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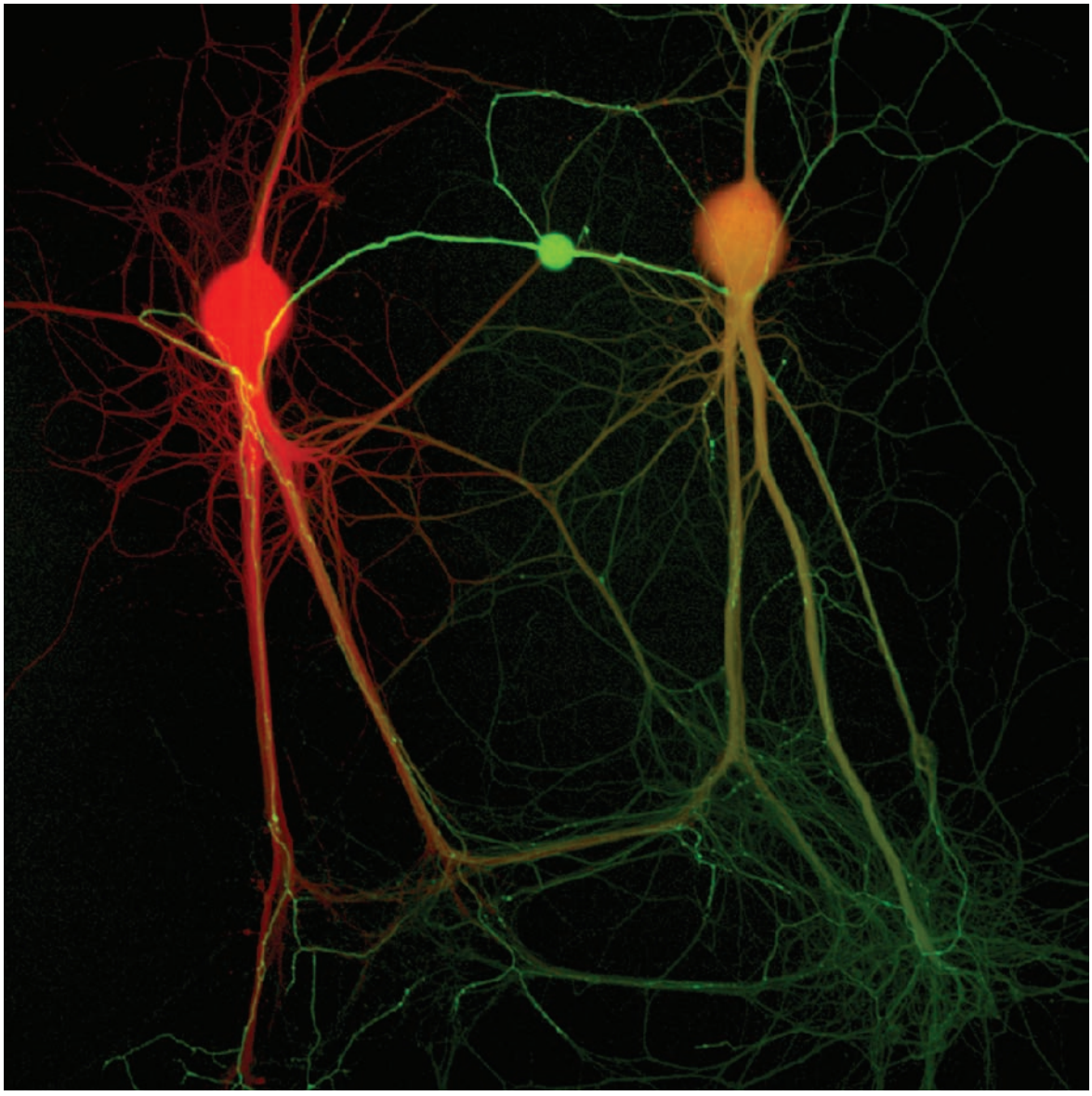
Part III



Preceding Page

A mechanosensory neuron (center, **green**) sends its axon to form excitatory synaptic connections with two motor neurons (**red**, **orange**) in cell culture, recapitulating the connections in the living animal. The neurons were isolated from the marine snail *Aplysia californica*. (Reproduced, with permission, from Harshad Vishwasrao and Eric R. Kandel.)

