He regarded this decision making as the brain's most fundamental operation (see Chapter 56).

Synaptic Inputs Are Integrated at the Axon Initial Segment

In most neurons, the decision to initiate an action potential output is made at one site: the axon initial segment. Here, the cell membrane has a lower threshold for action potential generation than at the cell body or dendrites because it has a higher density of voltage-dependent Na^+ channels (Figure 13–13). With each increment of membrane depolarization, more Na^+ channels open, providing a higher density of inward current (per unit area of membrane) at the axon initial segment than elsewhere in the cell.

At the initial segment, the depolarization increment required to reach the threshold for an action potential (–55 mV) is only 10 mV from the resting level of –65 mV. In contrast, the membrane of the cell body must be depolarized by 30 mV before reaching its threshold (–35 mV). Therefore, synaptic excitation first discharges the region of membrane at the initial segment, also called the *trigger zone.* The action potential generated at this site then depolarizes the membrane of the cell body to threshold and at the same time is propagated along the axon .

Because neuronal integration involves the summation of synaptic potentials that spread to the trigger zone, it is critically affected by two passive membrane properties of the neuron (Chapter 9). First, the membrane time constant helps determine the time course of the synaptic potential in response to the EPSC, thereby controlling *temporal summation*, the process by which consecutive synaptic potentials are added together in the postsynaptic cell. Neurons with a large membrane time constant have a greater capacity for temporal summation than do neurons with a shorter time constant (Figure 13–14A). As a result, the longer the time constant, the greater is the likelihood that two consecutive inputs will summate to bring the cell membrane to its threshold for an action potential.

Second, the *length* constant of the cell determines the degree to which the EPSP decreases as it spreads

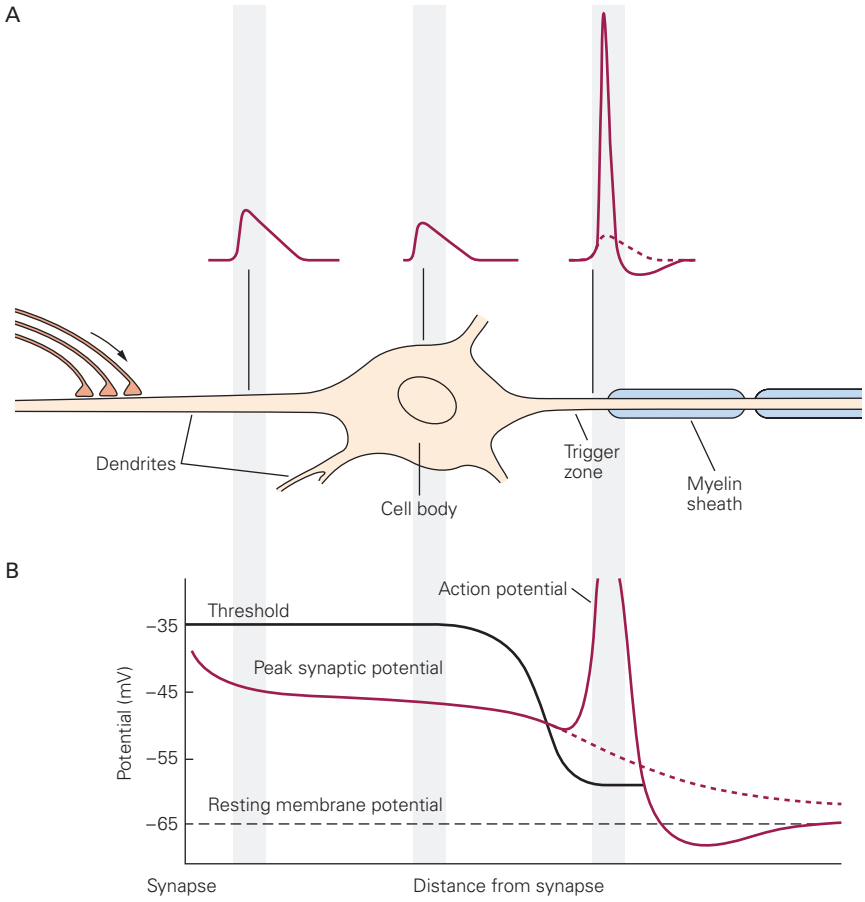

Figure 13–13 A synaptic potential arising in a dendrite can generate an action potential at the axon initial segment. (Adapted, with permission, from Eckert et al. 1988.)

