Cold and continuous pressure interrupt blood circulation (and hence the delivery of oxygen and nutrients) to neuron processes, impairing their ability to conduct impulses. For example, your fingers get numb when you hold an ice cube for more than a few seconds, and your foot "goes to sleep" when you sit on it. When you remove the cold object or pressure, impulses are transmitted again, leading to an unpleasant prickly feeling. ●

The Synapse

The operation of the nervous system depends on the flow of information through chains of neurons functionally connected by synapses. A **synapse** (sin'aps), from the Greek *syn*, "to clasp or join," is a junction that mediates information transfer from one neuron to the next or from a neuron to an effector cell—it's where the action is.

Synapses between the axonal endings of one neuron and the dendrites of other neurons are **axodendritic synapses** (Figure 11.17). Those between axonal endings of one neuron and cell bodies of other neurons are **axosomatic synapses.** Less common (and far less understood) are synapses between axons *(axoaxonic)*, between dendrites *(dendrodendritic)*, or between dendrites and cell bodies *(dendrosomatic)*.

The neuron conducting impulses toward the synapse is the **presynaptic neuron** and the neuron transmitting the electrical signal away from the synapse is the **postsynaptic neuron.** At a *given* synapse, the presynaptic neuron is the information sender, and the postsynaptic neuron is the information receiver. As you might anticipate, most neurons function both as presynaptic and postsynaptic neurons. Neurons have anywhere from 1000 to 10,000 axonal terminals making synapses and are stimulated by an equal number of other neurons. In the body periphery, the postsynaptic cell may be either another neuron or an effector cell (a muscle cell or gland cell).

There are two varieties of synapses: *electrical* and *chemical*. These are described next.

Electrical Synapses

Electrical synapses, the less common variety, correspond to the gap junctions found between certain other body cells (Figure 11.18). They contain protein channels, made of connexin subunits, that connect the cytoplasm of adjacent neurons and allow ions to flow directly from one neuron to the next. Neurons joined in this way are said to be *electrically coupled,* and transmission across these synapses is very rapid. Depending on the nature of the synapse, communication may be unidirectional or bidirectional.

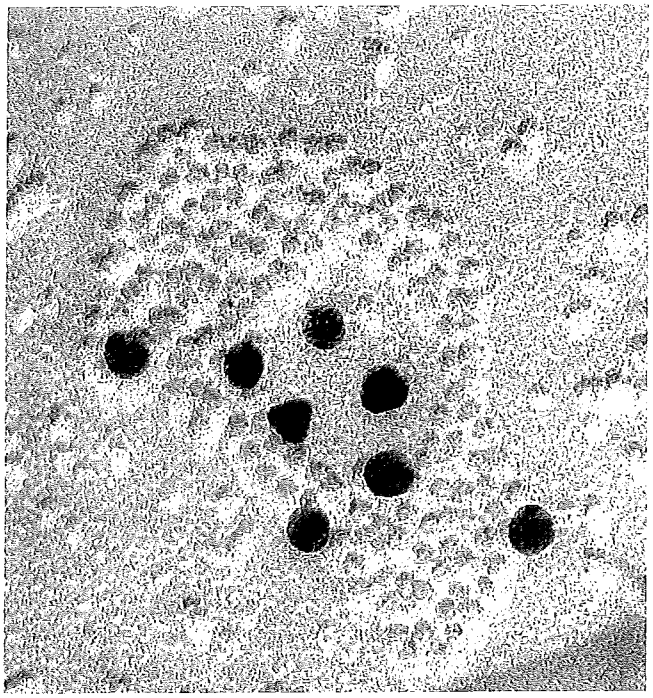


FIGURE 11.18 **Freeze-fracture image of an electrical synapse in an adult rat hippocampus.** The dark spheres are immunogold labels for the protein connexin36, which is the first connexin established as present in CNS electrical synapses (gap junctions) (200,000×). Photograph courtesy of John Rash, Ph.D.; Colorado State University.

A key feature of electrical synapses between neurons is that they provide a simple means of synchronizing the activity of all interconnected neurons. They appear to be important in CNS arousal from sleep and in mental attention and conscious perception. In adults, electrical synapses are found in regions of the brain responsible for certain stereotyped movements, such as the normal jerky movements of the eyes, and in axoaxonic synapses in the hippocampus, a region intimately involved in emotions and memory. They are far more abundant in embryonic nervous tissue, where they permit exchange of guiding clues during early neuronal development so that neurons can connect properly with one another. As the nervous system develops, some electrical synapses are replaced by chemical synapses. Electrical synapses also exist between glial cells of the CNS, where they play a role in ion and water homeostasis.

Chemical Synapses

In contrast to electrical synapses, which are specialized to allow the flow of ions between neurons,

chemical synapses are specialized for release and reception of chemical neurotransmitters. A typical chemical synapse is made up of two parts: (1) a knoblike *axonal terminal* of the presynaptic neuron, which contains many tiny, membrane-bounded sacs called **synaptic vesicles,** each containing thousands of neurotransmitter molecules; and (2) a neurotransmitter *receptor region* on the membrane of a dendrite or the cell body of the postsynaptic neuron.

Although close to each other, presynaptic and postsynaptic membranes are always separated by the **synaptic cleft,** a fluid-filled space approximately 30 to 50 nm (about one-millionth of an inch) wide. Because the current from the presynaptic membrane dissipates in the fluid-filled cleft, chemical synapses effectively prevent a nerve impulse from being *directly* transmitted from one neuron to another. Instead, transmission of signals across these synapses is a *chemical event* that depends on the release, diffusion, and receptor binding of neurotransmitter molecules and results in *unidirectional communication* between neurons. Thus, while transmission of nerve impulses along an axon and across electrical synapses is a purely electrical event, chemical synapses convert the electrical signals to chemical signals (neurotransmitters) that travel across the synapse to the postsynaptic cells, where they are converted back into electrical signals.