III Synaptic Transmission

In Part II, we examined how electrical signals are initiated and propagated within an individual neuron. We now turn to synaptic transmission, the process by which one nerve cell communicates with another.

With some exceptions, the synapse consists of three components: (1) the terminals of the presynaptic axon, (2) a target on the postsynaptic cell, and (3) a zone of apposition. Based on the structure of the apposition, synapses are categorized into two major groups: electrical and chemical. At electrical synapses, the presynaptic terminal and the postsynaptic cell are in very close apposition at regions termed *gap junctions*. The current generated by an action potential in the presynaptic neuron directly enters the postsynaptic cell through specialized bridging channels called *gap junction channels*, which physically connect the cytoplasm of the presynaptic and postsynaptic cells. At chemical synapses, a cleft separates the two cells, and the cells do not communicate through bridging channels. Rather, an action potential in the presynaptic cell leads to the release of a chemical transmitter from the nerve terminal. The transmitter diffuses across the synaptic cleft and binds to receptor molecules on the postsynaptic membrane, which regulates the opening and closing of ion channels in the postsynaptic cell. This leads to changes in the membrane potential of the postsynaptic neuron that can either excite or inhibit the firing of an action potential.

Receptors for transmitters can be classified into two major groups depending on how they control ion channels in the postsynaptic cell. One type, the ionotropic receptor, is an ion channel that opens when the transmitter binds. The second type, the metabotropic receptor, acts indirectly on ion channels by activating a biochemical second-messenger cascade within the postsynaptic cell. Both types of receptors can result in excitation or inhibition. The sign of the signal depends not on the identity of the transmitter but on the properties of the receptor with which the transmitter interacts. Most transmitters are low-molecular-weight molecules, but certain peptides also can act as messengers at synapses. The methods of electrophysiology, biochemistry, and molecular biology have been used to characterize the receptors in postsynaptic cells that respond to these various chemical messengers. These methods have also clarified how second-messenger pathways transduce signals within cells.

In this part of the book, we consider synaptic transmission in its most elementary forms. We first compare and contrast the two major classes of synapses, chemical and electrical (see Chapter 11). We then focus on a model chemical synapse in the peripheral nervous system, the neuromuscular junction between a presynaptic motor neuron and a postsynaptic skeletal muscle fiber (see Chapter 12). Next we examine chemical synapses between neurons in the central nervous system, focusing on the postsynaptic cell and its integration of synaptic signals from multiple presynaptic inputs acting on both ionotropic receptors (see Chapter 13) and metabotropic receptors (see Chapter 14). We then turn to the presynaptic terminal and consider the mechanisms by which neurons release transmitter from their presynaptic terminals, how transmitter release can be regulated by neural activity (see Chapter 15), and the chemical nature of the neurotransmitters (see Chapter 16). Because the molecular architecture of chemical synapses is complex, many inherited and acquired diseases can affect chemical synaptic transmission, which we consider in detail later in Chapter 57.

One key theme running throughout the chapters of this section, and indeed throughout the book, is the concept of plasticity. At all synapses, the strength of a synaptic connection is not fixed but can be modified in various ways by behavioral context or experience, through a variety of mechanisms referred to as synaptic plasticity. Some modifications result from the activity of the synapse itself (homosynaptic plasticity). Other modifications depend on extrinsic factors, often due to the release of a modulatory transmitter (heterosynaptic plasticity). In Chapters 53 and 54, we will see how such modifications provide a cellular substrate for different forms of memory storage that range in duration from seconds to a lifetime. In the chapters of Part IX, we will see how dysfunction in synaptic plasticity can contribute to a variety of neurological and psychiatric disorders.

Part Editor: Steven A. Siegelbaum

Part III

11

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. Synaptic transmission is fundamental to the neural functions we consider in this book, such as perception, voluntary movement, and learning.

