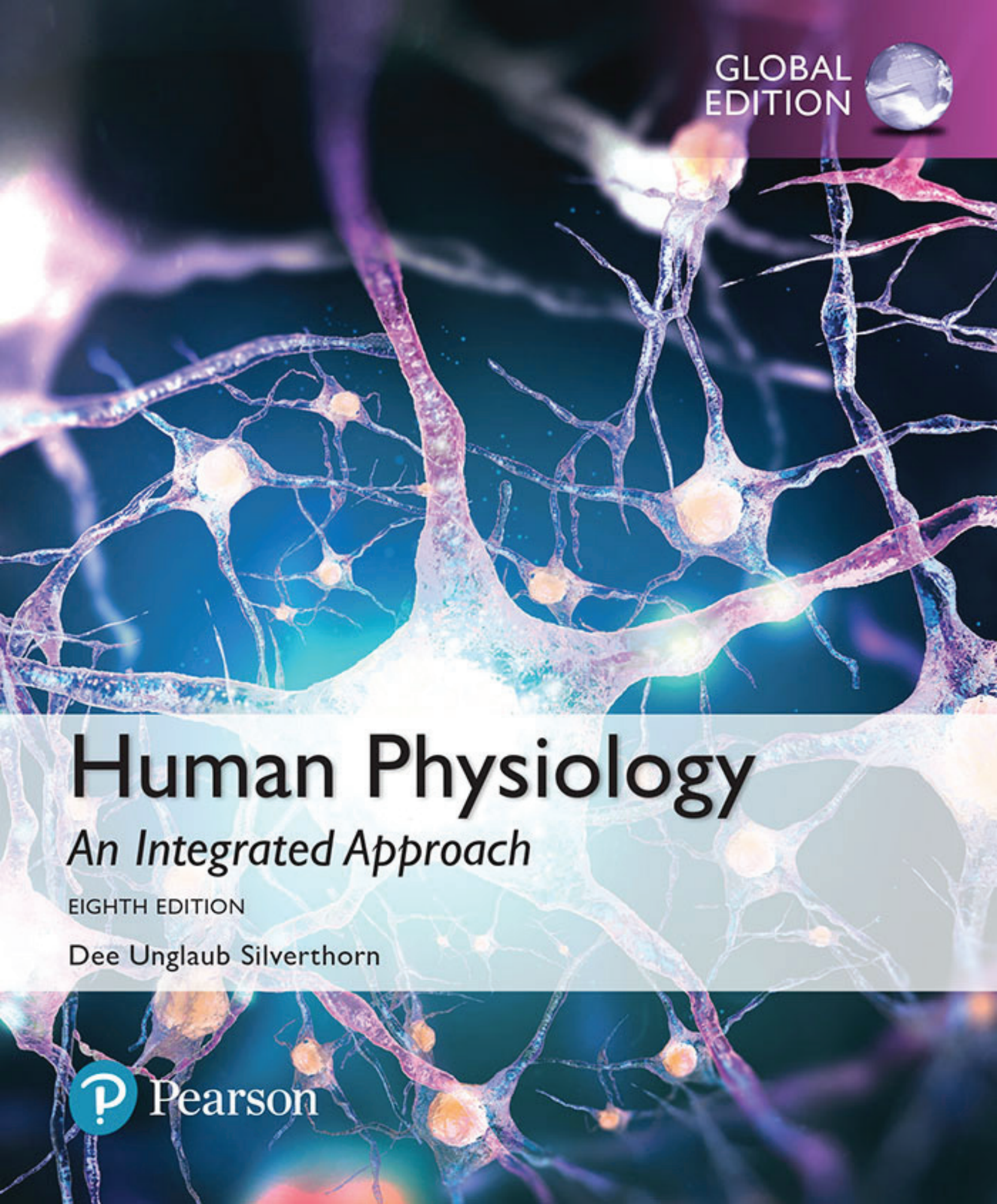

Human Physiology

An Integrated Approach

EIGHTH EDITION

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Contents in Brief

separated from their receptors. Other neurotransmitters are inactivated by enzymes in the synaptic cleft. For example, acetylcholine (ACh) in the extracellular fluid is rapidly broken down into choline and acetyl CoA by the enzyme **acetylcholinesterase (AChE)** in the extracellular matrix and in the membrane of the postsynaptic cell (**FIG. 8.20**). Choline from degraded ACh is transported back into the presynaptic axon terminal on a Na^+-dependent cotransporter. Once back in the axon terminal, it can be used to make new acetylcholine.