Information Transfer Across Chemical Synapses

When a nerve impulse reaches the axonal terminal, it sets into motion a chain of events that triggers neurotransmitter release. The neurotransmitter crosses the synaptic cleft and, on binding to receptors on the postsynaptic membrane, causes changes in the postsynaptic membrane permeability. The steps are shown in Figure 11.19:

① **Calcium channels open in the presynaptic axonal terminal.** When the nerve impulse reaches the axonal terminal, membrane depolarization opens not only Na^+ channels but voltage-gated Ca^{2+} channels as well. During the brief time the Ca^{2+} gates are open, Ca^{2+} floods into the terminal from the extracellular fluid.

② **Neurotransmitter is released.** The surge of Ca^{2+} into the axonal terminal acts as an intracellular messenger, directing docked synaptic vesicles to fuse with the axonal membrane and empty their contents by exocytosis into the synaptic cleft. The Ca^{2+} is then quickly removed from the terminal, either taken up into the mitochondria or ejected from the neuron by an active Ca^{2+} pump. The precise Ca^{2+} sensor that initiates neurotransmitter exocytosis is still a question, but a Ca^{2+}-binding protein called *synaptotagmin* found in the synaptic vesicles seems a likely candidate.

③ **Neurotransmitter binds to postsynaptic receptors.** The neurotransmitter diffuses across the synaptic cleft and binds reversibly to specific protein receptors clustered on the postsynaptic membrane.

④ **Ion channels open in the postsynaptic membrane.** As the receptor proteins bind neurotransmitter molecules, the three-dimensional shape of the proteins changes. This causes ion channels to open, and the resulting current flows produce local changes in the membrane potential. Depending on the receptor protein to which the neurotransmitter binds and the type of channel the receptor controls, the postsynaptic neuron may be either excited or inhibited.

For each nerve impulse reaching the presynaptic terminal, many vesicles (perhaps 300) are emptied into the synaptic cleft. The higher the impulse frequency (that is, the more intense the stimulus), the greater the number of synaptic vesicles that fuse and spill their contents, and the greater the effect on the postsynaptic cell.

Termination of Neurotransmitter Effects As long as it is bound to a postsynaptic receptor, a neurotransmitter continues to affect membrane permeability and to block reception of additional "messages" from presynaptic neurons. Thus, some means of "wiping the postsynaptic slate clean" is necessary. The effects of neurotransmitters last a few milliseconds before being terminated by one of three mechanisms. Depending on the particular neurotransmitter, the terminating mechanism may be

1. Degradation by enzymes associated with the postsynaptic membrane or present in the synapse. This is the case for acetylcholine.
2. Reuptake by astrocytes or the presynaptic terminal, where the neurotransmitter is stored or destroyed by enzymes, as with norepinephrine.
3. Diffusion away from the synapse.

Synaptic Delay Although some neurons can transmit impulses at 150 m/s (300 mph), neural transmission across a chemical synapse is comparatively slow and reflects the time required for neurotransmitter release, diffusion across the synapse, and binding to receptors. Typically, this **synaptic delay,** which lasts 0.3–5.0 ms, is the *rate-limiting* (slowest) step of neural transmission. Synaptic delay helps explain why transmission along short neural pathways involving only two or three neurons occurs rapidly, but transmission along multisynaptic pathways typical of higher mental functioning occurs much more slowly. However, in practical terms these differences are not noticeable.

