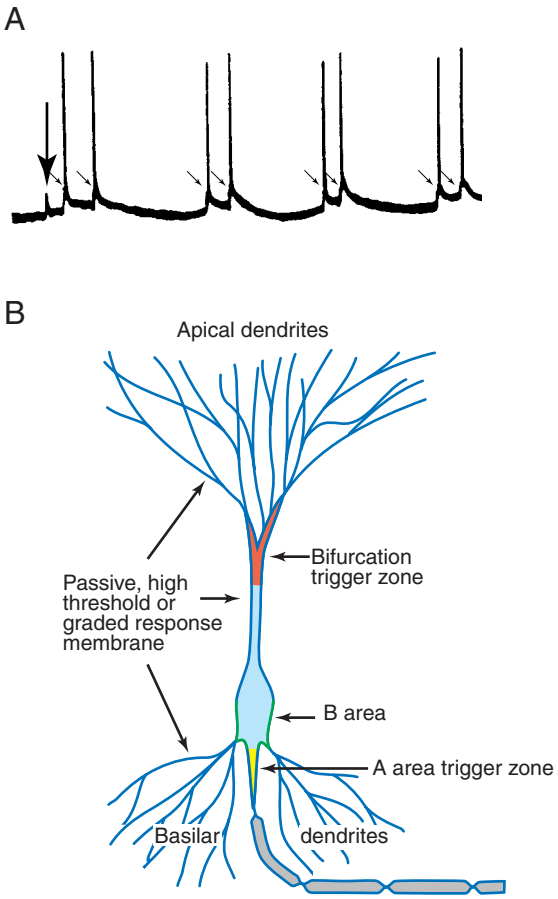

FIGURE 17.13 Early evidence for active dendritic properties in normal adult neurons. (A) Intracellular recordings from the soma of a hippocampal pyramidal neuron in an anesthetized cat; the large spontaneous action potentials are preceded by a small "fast prepotential" (small arrows), which occasionally occurs in isolation (large arrow). (B) Conceptual schema of how a "trigger zone" at bifurcating dendritic branches could give rise to the fast prepotential and boost the distal dendritic response. From Spencer and Kandel (1961).

slower all-or-nothing Ca^{2+} action potential. This large-amplitude, slow depolarization then spreads through the dendrites and back to the soma, triggering a train of action potentials that form a burst response.

This sequence of events is contained in a two-compartment model representing the soma and dendritic compartments (Fig. 17.15). The sequence emphasizes not only the importance of the interplay between the different types of channels, but also the critical role of the compartmentation of the neuron into dendritic and somatic compartments so that they can interact in controlling the intensity and time course of the impulse output.

Does the specific form of the input–output transformation depend on a specific distribution of active channels in the dendritic tree? Na^+ and Ca^{2+} channels are distributed widely in pyramidal neuron dendrites. In computational simulations, grouping channels in different distributions may have little effect on the input–output functions of a neuron (Mainen and

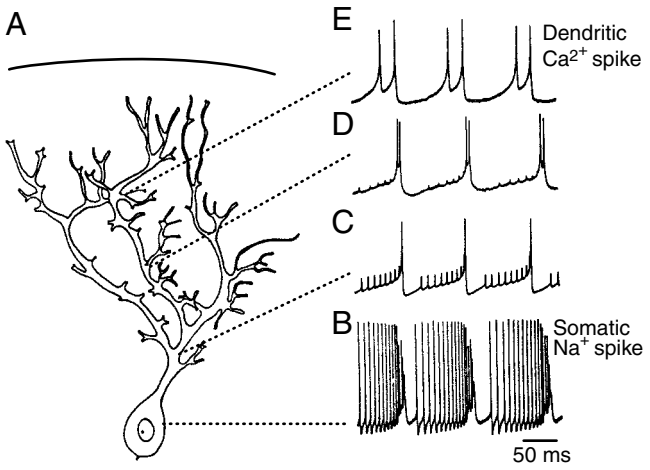

FIGURE 17.14 Classic demonstration of the difference between soma and dendritic action potentials. (A) Drawing of a Purkinje cell in the cerebellar slice. (B) Intracellular recordings from the soma, showing fast Na^+ spikes. (C–E) Intracellular recordings from progressively more distant dendritic sites; the fast soma spikes become small, owing to electrotonic decrement, and are replaced by large-amplitude dendritic Ca^{2+} spikes. Spread of these spikes to the soma causes an inactivating burst that interrupts the soma discharge. Adapted from Llinas and Sugimori (1980).

