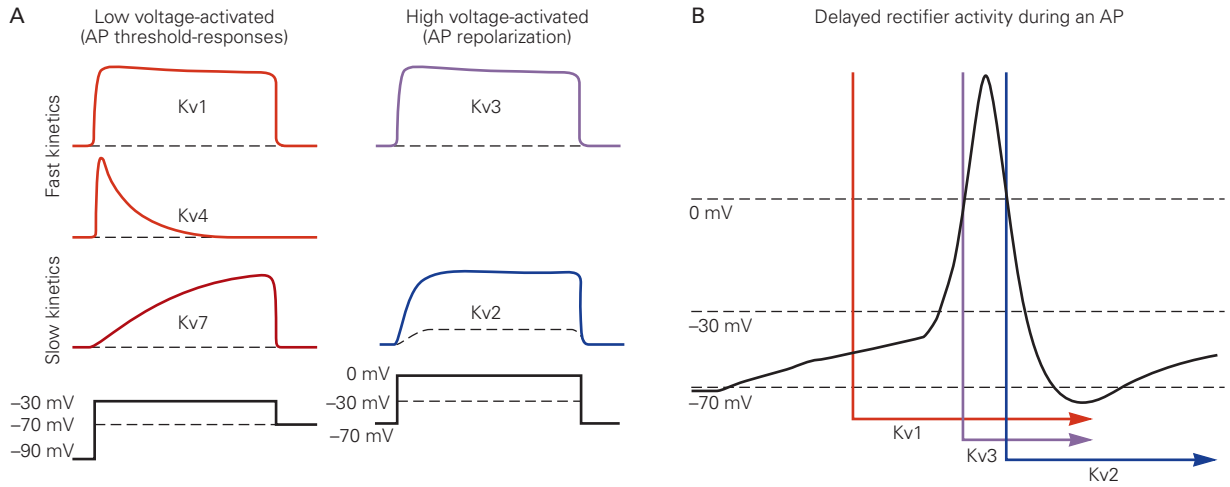

Figure 10–13 Different voltage dependence and kinetics of major classes of mammalian voltage-activated potassium channels.

A. Simplified generalization of the voltage dependence and kinetics of the major voltage-gated K^+ families. Because Kv1, Kv4, and Kv7 channels can be activated by relatively small depolarizations, they often help control action potential (AP) threshold. Kv2 and Kv3 channels require larger depolarizations to be activated. Kv1, Kv3, and Kv4 channels are activated relatively rapidly, whereas Kv7 and Kv2 channels are activated more slowly.

B. Simplified generalization of the differing activation times of the major components of delayed rectifier K^+ channels during an action potential. Kv1 channels require small depolarizations and are activated rapidly, sometimes significantly in advance of the action potential. Kv3 channels require large depolarizations and are activated late in the rising phase of the action potential and deactivated very rapidly thereafter. Kv2 channels are activated relatively slowly during the falling phase of the action potential and remain open during the afterhyperpolarization. (Adapted, with permission, from Johnston et al. 2010.)

A-type current is formed primarily by Kv4 family α-subunits, which form channels that inactivate over a range of time scales from a few milliseconds to tens of milliseconds. Kv1 channels that include Kv1.4 subunits or the auxiliary subunit Kvβ1 also mediate an inactivating component of current, which is highly expressed in some nerve terminals as well as some cell bodies.

As is the case for Na^+ channels and Cav3 family channels, A-type K^+ current not only inactivates during large depolarizations but is also subject to steady-state inactivation by small depolarizations from rest, providing a mechanism by which its amplitude can be modulated by small voltage changes around resting potential (see Figure 10–15B).

Kv7 subunits form non-inactivating channels that require only small depolarizations from rest to be activated and can even be activated significantly at the resting potential. In some neurons, Kv7 channels are downregulated by the transmitter acetylcholine acting through muscarinic G protein–coupled receptors (thus the origin of an alternative name of "M-current"). Kv7 channels typically activate relatively slowly, over tens of milliseconds, and provide little current during a single action potential but tend to suppress firing of subsequent action potentials (Chapter 14).

The KCNH gene family consists of three subfamilies of voltage-gated K^+ channels (Kv10, Kv11, and Kv12), which are also expressed in the brain. They influence resting potential, action potential threshold, and frequency and pattern of firing.