Many neurotransmitters are removed from the extracellular fluid by transport back into the presynaptic cell or into adjacent neurons or glia. For example, norepinephrine action is terminated when the intact neurotransmitter is transported back into the presynaptic axon terminal. Norepinephrine uptake uses an Na^+-dependent cotransporter. Once back in the axon terminal, norepinephrine is either transported back into vesicles or broken down by intracellular enzymes such as *monoamine oxidase* (MAO), found in mitochondria. Neurotransmitters and their components can be recycled to refill empty synaptic vesicles.

Concept Check

24. One class of antidepressant drugs is called selective serotonin reuptake inhibitors (SSRIs). What do these drugs do to serotonin activity at the synapse?

25. How does the axon terminal make acetyl CoA for acetylcholine synthesis? (*Hint:* see p. 143.)

26. Is Na^+-dependent neurotransmitter reuptake facilitated diffusion, primary active transport, or secondary active transport? Explain your reasoning.

Stronger Stimuli Release More Neurotransmitter

A single action potential arriving at the axon terminal releases a constant amount of neurotransmitter. Neurons therefore can use the frequency of action potentials to transmit information about the duration and strength of the stimuli that activated them. Duration of a stimulus is coded by the duration of a series of repeated action potentials. A stronger stimulus causes more action potentials per second to arrive at the axon terminal, which in turn may result in more neurotransmitter release.

For example, let's consider how a sensory neuron tells the CNS the intensity of an incoming stimulus. An above-threshold graded potential reaching the trigger zone of the sensory neuron does not trigger just one action potential. Instead, even a small graded potential that is above threshold triggers a burst of action potentials (**FIG. 8.21a**). As graded potentials increase in strength (amplitude), they trigger more frequent action potentials (Fig. 8.21b).

Electrical signaling patterns in the CNS are more variable. Brain neurons show different electrical personalities by firing action potentials in a variety of patterns, sometimes spontaneously, without an external stimulus to bring them to threshold. For example, some neurons are *tonically active* [p. 218], firing regular trains of action potentials (beating pacemakers). Other neurons exhibit *bursting*, bursts of action potentials rhythmically alternating with intervals of quiet (rhythmic pacemakers).

These different firing patterns in CNS neurons are created by ion channel variants that differ in their activation and inactivation voltages, opening and closing speeds, and sensitivity to neuromodulators. This variability makes brain neurons more dynamic and complicated than the simple somatic motor neuron we use as our model.

FIG. 8.20 Synthesis and recycling of acetylcholine

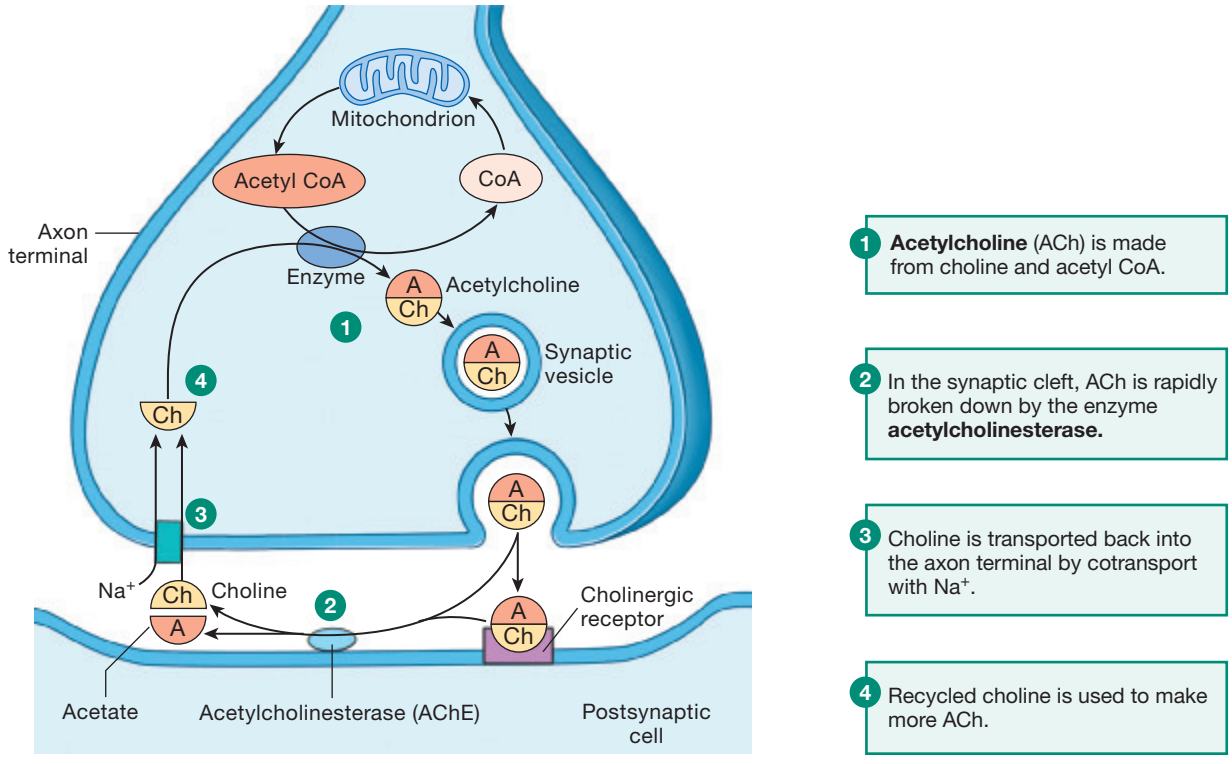
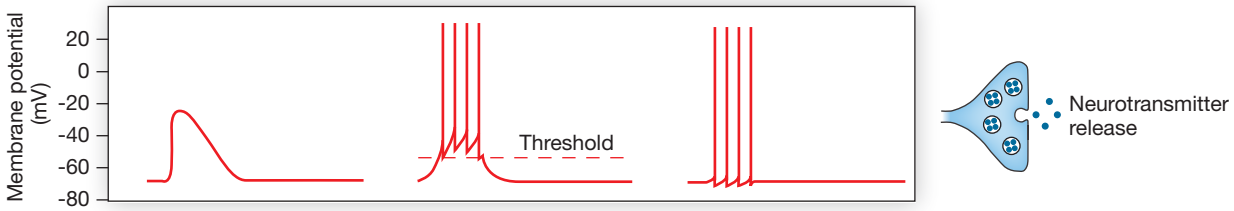


