

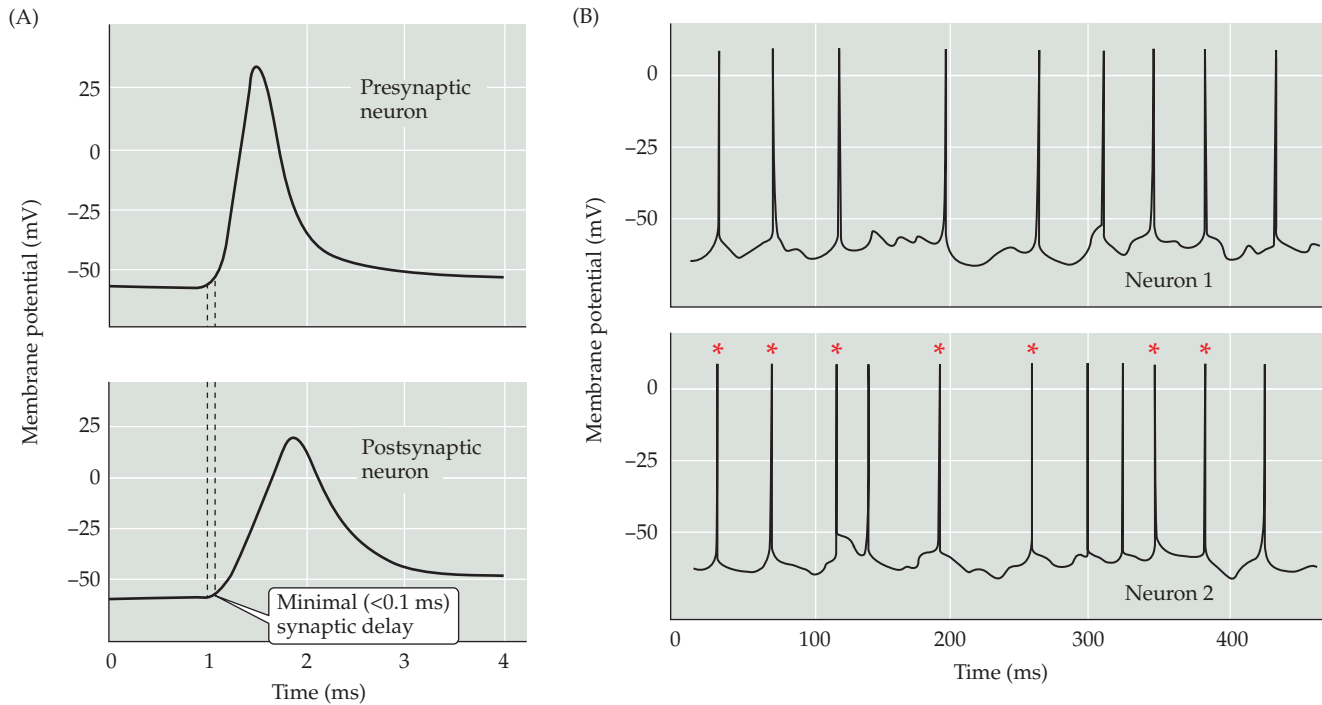


FIGURE 5.3 Function of gap junctions at electrical synapses. (A) Rapid transmission of signals at an electrical synapse in the crayfish. An action potential in the presynaptic neuron causes the postsynaptic neuron to be depolarized within a fraction of a millisecond. (B) Electrical synapses allow synchronization of electrical activity in hippocampal

current flow across connexons is virtually instantaneous, communication can occur without the delay that is characteristic of chemical synapses. The high speed of electrical synaptic transmission is apparent in the operation of the first electrical synapse to be discovered, which resides in the crayfish nervous system. A postsynaptic electrical signal is observed at this synapse within a fraction of a millisecond after the generation of a presynaptic action potential (Figure 5.3A). In fact, at least part of this brief synaptic delay is caused by propagation of the action potential into the presynaptic terminal, so there may be essentially no delay at all in the transmission of electrical signals across the synapse. Such synapses interconnect many of the neurons within the circuit that allows the crayfish to escape from its predators, thus minimizing the time between the presence of a threatening stimulus and a potentially life-saving motor response.