Voltage-Gated Hyperpolarization-Activated Cyclic Nucleotide-Gated Channels

Many neurons have cation channels that are slowly activated by hyperpolarization. This sensitivity to hyperpolarization is enhanced when intracellular cyclic nucleotides bind to the channel. Because these hyperpolarization-activated cyclic nucleotide-gated (HCN) channels have only two of the four negative binding sites found in the selectivity filter of K^+ channels, they are permeable to both K^+ and Na^+ and have a reversal potential around –40 to –30 mV. As a result, hyperpolarization from rest, as during strong synaptic inhibition or following an action potential, opens the channels to generate an inward depolarizing current referred to as I_h (see Figure 10–15D).

Gating of Ion Channels Can Be Controlled by Cytoplasmic Calcium

In a typical neuron, the opening and closing of certain ion channels can be modulated by various cytoplasmic factors, thus affording the neuron's excitability

properties greater flexibility. Changes in the levels of such cytoplasmic factors can result from the activity of the neuron itself or from the influences of other neurons (Chapters 14 and 15).

Intracellular Ca^{2+} concentration is one important factor that modulates ion channel activity. Although ionic currents through membrane channels during an action potential generally do not result in appreciable changes in the intracellular concentrations of most ion species, calcium is a notable exception to this rule. The concentration of free Ca^{2+} in the cytoplasm of a resting cell is extremely low, about 10^{-7} M, several orders of magnitude below the external Ca^{2+} concentration, which is approximately 2 mM. Thus, intracellular Ca^{2+} concentration may increase many-fold above its resting value as a result of voltage-gated Ca^{2+} influx.

Intracellular Ca^{2+} concentration controls the gating of a number of channels. Several kinds of channels are activated by increases in intracellular Ca^{2+}. For example, the Ca^{2+}-activated *BK channels* (named for their big single-channel conductance), which are widely expressed in neurons, are voltage-dependent K^+ channels that require a very large, nonphysiological depolarization to open in the absence of Ca^{2+}. The binding of Ca^{2+} to a site on the cytoplasmic surface of the channel shifts its voltage gating to allow the channel to open at more negative potentials. With the influx of Ca^{2+} during an action potential, BK channels can open and help repolarize the action potential. Another family of calcium-activated K^+ channels, the *SK channels* (named for their small single-channel conductance), are not voltage dependent but open only in response to increases in intracellular Ca^{2+}. SK channels can open in response to relatively small changes in intracellular Ca^{2+} but gate slowly, so their activation gradually builds up as more Ca^{2+} enters the cell during repeated action potential firing. Some Ca^{2+} channels are themselves sensitive to levels of intracellular Ca^{2+}, becoming inactivated when intracellular Ca^{2+} increases as a result of entry through the channel itself.

As is described in later chapters, changes in the intracellular concentration of Ca^{2+} can also influence a variety of cellular metabolic processes, as well as neurotransmitter release and gene expression.

Excitability Properties Vary Between Types of Neurons

Through the expression of a distinct complement of ion channels, the electrical properties of different neuronal types have evolved to match the dynamic demands of information processing. Thus, the function of a neuron is defined not only by its synaptic inputs and outputs but also by its intrinsic excitability properties.

Different types of neurons in the mammalian nervous system generate action potentials that have different shapes and fire in different characteristic patterns, reflecting different expression of voltage-gated channels. For example, cerebellar Purkinje neurons and GABAergic cortical interneurons are associated with high levels of expression of Kv3 channels. The rapid activation of these channels produces narrow action potentials. In dopaminergic and other monoaminergic neurons, there is a high level of expression of voltage-activated Ca^{2+} channels that open during the falling phase of the action potential. The inward Ca^{2+} current from these channels slows repolarization, resulting in broader action potentials.

In the squid axon, the action potential is followed by an *afterhyperpolarization* (see Figure 10–7). In some mammalian neurons, the afterhyperpolarization has slow components lasting tens or even hundreds of milliseconds, generated by calcium-activated K^+ channels or voltage-activated K^+ channels with slow deactivation kinetics. Slow afterhyperpolarizations mediated by SK channels can be enhanced by repeated action potentials, reflecting buildup in intracellular Ca^{2+} concentrations.