A. An excitatory synaptic potential originating in the dendrites decreases with distance as it propagates passively to the soma. Nevertheless, an action potential can be initiated at the trigger zone (the axon initial segment) because the density of the Na^+ channels in this region is high and thus the threshold for an action potential is low.

B. Comparison of the threshold for initiation of the action potential at different sites in the neuron (corresponding to drawing A). An action potential is generated when the amplitude of the synaptic potential exceeds the threshold. The **dashed line** shows the decay of the synaptic potential if no action potential is generated at the axon initial segment.

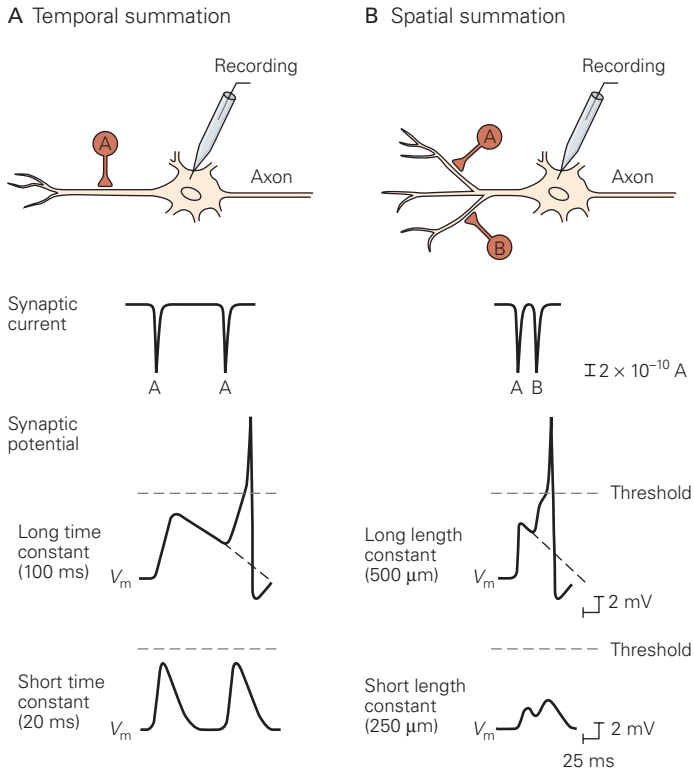

Figure 13–14 Central neurons are able to integrate a variety of synaptic inputs through temporal and spatial summation of synaptic potentials.

A. Temporal summation. The time constant of a postsynaptic cell (see Figure 9–10) affects the amplitude of the depolarization caused by consecutive EPSPs produced by a single presynaptic neuron (cell A). Here the synaptic current generated by the presynaptic neuron is nearly the same for both EPSPs. In a cell with a *long* time constant, the first EPSP does not fully decay by the time the second EPSP is triggered. In that instance, the depolarizing effects of both potentials are additive, bringing the membrane potential above the threshold and triggering an action potential. In a cell with a *short* time constant, the first EPSP decays to the resting potential before the second EPSP is triggered, and in that instance, the second EPSP alone does not cause enough depolarization to trigger an action potential.

B. Spatial summation. The length constant of a postsynaptic cell (see Figure 9–11B) affects the amplitudes of two excitatory postsynaptic potentials produced by two presynaptic neurons (cells A and B). For illustrative purposes, both synapses are the same distance (500 µm) from the postsynaptic cell's trigger zone, and the current produced by each synaptic contact is the same. If the distance between the site of synaptic input and the trigger zone in the postsynaptic cell is only one length constant (that is, the postsynaptic cell has a long length constant of 500 µm), the synaptic potentials produced by each of the two presynaptic neurons will decrease to 37% of their original amplitude by the time they reach the trigger zone. Summation of the two potentials results in enough depolarization to exceed threshold, triggering an action potential. If the distance between the synapse and the trigger zone is equal to two length constants (ie, the postsynaptic cell has a short length constant of
250 µm), each synaptic potential will be less than 15% of its initial amplitude, and summation will not be sufficient to trigger an action potential.

passively from a synapse along the length of the dendrite to the cell body and axon initial segment (the trigger zone). In cells with a longer length constant, signals spread to the trigger zone with minimal decrement; in cells with a short length constant, the signals decay rapidly with distance. Because the depolarization produced by one synapse is almost never sufficient to trigger an action potential at the trigger zone, the inputs from many presynaptic neurons acting at different sites on the postsynaptic neuron must be added together. This process is called *spatial summation.* Neurons with a large length constant are more likely to be brought to threshold by inputs arising from different sites than are neurons with a short length constant (Figure 13–14B).

