synapses begin to form, they often initiate the down-regulation of electrical transmission.

Both types of synapses also can coexist in neurons in the mature nervous system. The role of these two types of synapses is perhaps best understood in the circuitry of the retina. There, rod and cone photoreceptors release the neurotransmitter glutamate and form chemical synapses on a class of interneurons called bipolar cells. Each bipolar cell extends its dendrites horizontally, receiving chemical synaptic input from a number of overlying rods and cones that respond to light from a very small region of the visual field. The receptive field of a bipolar neuron, however, extends about twice as far as the receptive field of the photoreceptors from which it receives chemical synaptic input. This is a result of electrical synapses formed between neighboring bipolar cells and between bipolar cells and a second type of interneuron, the amacrine cell (Chapter 22).

Finally, the efficacy of gap junctions can be regulated by phosphorylation through different protein kinases, which generally enhances gap-junction coupling. For example, dopamine and other transmitters can increase or decrease gap-junction coupling by acting on metabotropic G protein–coupled receptors to regulate levels of cAMP and thereby enhance or decrease channel phosphorylation. Such complex signaling loops are a hallmark of many neural circuits and greatly expand their computational powers.

Highlights

1. Neurons communicate by two major mechanisms: electrical and chemical synaptic transmission.
2. Electrical synapses are formed at regions of tight apposition called gap junctions, which provide a direct pathway for charge to flow between the cytoplasm of communicating neurons. This results in very rapid synaptic transmission that is suited for synchronizing the activity of populations of neurons.
3. Neurons at electrical synapses are connected through gap-junction channels, which are formed from a pair of hemichannels, called connexons, one each contributed by the presynaptic and postsynaptic cells. Each connexon is a hexamer, composed of six subunits termed connexins.
4. At chemical synapses, a presynaptic action potential triggers the release of a chemical transmitter from the presynaptic cell through the process of exocytosis. Transmitter molecules then rapidly diffuse across the synaptic cleft to bind to and activate transmitter receptors in the postsynaptic cell.
5. Although slower than electrical synaptic transmission, chemical transmission allows for amplification of the presynaptic action potential through the release of tens of thousands of molecules of transmitter and the activation of hundreds to thousands of receptors in the postsynaptic cell.
6. There are two major classes of transmitter receptors. Ionotropic receptors are ligand-gated ion channels. Binding of transmitter to an extracellular binding site triggers a conformational change that opens the channel pore, generating an ionic current that excites (depolarizes) or inhibits (hyperpolarizes) the postsynaptic cell, depending on the receptor. Ionotropic receptors underlie fast chemical synaptic transmission that mediates rapid signaling in the nervous system.
7. Metabotropic receptors are responsible for the second major class of chemical synaptic actions. These receptors activate intracellular metabolic signaling pathways, often leading to the synthesis of second messengers, such as cAMP, that regulate levels of protein phosphorylation. Metabotropic receptors underlie slow, modulatory synaptic actions that contribute to changes in behavioral state and arousal.

Steven A. Siegelbaum
Gerald D. Fischbach

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12

Directly Gated Transmission: The Nerve-Muscle Synapse

MUCH OF OUR UNDERSTANDING of the principles that govern chemical synapses in the brain is based on studies of synapses formed by motor neurons on skeletal muscle cells. The landmark work of Bernard Katz and his colleagues over three decades beginning in 1950 defined the basic parameters of synaptic transmission and opened the door to modern molecular analyses of synaptic function. Therefore, before we examine the complexities of synapses in the central nervous system, we will examine the basic features of chemical synaptic transmission at the simpler nerve-muscle synapse.

The early studies capitalized on several experimental advantages offered by nerve-muscle preparations of various species. Muscles and attached motor axons are easy to dissect and maintain for several hours in vitro. Muscle cells are large enough to be penetrated with two or more fine-tipped microelectrodes, enabling precise analyses of synaptic potentials and underlying ionic currents. In most species, innervation is restricted to one site, the motor endplate, and in adult animals that site is innervated by only one motor axon. In contrast, central neurons receive many convergent inputs that are distributed throughout the dendritic arbor and the soma, and thus the impact of single inputs is more difficult to discern.

Most important, the chemical transmitter that mediates synaptic transmission between nerve and muscle, acetylcholine (ACh), was identified early in the 20th century. We now know that signaling at the nerve-muscle synapse involves a relatively simple mechanism: Neurotransmitter released from the presynaptic nerve binds to a single type of receptor in the postsynaptic membrane,

the nicotinic ACh receptor.[1] Binding of transmitter to the receptor directly opens an ion channel; both the receptor and channel are components of the same macromolecule. Synthetic and natural agents that activate or inhibit nicotinic ACh receptors have proven useful in analyzing not only the ACh receptors in muscle, but also cholinergic synapses in peripheral ganglia and in the brain. Moreover, such ligands can be useful therapeutic agents, including the treatment of inherited and acquired neurological diseases resulting from alterations in ACh receptor function or genetic mutations.