In many pyramidal neurons in the cortex and hippocampus, the action potential is followed by an *afterdepolarization*, a transient depolarization that sometimes follows an earlier faster afterhyperpolarization. If the afterdepolarization is large enough, it can trigger a second action potential, resulting in all-or-none burst firing. The afterdepolarization can be caused by a variety of ionic currents, including Na^+ and Ca^{2+} currents from a number of voltage-dependent channels.

The shape of the action potential in a neuron is not always invariant. In some cases it can be dynamically regulated either intrinsically (eg, by repetitive firing) or extrinsically (eg, by synaptic modulation) (Chapter 15).

The pattern of action potential firing evoked by depolarization varies widely between neurons. The input-output function of a neuron can be characterized by the frequency and pattern of action potential firing in response to a series of current injections of different magnitudes. In the mammalian cerebral cortex, glutamatergic pyramidal neurons typically fire rapidly at the beginning of the current pulse followed by progressive slowing of firing, a pattern known as *adaptation* (Figure 10–14A). In contrast, many GABAergic interneurons fire with very little change in frequency (Figure 10–14B). Other neurons have more complex firing patterns. Some pyramidal neurons in the cerebral cortex tend to fire with an initial burst of action potentials (Figure 10–14C); "chattering" cells respond with repetitive brief bursts of high-frequency firing (Figure 10–14D).