? *Why may such axonal terminals be referred to as "biological transducers"?*

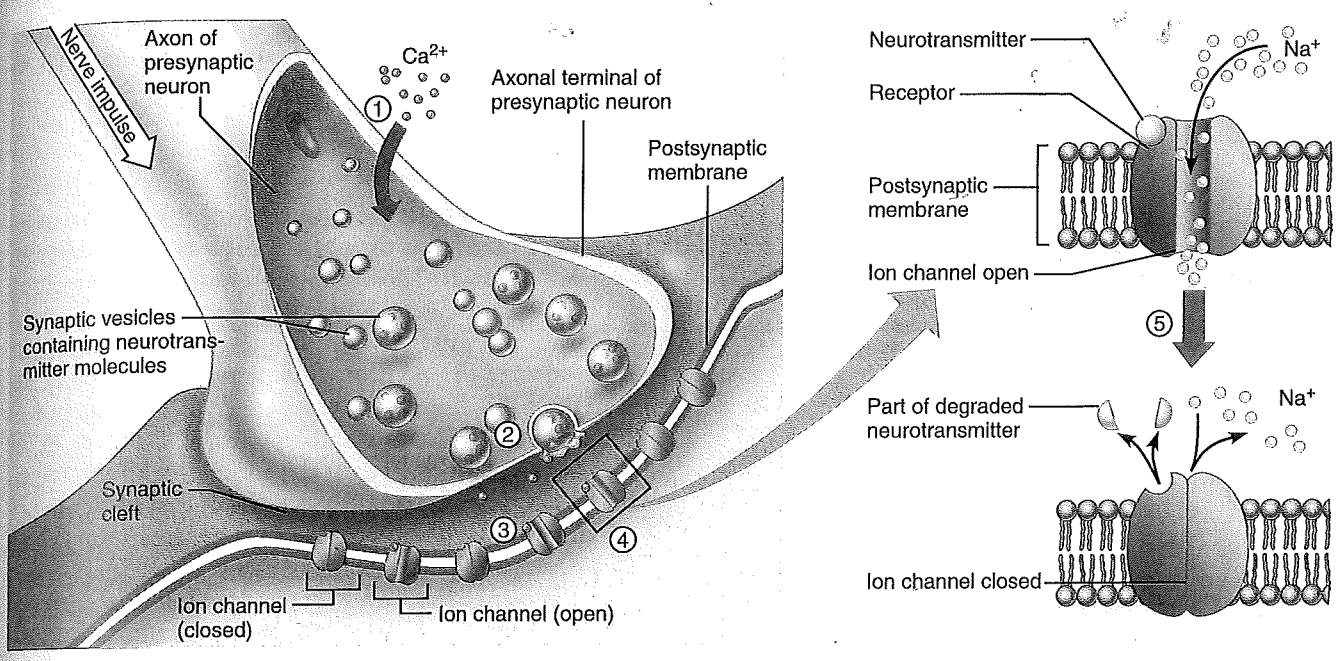


FIGURE 11.19 **Events at a chemical synapse in response to depolarization.** (1) Arrival of the depolarization wave (nerve impulse) opens calcium channels and allows Ca^{2+} influx into the axonal terminal. (2) Synaptic vesicles fuse with the presynaptic membrane and neurotransmitter is released into the synapse. (3) The neurotransmitter diffuses across the synaptic cleft and attaches to receptors on the postsynaptic membrane. (4) Binding of neurotransmitter opens ion channels in the postsynaptic membrane, resulting in voltage changes in that membrane. (5) Neurotransmitter is quickly destroyed by enzymes present at the synapse or taken back into the presynaptic terminal; depletion of neurotransmitter closes the ion channels and terminates the synaptic response.

Postsynaptic Potentials and Synaptic Integration

Many receptors present on postsynaptic membranes at chemical synapses are specialized to open ion channels, thereby converting chemical signals to electrical signals. Unlike the voltage-gated ion channels responsible for action potentials, however, these chemically gated channels are relatively insensitive to changes in membrane potential. Consequently, channel opening at postsynaptic membranes cannot possibly become self-amplifying or self-generating. Instead, neurotransmitter receptors mediate local changes in membrane potential that are *graded* according to the amount of neurotransmitter released and the time it remains in the area. Action potentials are compared with postsynaptic potentials in Table 11.2.

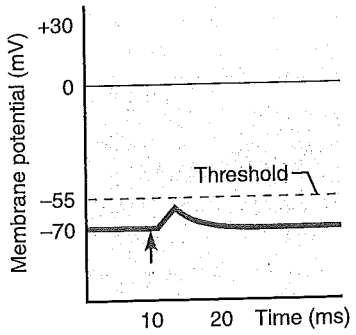
Chemical synapses are either excitatory or inhibitory, depending on how they affect the membrane potential of the postsynaptic neuron.

Excitatory Synapses and EPSPs

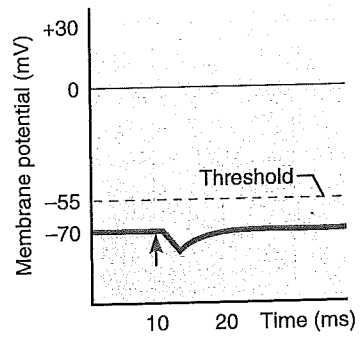
At excitatory synapses, neurotransmitter binding causes depolarization of the postsynaptic membrane. However, in contrast to what happens on axonal membranes, only a single type of channel opens on postsynaptic membranes (those of dendrites and neuronal cell bodies). This channel allows Na^+ and K^+ to diffuse *simultaneously* through the membrane in opposite directions. Although this two-way cation flow may appear to be self-defeating when depolarization is the goal, remember that the electrochemical gradient for sodium is much steeper than that for potassium. Hence, Na^+ influx is greater than K^+ efflux, and *net* depolarization occurs.

If enough neurotransmitter binds, depolarization of the postsynaptic membrane can successfully

Because they change the signal from an electrical current to a chemical signal (neurotransmitter), which in turn initiates an electrical current in the postsynaptic neuron. ■



(a) Excitatory postsynaptic potential (EPSP)



(b) Inhibitory postsynaptic potential (IPSP)

FIGURE 11.20 **Postsynaptic potentials.** **(a)** An excitatory postsynaptic potential (EPSP) is a local depolarization of the postsynaptic membrane that brings the neuron closer to threshold for AP generation. It is mediated by neurotransmitter binding that opens channels allowing the simultaneous passage of Na^+ and K^+ through the postsynaptic membrane. **(b)** An inhibitory postsynaptic potential results in hyperpolarization of the postsynaptic neuron and drives the neuron away from the threshold for firing. It is mediated by neurotransmitter binding that opens K^+ or Cl^- gates or both. The red vertical arrows represent stimulation.

reach 0 mV, which is well above an axon's threshold (about −50 mV) for "firing off" an action potential. However, *postsynaptic membranes do not generate action potentials; only axons* (with their voltage-gated channels) *have this capability.* The dramatic polarity reversal seen in axons never occurs in membranes containing *only* chemically gated channels because the opposite movements of K^+ and Na^+ prevent accumulation of excessive positive charge inside the cell. Hence, instead of action potentials, local graded depolarization events called **excitatory postsynaptic potentials (EPSPs)** occur at excitatory postsynaptic membranes (see Figure 11.20a). Each EPSP lasts a few milliseconds and then the membrane returns to its resting potential. The only function of EPSPs is to help trigger an action potential distally at the axon hillock of the postsynaptic neuron. Although currents created by individual EPSPs decline with distance, they can and often *do* spread all the way to the axon hillock. If currents reaching the hillock are strong enough to depolarize the axon to threshold, axonal voltage-gated channels open and an action potential is generated.

Inhibitory Synapses and IPSPs

Binding of neurotransmitters at inhibitory synapses *reduces* a postsynaptic neuron's ability to generate an action potential. Most inhibitory neurotransmitters induce hyperpolarization of the postsynaptic membrane by making the membrane more permeable to K^+ and/or Cl^-. Sodium ion permeability is not affected. If K^+ channels are opened, K^+ moves out of the cell; if Cl^- channels are opened, Cl^- moves in. In either case, the charge on the inner face of the membrane becomes more negative. As the membrane potential increases and is driven farther from the axon's threshold, the postsynaptic neuron becomes less and less likely to "fire" and larger depolarizing currents are required to induce an action potential. Such changes in potential are called **inhibitory postsynaptic potentials (IPSPs)** (see Figure 11.20b).