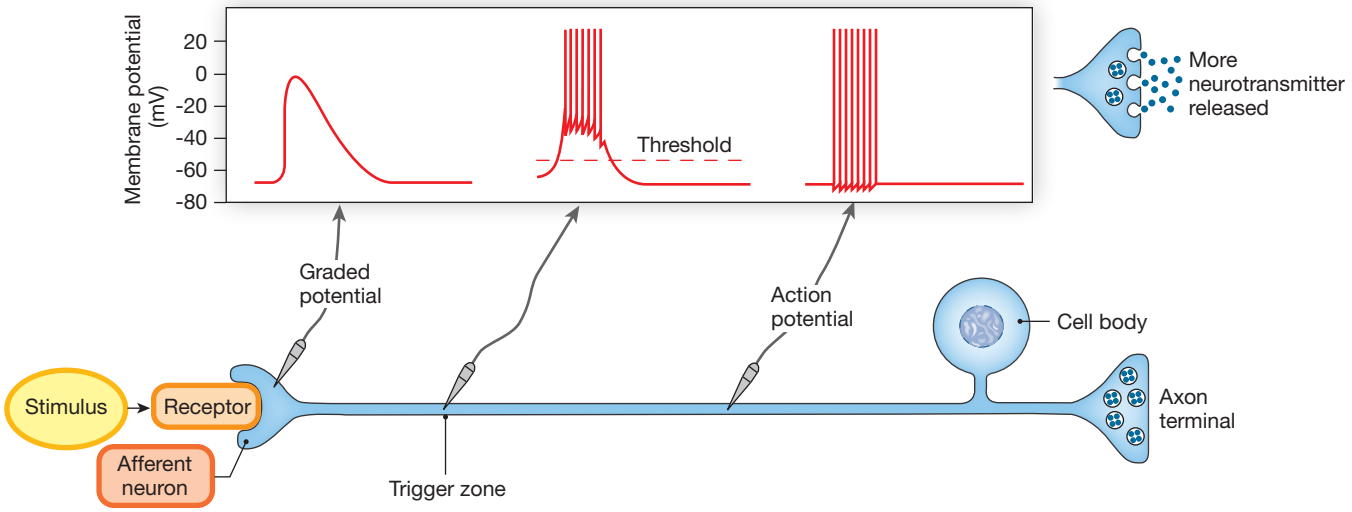
FIG. 8.21 Coding the strength of a stimulus

The frequency of action potential firing indicates the strength of a stimulus.

(a) Weak stimulus releases little neurotransmitter.



(b) Strong stimulus causes more action potentials and releases more neurotransmitter.