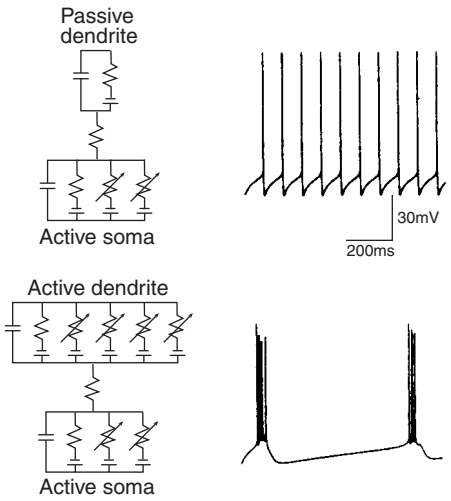

FIGURE 17.15 Generation of a burst response by interactions between soma and dendrites. From Pinsky and Rinzel (1994).

Sejnowski, 1995). However, there is evidence that subthreshold amplification by voltage-gated channels may tend to occur in the more proximal dendrites of some neurons (Yuste and Denk, 1995). In addition, the dendritic trees of some neurons are clearly divided into different anatomical and functional subdivisions, as discussed in the next section.

Medium Spiny Cells

A third instructive example of the role of active dendritic properties is found in the medium spiny cell of the neostriatum (Figs. 17.16A,B). The passive electrotonic properties of this cell are described in Chapter 4 (Fig. 4.12). Inputs to a given neuron from the cortex are widely distributed, meaning that a given neuron must summate a significant number of synaptic inputs before generating an impulse response. The responsiveness of the cell is controlled by its cable properties; individual responses in the spines are filtered out by the large capacitance of the many dendritic spines, so individual EPSPs recorded at the soma are small.

With synchronous specific inputs, the larger summated EPSPs depolarize the dendritic membrane strongly. The dendritic membrane contains inwardly rectifying channels (I_h) (Fig. 17.16C), which reduce their conductance on depolarization and thereby increase the effective membrane resistance and shorten the electrotonic length of the dendritic tree. The large depolarization also activates HT Ca^{2+} channels, which contribute to the large-amplitude, slow depolarizations. These combined effects change the neuron from a state in which it is insensitive to small noisy inputs into a state in which it gives a large response to a specific input and is maximally sensitive to additional inputs. Through this voltage-gated mechanism a neuron can enhance the effectiveness of distal dendritic inputs, not by boosting inward Na^+ and K^+ currents, but by reducing outward shunting K^+ currents. This exemplifies the principle of dynamic control over dendritic properties mentioned earlier (see above).

Multiple Impulse Initiation Sites Are under Dynamic Control

Can the active properties of dendrites give rise to full dendritic action potentials that propagate toward the cell body and precede the action potential in the soma–axon hillock–initial segment region? Evidence for this began with extracellular recordings of a "population spike" that appears to propagate along the apical dendrites toward the cell body in hippocampal pyramidal cells (Anderson, 1960), supported by the recording of "fast prepotentials" (see above) and by current source density calculations in cortical pyramidal neurons (Herreras, 1990). However, because of the indirect nature of this evidence, it is possible (Stuart *et al.*, 1997) that these active properties of distal dendrites can boost dendritic synaptic responses but may be too slow to lead to action potential initiation and forward propagation.