The Neuromuscular Junction Has Specialized Presynaptic and Postsynaptic Structures

As the motor axon approaches the *end-plate*, the site of contact between nerve and muscle (also known as the *neuromuscular junction*), it loses its myelin sheath and divides into several fine branches. At their ends, these fine branches form multiple expansions or varicosities called *synaptic boutons* (Figure 12–1) from which the motor axon releases its transmitter. Although myelin ends some distance from the sites of transmitter release, Schwann cells cover and partially enwrap the nerve terminal. A terminal "arbor" defines the area of the motor end-plate. In different species, end-plates range from compact elliptical structures about 20 µm across to linear arrays more than 100 µm in length.

The nerve terminals lie in grooves, the primary folds, along the muscle surface. The membrane under each synaptic bouton is further invaginated to form a series of secondary or junctional folds (Figure 12–1). The muscle cytoplasm beneath the nerve terminals contains many round muscle nuclei that likely are involved in synthesis of synapse-specific molecules. They are different from the flat nuclei located away from the synapse along the length of the muscle fiber.

Action potentials in the axon are conducted to the tips of the fine branches where they trigger the release of ACh. The synaptic boutons contain all the machinery required to synthesize and release ACh. This includes the synaptic vesicles containing the transmitter ACh and the active zones where the synaptic vesicles are clustered. In addition, each active zone contains voltage-gated Ca^{2+} channels that conduct Ca^{2+} into the terminal with each action potential. This influx of Ca^{2+} triggers the fusion of the synaptic vesicles with the plasma membrane at the active zones, releasing the contents of the synaptic vesicles into the synaptic cleft by the process of exocytosis (Chapter 15).

The distribution of ACh receptors can be studied using α-bungarotoxin (αBTX), a peptide isolated from the venom of the snake *Bungarus multicinctus* that binds tightly and specifically to the ACh receptors at the neuromuscular junction (Figure 12–2B). Quantitative autoradiography of iodinated BTX (^{125}I-αBTX) showed that the ACh receptors are packed at the crests of the secondary folds at a surface density in excess of 10,000/µm^2 (Figure 12–3). The factors responsible for localizing the receptor are discussed in Chapter 48, where we consider the development of synaptic connections.

Presynaptic and postsynaptic membranes at the neuromuscular junction are separated by a cleft approximately 100 nm wide. Although such a gap was postulated by Ramón y Cajal in the last years of the 19th century, it was not visualized until synapses were examined by electron microscopy more than 50 years later! A basement membrane (basal lamina) composed of collagen and other extracellular matrix proteins is present throughout the synaptic cleft. Acetylcholinesterase (AChE), an enzyme that rapidly hydrolyzes ACh, is anchored to collagen fibrils within the basement membrane. The ACh released into the synaptic cleft must run a "gauntlet" of AChE before it reaches the ACh receptors in the muscle membrane. As AChE is inhibited by high concentrations of ACh, most molecules get through. Nevertheless, the enzyme limits the action of ACh to "one hit" because AChE hydrolyzes transmitter as soon as it dissociates from its receptor in the postsynaptic membrane.

The Postsynaptic Potential Results From a Local Change in Membrane Permeability

Once ACh is released from a synaptic terminal, it rapidly binds to and opens the ACh receptor-channels in the end-plate membrane. This produces a dramatic increase in the permeability of the muscle membrane to cations, which leads to the entry of positive charge into the muscle fiber and a rapid depolarization of the end-plate membrane. The resulting excitatory postsynaptic potential (EPSP) is very large; stimulation of a single motor axon produces an EPSP of approximately 75 mV. At the nerve-muscle synapse, the EPSP is also referred to as the *end-plate potential*.

This change in membrane potential usually is large enough to rapidly activate the voltage-gated Na^+

[1]There are two basic types of receptors for ACh: nicotinic and muscarinic, so called because the alkaloids nicotine and muscarine bind exclusively to and activate one or the other type of ACh receptor. The nicotinic ACh receptor is ionotropic, whereas the muscarinic receptor is metabotropic. We shall learn more about muscarinic ACh receptors in Chapter 14.