8.5 Integration of Neural Information Transfer

Communication between neurons is not always a one-to-one event as we have been describing. Frequently, the axon of a presynaptic neuron branches, and its collaterals (branches) synapse on multiple target neurons. This pattern is known as **divergence** (FIG. 8.22a). On the other hand, when a group of presynaptic neurons provide input to a smaller number of postsynaptic neurons, the pattern is known as **convergence** (Fig. 8.22b).

Combination of convergence and divergence in the CNS may result in one postsynaptic neuron with synapses from as many as 10,000 presynaptic neurons (Fig. 8.22c). For example, the Purkinje neurons of the CNS have highly branched dendrites so that they can receive information from many neurons (Fig. 8.22d).

In addition, we now know that the traditional view of chemical synapses as sites of one-way communication, with all messages moving from presynaptic cell to postsynaptic cell, is not always correct. In the brain, there are some synapses where cells on both sides of the synaptic cleft release neurotransmitters that act on the opposite cell. Perhaps more importantly, we have learned that many postsynaptic cells "talk back" to their presynaptic neurons by sending neuromodulators that bind to presynaptic receptors. Variations in synaptic activity play a major role in determining how communication takes place in the nervous system.

The ability of the nervous system to change activity at synapses is called **synaptic plasticity** {*plasticus*, that which may be molded}. Synaptic plasticity occurs primarily in the CNS. Short-term plasticity may enhance activity at the synapse (facilitation) or decrease it (depression). For example, in some cases of sustained activity at a synapse, neurotransmitter release decreases over time because the axon cannot replenish its neurotransmitter supply rapidly enough, resulting in synaptic depression.

Sometimes changes at the synapse persist for significant periods of time (long-term depression or long-term potentiation, described later in this section). In the sections that follow, we examine some of the ways that communication at synapses can be modified.

Postsynaptic Responses May Be Slow or Fast

A neurotransmitter combining with its receptor sets in motion a series of responses in the postsynaptic cell (FIG. 8.23). Neurotransmitters that bind to G protein-coupled receptors linked to second messenger systems initiate slow postsynaptic responses.

(a) Divergent Pathway

In a **divergent pathway,** one presynaptic neuron branches to affect a larger number of postsynaptic neurons.

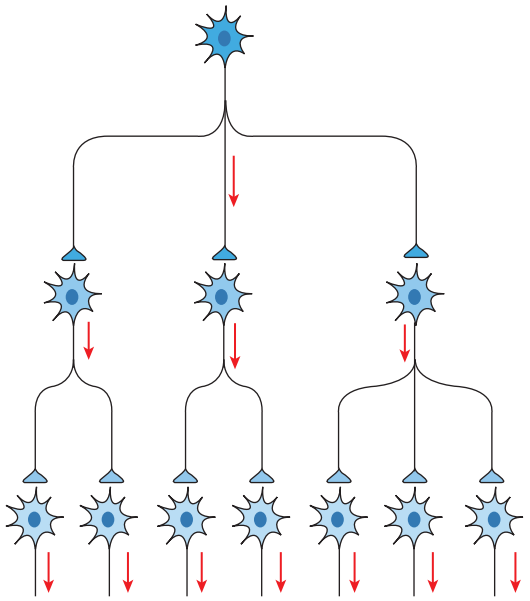
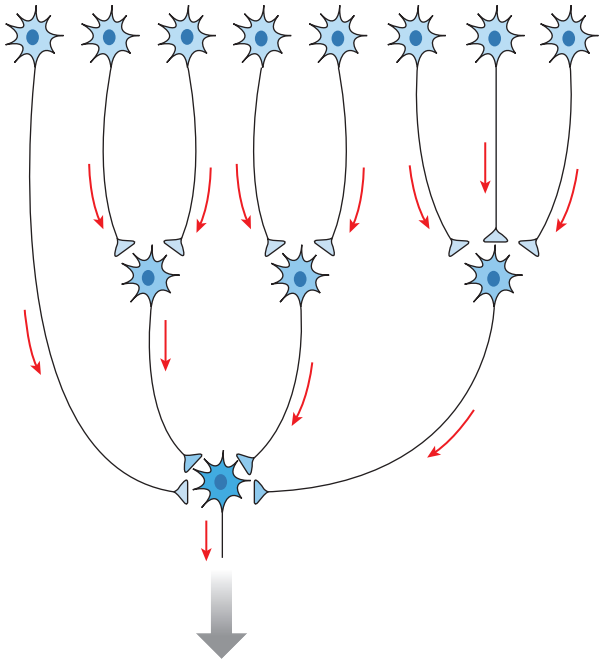


FIGURE QUESTION

The pattern of divergence in (a) is similar to _____ in a second messenger system.