Integration and Modification of Synaptic Events

Summation by the Postsynaptic Neuron A single EPSP cannot induce an action potential in the postsynaptic neuron. But if thousands of excitatory axonal terminals are firing on the same postsynaptic membrane, or if a smaller number of terminals are delivering impulses rapidly, the probability of reaching threshold depolarization increases greatly. Thus, EPSPs can add together, or **summate,** to influence the activity of a postsynaptic neuron (Figure 11.21). Nerve impulses would never be initiated if this were not so.

Two types of summation occur. **Temporal summation** occurs when one or more presynaptic neurons transmit impulses in rapid-fire order and bursts of neurotransmitter are released in quick succession. The first impulse produces a slight EPSP, and before it dissipates, successive impulses trigger more EPSPs. These summate, producing a much greater depolarization of the postsynaptic membrane than would result from a single EPSP.

Spatial summation occurs when the postsynaptic neuron is stimulated at the same time by a large number of terminals from the same or, more commonly, different neurons. Huge numbers of its receptors bind neurotransmitter and simultaneously initiate EPSPs, which summate and dramatically enhance depolarization.

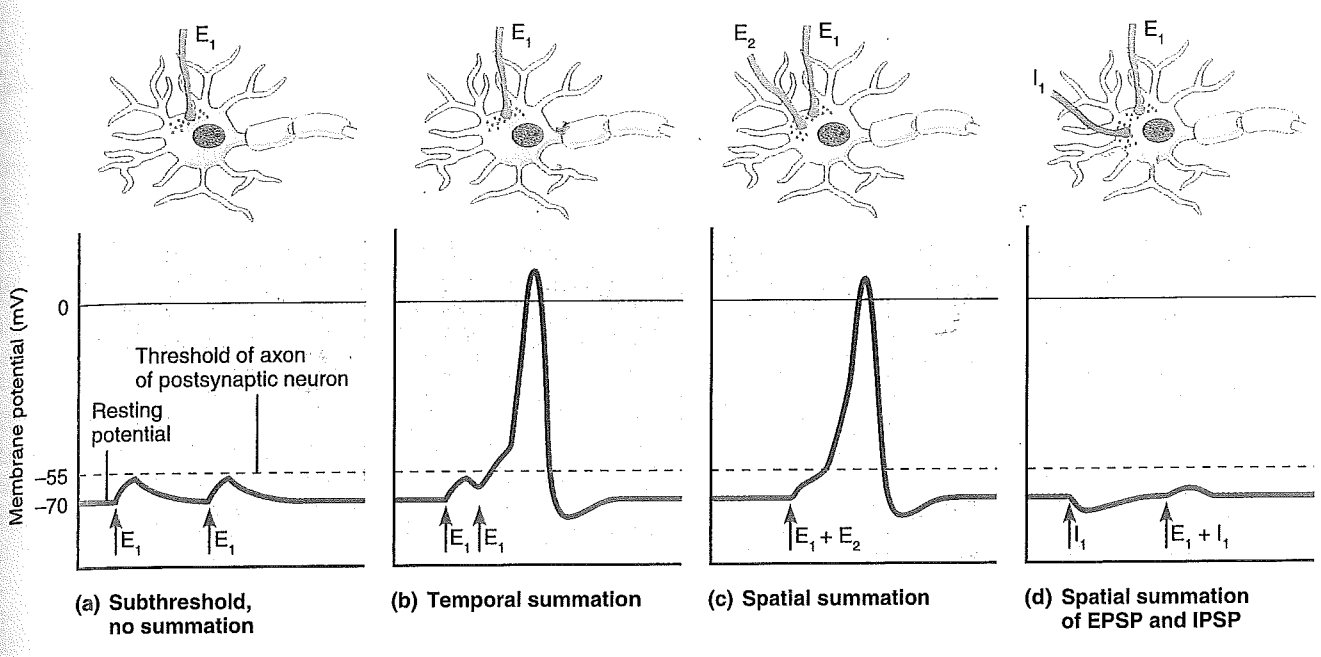


FIGURE 11.21 **Neural integration of EPSPs and IPSPs.** Synapses E_1 and E_2 are excitatory; synapse I_1 is inhibitory. Each individual impulse is subthreshold. **(a)** Synapse E_1 is stimulated and then stimulated again shortly thereafter. The two EPSPs do not overlap in time, so no summation occurs; threshold is not reached in the axon of the postsynaptic neuron. **(b)** Synapse E_1 is stimulated a second time before the initial EPSP has died away; temporal summation occurs, and the axon's threshold is reached, causing an action potential to be generated. **(c)** Synapses E_1 and E_2 are stimulated simultaneously (spatial summation), resulting in a threshold depolarization. **(d)** Synapse I_1 is stimulated, resulting in a short-lived IPSP (hyperpolarization). When E_1 and I_1 are simultaneously stimulated, the changes in potential cancel each other.

Although we have focused on EPSPs here, IPSPs also summate, both temporally and spatially. In this case, the postsynaptic neuron is inhibited to a greater degree.

Most neurons receive both stimulatory and inhibitory inputs from thousands of other neurons. Additionally, the same fiber may form different types of synapses (in terms of biochemical and electrical characteristics) with different types of target neurons. How is all this conflicting information sorted out? Each neuron's axon hillock appears to keep a running account of all the signals it receives (Figure 11.21d). Not only do EPSPs summate and IPSPs summate, but also EPSPs summate with IPSPs. If the stimulatory effects of EPSPs dominate the membrane potential enough to reach threshold, the neuron will fire. If summation yields only subthreshold depolarization or hyperpolarization, the neuron fails to generate an action potential. However, partially depolarized neurons are **facilitated**—that is, more easily excited by successive depolarization events—because they are already near threshold. Thus, axon hillock membranes function as *neural integrators*, and their potential at any time reflects the sum of all incoming neural information.

Because EPSPs and IPSPs are graded potentials that diminish in strength the farther they spread, we might expect that the most effective synapses are those closest to the axon hillock. What we find, however, is that distal synapses do count as much as more proximal ones (those on the cell body), because synapses get stronger with increasing distance from the cell body. Consequently, amplitude of synaptic responses at the cell body is homogeneous regardless of the site of input.