Subclasses of GABAergic Neurons Target Distinct Regions of Their Postsynaptic Target Neurons to Produce Inhibitory Actions With Different Functions

In contrast to the relatively few types of glutamatergic pyramidal neurons, the mammalian central nervous

system has a large variety of GABAergic inhibitory interneurons that differ in developmental origin, molecular composition, morphology, and connectivity (Figure 13–15). Up to 20 different subtypes of GABAergic neurons have been identified in one subregion of the hippocampus alone. The different types of GABAergic interneurons form extensive synaptic connections with their neighboring excitatory and inhibitory neurons. Thus, even though only 20% of all neurons are inhibitory, the overall levels of inhibition and excitation tend to be nearly balanced in most brain regions. This results in the tuning of neural circuits to respond to only the most salient excitatory information. While the diversity of interneurons is challenging to understand, it is clear that different types of interneurons selectively target different regions of their postsynaptic neurons.

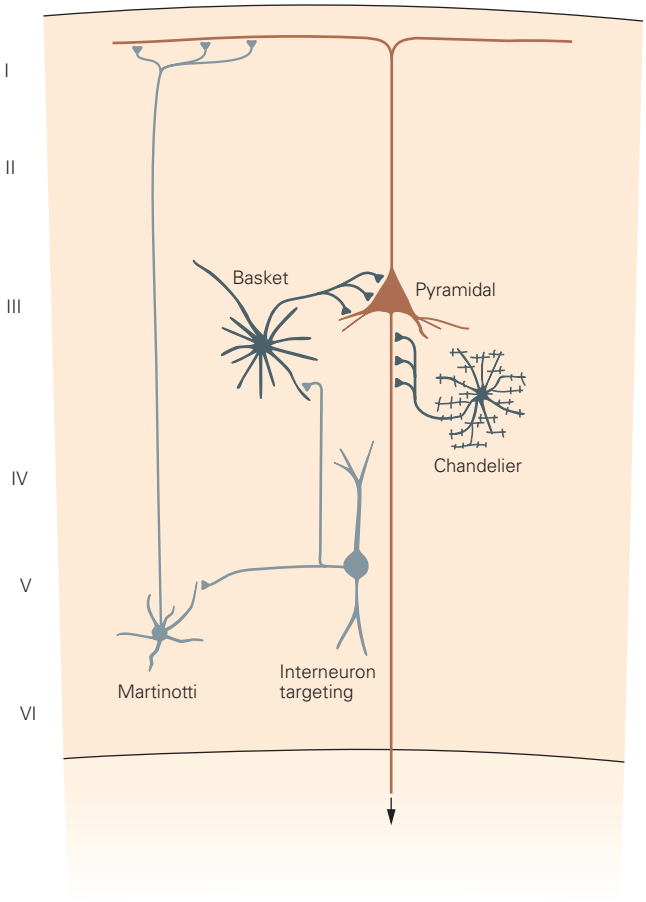

Figure 13–15 Different GABAergic inhibitory neurons target different regions of a postsynaptic cell. A diverse array of interneurons can be distinguished by their morphology, expression of different molecular markers, and their preferred site of targeting of postsynaptic neurons. *Basket cells* send their axons to form synapses on the cell body and proximal dendrites of postsynaptic neurons. The dendrites of the basket cells are shown as short lines radiating from the soma. *Axo-axonic cells*, also called *chandelier cells*, send their axons to form clusters of synapses along the axon initial segment of their targets. Both basket cells and chandelier cells express the calcium-binding protein parvalbumin. *Dendrite-targeting cells*, also called *Martinotti cells*, send their axons to form synapses on the distal dendrites of pyramidal cells. These cells also release the neuropeptide somatostatin. Other classes of GABAergic neurons selectively form synapses onto other inhibitory interneurons. These interneuron-targeting inhibitory neurons often release neuropeptide Y in addition to GABA.

This selective targeting is important because the location of inhibitory inputs in relation to excitatory synapses is critical in determining the effectiveness of inhibition (Figure 13–16). Inhibition of action potential output in response to excitatory input is more effective when inhibition is initiated at the cell body or near the axon trigger zone. The depolarization produced by an excitatory current from a dendrite must pass along the cell body membrane as it moves toward the axon. Inhibitory actions at the cell body or axon initial segment open Cl^- channels, thus increasing Cl^- conductance and reducing (by shunting) much of the depolarization produced by the spreading excitatory current. In addition, the size of the hyperpolarization at the cell body in response to an IPSP is largest when the inhibitory input targets the cell body, not a dendrite, owing to the attenuation of the dendritic IPSP by the cable properties of the dendrite.