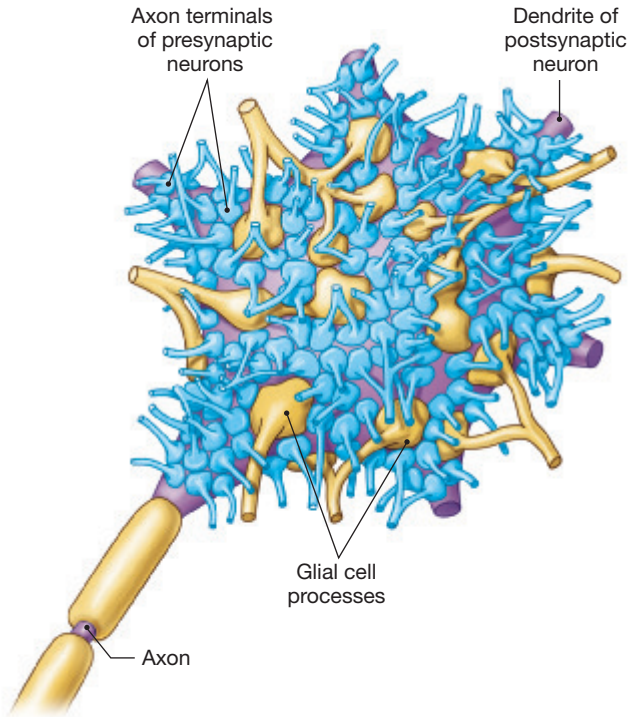
(b) Convergent Pathway

In a **convergent pathway,** many presynaptic neurons provide input to influence a smaller number of postsynaptic neurons.



(c) Synapses on a Cell Body

The cell body of a somatic motor neuron is nearly covered with synapses providing input from other neurons.



(d) Purkinje Cells

The highly branched dendrites of a Purkinje cell (neuron) demonstrate convergence of signals from many synapses onto a cell body.

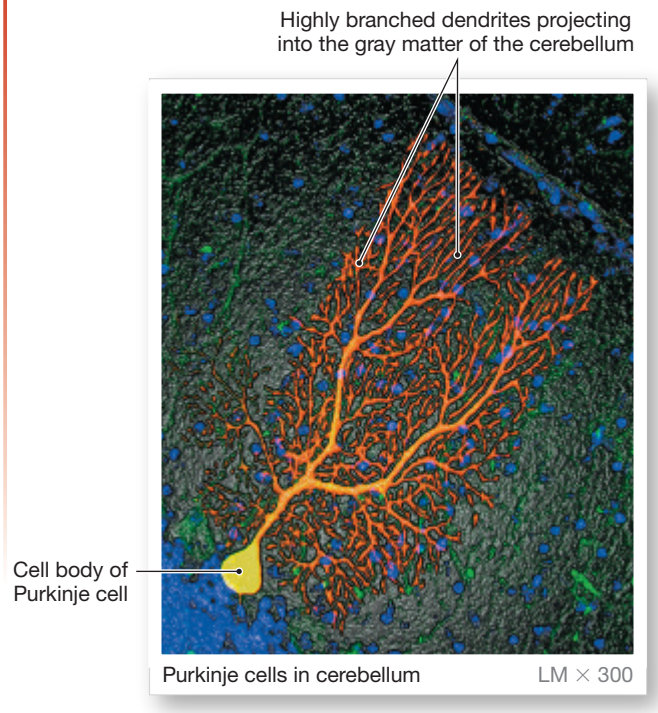
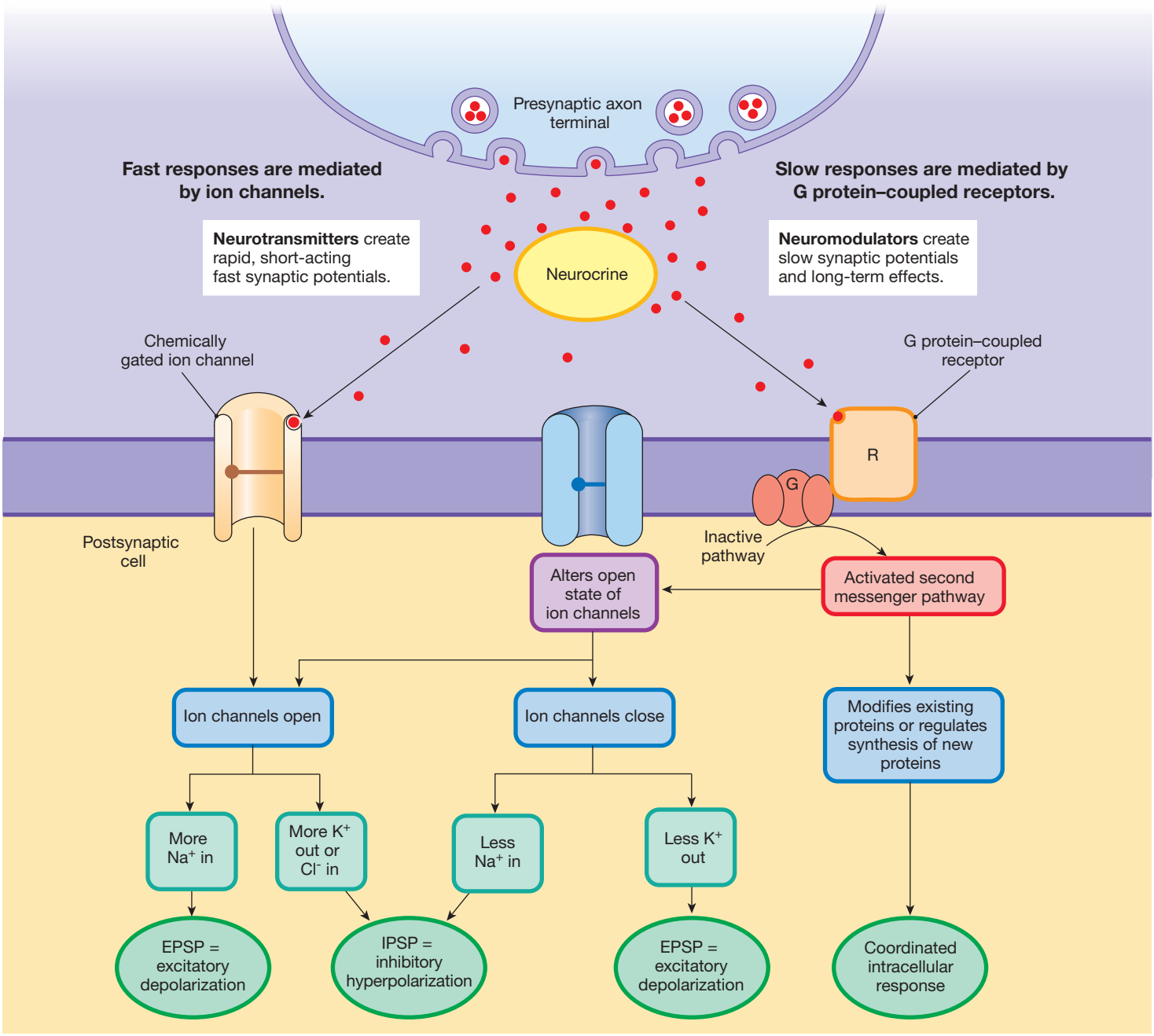