Synaptic Potentiation Repeated or continuous use of a synapse (even for short periods) enhances the presynaptic neuron's ability to excite the postsynaptic neuron, producing larger than expected postsynaptic potentials. This phenomenon is called **synaptic potentiation.** The presynaptic terminals at such synapses contain relatively high Ca^{2+} concentrations, a condition that (presumably) triggers the release of more neurotransmitter, which in turn produces larger EPSPs. Furthermore, synaptic potentiation increases Ca^{2+} influx via dendritic spines in the postsynaptic neuron as well. Brief high-frequency stimulation specifically activates voltage-regulated receptors called *NMDA (N-methyl-D-aspartate) receptors*, which are located on the postsynaptic membrane and couples the depolarization to increased Ca^{2+} entry. Theoretically, as Ca^{2+} floods into the cell, it activates certain kinase enzymes that

TABLE 11.2 Comparison of Action Potentials with Postsynaptic Potentials

Characteristic	Action Potential	Postsynaptic Potential	
		Excitatory (EPSP)	Inhibitory (IPSP)
Function	Long-distance signaling; constitutes the nerve impulse	Short-distance signaling; depolarization that spreads to axon hillock; moves membrane potential *toward* threshold for generation of action potential	Short-distance signaling; hyperpolarization that spreads to axon hillock; moves potential *away from* threshold for generation of action potential
Stimulus for opening of ionic gates	Voltage (depolarization)	Chemical (neurotransmitter)	Chemical (neurotransmitter)
Initial effect of stimulus	First opens sodium gates, then potassium gates	Opens channels that allow simultaneous sodium and potassium fluxes	Opens potassium or chloride channels or both
Repolarization	Voltage regulated; closing of sodium gates followed by opening of potassium gates	Dissipation of membrane changes with time and distance	
Conduction distance	Not conducted by local current flows; continually regenerated (propagated) along entire axon; intensity does not decline with distance	1–2 mm; local electrical events; intensity declines with distance	
Positive feedback cycle	Present	Absent	Absent
Peak membrane potential	+40 to +50 mV	0 mV	Becomes hyperpolarized; moves toward −90 mV
Summation	None; an all-or-none phenomenon	Present; produces graded depolarization	Present; produces graded hyperpolarization
Refractory period	Present	Absent	Absent

promote changes that result in more efficient responses to subsequent stimuli.

Synaptic potentiation, also called *post-tetanic potentiation,* can be viewed as a learning process that increases the efficiency of neurotransmission along a particular pathway. Indeed, the hippocampus of the brain, which plays a special role in memory and learning, exhibits especially long post-tetanic potentiations.

Another facet of synaptic potentiation appears to occur under certain conditions and at certain brain synapses. Dendrites of pyramidal neurons of the cerebral cortex and hippocampal neurons have fast voltage-gated sodium channels and high-threshold gates for Ca^{2+} currents that act in synaptic integration and influence the strength and plasticity of their synapses. Apparently as a neuron shoots off an AP, a back-propagating AP travels from the cell body to the dendrites. This current flow alters the efficiency of the synapses, promoting synaptic potentiation.

Presynaptic Inhibition and Neuromodulation

Postsynaptic activity can also be influenced by events occurring at the presynaptic membrane.

Presynaptic inhibition occurs when the release of excitatory neurotransmitter by one neuron is inhibited by the activity of another neuron via an axoaxonic synapse. More than one mechanism is involved, but the end result is that less neurotransmitter is released and bound, and smaller EPSPs are formed. Notice that this is the opposite of what we see with synaptic potentiation. In contrast to postsynaptic inhibition by IPSPs, which decreases the excitability of the postsynaptic neuron, presynaptic inhibition is more like a functional synaptic "pruning." Events at the presynaptic neuron reduce excitatory stimulation of the postsynaptic neuron.

Neuromodulation, another presynaptic event that affects postsynaptic activity, occurs when a neurotransmitter acts via slow changes in target cell metabolism or when chemicals other than neurotransmitters modify neuronal activity. Some *neuromodulators* influence the synthesis, release, degradation, or reuptake of neurotransmitter by a presynaptic neuron. Others alter the sensitivity of the postsynaptic membrane to the neurotransmitter. Some neuromodulators are hormones that act at sites far from their release site.

Neurotransmitters and Their Receptors

Neurotransmitters, along with electrical signals, are the "language" of the nervous system—the means by which each neuron communicates with others to process and send messages to the rest of the body. Sleep, thought, rage, hunger, memory, movement, and even your smile reflect the "doings" of these versatile molecules. Most factors that affect synaptic transmission do so by enhancing or inhibiting neurotransmitter release or destruction, or by blocking their binding to receptors. Just as speech defects may hinder interpersonal communication, interferences with neurotransmitter activity may short-circuit the brain's "conversations" or internal talk (see *A Closer Look* on pp. 424–425).

At present, more than 50 neurotransmitters or neurotransmitter candidates have been identified. Although some neurons produce and release only one kind of neurotransmitter, most make two or more and may release any one or all of them. It appears that in most cases, different neurotransmitters are released at different stimulation frequencies, a restriction that avoids producing a jumble of nonsense messages. However, co-release of two neurotransmitters from the same vesicles has been documented. The coexistence of more than one neurotransmitter in a single neuron makes it possible for that cell to exert several influences rather than one discrete effect.

Neurotransmitters are classified chemically and functionally. Table 11.3 provides a fairly detailed overview of neurotransmitters, some of which are described here. No one expects you to memorize this table at this point, but it will be a handy reference for you to look back to when neurotransmitters are mentioned in subsequent chapters.

Classification of Neurotransmitters by Chemical Structure

Neurotransmitters fall into several chemical classes based on molecular structure.