Evidence on this question has been obtained from the olfactory mitral cell, whose excitatory inputs are

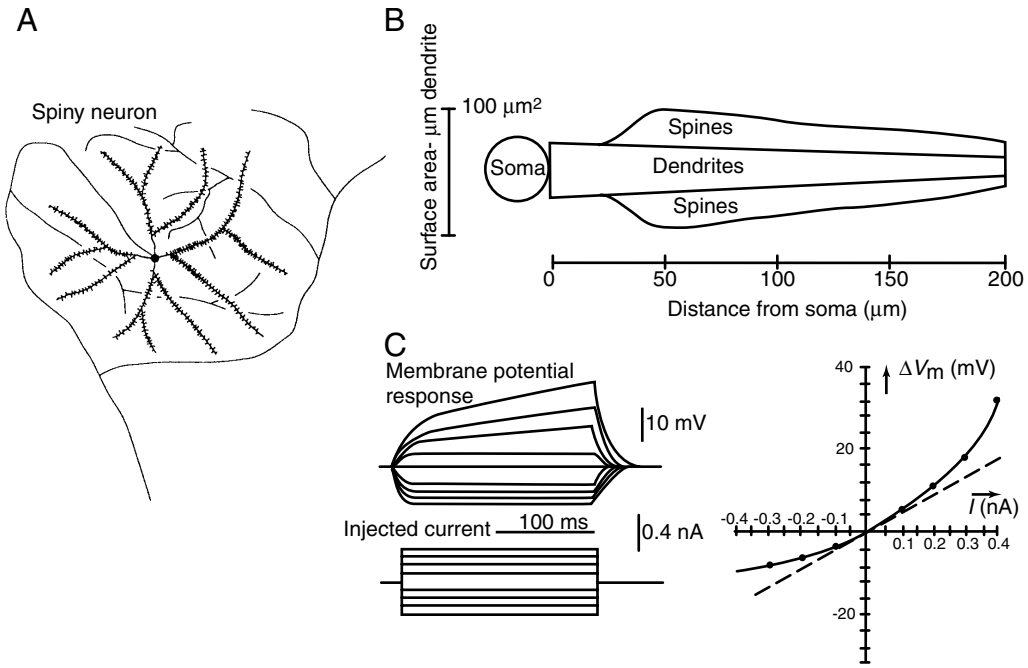

FIGURE 17.16 Dendritic spines and dendritic membrane properties interact to control neuronal excitability. (A) Diagram of a medium spiny neuron in the caudate nucleus. (B) Plot of surface areas of different compartments, showing large increase in surface area due to spines. (C) Intracellular patch-clamp analysis of medium spiny neuron, showing inward rectification of the membrane that controls the response of the dendrites to excitatory synaptic inputs (cf. Chapter 4, Fig. 4.12). From Wilson (1998).

on its distal dendritic tuft (see Fig. 17.17A). At weak levels of electrical shocks to the olfactory nerves, the site of action potential initiation is at or near the soma, as in the classic model (trace labeled 17 μA in Fig. 17.17B). This shows that despite its long length, the primary dendrite is not an impediment to the transfer of the EPSP carrying specific sensory information from the distal dendrite to the soma and initial axonal segment. It adds another nail to the coffin of the common misconception that in neurons with axons specific excitatory inputs must be targeted near the axon hillock and that distal dendrites can mediate only slow background modulation of that site.