Two classes of inhibitory neurons, basket cells and chandelier cells, exert strong control over neuronal output by specifically targeting the soma and axon initial segment, respectively (Figure 13–15). Basket cells often express the calcium-binding protein parvalbumin and are the most common type of inhibitory neuron in the brain. Chandelier cells, which also express parvalbumin, have axonal arbors with a branching pattern and clustering of synaptic terminals that resemble the numerous candles of a chandelier. Under some circumstances, the chandelier cells may paradoxically enhance neuronal firing because the Cl^- reversal potential in some axons can be positive to the threshold for action potential firing.

A third class of interneurons, the Martinotti cells, specifically targets distal dendrites and spines. These common interneurons release the neuropeptide somatostatin in addition to GABA. Inhibitory actions at a remote part of a dendrite act to decrease the local depolarization produced by a nearby excitatory input, with less of an effect on EPSPs generated on other dendritic branches. Somatostatin-positive interneurons activate slowly in response to an excitatory input and generate IPSPs that increase in size with repetitive activation (synaptic facilitation). In contrast, parvalbumin-expressing interneurons fire rapidly and generate

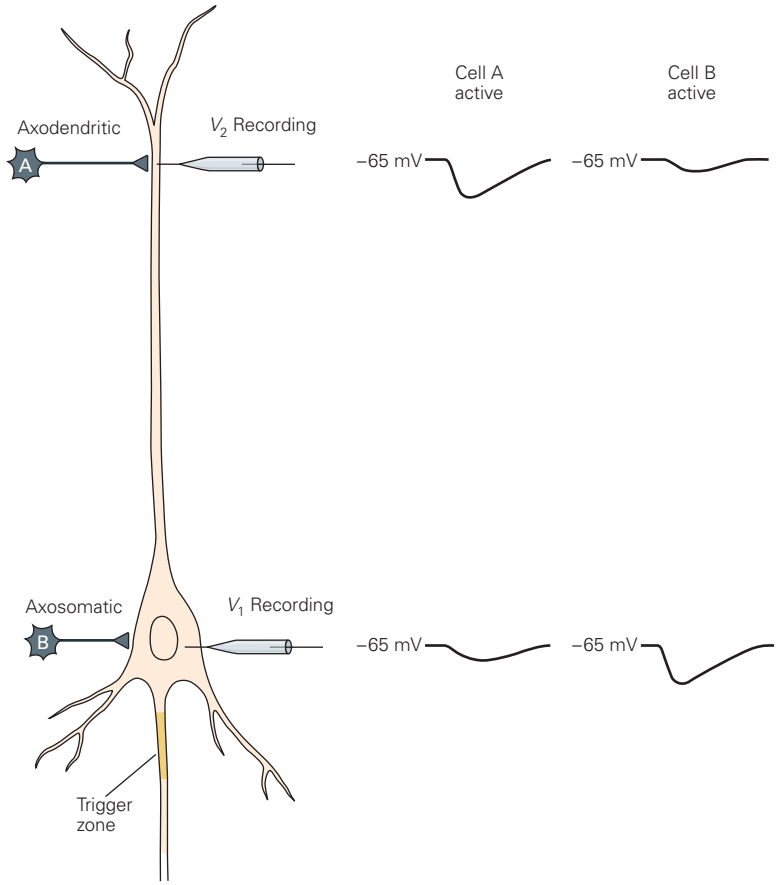

Figure 13–16 **The effect of an inhibitory current in the postsynaptic neuron depends on the distance the current travels from the synapse to the cell's trigger zone.** In this hypothetical experiment, the inputs from inhibitory axosomatic and axodendritic synapses are compared by recording from both the cell body (V_1) and a dendrite (V_2) of the postsynaptic cell. Stimulating cell B (the axosomatic synapse) produces a large IPSP in the cell body. The IPSP decays as it propagates up the dendrite, producing only a small hyperpolarization at the site of dendritic recording. Stimulating cell A activates an axodendritic synapse, producing a large local IPSP in the dendrite but only a small IPSP in the cell body, because the synaptic potential decays as it propagates down the dendrite. Thus, the axosomatic IPSP is more effective than the axodendritic IPSP in inhibiting action potential firing in the postsynaptic cell, whereas the axodendritic IPSP is more effective in preventing local dendritic depolarization.

IPSPs that decrease in size with repetitive activation (synaptic depression). These properties allow the somatostatin and parvalbumin interneurons to control the spread through neural circuits of later and earlier phases of neural signals, respectively.