Acetylcholine (ACh) **Acetylcholine** (as″ĕ-til-ko′lēn) was the first neurotransmitter identified. It is still the best understood because it is released at neuromuscular junctions, which are much easier to study than synapses buried in the CNS. ACh is synthesized and enclosed in synaptic vesicles in axonal terminals in a reaction catalyzed by the enzyme *choline acetyltransferase*. Acetic acid is bound to coenzyme A (CoA) to form acetyl-CoA, which then combines with choline. Then coenzyme A is released.

$$\text{Acetyl-CoA} + \text{choline} \xrightarrow[\text{acetyltransferase}]{\text{choline}} \text{ACh} + \text{CoA}$$

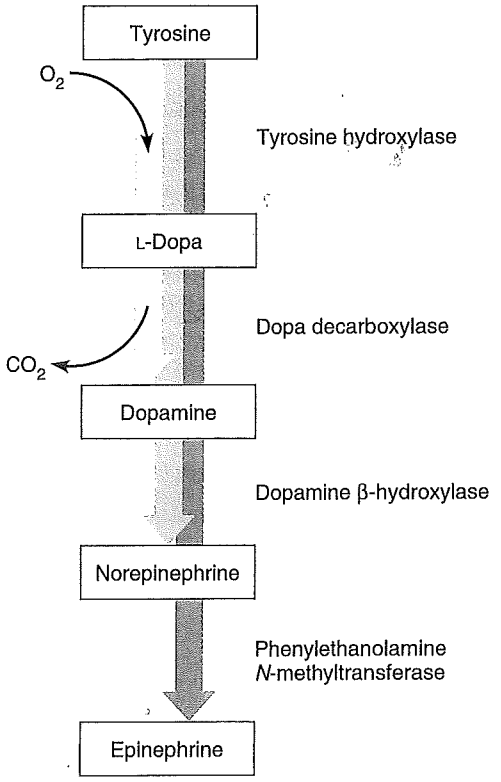


FIGURE 11.22 **Common pathway for synthesis of dopamine, norepinephrine, and epinephrine.** How far synthesis proceeds along the pathway depends on the enzymes present in the cell.

Once released by the presynaptic terminal, ACh binds to the postsynaptic receptors briefly. Then it is released and degraded to acetic acid and choline by the enzyme **acetylcholinesterase (AChE)**, located in the synaptic cleft and on postsynaptic membranes. The released choline is recaptured by the presynaptic terminals and reused to synthesize more ACh.

ACh is released by all neurons that stimulate skeletal muscles and by some neurons of the autonomic nervous system. ACh-releasing neurons are also prevalent in the CNS.

Biogenic Amines The **biogenic amines** (bi″o-jen′ik) include the **catecholamines** (kat″ĕ-kol′ah-mēnz), such as dopamine, norepinephrine (NE), and epinephrine, and the **indolamines,** which include serotonin and histamine. As illustrated in Figure 11.22, *dopamine* and *NE* are synthesized from the amino acid tyrosine in a common pathway consisting of several steps. Apparently, neurons contain only the enzymes needed to produce their own neurotransmitter(s). Thus, the sequence stops at dopamine in dopamine-releasing neurons but continues on to NE in NE-releasing neurons. The same pathway is used by the epinephrine-releasing cells of

TABLE 11.3 Neurotransmitters

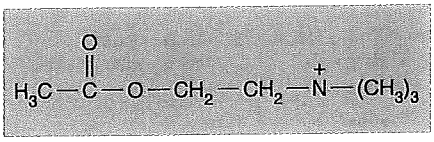
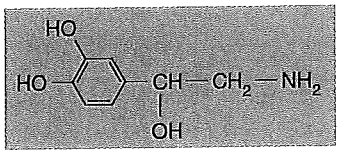
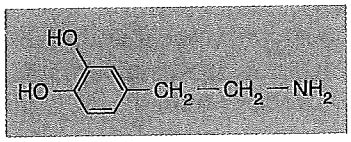
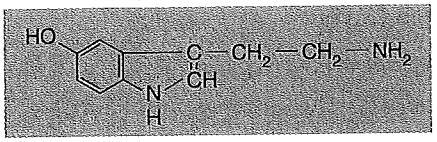
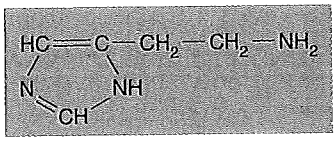
Neurotransmitter	Functional Classes	Sites Where Secreted	Comments
Acetylcholine			
	Excitatory to skeletal muscles; excitatory or inhibitory to visceral effectors, depending on receptors bound Direct action at nicotinic receptors; indirect action via second messengers at muscarinic receptors	CNS: basal nuclei and some neurons of motor cortex of brain PNS: all neuromuscular junctions with skeletal muscle; some autonomic motor endings (all preganglionic and parasympathetic postganglionic fibers)	Effects prolonged (leading to tetanic muscle spasms and neural "frying") by nerve gas and organophosphate insecticides (malathion); release inhibited by botulinus toxin and barbiturates; binding to receptors inhibited by curare (a muscle paralytic agent) and some snake venoms; decreased ACh levels in certain brain areas in Alzheimer's disease; ACh receptors destroyed in myasthenia gravis; binding of nicotine to nicotinic ACh receptors in the brain enhances excitatory neurotransmitter (glutamate, ACh) release by enhancing presynaptic Ca^{2+} levels; may account for behavioral effects of nicotine in smokers; atropine competes with ACh for binding sites
Biogenic Amines			
Norepinephrine 	Excitatory or inhibitory, depending on receptor type bound Indirect action via second messengers	CNS: brain stem, particularly in the locus coeruleus of the midbrain; limbic system; some areas of cerebral cortex PNS: main neurotransmitter of ganglion cells in the sympathetic nervous system	A "feeling good" neurotransmitter; release enhanced by amphetamines; removal from synapse blocked by tricyclic antidepressants [amitriptyline (Elavil) and others] and cocaine; brain levels reduced by reserpine (an antihypertensive drug), leading to depression
Dopamine 	Excitatory or inhibitory depending on the receptor type bound Indirect action via second messengers	CNS: substantia nigra of midbrain; hypothalamus; is the principal neurotransmitter of extrapyramidal system PNS: some sympathetic ganglia	A "feeling good" neurotransmitter; release enhanced by L-dopa and amphetamines; reuptake blocked by cocaine; deficient in Parkinson's disease; may be involved in pathogenesis of schizophrenia
Serotonin (5-HT) 	Mainly inhibitory Indirect action via second messengers; direct action at 5-HT_3 receptors	CNS: brain stem, especially midbrain; hypothalamus; limbic system; cerebellum; pineal gland; spinal cord	Activity blocked by LSD; may play a role in sleep, appetite, nausea, migraine headaches, and regulation of mood; drugs that block its uptake (Prozac) relieve anxiety and depression
Histamine 	Indirect action via second messengers	CNS: hypothalamus	Also released by mast cells during inflammation and acts as powerful vasodilator

