8
Overview of Synaptic Transmission

WHAT GIVES NERVE CELLS THEIR SPECIAL ABILITY to communicate with one another rapidly and with such great precision? We have already seen how signals are propagated *within* a neuron, from its dendrites and cell body to its axonal terminals. With this chapter we begin to consider the signaling *between* neurons through the process of synaptic transmission.

The specialized site at which one neuron communicates with another is called a *synapse*, and synaptic transmission is fundamental to the neural functions we consider later in the book, such as perception, voluntary movement, and learning.

The average neuron forms several thousand synaptic connections and receives a similar number. The Purkinje cell of the cerebellum receives up to 100,000 synaptic inputs. Although many of these connections are highly specialized, all neurons make use of one of the two basic forms of synaptic transmission: electrical or chemical. Moreover, the strength of both forms of synaptic transmission can be enhanced or diminished by cellular activity. This *plasticity* of synapses is crucial to memory and other higher brain functions.

Electrical synapses are employed primarily to send rapid and stereotyped depolarizing signals. In contrast, chemical synapses are capable of more variable signaling and thus can produce more complex behaviors. They can mediate either excitatory or inhibitory actions in postsynaptic cells and produce electrical changes in the postsynaptic cell that last from milliseconds to many minutes. Chemical synapses also serve to amplify neuronal signals, so even a small presynaptic nerve terminal can alter the response of large postsynaptic cells. Not surprisingly, most synapses in the brain are chemical. Because chemical synaptic transmission is so central to understanding brain and behavior, it is examined in detail in the next four chapters.

Synapses Are Either Electrical or Chemical

The term *synapse* was introduced at the beginning of the twentieth century by Charles Sherrington to describe the specialized zone of contact at which one neuron communicates with another. This site had first been described histologically at the level of light microscopy by Ramón y Cajal in the late 19th century.

All synapses were initially thought to operate by means of electrical transmission. In the 1920s, however, Otto Loewi discovered that the chemical compound acetylcholine (ACh) conveys signals from the vagus nerve to the heart. Loewi's discovery provoked considerable debate in the 1930s over whether chemical signaling existed at other synapses, including synapses between motor nerve and skeletal muscle as well as synapses in the brain.

Two schools of thought emerged, one physiological and the other pharmacological. Each championed a single mechanism for all synaptic transmission. Led by John Eccles (Sherrington's student), the physiologists argued that synaptic transmission is electrical, that the action potential in the presynaptic neuron generates a current that flows passively into the postsynaptic cell. The pharmacologists, led by Henry Dale, argued that transmission is chemical, that the action potential in the presynaptic neuron leads to the release of a chemical substance that in turn initiates

current in the postsynaptic cell. When physiological and ultrastructural techniques improved in the 1950s and 1960s, it became clear that both forms of transmission exist. Although a chemical transmitter is used at most synapses, some operate purely by electrical means.

Once the fine structure of synapses was made visible with the electron microscope, chemical and electrical synapses were found to have different structures. At chemical synapses the presynaptic and postsynaptic neurons are completely separated by a small space, called the synaptic cleft; there is no continuity between the cytoplasm of one cell and the next. In contrast, at electrical synapses the pre- and postsynaptic cells communicate through special channels, the *gap-junction channels*, that directly connect the cytoplasm of the two cells.

The main functional properties of the two types of synapses are summarized in Table 8–1. The most important difference can be observed by injecting a positive current into the presynaptic cell to elicit a depolarization. At both types of synapses outward current across the presynaptic cell membrane deposits positive charge on the inside of the presynaptic cell membrane, thereby depolarizing the cell (see Chapter 6). At electrical synapses some of the current will enter the postsynaptic cell through the gap-junction channels, depositing a positive charge on the inside of the membrane and depolarizing it. The current leaves the postsynaptic cell across the membrane capacitance and through resting channels (Figure 8–1A). If the depolarization exceeds threshold, voltage-gated ion channels in the postsynaptic cell open and generate an action potential. By contrast, at chemical synapses there is no direct low-resistance pathway between the pre- and postsynaptic cells. Instead, the action potential in the presynaptic neuron initiates the release of a chemical transmitter, which diffuses across the synaptic cleft to interact with receptors on the membrane of the postsynaptic cell (Figure 8-1B).

Table 8–1 Distinguishing Properties of Electrical and Chemical Synapses

Type of synapse	Distance between pre- and postsynaptic cell membranes	Cytoplasmic continuity between pre- and postsynaptic cells	Ultrastructural components	Agent of transmission	Synaptic delay	Direction of transmission
Electrical	4 nm	Yes	Gap-junction channels	Ion current	Virtually absent	Usually bidirectional
Chemical	20–40 nm	No	Presynaptic vesicles and active zones; postsynaptic receptors	Chemical transmitter	Significant: at least 0.3 ms, usually 1–5 ms or longer	Unidirectional

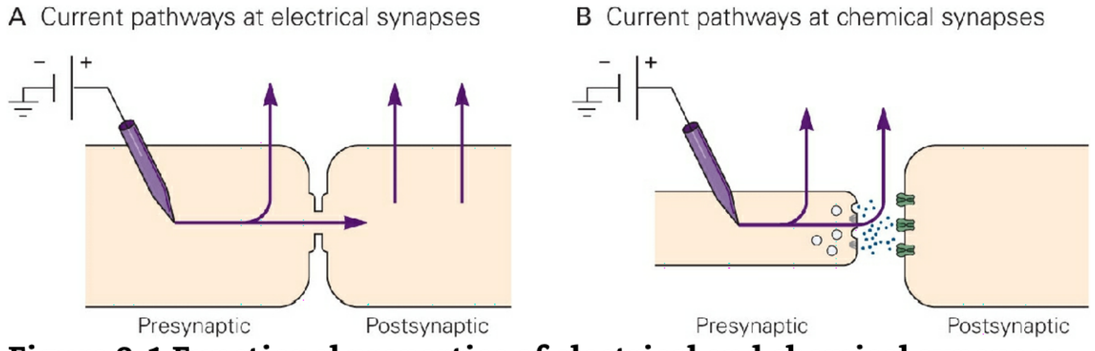

Figure 8-1 Functional properties of electrical and chemical synapses.

A. At an electrical synapse some current injected into the presynaptic cell escapes through resting (nongated) ion channels in the cell membrane. However, some current also enters the postsynaptic cell through gap-junction channels that connect the cytoplasm of the pre- and postsynaptic cells and that provide a low-resistance (high-conductance) pathway for electrical current.

B. At chemical synapses all current injected into the presynaptic cell escapes into the extracellular fluid. However, the resulting depolarization of the presynaptic cell membrane can produce an action potential that causes the release of neurotransmitter molecules that bind receptors on the postsynaptic cell. This binding opens ion channels that initiate a change in membrane potential in the postsynaptic cell.