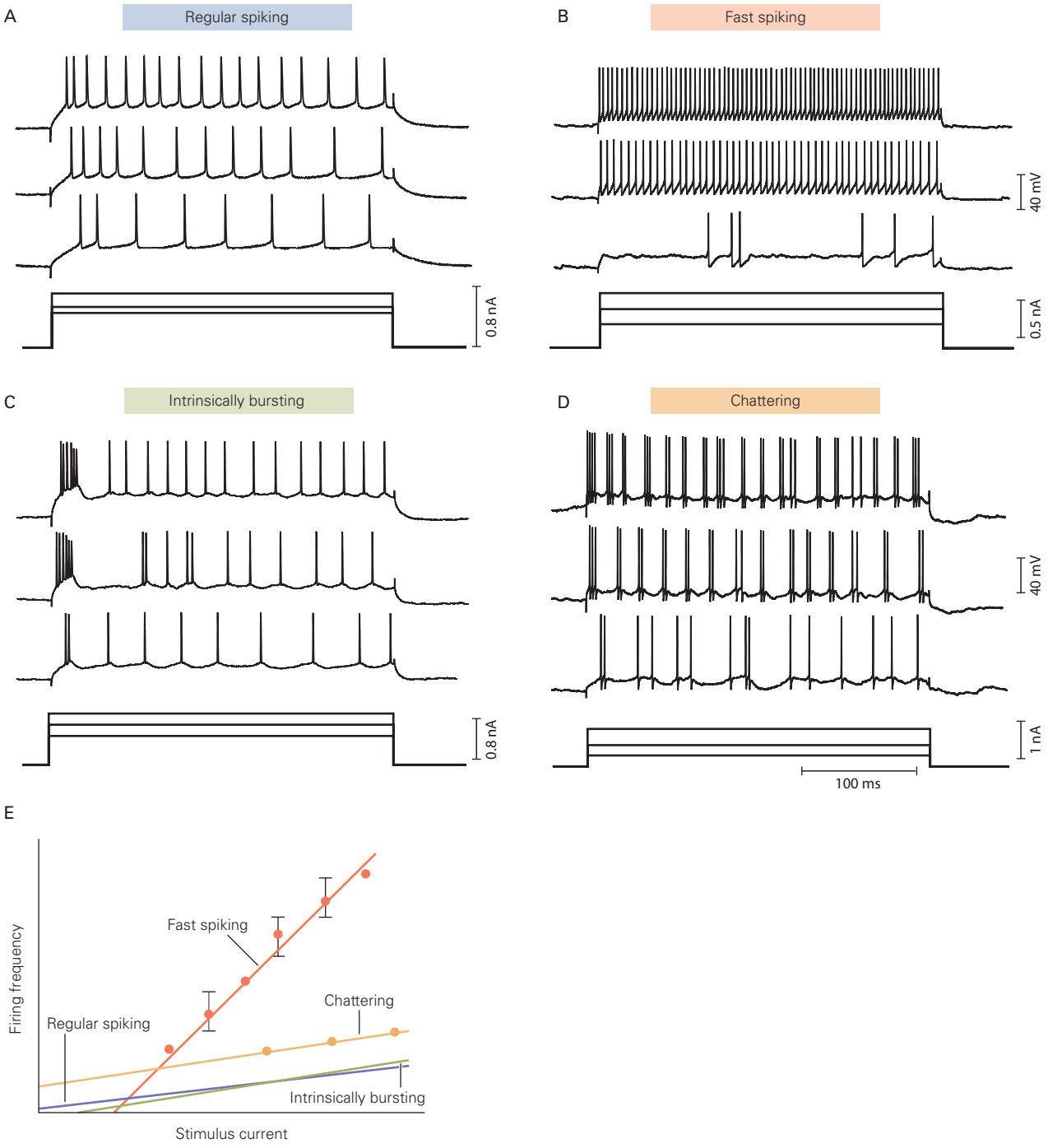

Figure 10–14 Different firing patterns in four types of cortical neurons. Three steps of depolarizing current, each of different amplitude, were injected into each cell to evoke firing. (Adapted, with permission, from Nowak et al. 2003.)

A. A cortical neuron with a firing pattern typical of many glutamatergic cortical pyramidal neurons, illustrating characteristic adaptation.

B. A firing pattern typical of many GABAergic interneurons, illustrating maintained high-frequency repetitive firing.

C. Firing in an intrinsically bursting neuron, a subtype of pyramidal neuron in cortical layer II/III.

D. Firing in a chattering cell, a subtype of pyramidal neuron in cortical layer V.

E. Firing frequency versus stimulus current for these four cell types, showing their different sensitivities to increasing stimulus strength.

The sensitivity of these four classes of neurons to excitatory input can also be characterized by their frequency–current relationships. The fast spiking neurons are the most sensitive to increases in depolarizing excitatory current.

Some neurons can sustain repetitive firing at high frequencies up to 500 Hz. Such *fast-spiking* neurons occur throughout the mammalian central nervous system, including many principal neurons in the auditory system, where neurons must respond to sound waves of very high frequencies. The ability to fire repetitively at high frequencies is correlated with high expression levels of Kv3 family channels, which produce rapid repolarization and close extremely rapidly following repolarization, resulting in a minimal afterhyperpolarization and a brief refractory period.

The different firing patterns of neurons can be understood in terms of the expression and gating properties of particular channels. For example, adaptation of firing frequency during a maintained current pulse can be produced by activation of particular Kv1 family channels, which are strongly activated following an action potential and thus impede firing of a subsequent spike (Figure 10–15A). Because many channels are controlled by a process of inactivation that regulates their availability for activation, synaptic inputs that produce small voltage changes around the resting potential can greatly modify the cell's excitability. For example, in some neurons, a steady hyperpolarizing synaptic input makes the cell less excitable by reducing the extent of inactivation of the A-type K^+ channels at the normal resting potential of the cell (Figure 10–15B). In other neurons, such a steady hyperpolarization makes the cell *more* excitable because it reduces the inactivation of Cav3 voltage-gated Ca^{2+} channels (Figure 10–15C).

A surprisingly large number of neurons in the mammalian brain fire spontaneously in the absence of any synaptic input. When such activity is regular and rhythmic, it is often referred to as "pacemaking," by analogy to the rhythmic spontaneous firing of the cardiac pacemaker in the sinoatrial node of the heart. Many neurons that release modulatory neurotransmitters, such as dopamine, serotonin, norepinephrine, and acetylcholine, fire spontaneously, typically at frequencies of 0.5 to 5 Hz, resulting in constant tonic release of transmitter in the target areas of the neuron.

One mechanism causing spontaneous firing is exemplified by neurons in the suprachiasmatic nucleus of the hypothalamus, which helps control the circadian rhythm of overall metabolism and the sleep–wake cycle. These neurons fire spontaneously, with faster firing during the daytime than the nighttime (Chapter 44). Pacemaking in these cells is driven in part by subthreshold *persistent Na^+ current*, a small voltage-dependent current which flows through Na^+ channels at voltages as negative as –70 mV. This current can slowly depolarize the neuron to the point where a fast action potential fires (Figure 10–15E). In the same neurons, there are non–voltage-dependent channels that conduct Na^+ "leak" current, which depolarizes the cells into the voltage range where voltage-dependent persistent Na^+ current is activated. The higher expression level in the cell membrane of such Na^+ leakage channels during the daytime leads to the day–night difference in firing rate.