A fourth major type of inhibitory interneuron expresses the neuropeptide vasoactive intestinal peptide (VIP). These interneurons selectively target other interneurons and thus serve to decrease the level of inhibition in a neural circuit, thereby enhancing overall excitation, a process termed disinhibition.

Dendrites Are Electrically Excitable Structures That Can Amplify Synaptic Input

Propagation of signals in dendrites was originally thought to be purely passive. However, intracellular recordings from the cell body of neurons in the 1950s and from dendrites beginning in the 1970s demonstrated that dendrites could produce action potentials. Indeed, we now know that the dendrites of most neurons contain voltage-gated Na^+, K^+, and Ca^{2+} channels in addition to ligand-gated channels and resting channels. In fact, the rich diversity of dendritic conductances suggests that central neurons rely on a sophisticated repertory of electrophysiological properties to integrate synaptic inputs.

One function of the voltage-gated Na^+ and Ca^{2+} channels in dendrites is to amplify the EPSP. In some neurons, there is a sufficient density of voltage-gated channels in the dendritic membrane to serve as a local trigger zone. This can produce nonlinear electrical responses that enhance the depolarization generated by excitatory inputs that arrive at remote parts of the dendrite. When a cell has several dendritic trigger zones, each one sums the local excitation and inhibition produced by nearby synaptic inputs; if the net input is above threshold, a dendritic action potential may be generated, usually by voltage-gated Na^+ or Ca^{2+} channels (Figure 13–17A). Nevertheless, the number of voltage-gated Na^+ or Ca^{2+} channels in the dendrites is usually not sufficient to support all-or-none regenerative propagation of an action potential to the cell body. Rather, action potentials generated in the dendrites are usually local events that spread electrotonically to the cell body and axon initial segment, producing a