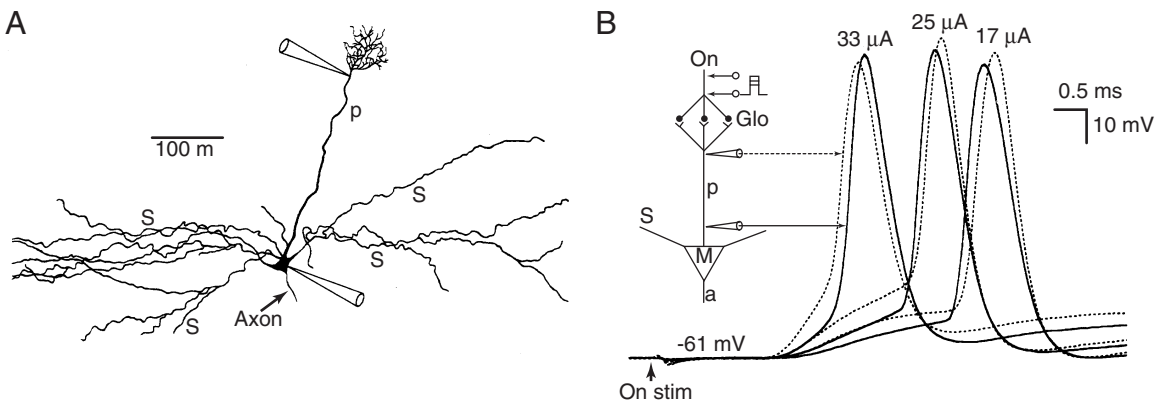

FIGURE 17.17 Shift of action potential initiation site between soma and distal dendrite. (A) A mitral cell in a slice preparation from the rat olfactory bulb stained with biocytin, showing placement of dual patch recording electrodes, one on the soma and one at the distal end of the primary dendrite 300 μm from the soma near the distal dendritic tuft in the glomerulus. (B) In another cell, an electrode site near the soma is paired with a distal dendritic site. With weak shocks to the olfactory nerves (17 μA) the soma action potential arises first; as the shocks are strengthened to 33 μA, the action potential initiation shifts to the distal dendrite recording site. Abbreviations: M, mitral cell; p, primary dendrite; s, secondary dendrite; a, axon; On, olfactory nerves; Glo, glomerulus. From Chen *et al.* (1997).

As the level of distal excitatory input is increased, the dual patch recordings show clearly that the action potential initiation site is not fixed; instead, the site shifts gradually from the soma to the distal dendrite (see 25- and 33-μA traces in Fig. 17.17B). Thus, the site of impulse initiation is not fixed in the mitral cell, but varies with the intensity of distal excitatory input. The action potential is due to tetrodotoxin-sensitive Na^+ channels distributed along the extent of the primary dendrite. The way that passive potential spread along the dendrite controls the site of action potential initiation in these experiments has been discussed in Chapter 4 (Fig. 4.15). The site can also be shifted to the distal dendrites by synaptic inhibition applied to the soma through the dendrodendritic synapses.

Summary

These are only a few examples of the range of operations carried out by complex dendrites. These dendritic operations are embedded in the circuits that control behavior. Many further examples could be mentioned; for instance, the way that motoneuron intrinsic properties are involved in the activation patterns of motor units controlling the limbs (Gorassini *et al.*, 1999). Thus, for each neuron, the dendritic tree constitutes an expanded unit essential to the circuits underlying behavior.

Dendritic Spines Are Multifunctional Microintegrative Units

The very small size of dendritic spines has made it difficult to study them directly. However, examples have already been given of spines with complex information processing capacities, such as granule cell spines in the olfactory bulb and spines of medium spiny neurons in the striatum. In cortical neurons, spines have been implicated in cognitive functions from observations of dramatic changes in spine morphology in relation to different types of mental retardation and different hormonal exposures. Activity-dependent changes in spine morphology could be a mechanism contributing to learning and memory [summarized in Harris and Kater (1994), Shepherd (1996), Yuste and Denk (1995); see also Chapter 18].

Computational models have been very useful in testing these hypotheses, as well as suggesting other possible functions, such as the dynamic changes of electrotonic structure in medium spiny cells of the basal ganglia (see above). With the development of more powerful light microscopical methods, such as two-photon laser confocal microscopy, it has become possible to image Ca^{2+} fluxes in individual spines in relation to synaptic inputs and neuronal activity

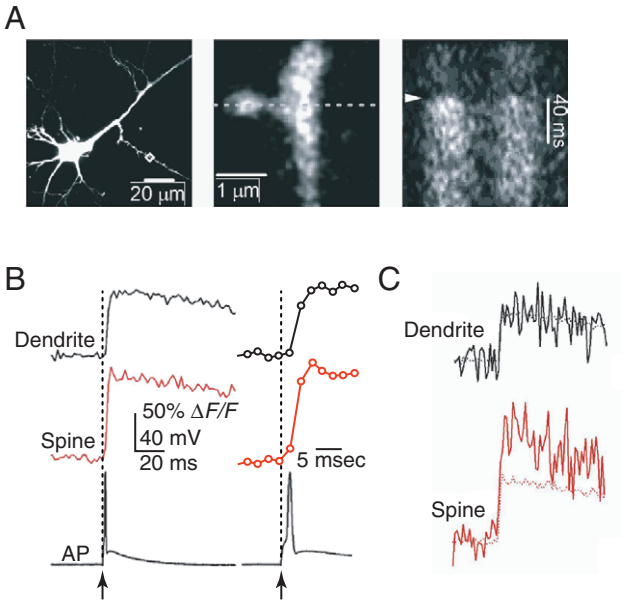

FIGURE 17.18 Calcium transients can be imaged in single dendritic spines in a rat hippocampal slice. (A) Fluo-4, a calcium sensitive dye, injected into a neuron enables an individual spine to be imaged under two-photon microscopy. (B) An action potential (AP) induces an increase in Ca^{2+} in the dendrite and a larger increase in the spine (averaged responses). Fluctuation analysis indicated that spines likely contain up to 20 voltage-sensitive Ca channels; single-channel openings could be detected, which had a high (0.5) probability of opening following a single action potential. From Sabatini and Svoboda (2000).