In dopaminergic neurons of the substantia nigra, pacemaking is unusual in being driven partly by voltage-dependent Ca^{2+} currents. The continual entry of Ca^{2+} during the lifetime of the neurons may contribute to metabolic stress associated with death of these neurons in Parkinson disease (Chapter 63).

Excitability Properties Vary Between Regions of the Neuron

Different regions of a neuron have different types of ion channels that support the specialized functions of each region. The axon, for example, functions as a relatively simple relay line. In contrast, the input, integrative, and output regions of a neuron typically perform more complex processing of the information they receive before passing it along (Chapter 3).

The trigger zone at the axon initial segment has the lowest threshold for action potential generation, in part because it has an exceptionally high density of voltage-gated Na^+ channels. In addition, it typically has voltage-gated ion channels that are sensitive to relatively small deviations from the resting potential. These channels thus play a critical role in transforming graded synaptic or receptor potentials into a train of all-or-none action potentials. Channels highly expressed at the axon initial segment of many neurons include Nav1.6, Kv1, Kv7, and low voltage-activated T-type Ca^{2+} channels.

Dendrites in many types of neurons have voltage-gated ion channels, including Ca^{2+}, K^+, HCN, and Na^+ channels (Chapter 13). When activated, these channels help shape the amplitude, time course, and propagation of the synaptic potentials to the cell body. In some neurons, the density of voltage-gated channels in the dendrites is sufficient to support local action potentials, typically with relatively high threshold voltages.