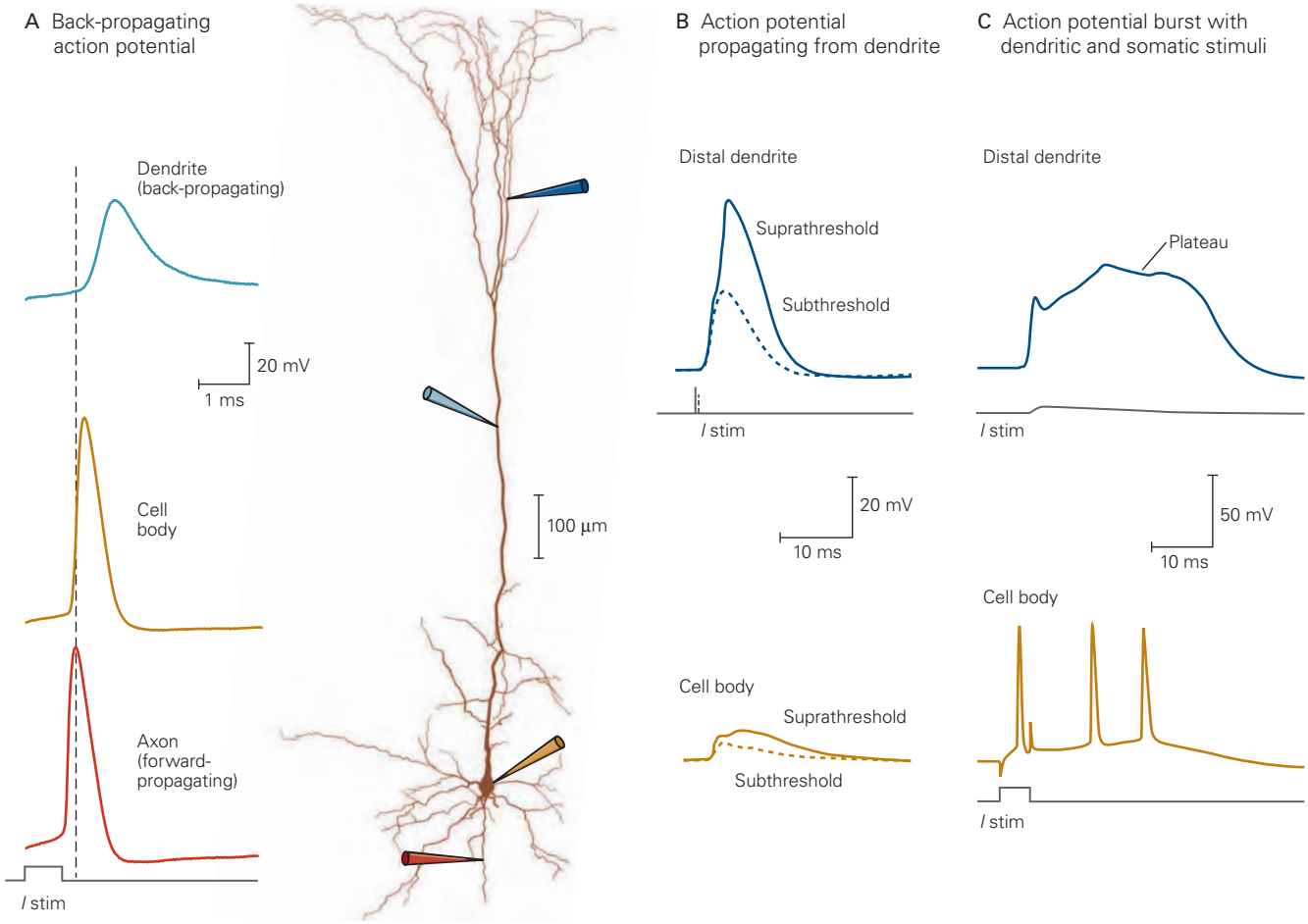

Figure 13–17 **Active properties of dendrites can amplify synaptic inputs and support propagation of electrical signals to and from the axon initial segment.** The figure illustrates an experiment in which several electrodes are used to record membrane voltage and pass stimulating current in the axon, cell body, and at several locations along the dendritic tree. The recording electrodes and corresponding voltage traces are matched by color. Stimulating current pulses are also indicated (***I* stim**). (Panels A and B adapted from Stuart et al. 2016.)

A. An action potential initiated in the axon initial segment can propagate to the dendrites. Such backpropagation depends on activation of voltage-gated Na^+ channels in the dendrites. Unlike the nondecrementing action potential that is continually regenerated along an axon, the amplitude of a back-propagating action potential decreases as it travels along a dendrite due to its relatively low density of voltage-gated Na^+ channels.

B. A strong depolarizing EPSP at a dendrite can generate a dendritic action potential that travels to the cell body. Such action potentials are often generated by dendritic voltage-gated Ca^{2+} channels and have a high threshold. They propagate relatively slowly and attenuate with distance, often failing to reach the cell body. The **solid blue line** shows a suprathreshold response generated in the dendrite in response to a large depolarizing current pulse, and the **dotted blue line** shows a subthreshold response to a weaker current stimulus. The **solid and dotted orange lines** show the corresponding voltage responses recorded in the cell body.

C. Near simultaneous injection of a subthreshold stimulating current resembling a weak EPSC into the dendrite and a strong brief suprathreshold stimulating current into the cell body (which by itself evokes a single somatic action potential) triggers a long-lasting plateau potential in the dendrite and the firing of a burst of action potentials in the cell body. (Adapted, with permission from Larkum et al. 1999. Copyright © 1999 Springer Nature.)

subthreshold somatic depolarization that is integrated with other input signals in the cell.

Dendritic voltage-gated channels also permit action potentials generated at the axon initial segment to propagate backward into the dendritic tree (Figure 13–17B). These *backpropagating* action potentials are largely generated by dendritic voltage-gated Na^+ channels. Although the precise role of these action

potentials is unclear, they may provide a temporally precise mechanism for enhancing current through NMDA receptor-channels by providing the depolarization necessary to remove the Mg^{2+} block, thereby contributing to the induction of synaptic plasticity (Figure 13–10).

NMDA receptors are able to mediate another type of nonlinear integration in dendrites as a result of their voltage dependence. Moderate synaptic stimuli are able to activate a sufficient number of AMPA receptors to produce an intermediate level of depolarization that is able to lead to expulsion of Mg^{2+} from a fraction of NMDA receptors. As these receptors begin to conduct cations into the postsynaptic dendrite, they produce a further depolarization that leads to even greater unblocking of Mg^{2+}, increasing further the size of the NMDA receptor EPSC, resulting in even greater depolarization. In some instances, this leads to a local regenerative depolarization, referred to as an NMDA spike. Such NMDA spikes are purely local events—they cannot propagate actively in the absence of synaptic stimulation because they require glutamate release. NMDA spikes have been implicated in different forms of synaptic plasticity and in the enhancement of dendritic integration of synaptic inputs.