(Fig. 17.18). The evidence for active properties of dendrites has suggested that the spines may also have active properties. Thus, spines may be devices for nonlinear thresholding operations, either through voltage-gated ion channels or through voltage-dependent synaptic properties such as *N*-methyl-D-aspartate (NMDA) receptors. On the other hand, spines may function as compartments to isolate changes at the synapse, such as excess Ca^{2+}, that would be harmful to the rest of the neuron (Volfovsky *et al.*, 1999).

The range of functions that have been hypothesized for spines is partly a reflection of how little direct evidence we have of specific properties of spines. It also indicates that the answer to the question "What is the function of the dendritic spine?" is unlikely to be only one function but rather a range of functions that is tuned in a given neuron to the specific operations of that neuron. The spine is increasingly regarded as a microcompartment that integrates a range of functions (Segev and London, 2000; Harris and Kater, 1994; Shepherd, 1996; Yuste and Denk, 1995). A spiny dendritic tree is thus covered with a large population of microintegrative units. As previously discussed, the effect of any given one of these units on the action potential output of the neuron should therefore not be assessed with regard

only to the far-off cell body and axon hillock, but rather with regard first to its effect on its neighboring microintegrative units.

SUMMARY: THE DENDRITIC TREE AS A COMPLEX INFORMATION PROCESSING SYSTEM

Dendrites are the primary information processing substrate of the neuron. They allow the neuron wide flexibility in carrying out the operations needed for processing information in the spatial and temporal domains within nervous centers. The main constraints on these operations are the rules of passive electrotonic spread (Chapter 4) and the rules of nonlinear thresholding at multiple sites within the complex geometry of dendritic trees discussed in this chapter. Cells with and without axons and action potentials demonstrate many specific types of information processing that are possible in dendrites, such as motion detection, oscillatory activity, lateral inhibition, and