FIG. 8.23 ESSENTIALS Fast and Slow Postsynaptic Responses



Some second messengers act from the cytoplasmic side of the cell membrane to open or close ion channels. Changes in membrane potential resulting from these alterations in ion flow are called **slow synaptic potentials** because the response of the second messenger pathway takes longer than the direct opening or closing of a channel. In addition, the response itself lasts longer, usually seconds to minutes.

Slow postsynaptic responses are not limited to altering the open state of ion channels. Neurotransmitters acting on GPCRs may also modify existing cell proteins or regulate the production of new cell proteins. These types of slow response have been linked to the growth and development of neurons and to the mechanisms underlying long-term memory.

Fast synaptic responses are always associated with the opening of ion channels. In the simplest response, the neurotransmitter binds to and opens a receptor-channel on the postsynaptic cell, allowing ions to move between the postsynaptic cell and the extracellular fluid. The resulting change in membrane potential is called a **fast synaptic potential** because it begins quickly and lasts only a few milliseconds.

If the synaptic potential is depolarizing, it is called an **excitatory postsynaptic potential** (**EPSP**) because it makes the cell more likely to fire an action potential. If the synaptic potential is

hyperpolarizing, it is called an **inhibitory postsynaptic potential (IPSP)** because hyperpolarization moves the membrane potential away from threshold and makes the cell less likely to fire an action potential.

Pathways Integrate Information from Multiple Neurons

When two or more presynaptic neurons converge on the dendrites or cell body of a single postsynaptic cell, the response of the postsynaptic cell is determined by the summed input from the presynaptic neurons. **FIGURE 8.24c** shows the three-dimensional reconstruction of dendritic spines of a postsynaptic neuron, with numerous excitatory and inhibitory synapses providing input. The summed input from these synapses determines the activity of the postsynaptic neuron.