Under what conditions do active conductances influence dendritic integration? There is now evidence that dendrites may switch between passive and active integration depending on the precise timing and strength of synaptic inputs. One interesting example of such a switch is the way some cortical neurons respond to inputs arriving at their distal and proximal dendrites. In many neurons, inputs from relatively nearby neurons arrive at more proximal regions of the dendrites, closer to the cell body. Inputs from more distant brain areas arrive at the distal tips of dendrites. Although excitatory synaptic inputs to the distal dendrites usually produce only a very small depolarizing response at the soma, due to electronic decay along the dendritic cable, these inputs can significantly enhance spike firing when paired with excitatory inputs to more proximal regions of the dendrites. Thus, a single strong EPSP at a proximal site (or a single brief somatic current pulse) normally produces a single action potential at the axon initial segment, which can then backpropagate into the dendrites. However, when a distal stimulus is paired with a proximal stimulus, the backpropagating spike summates with the distal EPSP to trigger a long-lasting type of dendritic spike called a plateau potential, which depends on activation of voltage-gated Ca^{2+} channels and NMDA receptors. When the plateau potential arrives at the cell body, it can trigger a brief burst of three or more spikes at rates as high as 100 Hz (Figure 13–17C). These spike bursts are thought to provide a very potent means of inducing long-term synaptic plasticity and releasing transmitter as the burst propagates to the presynaptic terminal.

A more localized form of synaptic integration occurs in dendritic spines. Even though some excitatory inputs occur on dendritic shafts, close to 95% of all excitatory inputs in the brain terminate on spines, surprisingly avoiding dendritic shafts (see Figure 13–2). Although the function of spines is not completely understood, their thin necks provide a barrier to diffusion of various signaling molecules from the spine head to the dendritic shaft. As a result, a relatively small Ca^{2+} current through the NMDA receptors can lead to a relatively large increase in $[Ca^{2+}]$ that is localized to the head of the individual spine that is synaptically activated (Figure 13–18A). Moreover, because action potentials can backpropagate from the cell body to the dendrites, spines also serve as sites at which information about presynaptic and postsynaptic activity is integrated.

Indeed, when a backpropagating action potential is paired with presynaptic stimulation, the spine Ca^{2+} signal is greater than the linear sum of the individual Ca^{2+} signals from synaptic stimulation alone or action potential stimulation alone. This "supralinearity" is specific to the activated spine and occurs because depolarization during the action potential causes Mg^{2+} to be expelled from the NMDA receptor-channel, allowing it to conduct Ca^{2+} into the spine. The resultant Ca^{2+} accumulation thus provides, at an individual synapse, a biochemical detector of the near simultaneity of the input (EPSP) and output (backpropagating action potential), which is thought to be a key requirement of memory storage (Chapter 54).

Because the thin spine neck restricts, at least partly, the rise in Ca^{2+} and, thus, long-term plasticity to the spine that receives the synaptic input, spines also ensure that activity-dependent changes in synaptic function, and thus memory storage, are restricted to the synapses that are activated. The ability of spines to implement such synapse-specific local learning rules may be of fundamental importance for the ability of neural networks to store meaningful information (Chapter 54). Finally, in some spines, local synaptic potentials are filtered as they propagate through the spine neck and enter the dendrite, such that the size of the EPSP at the cell body is reduced. The regulation of this electrical filtering could provide another means of controlling the efficacy with which a given synaptic conductance is able to excite the cell body.