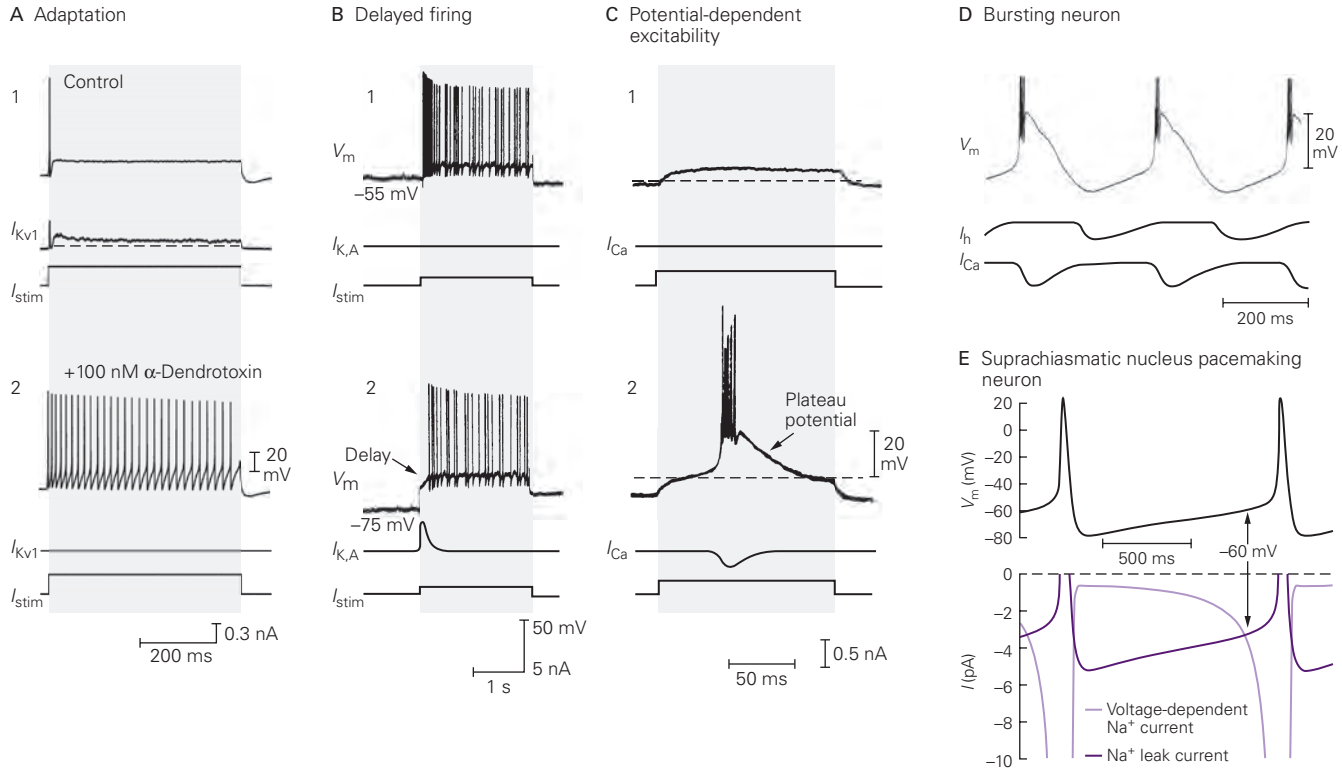

Figure 10–15 Regulation of firing pattern by a variety of voltage-gated channels.

A. Activation of Kv1 channels normally prevents firing of a second action potential by increasing spike threshold in a mouse dorsal root ganglion neuron (**1**). Blocking Kv1 channels with the snake toxin α-dendrotoxin changes the firing pattern from strong adaptation to maintained repetitive firing in response to a steady stimulating current (I_{stim}) (**2**). (Data from Pin Liu.)

B. Injection of a depolarizing current pulse (I_{stim}) into a neuron in the nucleus tractus solitarius normally triggers an immediate train of action potentials (**1**). If the cell is first held at a hyperpolarized membrane potential, the spike train is delayed (**2**). The delay is caused when A-type K^+ channels are activated by the depolarizing current pulse. The channels generate a transient outward K^+ current, $I_{K,A}$, that briefly slows the approach of V_m to threshold. These channels typically are inactivated at the resting potential (–55 mV), but steady hyperpolarization removes the inactivation. (Adapted with permission, from Dekin and Getting 1987.)

C. A small depolarizing current pulse injected into a thalamic neuron at rest generates a subthreshold depolarization (**1**). If the membrane potential is held at a hyperpolarized level, the same current pulse triggers a burst of action potentials (**2**). The effectiveness of the current pulse is enhanced because the hyperpolarization causes a type of voltage-gated Ca^{2+} channel to recover from inactivation. Depolarizing inward current through these Ca^{2+} channels (I_{Ca}) generates a plateau potential of about 20 mV that triggers a burst of action potentials. The **dashed line** indicates the level of the normal resting potential. (Adapted with permission, from Llinás and Jahnsen 1982.)

The data in parts **B** and **C** demonstrate that steady hyperpolarization, such as might be produced by inhibitory synaptic input to a neuron, can profoundly affect the spike train pattern of a neuron. This effect varies greatly among cell types and depends on the presence or absence of particular types of voltage-gated Ca^{2+} and K^+ channels.

D. In the absence of synaptic input, thalamocortical relay neurons can fire spontaneously in brief bursts of action potentials. These bursts are produced by current through two types of voltage-gated ion channels. The gradual depolarization that leads to a burst is driven by inward current (I_h) through HCN channels, which open in response to hyperpolarization. The burst is triggered by an inward Ca^{2+} current through voltage-gated Cav3 channels, which are activated at relatively low levels of depolarization. This Ca^{2+} influx generates sufficient depolarization to reach threshold and drive a brief burst of Na^+-dependent action potentials. The strong depolarization during the burst causes the HCN channels to close and inactivates the Ca^{2+} channels, allowing hyperpolarization to develop between bursts of firing. This hyperpolarization then opens the HCN channels, initiating the next cycle in the rhythm. (Adapted, with permission, from McCormick and Huguenard 1992.)

E. Neurons from the suprachiasmatic nucleus of the hypothalamus generate spontaneous pacemaker potentials. Following an action potential, the neuron spontaneously depolarizes, first slowly and then more rapidly, resulting in another action potential. The depolarization is driven by two inward Na^+ currents during the interspike interval. One is "persistent Na^+ current," which flows through voltage-dependent sodium channels sensitive to block by tetrodotoxin, probably the same population of channels that underlie the much larger sodium current during the upstroke of the action potential. The second current flows through non–voltage-activated sodium leak nonselective (*NALCN*) channels, which provide a steady conductance pathway for Na^+ and K^+ ions. At negative voltages, Na^+ driving force is large and K^+ driving force is small, so the leak current is carried predominantly by Na^+ ions. This inward current depolarizes the neuron to the point at which voltage-dependent persistent Na^+ current becomes dominant (around –60 mV). (Adapted, with permission, from Jackson et al. 2004. Copyright © 2004 Society for Neuroscience.)