Electrical Synapses Provide Instantaneous Signal Transmission

During excitatory synaptic transmission at an electrical synapse, voltage-

gated ion channels in the presynaptic cell generate the current that depolarizes the postsynaptic cell. Thus these channels not only depolarize the presynaptic cell above the threshold for an action potential but also generate sufficient ionic current to produce a change in potential in the postsynaptic cell.

To generate such a large current, the presynaptic terminal must be big enough for its membrane to contain many ion channels. At the same time, the postsynaptic cell must be relatively small. This is because a small cell has a higher input resistance (R_{in}) than a large cell and, according to Ohm's law ($\Delta V = I \times R_{in}$), undergoes a greater voltage change (ΔV) in response to a given presynaptic current (I).

Electrical synaptic transmission was first described by Edwin Furshpan and David Potter in the giant motor synapse of the crayfish, where the presynaptic fiber is much larger than the postsynaptic fiber (Figure 8–2A). An action potential generated in the presynaptic fiber produces a depolarizing postsynaptic potential that often exceeds the threshold to fire an action potential. At electrical synapses, the synaptic delay—the time between the presynaptic spike and the postsynaptic potential—is remarkably short (Figure 8-2B).

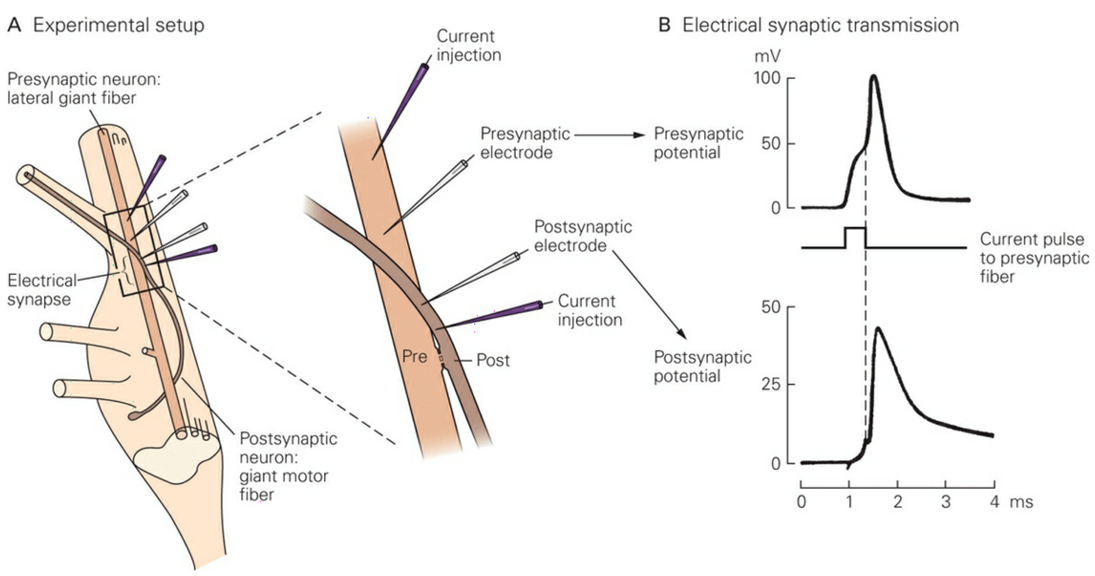

Figure 8-2 Electrical synaptic transmission was first demonstrated at the giant motor synapse in the crayfish. (Adapted, with permission, from Furshpan and Potter 1957 and 1959.)

A. The lateral giant fiber running down the nerve cord is the presynaptic neuron. The giant motor fiber, which projects from the cell body in the ganglion to the periphery, is the postsynaptic neuron. Electrodes for passing current and for recording voltage are placed within the pre- and postsynaptic cells.

B. Transmission at an electrical synapse is virtually instantaneous—the postsynaptic response follows presynaptic stimulation in a fraction of a millisecond. The **dashed line** shows how the responses of the two cells correspond in time. At chemical synapses there is a delay (the synaptic delay) between the pre- and postsynaptic potentials (see Figure 8-8).

Such a short latency is not possible with chemical transmission, which requires several biochemical steps: release of a transmitter from the presynaptic neuron, diffusion of transmitter molecules to the postsynaptic cell, binding of transmitter to a specific receptor, and subsequent gating of ion channels (all described later in this chapter). Only current passing directly from one cell to another can produce the near-instantaneous transmission observed at the giant motor synapse.

Another feature of electrical transmission is that the change in potential of the postsynaptic cell is directly related to the size and shape of the change in potential of the presynaptic cell. Even when a weak subthreshold depolarizing current is injected into the presynaptic neuron, some current enters the postsynaptic cell and depolarizes it (Figure 8–3). In contrast, at a chemical synapse the current in the presynaptic cell must reach the threshold for an action potential before it can release transmitter and elicit a response in the postsynaptic cell.

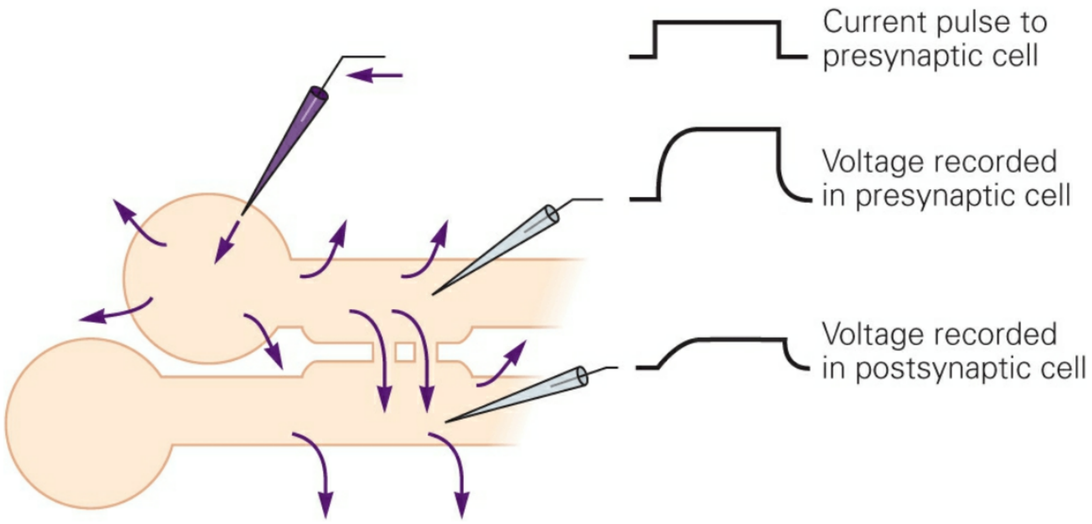

Figure 8-3 Electrical transmission is graded and occurs even when the current in the presynaptic cell is below the threshold for an action potential. This can be demonstrated by depolarizing the presynaptic cell with a small current pulse through one electrode while the membrane potential is recorded with a second electrode. A subthreshold depolarizing stimulus causes a passive depolarization in the presynaptic and postsynaptic cells. (Depolarizing or outward current is indicated by an upward deflection.)