TABLE 11.3 *(continued)*

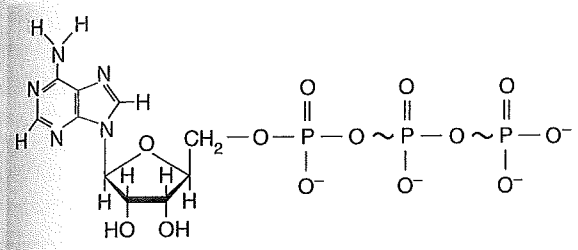
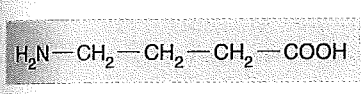
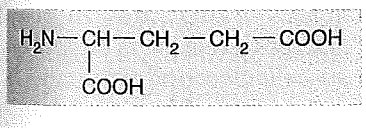
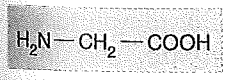
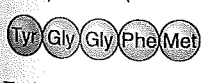
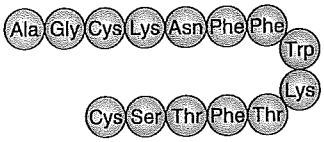
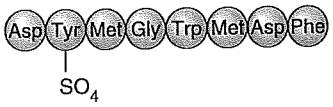
Neurotransmitter	Functional Classes	Sites Where Secreted	Comments
ATP	Excitatory or inhibitory depending on receptor type bound Direct and indirect actions via second messengers	CNS: basal nuclei, induces Ca^{2+} wave propagation in astrocytes PNS: dorsal root ganglion neurons	ATP released by sensory neurons (as well as that released by injured cells) provokes pain sensation
			
Amino Acids			
GABA (γ-aminobutyric acid)	Generally inhibitory Direct action	CNS: hypothalamus; Purkinje cells of cerebellum; spinal cord; granule cells of olfactory bulb; retina	Principal inhibitory neurotransmitter in the brain; important in presynaptic inhibition at axoaxonal synapses; inhibitory effects augmented by alcohol (resulting in impaired motor coordination) and antianxiety drugs of the benzodiazepine class (e.g., Valium); substances that block its synthesis, release, or action induce convulsions
			
Glutamate	Generally excitatory Direct action	CNS: spinal cord; widespread in brain where it represents the major excitatory neurotransmitter	Important in learning and memory; the "stroke neurotransmitter"—excessive release produces excitotoxicity: neurons literally stimulated to death; most commonly caused by ischemia (oxygen deprivation, usually due to a blocked blood vessel); when released by gliomas aids tumor advance
			
Glycine	Generally inhibitory Direct action	CNS: spinal cord and brain stem; retina	Strychnine blocks glycine receptors, resulting in uncontrolled convulsions and respiratory arrest
			
Peptides			
Endorphins, dynorphin, enkephalins (illustrated)	Generally inhibitory Indirect action via second messengers	CNS: widely distributed in brain; hypothalamus; limbic system; pituitary; spinal cord	Natural opiates; inhibit pain by inhibiting substance P; effects mimicked by morphine, heroin, and methadone
			
Tachykinins: Substance P (illustrated), neurokinin A (NKA)	Excitatory Indirect action via second messengers	CNS: basal nuclei; midbrain; hypothalamus; cerebral cortex PNS: certain sensory neurons of dorsal root ganglia of spinal cord (pain afferents)	Substance P mediates pain transmission in the PNS; in the CNS tachykinins are involved in respiratory and cardiovascular controls and in mood
			

TABLE 11.3 **Neurotransmitters** *(continued)*

Neurotransmitter	*Functional Classes*	*Sites Where Secreted*	*Comments*
Somatostatin	Generally inhibitory Indirect action via second messengers	CNS: hypothalamus; retina and other parts of brain Pancreas	Inhibits release of growth hormone; a gut-brain peptide
			
Cholecystokinin (CCK)	Possible neurotransmitter	Cerebral cortex Small intestine	May be related to feeding behaviors; a gut-brain peptide
			
Dissolved Gases			
Nitric oxide (NO)	Excitatory Indirect action via second messengers	CNS: brain spinal cord PNS: adrenal gland; nerves to penis	Its release potentiates stroke damage; some types of male impotence treated by stimulating NO release
Carbon monoxide (CO)	Excitatory Indirect action via second messengers	Brain and some neuromuscular and neuroglandular synapses	—

the brain and the adrenal medulla. *Serotonin* is synthesized from the amino acid tryptophan. *Histamine* is synthesized from the amino acid histidine.

Biogenic amine neurotransmitters are broadly distributed in the brain, where they play a role in emotional behavior and help regulate the biological clock. Additionally, catecholamines (particularly NE) are released by some motor neurons of the autonomic nervous system. Imbalances of these neurotransmitters are associated with mental illness; for example, overproduction of dopamine occurs in schizophrenia. Additionally, certain psychoactive drugs (LSD and mescaline) can bind to biogenic amine receptors and induce hallucinations.

Amino Acids It is difficult to prove a neurotransmitter role when the suspect is an *amino acid,* because amino acids occur in all cells of the body and are important in many biochemical reactions. The amino acids for which a neurotransmitter role is certain include **gamma (γ)-aminobutyric acid (GABA), glycine, aspartate,** and **glutamate,** but there are others. Amino acid neurotransmitters have so far been found only in the CNS.