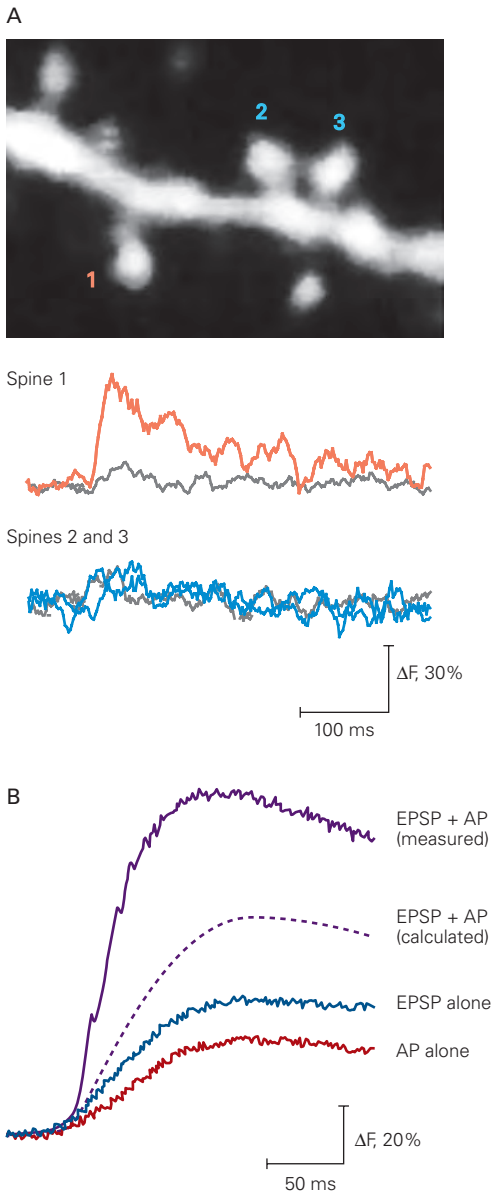

Figure 13–18 Dendritic spines compartmentalize calcium influx through NMDA receptors.

A. This fluorescence image of a hippocampal CA1 pyramidal neuron filled with a calcium-sensitive dye shows the outline of a dendritic shaft with several spines. When the dye binds Ca^{2+}, its fluorescence intensity increases. The traces plot fluorescence intensity over the time following the extracellular stimulation of the presynaptic axon. Spine 1 shows a large, rapid increase in fluorescence (**ΔF**) in response to synaptic stimulation (**red trace**), reflecting Ca^{2+} influx through the NMDA receptors. In contrast, there is little change in the fluorescence intensity in the neighboring dendrite shaft (**gray trace**), showing that Ca^{2+} accumulation is restricted to the head of the spine. Spines 2 and 3 show little increase in fluorescence in response to synaptic stimulation because their presynaptic axons were not activated. (Reproduced, with permission, from Lang et al. 2004. Copyright © 2004 National Academy of Sciences.)

B. Calcium accumulation is greatest in spines when synaptic stimulation is paired with postsynaptic action potentials. The Ca^{2+} signal generated when an EPSP and a backpropagating action potential are evoked at the same time is greater than the expected sum of the individual Ca^{2+} signals when either an EPSP or a backpropagating action potential (**AP**) alone is evoked. (Adapted, with permission, from Yuste and Denk 1995.)

Highlights

1. A typical central neuron integrates a large number of excitatory and inhibitory synaptic inputs. The amino acid transmitter glutamate is responsible for most excitatory synaptic actions in the central nervous system, with the inhibitory amino acids GABA and glycine mediating inhibitory synaptic actions.
2. Glutamate activates families of ionotropic and metabotropic receptors. The three major classes of ionotropic glutamate receptors—AMPA, NMDA, and kainate—are named for the chemical agonists that activate them.
3. The ionotropic glutamate receptors are tetramers composed of subunits encoded by homologous genes. Each subunit has a large extracellular amino terminus, with three membrane-spanning segments and a large cytoplasmic tail. A pore-forming loop dips into and out of the membrane between the first and second transmembrane segments.
4. Binding of glutamate to all three ionotropic receptors opens a nonselective cation channel equally permeable to Na^+ and K^+. The NMDA receptor-channel also has a high permeability to Ca^{2+}.
5. The NMDA receptor acts as a coincidence detector. It is normally blocked by extracellular Mg^{2+}

lodged in its pore; it only conducts when glutamate is released *and* the postsynaptic membrane is sufficiently depolarized to expel the Mg^{2+} ion by electrostatic repulsion.

6. Calcium influx through the NMDA receptor during strong synaptic activation can trigger intracellular signaling cascades, leading to long-term synaptic plasticity, which can potentiate synaptic transmission for a period of hours to days, providing a potential mechanism for memory storage.
7. Inhibitory synaptic actions in the brain are mediated by the binding of GABA to both ionotropic ($GABA_A$) and metabotropic ($GABA_B$) receptors. The $GABA_A$ receptors are pentamers, whose subunits are homologous to those of the nicotinic ACh receptors. Glycine ionotropic receptors are structurally similar to $GABA_A$ receptors and are largely confined to inhibitory synapses in the spinal cord.
8. Binding of GABA or glycine to its receptor activates a Cl^- selective channel. In most cells, the Cl^- equilibrium potential is slightly negative to the resting potential. As a result, inhibitory synaptic actions hyperpolarize the cell membrane away from threshold for firing an action potential.
9. The decision as to whether a neuron fires an action potential depends on spatial and temporal summation of the various excitatory and inhibitory inputs and is determined by the size of the resulting depolarization at the axon initial segment, the region of the neuron with the lowest threshold.
10. Dendrites also have voltage-gated channels, enabling them to fire local action potentials in some circumstances. This can amplify the size of the local EPSP to produce a larger depolarization at the cell body.

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