Most electrical synapses can transmit both depolarizing and hyperpolarizing currents. A presynaptic action potential with a large hyperpolarizing afterpotential produces a biphasic (depolarizing-hyperpolarizing) change in potential in the postsynaptic cell. Signal transmission at electrical synapses is similar to the passive propagation of subthreshold electrical signals along axons (see Chapter 6) and therefore is also referred to as *electrotonic transmission*. At some specialized gap junctions the channels have voltage-dependent gates that permit them to conduct depolarizing current in only one direction, from the presynaptic cell to the postsynaptic cell. These junctions are called *rectifying synapses*. (The crayfish giant motor synapse is an example.)

Cells at an Electrical Synapse Are Connected by Gap-Junction Channels

The specialized region of contact between two neurons at an electrical synapse is termed the *gap junction*. Here the separation between the two neurons (4 nm) is much less than the normal nonsynaptic space between neurons (20 nm). This narrow gap is bridged by the gap-junction channels, specialized protein structures that conduct ionic current from the presynaptic to the postsynaptic cell.

A gap-junction channel consists of a pair of *hemichannels*, or connexons, one in the presynaptic and the other in the postsynaptic cell membrane. These hemichannels thus form a continuous bridge that provides a direct communication path between the two cells (Figure 8–4). The pore of the channel has a large diameter of approximately 1.5 nm, which permits inorganic ions and small organic molecules and experimental markers such as fluorescent dyes to pass between the two cells.

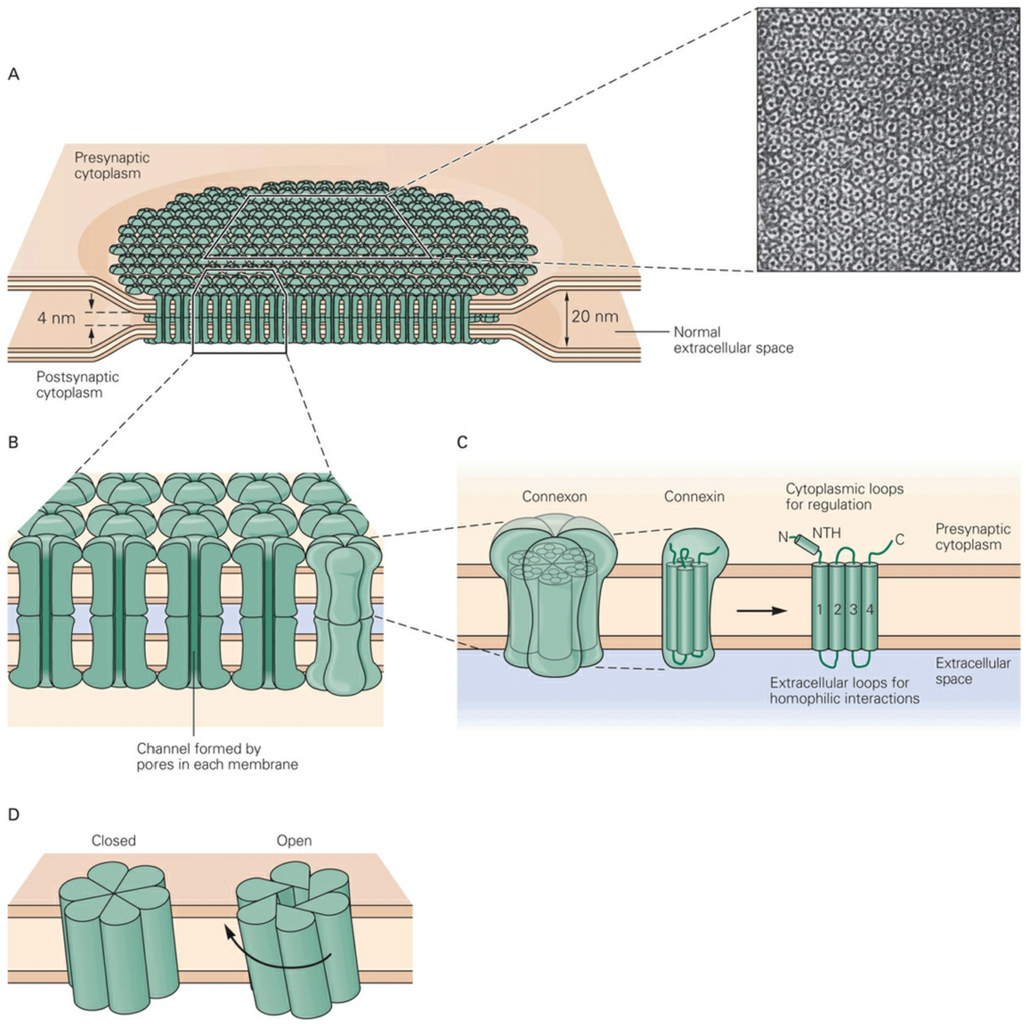

Figure 8-4 A three-dimensional model of the gap-junction channel, based on X-ray and electron diffraction studies.

A. The electrical synapse, or gap junction, is composed of numerous specialized channels that span the membranes of two neurons. These gap-junction channels allow current to pass directly from one cell to the other. The array of channels shown in the electron micrograph was isolated from the membrane of a rat liver. The tissue has been negatively stained, a technique that darkens the area around the channels and in the pores. Each channel appears hexagonal in outline. Magnification × 307,800. (Reproduced, with permission, from N. Gilula.)

B. A gap-junction channel is actually a pair of hemichannels, one in each apposite cell that connects the cytoplasm of the two cells. (Adapted, with permission, from Makowski et al. 1977.)

C. Each hemichannel, or connexon, is made up of six identical subunits called connexins. Each connexin is approximately 7.5 nm long and spans the cell membrane. A single connexin has intracellular N- and C-termini, including a short intracellular N-terminal α-helix (NTH), and four membrane-spanning α-helixes (1–4). There are regions of similarity in the amino acid sequences of gap-junction proteins from many different kinds of tissue. These include the transmembrane helixes and the extracellular regions, which are involved in the homophilic matching of apposite hemichannels.

D. The connexins are arranged in such a way that a pore is formed in the center of the structure. The resulting connexon, with a pore diameter of approximately 1.5 to 2 nm, has a characteristic hexagonal outline, as shown in part A. In some gap-junction channels the pore is opened when the subunits rotate approximately 0.9 nm at the cytoplasmic base in a clockwise direction. (Reproduced, with permission, from Unwin and Zampighi 1980.)