Neurons communicate with one another at a specialized site called a *synapse*. The average neuron forms several thousand synaptic connections and receives a similar number of inputs. However, this number can vary widely depending on the particular type of neuron. Whereas the Purkinje cell of the cerebellum receives up to 100,000 synaptic inputs, the neighboring granule neurons, the most numerous class of neurons in the brain, receive only around four excitatory inputs. Although many of the synaptic connections in the central and peripheral nervous systems 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 is not fixed, but can be enhanced or diminished by neuronal activity. This synaptic *plasticity* is crucial for memory and for 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 interactions. They can produce either excitatory or inhibitory actions in postsynaptic cells and initiate changes in the postsynaptic cell that last from milliseconds to hours. Chemical synapses also serve to amplify neuronal signals, so even a small presynaptic nerve terminal can alter the response of large postsynaptic cells. Because chemical synaptic transmission is so central to understanding brain and behavior, it is examined in detail in the next four chapters.

Synapses Are Predominantly Electrical or Chemical

The term *synapse* was introduced at the beginning of the 20th century by Charles Sherrington to describe the specialized zone of contact at which one neuron communicates with another. This site had first been

Table 11–1 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

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 a chemical compound, most likely acetylcholine (ACh), conveys signals from the vagus nerve to slow the beating heart. Loewi's discovery provoked considerable debate in the 1930s over whether chemical signaling existed at the fast 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. While most neurons initiate electrical signaling with a chemical transmitter, many others produce an electrical signal directly in the postsynaptic cell.

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, 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 that directly connect the cytoplasm of the two cells.

The main functional properties of the two types of synapses are summarized in Table 11–1. 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 its membrane, thereby depolarizing the cell (Chapter 9). 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 through resting channels (Figure 11–1A). 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 and binds with receptors on the membrane of the postsynaptic cell (Figure 11–1B).

Electrical Synapses Provide Rapid 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

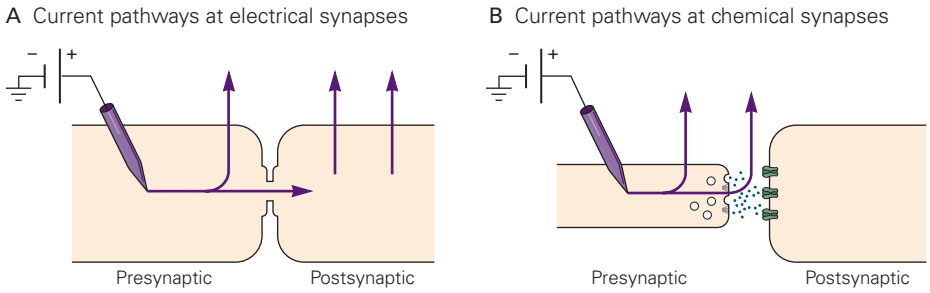


Figure 11–1 Functional properties of electrical and chemical synapses.

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.

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 11–2A). An action potential generated in the presynaptic fiber produces a depolarizing postsynaptic potential that often exceeds the threshold to fire an action