With moderate synaptic stimulation, full-blown action potentials are first generated at the trigger zone at the initial segment of the axon and then propagate back into the dendrites, serving as a signal to the synaptic regions that the cell has fired.

Conduction of the action potential down the axon is mediated primarily by voltage-gated Na^+ and K^+ channels that function much like those in the squid axon. In myelinated axons, the nodes of Ranvier have a high density of Na^+ channels but a low density of voltage-activated K^+ channels. There is a higher density of voltage-activated K^+ channels under the myelin sheath near the two ends of each internodal segment. The normal function of these K^+ channels is to suppress generation of action potentials in portions of the axon membrane under the myelin sheath. In demyelinating diseases, these channels become exposed and thus may inhibit the ability of the bare axon to conduct action potentials (Chapters 9 and 57).

Presynaptic nerve terminals at chemical synapses have a high density of voltage-gated Ca^{2+} channels, most commonly Cav2.1 (P/Q-type) channels, Cav2.2 (N-type) channels, or a mixture of the two. Arrival of an action potential in the terminal opens these channels, causing an influx of Ca^{2+} that triggers transmitter release (Chapter 15).

Neuronal Excitability Is Plastic

The expression, localization, and functional state of voltage-gated ion channels controlling the rate and pattern of action potential firing in a particular neuron are not always fixed, but can change in response to changes in the neuron's synaptic input, its activity, or its environment, as well as in response to injury or disease. For example, synaptic input that causes channel phosphorylation via second messenger pathways can lead to transient changes in a channel's functional properties, which in turn modulate cell excitability (Chapter 14). Plasticity can also occur on a longer time scale, such as when increased activity of a neuronal network as a whole leads to decreased excitability of individual neurons—a homeostatic feedback system. In some cases, activity-induced structural changes, such as change in length of the axon initial segment or its migration relative to the soma, can also affect excitability. The molecular mechanisms of homeostatic changes in neuronal excitability are not well understood but likely involve intracellular calcium signaling pathways that control transcription or cellular trafficking of specific ion channels. Dysfunction of such regulatory pathways may underlie some types of epilepsy and hyperexcitability associated with conditions such as neuropathic pain.

Highlights

1. An action potential is a transient depolarization of membrane voltage lasting about 1 ms that is produced when ions move across the cell membrane through voltage-gated channels and thereby change the charge separation across the membrane.
2. The depolarizing phase of the action potential results from rapid, regenerative opening of voltage-activated Na^+ channels. Repolarization is due to inactivation of Na^+ channels and activation of K^+ channels.
3. The sharp threshold for action potential generation occurs at a voltage at which inward Na^+ channel current just exceeds outward currents through leak channels and voltage-gated K^+ channels.
4. The refractory period reflects Na^+ channel inactivation and K^+ channel activation continuing after the action potential. The refractory period limits the action potential firing rate.
5. The conformational changes of channel proteins underlying voltage-dependent activation and inactivation are not yet completely understood, but key regions involved in channel gating have been identified.
6. Voltage-gated sodium channels select for sodium on the basis of size, charge, and energy of hydration of the ion.
7. Most neurons express multiple kinds of voltage-gated Na^+, Ca^{2+}, K^+, HCN, and Cl^- channels, with especially large diversity in the properties of K^+ channels.
8. The diversity of voltage-dependent channels reflects the expression of multiple genes, formation of heteromeric channels from multiple gene products, alternative splicing of gene transcripts, mRNA editing, and combination of pore-forming subunits with a variety of accessory proteins.
9. Activity of some voltage-gated ion channels can be modulated by cytoplasmic Ca^{2+}.
10. The diversity in expression of voltage-gated ion channels results in differences in excitability properties of different types of neurons and in different regions of the same neuron.
11. The regional expression and functional state of ion channels can be regulated in response to cell

activity, changes in cell environment, or pathological processes, resulting in plasticity of the intrinsic excitability of neurons.

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