Each hemichannel or connexon is composed of six identical subunits, called *connexins*. Connexins in different tissues are encoded by a large gene family containing more than 20 members. All connexin subunits have an intracellular N- and C-terminus with four interposed α-helixes that span the cell membrane (Figure 8-4C). Many gap-junction channels in different cell types are formed by the products of different connexin genes and thus respond differently to modulatory factors that control their opening and closing. For example, although most gap-junction channels close in response to lowered cytoplasmic pH or elevated cytoplasmic Ca^{2+}, the sensitivity of different channel isoforms to these factors varies widely. This pH and Ca^{2+}-dependent closing of gap-junction channels plays an important role in the decoupling of damaged cells from healthy cells, because damaged cells contain elevated Ca^{2+} levels and a high concentration of protons. Finally, neurotransmitters released from nearby chemical synapses can modulate the opening of gap-junction channels through intracellular metabolic reactions (see Chapter 11).

The three-dimensional structure of a gap-junction channel formed by the human connexin 26 subunit has recently been determined by X-ray crystallography. This structure shows in detail how the membrane-spanning α-helixes assemble to form the central pore of the channel and how the extracellular loops connecting the transmembrane helixes interdigitate to connect the two hemichannels (Figure 8–5). The pore is lined with polar residues that facilitate the movement of ions. An N-terminal α-helix may serve as the voltage gate of the connexin 26 channel, plugging the cytoplasmic mouth of the pore in the closed state. A separate gate at the extracellular side of the channel, formed by the extracellular loop connecting the first two membrane helixes, has been inferred from functional studies. This loop gate is thought to close isolated hemichannels that are not docked to a hemichannel partner in the apposing cell.

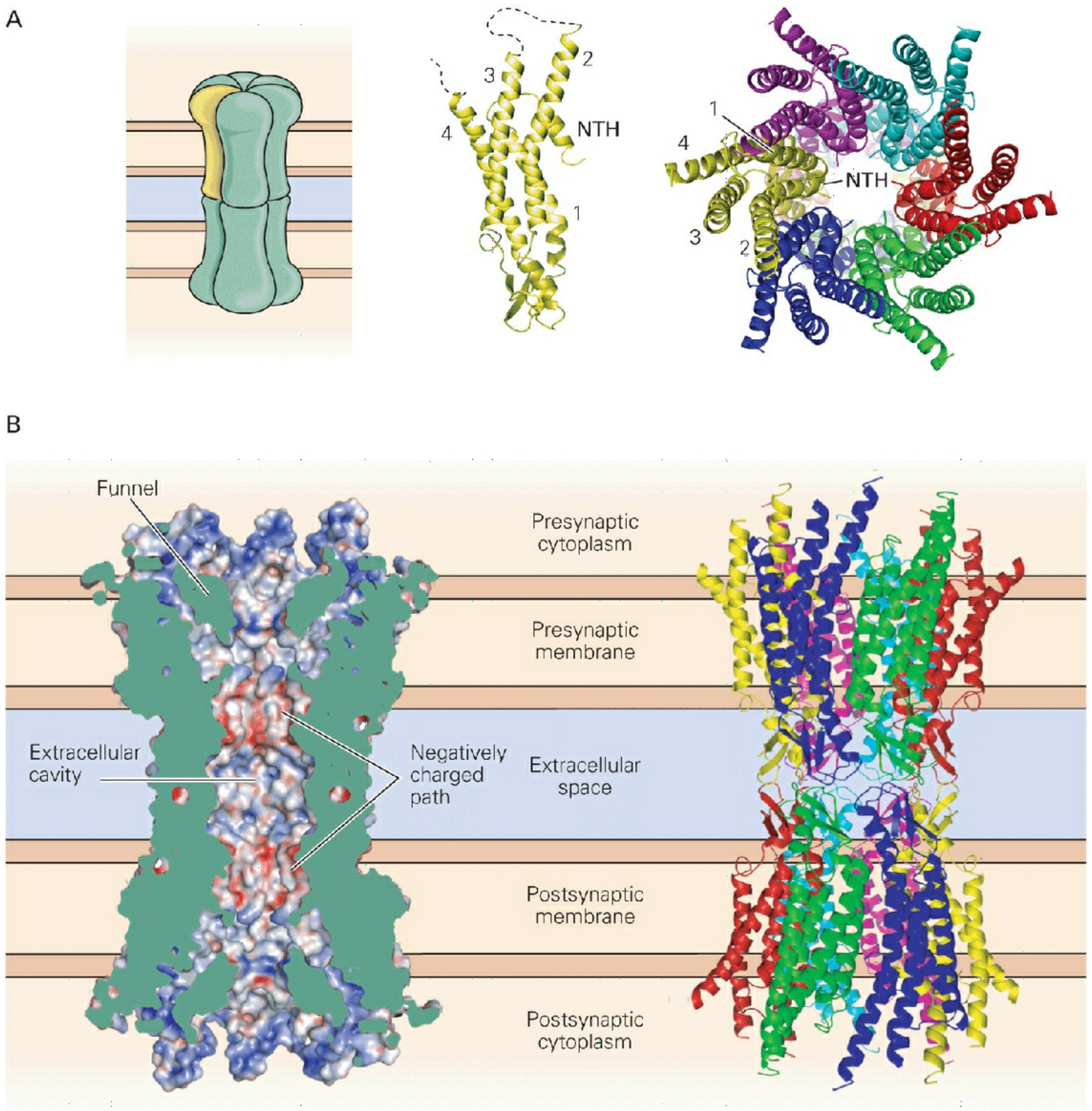

Figure 8-5 High-resolution three-dimensional structure of a gap-junction channel. All structures were determined by X-ray crystallography of gap-junction channels formed by the human connexon 26 subunit. (Reproduced, with permission, from Maeda et al., 2009.)

A. Left: Diagram of an intact gap-junction channel showing the pair of apposed hemichannels in the pre- and postsynaptic cells. **Middle**: High-resolution structure of a single connexin subunit showing the presence of four transmembrane α-helixes (1–4) and a short N-terminal helix (NTH). The orientation of the subunit corresponds to that of the yellow subunit in the diagram to the left. **Right**: Bottom-up view looking into a hemichannel from the cytoplasm. Each of the six subunits has a different color. The helixes of the yellow subunit are numbered. The orientation corresponds to that of the yellow hemichannel in the diagram at left, following a 90° rotation toward the viewer.