The combination of several nearly simultaneous graded potentials is called **spatial summation**. The word *spatial* {*spatium*, space} refers to the fact that the graded potentials originate at different locations (spaces) on the neuron.

Figure 8.24d illustrates spatial summation when three presynaptic neurons releasing excitatory neurotransmitters ("excitatory neurons") converge on one postsynaptic neuron. Each neuron's EPSP is too weak to trigger an action potential by itself, but if the three presynaptic neurons fire simultaneously, the sum of the three EPSPs is above threshold and creates an action potential.

Spatial summation is not always excitatory. If summation prevents an action potential in the postsynaptic cell, the summation is called **postsynaptic inhibition**. This occurs when presynaptic neurons release inhibitory neurotransmitter. For example, Figure 8.24e shows three presynaptic neurons, two excitatory and one inhibitory, converging on a postsynaptic cell. The neurons fire, creating one IPSP and two EPSPs that sum as they reach the trigger zone. The IPSP counteracts the two EPSPs, creating an integrated signal that is below threshold. As a result, no action potential is generated at the trigger zone.

Temporal Summation Summation of graded potentials does not always require input from more than one presynaptic neuron. Two subthreshold graded potentials from the same presynaptic neuron can be summed if they arrive at the trigger zone close enough together in time. Summation that occurs from graded potentials overlapping in time is called **temporal summation** {*tempus*, time}. Let's see how this can happen.

Figure 8.24a shows recordings from an electrode placed in the trigger zone of a neuron. A stimulus (X_1) starts a subthreshold graded potential on the cell body at the time marked on the *x*-axis. The graded potential reaches the trigger zone and depolarizes it, as shown on the graph (A_1), but not enough to trigger an action potential. A second stimulus (X_2) occurs later, and its subthreshold graded potential (A_2) reaches the trigger zone sometime after the first. The interval between the two stimuli is so long that the two graded potentials do not overlap. Neither potential by itself is above threshold, so no action potential is triggered.

In Figure 8.24b, the two stimuli occur closer together in time. As a result, the two subthreshold graded potentials arrive at the trigger zone at almost the same time. The second graded potential adds its depolarization to that of the first, causing the trigger zone to depolarize to threshold.

In many situations, graded potentials in a neuron incorporate both temporal and spatial summation. The summation of graded potentials demonstrates a key property of neurons: *postsynaptic integration*. When multiple signals reach a neuron, postsynaptic integration creates a signal based on the relative strengths and durations of the signals. If the integrated signal is above threshold, the neuron fires an action potential. If the integrated signal is below threshold, the neuron does not fire.

Concept Check

27. In Figure 8.24e, assume the postsynaptic neuron has a resting membrane potential of −70 mV and a threshold of −55 mV. If the inhibitory presynaptic neuron creates an IPSP of −5 mV and the two excitatory presynaptic neurons have EPSPs of 10 and 12 mV, will the postsynaptic neuron fire an action potential?

28. In the graphs of Figure 8.24a, b, why doesn't the membrane potential change at the same time as the stimulus?

Synaptic Activity Can Be Modified

The examples of synaptic integration we just discussed all took place on the postsynaptic side of a synapse, but the activity of presynaptic cells can also be altered, or *modulated*. When a modulatory neuron terminates on a presynaptic cell, the IPSP or EPSP created by the modulatory neuron can alter the action potential reaching the axon terminals of the presynaptic cell and modulate neurotransmitter release. In *presynaptic facilitation*, input from an excitatory neuron increases neurotransmitter release by the presynaptic cell.

If modulation of a neuron decreases its neurotransmitter release, the modulation is called *presynaptic inhibition*. Presynaptic inhibition may be global or selective. In global presynaptic inhibition (Fig. 8.24f), input on the dendrites and cell body of a neuron decreases neurotransmitter release by all collaterals and all target cells of the neuron are affected equally.

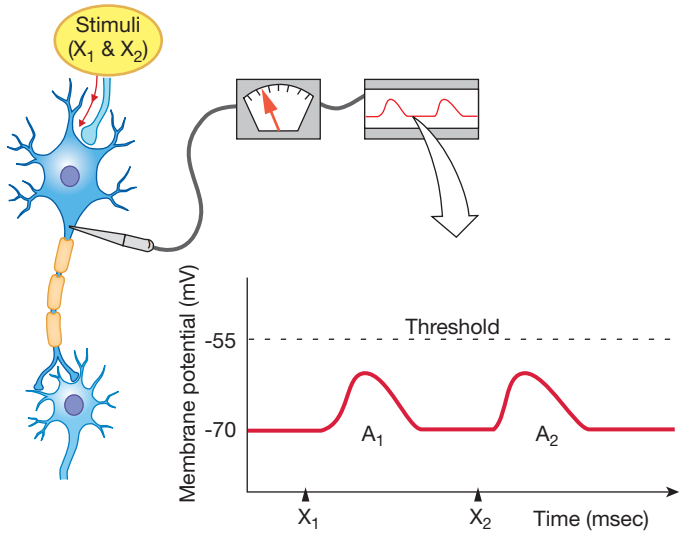
In selective modulation, one collateral can be inhibited while others remain unaffected. Selective presynaptic alteration of neurotransmitter release provides a more precise means of control than global modulation. For example, Figure 8.24g shows selective presynaptic modulation of a single collateral's axon terminal so that only its target cell fails to respond.