Another unique advantage of electrical synapses is that transmission can be bidirectional; although some connexons have special features for unidirectional transmission, in most cases current can flow in either direction, depending on which member of the coupled pair is invaded by an action potential. This allows electrical synapses to synchronize electrical activity among populations of neurons.

interneurons. In a pair of interneurons connected by electrical synapses, generation of an action potential in one neuron often results in the synchronized firing of an action potential in another neuron (asterisks). (A after Furshpan and Potter, 1959; B after Beierlein et al., 2000.)

For example, the brainstem neurons that generate rhythmic electrical activity underlying breathing are synchronized by electrical synapses, as are populations of interneurons in the cerebral cortex, thalamus, cerebellum, and other brain regions (Figure 5.3B). Electrical transmission between vasopressin- and oxytocin-secreting neurons in the hypothalamus ensures that all cells fire action potentials at about the same time, thus facilitating a synchronized burst of secretion of these hormones into the circulation (see Box 21A). The fact that connexon pores are large enough to allow second messengers to diffuse between cells also permits electrical synapses to synchronize the intracellular signaling of coupled cells. This feature may be particularly important for glial cells, which form large intracellular signaling networks via their gap junctions.

Signaling Transmission at Chemical Synapses

Figure 5.4A shows an electron micrograph of a chemical synapse in the cerebral cortex. This image illustrates the presynaptic terminal, with its abundance of synaptic vesicles, as well as the postsynaptic cell separated by a synaptic cleft. A three-dimensional rendering of this chemical

synapse, constructed from many images including the one in Figure 5.4A, reveals these features as well as many more structures, including filamentous elements in both pre- and postsynaptic processes, as well as structures in the synaptic cleft (Figure 5.4B). In the presynaptic terminal, dense projections (dark blue) are associated with the **active zone**, the place where synaptic vesicles discharge their neurotransmitters into the synaptic cleft, while the blue structure on the postsynaptic side represents the **post-synaptic density**, a structure important for postsynaptic signaling at excitatory synapses (see Box 7B).

Transmission at chemical synapses is based on the elaborate sequence of events depicted in Figure 5.4C. Prior to transmission, synaptic vesicles are formed and filled with neurotransmitter. Synaptic transmission is initiated when an action potential invades the terminal of the presynaptic neuron. The change in membrane potential caused by the arrival of the action potential leads to the opening of voltage-gated calcium channels in the presynaptic membrane. Because of the steep concentration gradient of Ca^{2+} across the presynaptic membrane (the external Ca^{2+} concentration is approximately $10^{-3} M$, whereas the internal Ca^{2+} concentration is approximately $10^{-7} M$), the opening of these channels causes a rapid influx of Ca^{2+} into the presynaptic terminal, with the result that the Ca^{2+} concentration of the cytoplasm in the terminal transiently rises to a much higher value. Elevation of the presynaptic Ca^{2+} concentration, in turn, allows synaptic vesicles to fuse with the plasma membrane of the presynaptic neuron. The Ca^{2+} -dependent fusion of synaptic vesicles with the terminal membrane causes their contents, most importantly neurotransmitters, to be released into the synaptic cleft, a process called **exocytosis**.

Following exocytosis, transmitters diffuse across the synaptic cleft and bind to specific receptors on the membrane of the postsynaptic neuron. The binding of neurotransmitter to the receptors causes channels in the postsynaptic membrane to open (or sometimes to close), thus changing the ability of ions to flow across the postsynaptic membrane. The resulting neurotransmitter-induced current flow alters the conductance and (usually) the membrane potential of the postsynaptic neuron, increasing or decreasing the probability that the neuron will fire an action potential. Subsequent removal of the neurotransmitter from the synaptic cleft, by uptake into glial cells or by enzymatic degradation, terminates the action of the neurotransmitter. In this way, information is transmitted transiently from one neuron to another.