B. Two side views of the gap-junction channel in the plane of the membrane show the two apposed hemichannels. The orientation is the same as in the panel of part A. **Left**: Cross-section through the channel shows the internal surface of the channel pore. **Blue** indicates positively charged surfaces, and **red** indicates negatively charged surfaces. The **green mass** inside the pore at the cytoplasmic entrance (funnel) is thought to represent the channel gate formed by the N-terminal helix. **Right**: A side view of the channel shows each of the six connexin subunits in the same color scheme as in part A. The entire gap-junction channel is approximately 9 nm wide by 15 nm tall.

Electrical Transmission Allows the Rapid and Synchronous Firing of Interconnected Cells

How are electrical synapses useful? As we have seen, transmission across electrical synapses is extremely rapid because it results from the direct passage of current between cells. Speed is important for escape responses. For example, the tail-flip response of goldfish is mediated by a giant neuron in the brain stem (known as the Mauthner cell), which receives sensory input at electrical synapses. These electrical synapses rapidly depolarize the Mauthner cell, which in turn activates the motor neurons of the tail, allowing rapid escape from danger.

Electrical transmission is also useful for orchestrating the actions of large groups of neurons. Because current crosses the membranes of all electrically coupled cells at the same time, several small cells can act coordinately as one large cell. Moreover, because of the electrical coupling between the cells, the effective resistance of the coupled network of neurons is smaller than the resistance of an individual cell. Thus, from Ohm's law, the synaptic current required to fire electrically coupled cells is larger than that necessary to fire an individual cell. That is, electrically

coupled cells have a higher firing threshold. Once this high threshold is surpassed, however, electrically coupled cells fire synchronously because voltage-activated Na^+ currents generated in one cell are very rapidly conducted to other cells.

Thus a behavior controlled by a group of electrically coupled cells has an important adaptive advantage: It is triggered explosively. For example, when seriously perturbed, the marine snail *Aplysia* releases massive clouds of purple ink that provide a protective screen. This stereotypic behavior is mediated by three electrically coupled motor cells that innervate the ink gland. Once the action potential threshold is exceeded in these cells, they fire synchronously (Figure 8–6). In certain fish, rapid eye movements (called saccades) are also mediated by electrically coupled motor neurons firing together. Gap junctions are also important in the mammalian brain, where the synchronous firing of electrically coupled inhibitory interneurons generates synchronous, high-frequency oscillations.

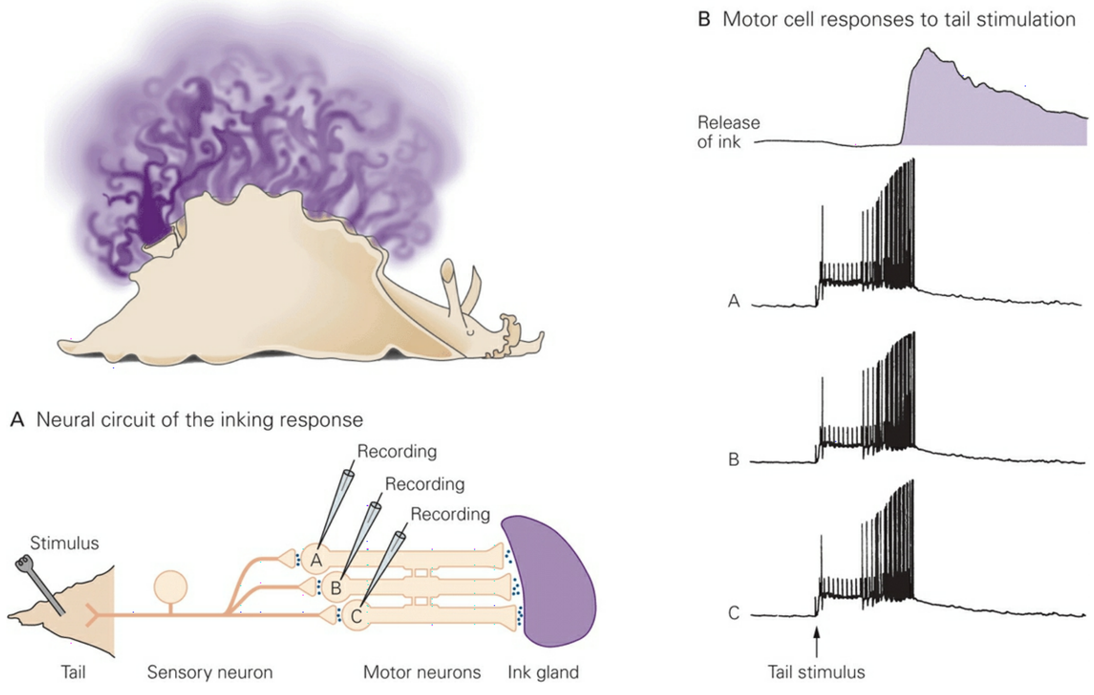

Figure 8-6 Electrically coupled motor neurons firing together can produce synchronous behaviors. (Adapted, with permission, from Carew and Kandel 1976.)

A. In the marine snail *Aplysia* sensory neurons from the tail ganglion form synapses with three motor neurons that innervate the ink gland. The motor neurons are interconnected by electrical synapses.

B. A train of stimuli applied to the tail produces a synchronized discharge in all three motor neurons that results in the release of ink.

In addition to providing speed or synchrony in neuronal signaling, electrical synapses also can transmit metabolic signals between cells. Because gap-junction channels are relatively large and nonselective, they conduct a variety of inorganic cations and anions, including the second messenger Ca^{2+}, and even allow moderate-sized organic compounds (less than 1,000 Da molecular weight)—such as the second messengers inositol 1,4,5-trisphosphate (IP_3), cyclic adenosine monophosphate (cAMP), and even small peptides—to pass from one cell to the next.

Gap Junctions Have a Role in Glial Function and Disease

Gap junctions are formed between glial cells as well as between neurons. In glia the gap junctions mediate both intercellular and intracellular communication. In the brain individual astrocytes are connected to each other through gap junctions, which mediate communication between them, forming a glial cell network. Electrical stimulation of neuronal pathways in brain slices can release neurotransmitters that trigger a rise in intracellular Ca^{2+} in certain astrocytes. This produces a wave of Ca^{2+} that propagates at a rate of approximately 1 μm/s, traveling from astrocyte to astrocyte by diffusion through gap-junction channels. Although the precise function of the waves is unknown, their existence suggests that glia may play an active role in signaling in the brain.

Gap-junction channels also enhance communication *within* certain glial cells, the Schwann cells that produce the myelin sheath of axons in the peripheral nervous system. Successive layers of myelin formed by a single Schwann cell are connected by gap junctions. These gap junctions may help to hold the layers of myelin together and promote the passage of small metabolites and ions across the many layers of myelin. The importance of the Schwann cell gap-junction channels is underscored by certain genetic diseases. For example, the X chromosome-linked form of Charcot-Marie-Tooth disease, a demyelinating disorder, is caused by sin-

gle mutations in a connexin gene (*connexin 32*) expressed in the Schwann cell that blocks gap-junction channel function. Inherited mutations that prevent the function of a connexin expressed in the cochlea (connexin 26) underlie up to half of all instances of congenital deafness. This connexin normally forms gap-junction channels that are important for fluid secretion in the inner ear.