Synaptic activity can also be altered by changing the target (postsynaptic) cell's responsiveness to neurotransmitter. This may be accomplished by changing the structure, affinity, or number of neurotransmitter receptors. Modulators can alter all of these parameters by influencing the synthesis of enzymes, membrane transporters, and receptors. Most neuromodulators act through second messenger systems that alter existing channels, and their effects last much longer than do those of neurotransmitters. One signal molecule can act as either a neurotransmitter or a neuromodulator, depending on its receptor (Fig. 8.23).

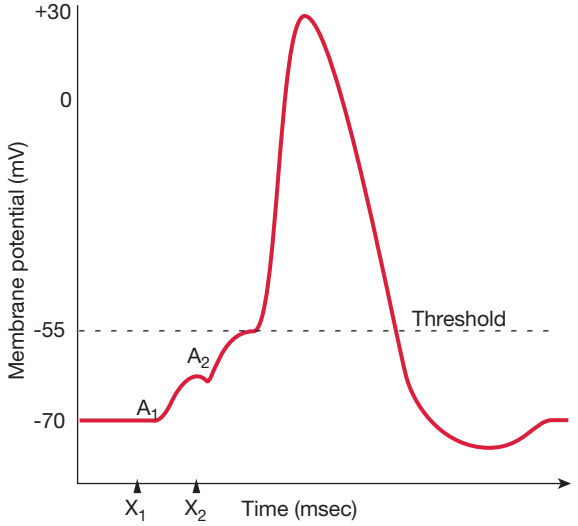
Temporal Summation

Temporal summation occurs when two graded potentials from one presynaptic neuron occur close together in time.

(a) No summation. Two subthreshold graded potentials will not initiate an action potential if they are far apart in time.



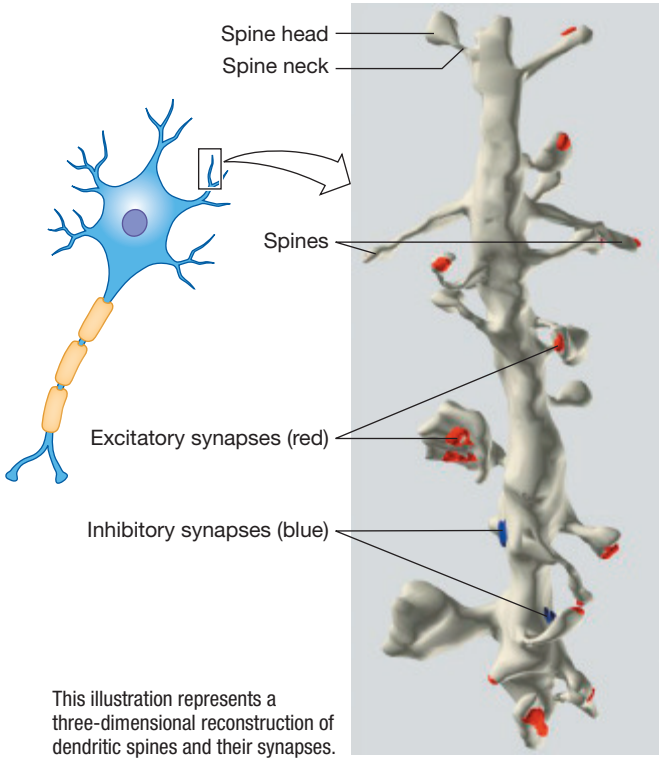
(b) Summation causing action potential. If two subthreshold potentials arrive at the trigger zone within a short period of time, they may sum and initiate an action potential.



Spatial Summation

Spatial summation occurs when the currents from nearly simultaneous graded potentials combine.

(c) Multiple presynaptic neurons provide input on the dendrites and cell body of the postsynaptic neurons.



This illustration represents a three-dimensional reconstruction of dendritic spines and their synapses.

(d) Summation of several subthreshold signals results in an action potential.