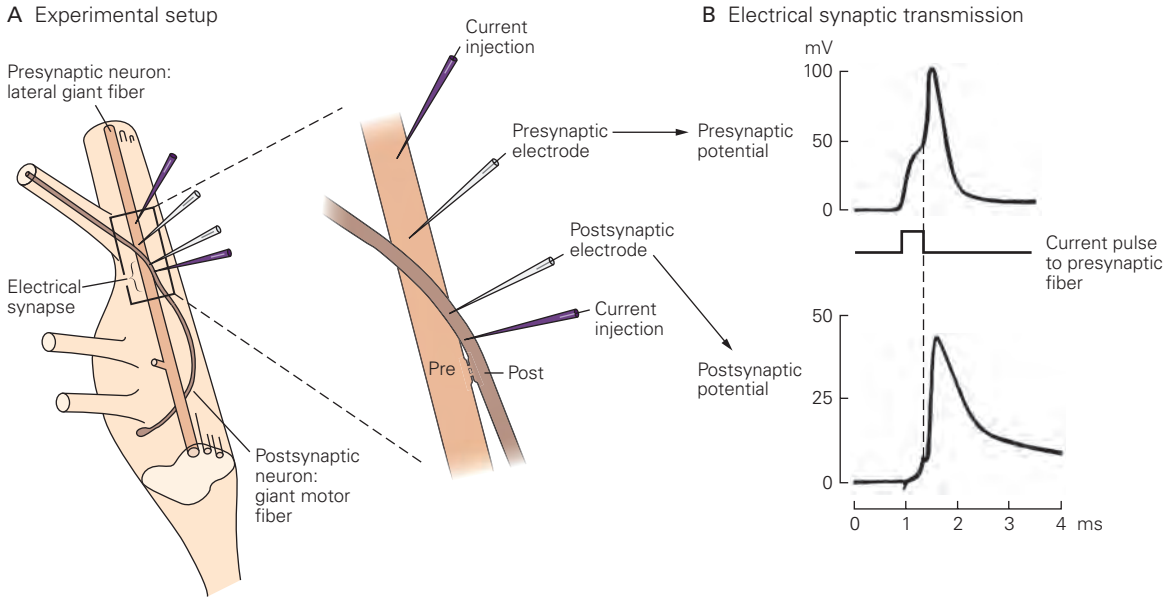


Figure 11–2 Electrical synaptic transmission was first demonstrated at the giant motor synapse in the crayfish. (Adapted, with permission, from Furshpan and Potter 1957 and 1959.)

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 11–8).

potential. At electrical synapses, the synaptic delay—the time between the presynaptic spike and the postsynaptic potential—is remarkably short (Figure 11–2B).

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 across the synaptic cleft to the postsynaptic cell, binding of transmitter to a specific receptor, and subsequent gating of ion channels (all described in this and the next chapter). Only current passing directly from one cell to another can produce the near-instantaneous transmission observed at the giant motor electrical 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 11–3). 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.

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 (Chapter 9) 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.)

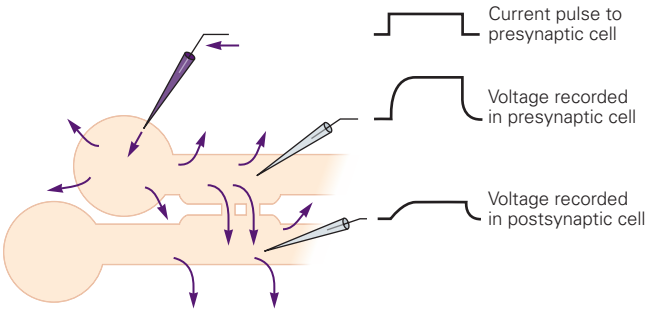


Figure 11–3 Electrical transmission is graded. It occurs even when the current in the presynaptic cell is below the threshold for an action potential. As demonstrated by single-cell recordings, a subthreshold depolarizing stimulus causes a passive depolarization in the presynaptic and postsynaptic cells. (Depolarizing or outward current is indicated by an upward deflection.)

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

At an electrical synapse, the pre- and postsynaptic components are apposed at the *gap junction*, where 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 *gap-junction channels*, specialized protein structures that conduct ionic current directly 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 between the two cells (Figure 11–4). The pore of the channel has a large diameter of approximately 1.5 nm, much larger than the 0.3- to 0.5-nm diameter of ion-selective ligand-gated or voltage-gated channels. The large pore of gap-junction channels does not discriminate among inorganic ions and is even wide enough to permit small organic molecules and experimental markers such as fluorescent dyes to pass between the two cells.

Each connexon is composed of six identical subunits, called *connexins*. Connexins in different tissues are encoded by a large family of 21 separate but related genes. In mammals, the most common connexon in neurons is formed from the product of *connexin 36.* Connexin genes are named for their predicted molecular weight, in kilodaltons, based on their primary amino acid sequence. All connexin subunits have an intracellular N- and C-terminus with four interposed α-helixes that span the cell membrane (Figure 11–4C).

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. The closing of gap-junction channels in response to pH and Ca^{2+} plays an important role in the decoupling of damaged cells from healthy cells, as 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 (Chapter 14).