Chemical Synapses Can Amplify Signals

In contrast to electrical synapses, at chemical synapses there is no structural continuity between pre- and postsynaptic neurons. In fact, the separation between the two cells at a chemical synapse, the synaptic cleft, is usually wider (20–40 nm) than the nonsynaptic intercellular space (20 nm). Chemical synaptic transmission depends on the diffusion of a neurotransmitter across the synaptic cleft. A neurotransmitter is a chemical substance that binds receptors in the postsynaptic membrane of the target cell. At most chemical synapses transmitter is released from specialized swellings of the axon, the presynaptic terminals, which typically contain 100 to 200 synaptic vesicles, each of which is filled with several thousand molecules of the neurotransmitter (Figure 8–7).

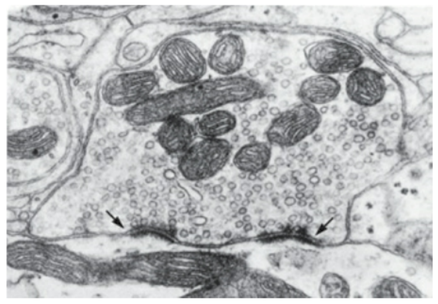

Figure 8-7 The fine structure of a presynaptic terminal. This electron micrograph shows a synapse in the cerebellum. The large dark structures are mitochondria. The many small round bodies are vesicles that contain neurotransmitter. The fuzzy dark thickenings along the presynaptic membrane (arrows) are the active zones, specialized areas that are thought to be docking and release sites for synaptic vesicles. The synaptic cleft is the space just outside the presynaptic terminal separating the pre- and postsynaptic cell membranes. (Reproduced, with permission, from J. E. Heuser and T. S. Reese.)

The synaptic vesicles are clustered at specialized regions of the presynaptic membrane called *active zones*, which are the sites of neurotransmitter release. During a presynaptic action potential, voltage-gated Ca^{2+} channels at the active zone open, allowing Ca^{2+} to enter the presynaptic terminal. The rise in intracellular Ca^{2+} concentration triggers a biochemical reaction that causes the vesicles to fuse with the presynaptic membrane and release neurotransmitter into the synaptic cleft, a process termed *exocytosis*. The transmitter molecules then diffuse across the synaptic cleft and bind to their receptors on the postsynaptic cell membrane. This in turn activates the receptors, leading to the opening or closing of ion channels. The resulting flux of ions alters the membrane conductance and potential of the postsynaptic cell (Figure 8–8).

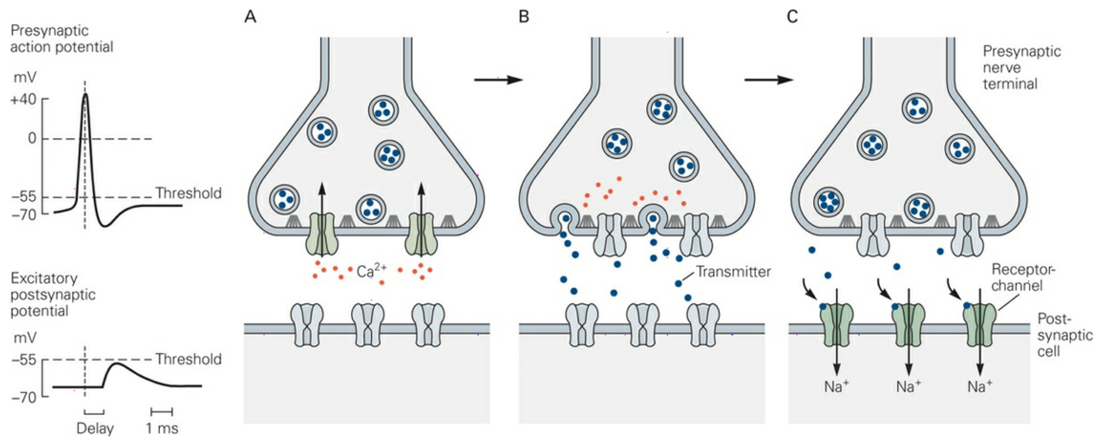

Figure 8-8 Synaptic transmission at chemical synapses involves several steps. The complex process of chemical synaptic transmission accounts for the delay between an action potential in the presynaptic cell and the synaptic potential in the postsynaptic cell compared with the virtually instantaneous transmission of signals at electrical synapses (see Figure 8-2B).

A. An action potential arriving at the terminal of a presynaptic axon causes voltage-gated Ca^{2+} channels at the active zone to open. The **gray filaments** represent the docking and release sites of the active zone.

B. The Ca^{2+} channel opening produces a high concentration of intracellular Ca^{2+} near the active zone, causing vesicles containing neurotransmitter to fuse with the presynaptic cell membrane and release their

contents into the synaptic cleft (a process termed *exocytosis*).

C. The released neurotransmitter molecules then diffuse across the synaptic cleft and bind specific receptors on the postsynaptic membrane. These receptors cause ion channels to open (or close), thereby changing the membrane conductance and membrane potential of the postsynaptic cell.

These several steps account for the synaptic delay at chemical synapses, a delay that can be as short as 0.3 ms but often lasts several milliseconds. Although chemical transmission lacks the speed of electrical synapses, it has the important property of *amplification*. Just one synaptic vesicle releases several thousand molecules of transmitter that together can open thousands of ion channels in the target cell. In this way a small presynaptic nerve terminal, which generates only a weak electrical current, can depolarize a large postsynaptic cell.

Neurotransmitters Bind to Postsynaptic Receptors

Chemical synaptic transmission can be divided into two steps: a transmitting step, in which the presynaptic cell releases a chemical messenger, and a receptive step, in which the transmitter binds to and activates the receptor molecules in the postsynaptic cell. The transmitting process resembles endocrine hormone release. Indeed, chemical synaptic transmission can be seen as a modified form of hormone secretion. Both endocrine glands and presynaptic terminals release a chemical agent with a signaling function, and both are examples of regulated secretion (Chapter 4). Similarly, both endocrine glands and neurons are usually some distance from their target cells. There is one important difference, however, between endocrine and synaptic signaling. Whereas the hormone released by a gland travels through the blood stream until it interacts with all cells that contain an appropriate receptor, a neuron usually communicates only with the cells with which it forms synapses. Because the presynaptic action potential triggers the release of a chemical transmitter onto a target cell across a distance of only 20 nm, the chemical signal travels only a small distance to its target. Therefore, neuronal signaling has two special features: It is fast and precisely directed.