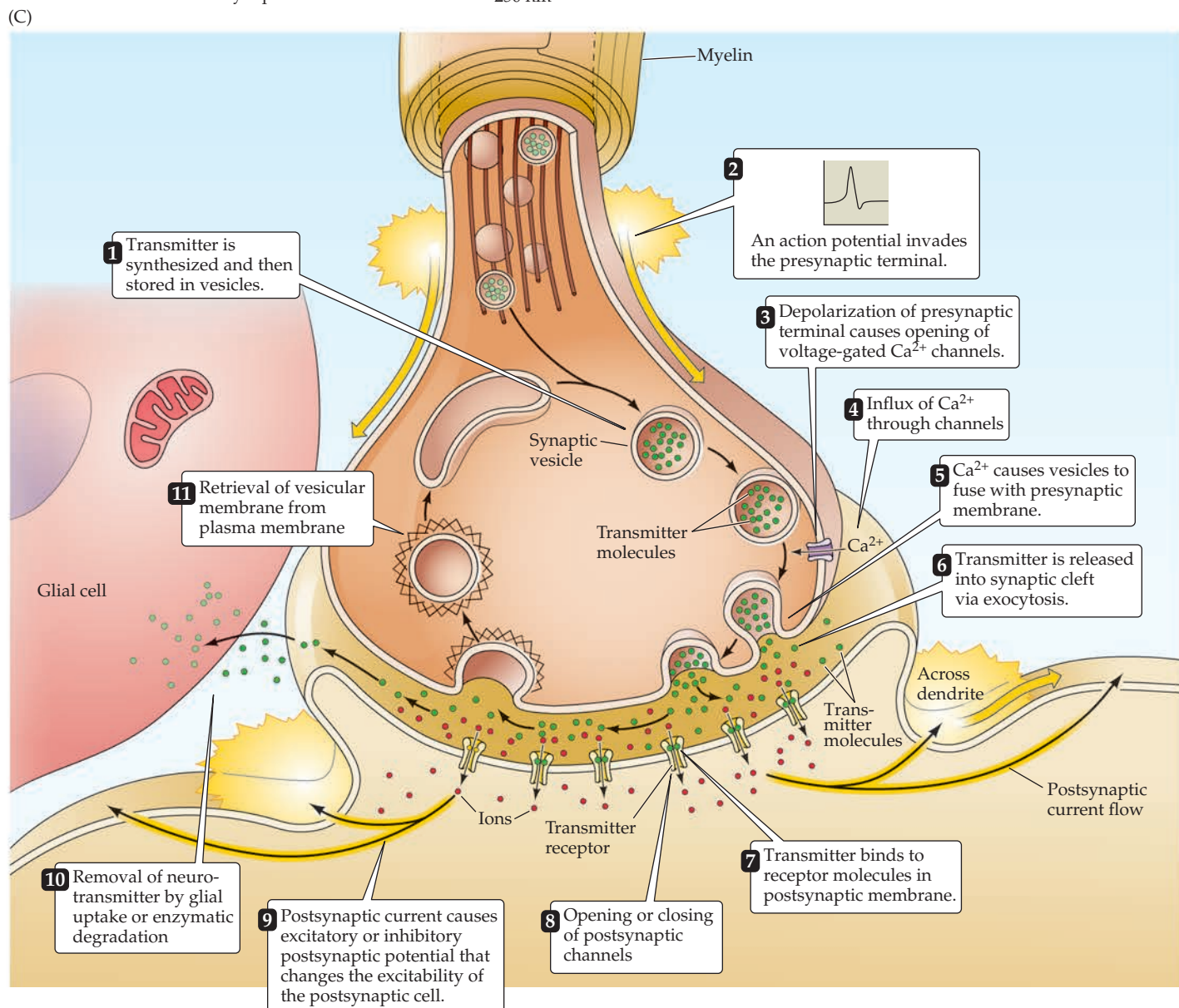
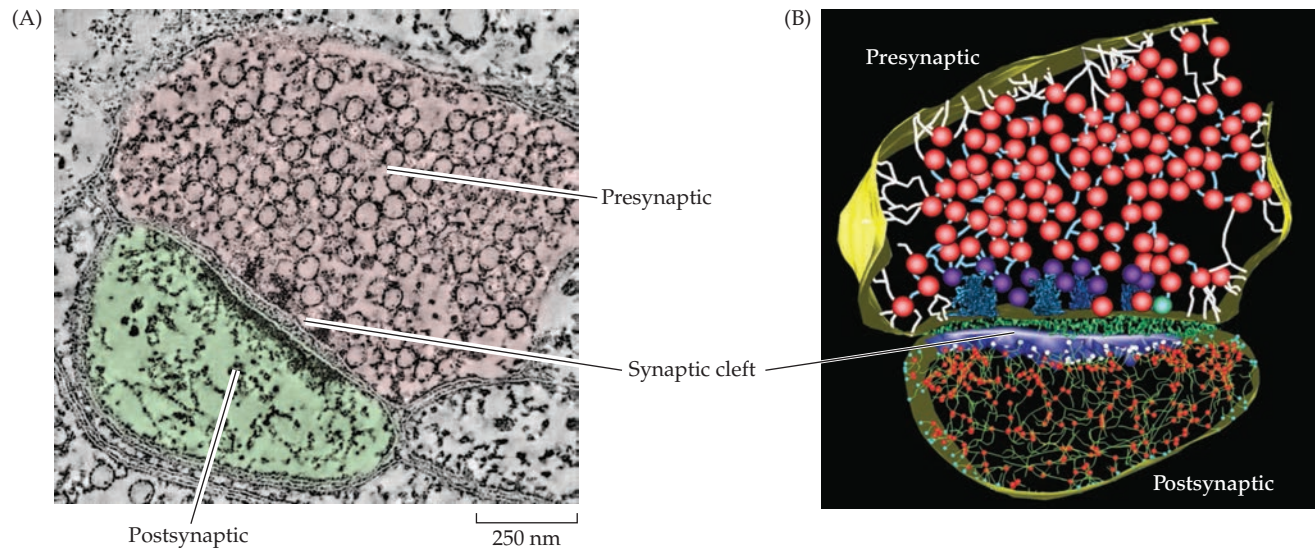
Properties of Neurotransmitters