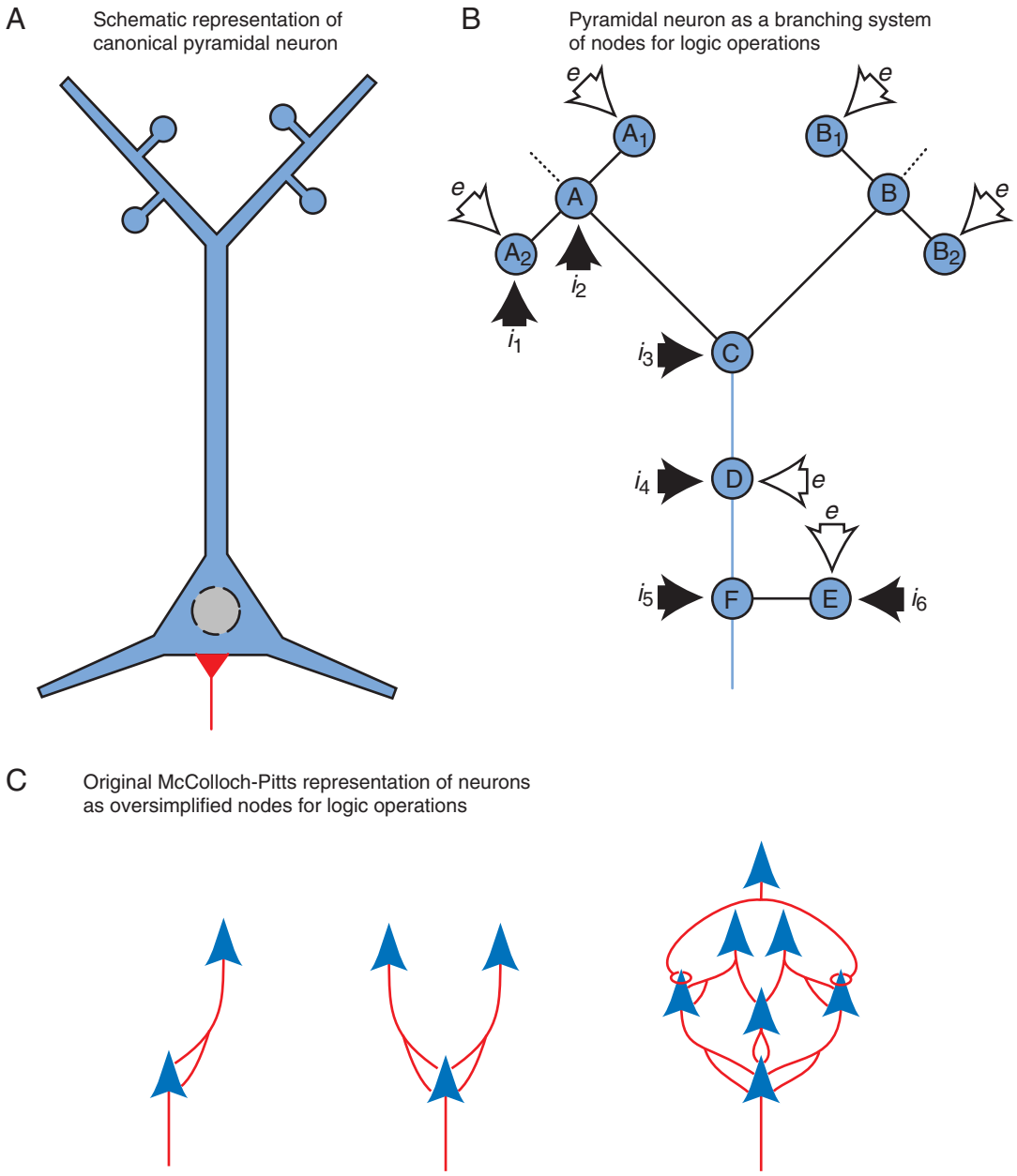

FIGURE 17.19 The dendritic tree as a computational system. Dendritic tree of a cortical pyramidal neuron (A) represented as a system of computational nodes (B). These new concepts illustrated in (B) contrast with (C), which depicts the earlier concept of McCulloch and Pitts (1943) in which the dendritic tree is ignored and the entire neuron is reduced to a single computational node. Abbreviations: e, excitatory synapse; i, inhibitory synapse. From Shepherd (1994).

network control of sensory processing and motor control. These types and more are possible for cells with axons, which in addition operate within constraints that govern local versus global outputs and subthreshold versus suprathreshold activities.

Spines add a dimension of local computation to dendritic function that is especially relevant to mechanisms for learning and memory (see Chapter 18). Although spines seem to distance synaptic responses from directly affecting axonal output, in fact many cells demonstrate that distal spine inputs carry specific information.

The key to understanding how all parts of the dendritic tree, including its distal branches and spines, can participate in mediating specific types of information processing is to recognize the tree as a complex system of active nodes. From this perspective, if a spine can affect its neighbor and that spine its neighbor, a dendritic tree becomes a cascade of decision points, with multiple cascades operating over multiple overlapping time scales. As illustrated in Fig. 17.19, a neocortical pyramidal neuron can be reduced to a canonical form (A) and then represented as a system of computational nodes. In this system, each node receiving excitatory (e) input is subjected to gating by inhibitory input at that site (i 1–6), and to further modulation and gating by inhibition between that site and the site of global output from the soma and axon hillock (site i 5). Thus, far from being a single node, as in the classic concept of McCulloch and Pitts (1943) and the classic neural network models, the complex neuron is a system of nodes in itself, within which *the dendrites constitute a kind of neural microchip for complex computations*. The neuron as a single node, so feeble in its information processing capacities, is replaced by the neuron as a complex multinodal system. The range of operations of which this complex system is capable continues to expand (see Shepherd, 1994). Exploring the information processing capacities of the brain at the level of real dendritic systems, by both experimental and theoretical methods, thus presents one of the most exciting challenges for neuroscientists in the future.

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