To accomplish this directed or focused release, most neurons have specialized secretory machinery, the active zones, which are directly apposed to the transmitter receptors in the postsynaptic cell. In neurons without active zones, the distinction between neuronal and hormonal transmission becomes blurred. For example, the neurons in the autonomic nervous system that innervate smooth muscle reside at some distance from their postsynaptic cells and do not have specialized release sites in their terminals. Synaptic transmission between these cells is slower and relies on a more widespread diffusion of transmitter. Furthermore, the same transmitter substance can be released differently from different cells. From one cell a substance can be released as a conventional transmitter acting directly on neighboring cells. From other cells it can be released in a less focused way as a modulator, producing a more diffuse action; and from still other cells it can be released into the blood stream as a neurohormone.

Although a variety of chemicals serve as neurotransmitters, including both small molecules and peptides (see Chapter 13), the action of a transmitter depends on the properties of the postsynaptic receptors that recognize and bind the transmitter, not the chemical properties of the transmitter. For example, ACh can excite some postsynaptic cells and inhibit others, and at still other cells it can produce both excitation and inhibition. It is the receptor that determines the action of ACh, including whether a cholinergic synapse is excitatory or inhibitory.

Within a group of closely related animals, a transmitter substance binds conserved families of receptors and can be often associated with specific physiological functions. In vertebrates ACh acts on excitatory ACh receptors at all neuromuscular junctions to trigger contraction and it acts on inhibitory ACh receptors to slow the heart.

The notion of a receptor was introduced in the late 19th century by the German bacteriologist Paul Ehrlich to explain the selective action of toxins and other pharmacological agents and the great specificity of immunological reactions. In 1900 Ehrlich wrote: “Chemical substances are only able to exercise an action on the tissue elements with which they are able to establish an intimate chemical relationship … [This relationship] must be specific. The [chemical] groups must be adapted to one another … as lock and key.”

In 1906 the English pharmacologist John Langley postulated that the

sensitivity of skeletal muscle to curare and nicotine was caused by a "receptive molecule." A theory of receptor function was later developed by Langley's students (in particular, A.V. Hill and Henry Dale), a development that was based on concurrent studies of enzyme kinetics and cooperative interactions between small molecules and proteins. As we shall see in the next chapter, Langley's "receptive molecule" has been isolated and characterized as the ACh receptor of the neuromuscular junction.

All receptors for chemical transmitters have two biochemical features in common:

1. They are membrane-spanning proteins. The region exposed to the external environment of the cell recognizes and binds the transmitter from the presynaptic cell.
2. They carry out an effector function within the target cell. The receptors typically influence the opening or closing of ion channels.

Postsynaptic Receptors Gate Ion Channels Either Directly or Indirectly

Neurotransmitters control the opening of ion channels in the postsynaptic cell either directly or indirectly. These two classes of transmitter actions are mediated by receptor proteins derived from different gene families.

Receptors that gate ion channels directly, such as the ACh receptor at the neuromuscular junction, are composed of four or five subunits that form a single macromolecule. Such receptors contain both an extracellular domain that forms the binding site for the transmitter and a membrane-spanning domain that forms an ion-conducting pore (Figure 8–9A). This kind of receptor is often referred to as *ionotropic*. Upon binding neurotransmitter, the receptor undergoes a conformational change that opens the channel. The actions of ionotropic receptors, also called *receptor-channels* or *ligand-gated channels*, are discussed in detail in Chapters 9 and 10.

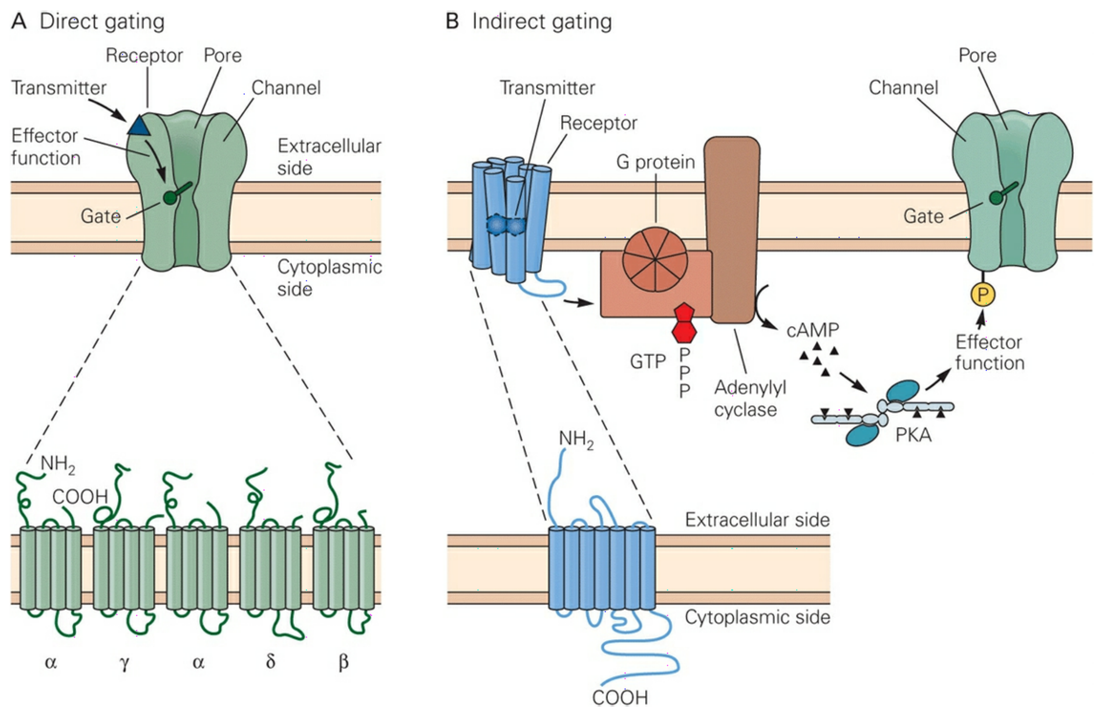

Figure 8-9 Neurotransmitters open postsynaptic ion channels either directly or indirectly.

A. A receptor that directly opens ion channels is an integral part of the macromolecule that also forms the channel. Many such ligand-gated channels are composed of five subunits, each of which is thought to contain four membrane-spanning α-helical regions.

B. A receptor that indirectly opens an ion channel is a distinct macromolecule separate from the channel it regulates. In one large family of such receptors, the receptors are composed of a single subunit with seven membrane-spanning α-helical regions that bind the ligand within the plane of the membrane. These receptors activate a guanosine triphosphate (GTP)–binding protein (G protein), which in turn activates a second-messenger cascade that modulates channel activity. In the cascade illustrated here the G protein stimulates adenylyl cyclase, which converts adenosine triphosphate (ATP) to cAMP. The cAMP activates the cAMP-dependent protein kinase (PKA), which phosphorylates the channel (P), leading to a change in function.