Peptides The **neuropeptides,** essentially strings of amino acids, include a broad spectrum of molecules with diverse effects. For example, a neuropeptide called **substance P** is an important mediator of pain signals. By contrast, **endorphins,** which include **beta endorphin, dynorphin,** and **enkephalins** (enkef'ah-linz), act as natural opiates, reducing our perception of pain under certain stressful conditions. Enkephalin activity increases dramatically in pregnant women in labor. Endorphin release is enhanced when an athlete gets a so-called second wind and is probably responsible for the "runner's high." Additionally, some researchers claim that the placebo effect is due to endorphin release. These pain-killing neurotransmitters remained undiscovered until investigators began to ask why morphine and other opiates reduce anxiety and pain, and found that these drugs attach to the same receptors that bind natural opiates, producing similar but stronger effects.

Some neuropeptides, such as somatostatin and cholecystokinin, are also produced by nonneural body tissues and are widespread in the gastrointestinal tract. Such peptides are commonly referred to as **gut-brain peptides.**

Novel Messengers Just a few years ago, it would have been scientific suicide to suggest that ATP, nitric oxide, and carbon monoxide—all ubiquitous molecules—might be neurotransmitters. Nonetheless, the discovery of these unlikely messengers has

opened up a whole new chapter in the story of neurotransmission.

Although it was well known that **adenosine triphosphate (ATP)**, the universal form of cellular energy, was stored in synaptic vesicles, its presence there was thought to promote synthesis or reuptake of other neurotransmitters. ATP is now recognized as a major neurotransmitter (perhaps the most primitive one) in both the CNS and PNS. Like glutamate and acetylcholine it produces a fast excitatory response at certain receptors. Depending on the ATP receptor type it binds to, ATP binding can mediate fast excitatory responses or trigger slow second-messenger responses.

Even more preposterous was the idea that **nitric oxide (NO)**, a short-lived toxic gas, could be a neurotransmitter. It defies all the official descriptions of neurotransmitters in that rather than being stored in vesicles and released by exocytosis, it is synthesized on demand and diffuses out of the cells making it. Instead of attaching to surface receptors, it zooms through the plasma membrane of nearby cells to bind with a peculiar intracellular receptor—iron in *guanylyl cyclase,* the enzyme that makes the second messenger *cyclic GMP.* The precise role of NO in the brain has been hard to pin down, but when the neurotransmitter glutamate binds to NMDA receptors, Ca^{2+} channels open to allow an influx of Ca^{2+} into the cell. The Ca^{2+} triggers reactions that activate *nitric oxide synthase (NOS),* the enzyme needed for NO synthesis. Many believe NO is the retrograde messenger involved in long-term potentiation (learning and memory)—that is, it may travel back from the postsynaptic neuron to the presynaptic neuron where it activates guanylyl cyclase. Excessive release of NO is responsible for much of the brain damage seen in stroke patients (see pp. 467–468). In the myenteric plexus of the intestine, NO causes intestinal smooth muscle to relax.

It may be that NO is just the first of a soon-to-be-discovered class of signaling gases that pass swiftly into cells, bind briefly to metal-containing enzymes, and then vanish. **Carbon monoxide (CO)**, another airy messenger, also stimulates synthesis of cyclic GMP, and some researchers speculate that CO is the main regulator of cyclic GMP levels in the brain. Though NO and CO are found in different brain regions and appear to act in different pathways, their mode of action is very similar. The proposed role of CO in neurotransmission leads to an interesting speculation: Heavy smokers who quit often bemoan the fact that they can't concentrate for weeks after. Because CO displaces oxygen in the blood, it would seem that they should think better after quitting. Perhaps the higher blood CO levels they were accustomed to enhanced neurotransmission in certain circuits involved in logic. Time will tell.

Classification of Neurotransmitters by Function

This text cannot begin to describe the incredible diversity of functions that neurotransmitters mediate. Therefore, we limit our discussion to two broad ways of classifying neurotransmitters according to function; more details will be added as appropriate in subsequent chapters.

Effects: Excitatory Versus Inhibitory We can summarize this classification scheme by saying that some neurotransmitters are excitatory (cause depolarization), some are inhibitory (cause hyperpolarization), and others exert both effects, depending on the specific receptor types with which they interact. For example, the amino acids GABA and glycine are usually inhibitory, while glutamate is typically excitatory (see Table 11.3). On the other hand, ACh and NE each bind to at least two receptor types that cause opposite effects. For example, acetylcholine is excitatory at neuromuscular junctions with skeletal muscle and inhibitory in cardiac muscle.

Mechanism of Action: Direct Versus Indirect Neurotransmitters that open ion channels are said to act *directly.* These neurotransmitters provoke rapid responses in postsynaptic cells by promoting changes in membrane potential. ACh and the amino acid neurotransmitters are direct-acting neurotransmitters.

Neurotransmitters that act *indirectly* promote broader, longer-lasting effects by acting through intracellular *second-messenger* molecules [typically via G protein mechanisms as described in Chapter 3 (p. 84)]. In this way their mechanism of action is similar to that of many hormones. The biogenic amines, neuropeptides, and the dissolved gases are indirect neurotransmitters.

Neurotransmitter Receptors

In Chapter 3, we introduced the various receptors involved in cell signaling. Now we are ready to pick up that thread again as we examine the action of receptors that bind neurotransmitters. For the most part, neurotransmitter receptors are either channel-linked receptors, which mediate fast synaptic transmission, or G protein–linked receptors, which oversee slow synaptic responses.

Mechanism of Action of Channel-Linked Receptors Equivalent to ligand-gated ion channels, **channel-linked receptors** mediate direct transmitter action. Also called *ionotropic receptors,* these receptors are composed of several protein subunits arranged in a "rosette" around a central pore. As the ligand binds to one (or more) receptor subunits, the proteins change shape. This event opens the central