The notion that electrical information can be transferred from one neuron to the next by means of chemical signaling was the subject of intense debate through the first half of the twentieth century. In 1926, the German physiologist

Otto Loewi performed a key experiment that supported this idea. Acting on an idea that allegedly came to him in the middle of the night, Loewi proved that electrical stimulation of the vagus nerve slows the heartbeat by releasing a chemical signal that was later shown to be **acetylcholine (ACh)**. ACh is now known to be a neurotransmitter that acts not only in the heart but also at a variety of postsynaptic targets in the central and peripheral nervous systems, preeminently at the neuromuscular junction of striated muscles and in the visceral motor system (see Chapters 6 and 21).

Formal criteria have been established to definitively identify a substance as a neurotransmitter. These criteria have led to the identification of more than 100 different neurotransmitters, which can be classified into two broad categories: small-molecule neurotransmitters, such as ACh, and neuropeptides (see Chapter 6). Having more than one transmitter diversifies the physiological repertoire of synapses. Multiple neurotransmitters can produce different types of responses on individual postsynaptic cells. For example, a neuron can be excited by one type of neurotransmitter and inhibited by another type of neurotransmitter. The speed of postsynaptic responses produced by different transmitters also differs, allowing control of electrical signaling over different timescales. In general, small-molecule neurotransmitters mediate rapid synaptic actions, whereas neuropeptides tend to modulate slower, ongoing neuronal functions. In some cases, neurons synthesize and release two or more different neurotransmitters; in this case, the molecules are called **co-transmitters**. Co-transmitters can be differentially released according to the pattern of synaptic activity, so that the signaling properties of such synapses change dynamically according to the rate of activity.

Effective synaptic transmission requires close control of the concentration of neurotransmitters within the synaptic cleft. Neurons have therefore developed a sophisticated ability to regulate the synthesis, packaging, release, and degradation (or removal) of neurotransmitters to achieve the desired levels of transmitter molecules. The synthesis of small-molecule neurotransmitters occurs locally within presynaptic terminals. The precursor molecules required to make new molecules of neurotransmitter are usually taken into the nerve terminal by transporters found in the plasma membrane of the terminal (see Figure 4.13E). The enzymes that synthesize these neurotransmitters are present in the cytoplasm of the presynaptic terminal, and the newly synthesized transmitters are then loaded into synaptic vesicles via another type of transporter located in the vesicular membrane. Most small-molecule neurotransmitters are packaged in vesicles 40 to 60 nm in diameter, the centers of which appear clear in electron micrographs (see Figure 5.4A); accordingly, these vesicles are referred to as **small clear-core vesicles**. Neuropeptides are synthesized in the cell body of a neuron, and peptide-filled