Receptors that gate ion channels indirectly, like the several types of receptors for norepinephrine or dopamine in neurons of the cerebral

cortex, are normally composed of one or at most two subunits that are distinct from the ion channels they regulate. These receptors, which commonly have seven membrane-spanning α-helixes, act by altering intracellular metabolic reactions and are often referred to as *metabotropic receptors*. Activation of these receptors often stimulates the production of second messengers, small freely diffusible intracellular metabolites such as cAMP or diacylglycerol. Many of these second messengers activate protein kinases, enzymes that phosphorylate different substrate proteins. In many instances the protein kinases directly phosphorylate ion channels, leading to their opening or closing (Figure 8-9B). The actions of metabotropic receptors are examined in detail in Chapter 11.

Ionotropic and metabotropic receptors have different functions. The ionotropic receptors produce relatively fast synaptic actions lasting only milliseconds. These are commonly found at synapses in neural circuits that mediate rapid behaviors, such as the stretch receptor reflex. The metabotropic receptors produce slower synaptic actions lasting seconds to minutes. These slower actions can modulate behavior by altering the excitability of neurons and the strength of the synaptic connections of the neural circuitry mediating behavior. Such modulatory synaptic actions often act as crucial reinforcing pathways in the process of learning.

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Selected Readings

Bennett MV, Zukin RS. 2004. Electrical coupling and neuronal synchronization in the mammalian brain. Neuron 19:495–511.

Colquhoun D, Sakmann B. 1998. From muscle endplate to brain synapses: a short history of synapses and agonist-activated ion channels. Neuron 20:381–387.

Cowan WM, Kandel ER. 2000. A brief history of synapses and synaptic transmission. In: MW Cowan, TC Südhof, CF Stevens (eds). *Synapses*, pp. 1–87. Baltimore and London: The Johns Hopkins Univ. Press.

Eccles JC. 1976. From electrical to chemical transmission in the central nervous system. The closing address of the Sir Henry Dale Centennial Symposium. Notes Rec R Soc Lond 30:219–230.

Furshpan EJ, Potter DD. 1959. Transmission at the giant motor synapses of the crayfish. J Physiol 145:289–325.

Goodenough DA, Paul DL. 2009. Gap junctions. Cold Spring Harb Perspect Biol 1:a002576.

Jessell TM, Kandel ER. 1993. Synaptic transmission: a bidirectional and a self-modifiable form of cell-cell communication. Cell 72:1–30.

Nakagawa S, Maeda S, Tsukihara T. 2010. Structural and functional studies of gap junction channels. Curr Opin Struct Biol 20:423–430

References

Beyer EC, Paul DL, Goodenough DA. 1987. Connexin 43: a protein from rat heart homologous to a gap junction protein from liver. J Cell Biol 105:2621–2629.

Bruzzone R, White TW, Scherer SS, Fischbeck KH, Paul DL. 1994. Null mutations of connexin 32 in patients with x-linked Charcot-Marie-Tooth disease. Neuron 13:1253–1260.

Carew TJ, Kandel ER. 1976. Two functional effects of decreased conductance EPSP's: synaptic augmentation and increased electrotonic coupling. Science 192:150–153.

Cornell-Bell AH, Finkbeiner SM, Cooper MS, Smith SJ. 1990. Glutamate induces calcium waves in cultured astrocytes: long-range glial signaling. Science 247:470–473.

Dale H. 1935. Pharmacology and nerve-endings. Proc R Soc Lond 28:319–332.

Eckert R. 1988. Propagation and transmission of signals. In: *Animal Physiology: Mechanisms and Adaptations*, 3rd ed., pp. 134–176. New York: Freeman.

Ehrlich P. 1900. On immunity with special reference to cell life. Croonian Lect Proc R Soc Lond 66:424–448.

Furshpan EJ, Potter DD. 1957. Mechanism of nerve-impulse transmission

at a crayfish synapse. Nature 180:342–343.

Harris AL. 2009. Gating on the outside. J Gen Physiol 133:549–553.

Heuser JE, Reese TS. 1977. Structure of the synapse. In: ER Kandel (ed). *Handbook of Physiology: A Critical, Comprehensive Presentation of Physiological Knowledge and Concepts*, Sect. 1. *The Nervous System*, Vol. 1 *Cellular Biology of Neurons*, Part 1, pp. 261–294. Bethesda, MD: American Physiological Society.

Jaslove SW, Brink PR. 1986. The mechanism of rectification at the electrotonic motor giant synapse of the crayfish. Nature 323:63–65.

Langley JN. 1906. On nerve endings and on special excitable substances in cells. Proc R Soc Lond B Biol Sci 78:170–194.

Loewi O, Navratil E. 1926. Über humorale Übertragbarkeit der Herznervenwirkung. X. Mitteilung: über das Schicksal des Vagusstoffs. Pflügers Arch 214:678–688; 1972. Translated in: On the humoral propagation of cardiac nerve action. Communication X. The fate of the vagus substance. In: I Cooke, M Lipkin Jr (eds). *Cellular Neurophysiology: A Source Book*, pp. 478–485. New York: Holt, Rinehart and Winston.

Maeda S, Nakagawa S, Suga M, Yamashita E, Oshima A, Fujiyoshi Y, Tsukihara T. 2009. Structure of the connexin 26 gap junction channel at 3.5 Å resolution. Nature 458:597–602.

Makowski L, Caspar DL, Phillips WC, Goodenough DA. 1977. Gap junction structures. II. Analysis of the X-ray diffraction data. J Cell Biol 74:629–645.

Pappas GD, Waxman SG. 1972. Synaptic fine structure: morphological correlates of chemical and electronic transmission. In: GD Pappas, DP Purpura (eds). *Structure and Function of Synapses*, pp. 1–43. New York: Raven.

Ramón y Cajal S. 1894. La fine structure des centres nerveux. Proc R Soc Lond 55:444–468.

Ramón y Cajal S. 1911. *Histologie du Système Nerveux de l'Homme & des Vertébrés*, Vol. 2. L Azoulay (transl). Paris: Maloine, 1955. Reprint. Madrid: Instituto Ramón y Cajal.

Sherrington C. 1947. *The Integrative Action of the Nervous System*, 2nd ed. New Haven: Yale Univ. Press.

Unwin PNT, Zampighi G. 1980. Structure of the junction between communicating cells. Nature 283:545–549.

Whittington MA, Traub RD. 2003. Interneuron diversity series: inhibitory interneurons and network oscillations in vitro. Trends Neurosci 26:676–682.