◀ **FIGURE 5.4 Structure and function of chemical synapses.** (A) Structure of a chemical synapse in the cerebral cortex. A presynaptic terminal (pink) forms a synapse with a postsynaptic dendrite (green). (B) Three-dimensional reconstruction of the synapse shown in (A). Inside the presynaptic terminal, spheres indicate synaptic vesicles at various stages of their trafficking cycle, linear elements indicate intracellular filaments, and dark blue indicates dense projections associated with the active zone. Inside the postsynaptic neuron, the blue structure is the postsynaptic density, green structures represent filaments, red spheres indicate points where the filaments branch. Green material within the synaptic cleft indicates structures of unknown function. (C) Sequence of events involved in transmission at a typical chemical synapse. (A,B from Burette et al., 2012.)

vesicles are transported along an axon and down to the synaptic terminal via **axonal transport**. Neuropeptides are packaged into synaptic vesicles that range from 90 to 250 nm in diameter. Because the centers of these vesicles appear electron-dense in electron micrographs, they are referred to as **large dense-core vesicles**.

After a neurotransmitter has been secreted into the synaptic cleft, it must be removed to enable the postsynaptic cell to engage in another cycle of synaptic transmission. The removal of neurotransmitters involves diffusion away from the postsynaptic receptors, in combination with reuptake into nerve terminals or surrounding glial cells, degradation by specific enzymes, or a combination of these mechanisms. Specific transporter proteins remove most

small-molecule neurotransmitters (or their metabolites) from the synaptic cleft, ultimately delivering them back to the presynaptic terminal for reuse (see Chapter 6).

Quantal Release of Neurotransmitters

Much of the evidence leading to the present understanding of chemical synaptic transmission was obtained from experiments examining the release of ACh at neuromuscular junctions. These synapses between spinal motor neurons and skeletal muscle cells are simple, large, and peripherally located, making them particularly amenable to experimental analysis. Such synapses occur at specializations called **end plates** because of the saucerlike appearance of the site on the muscle fiber where the presynaptic axon elaborates its terminals (Figure 5.5A). Most of the pioneering work on neuromuscular transmission was performed during the 1950s and 1960s by Bernard Katz and his collaborators at University College London. Although Katz worked primarily on the frog neuromuscular junction, numerous subsequent experiments have confirmed the applicability of his observations to transmission at all chemical synapses.

When an intracellular microelectrode is used to record the membrane potential of a muscle cell, an action potential in the presynaptic motor neuron can be seen to elicit a transient depolarization of the postsynaptic muscle fiber. This change in membrane potential, called an **end plate potential (EPP)**, is normally large enough to bring the membrane potential of the muscle cell well above the threshold

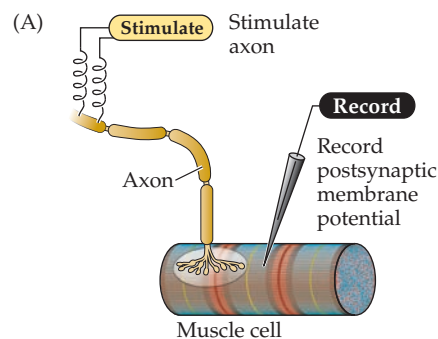


FIGURE 5.5 Synaptic transmission at the neuromuscular junction. (A) Experimental arrangement: The axon of the motor neuron innervating the muscle fiber is stimulated with an extracellular electrode, while an intracellular microelectrode is inserted into the postsynaptic muscle cell to record its electrical responses. (B) End plate potentials (shaded area) evoked by stimulation of a motor neuron are normally above threshold and therefore produce an action potential in the postsynaptic muscle cell. (C) Spontaneous miniature EPPs (MEPPs) occur in the absence of presynaptic stimulation. (D) When the neuromuscular junction is bathed in a solution that has a low concentration of Ca^{2+} , stimulating the motor neuron evokes EPPs whose amplitudes are reduced to about the size of MEPPs. (After Fatt and Katz, 1952.)