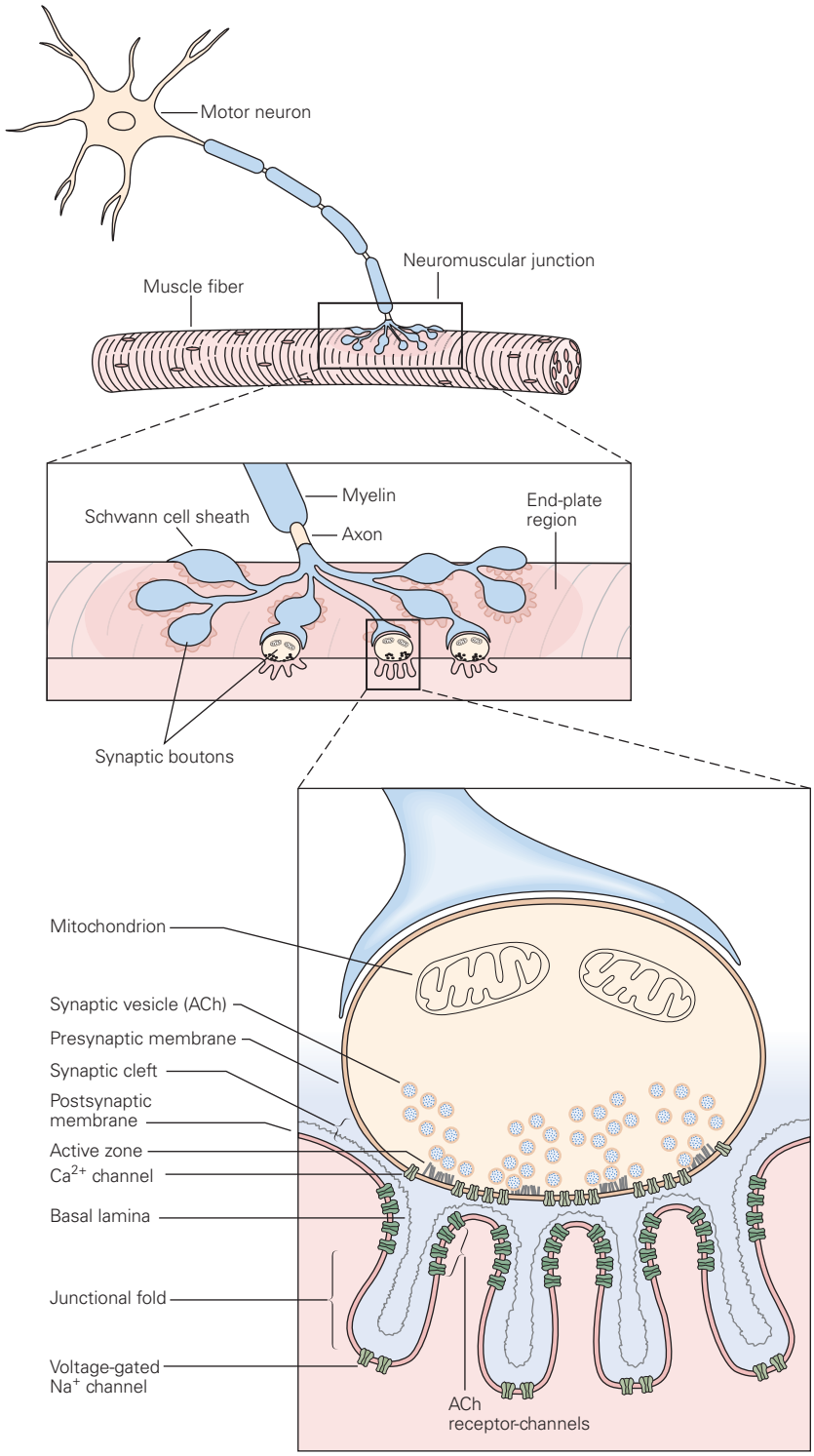

Figure 12–1 The neuromuscular junction is an ideal site for studying chemical synaptic signaling. At the muscle, the motor axon ramifies into several fine branches approximately 2 μm thick. Each branch forms multiple swellings called *synaptic boutons*, which are covered by a thin layer of Schwann cells. The boutons contact a specialized region of the muscle fiber membrane, the *end-plate*, and are separated from the muscle membrane by a 100-nm synaptic cleft. Each bouton contains mitochondria and synaptic vesicles clustered around *active zones*, where the neurotransmitter acetylcholine (**ACh**) is released. Immediately under each bouton in the end-plate are several junctional folds, the crests of which contain a high density of ACh receptors.

The muscle fiber and nerve terminal are covered by a layer of connective tissue, the basal lamina, consisting of collagen and glycoproteins. Unlike the cell membrane, the basal lamina is freely permeable to ions and small organic compounds, including the ACh transmitter. Both the presynaptic terminal and the muscle fiber secrete proteins into the basal lamina, including the enzyme acetylcholinesterase, which inactivates the ACh released from the presynaptic terminal by breaking it down into acetate and choline. The basal lamina also organizes the synapse by aligning the presynaptic boutons with the postsynaptic junctional folds. (Adapted from McMahan and Kuffler 1971.)

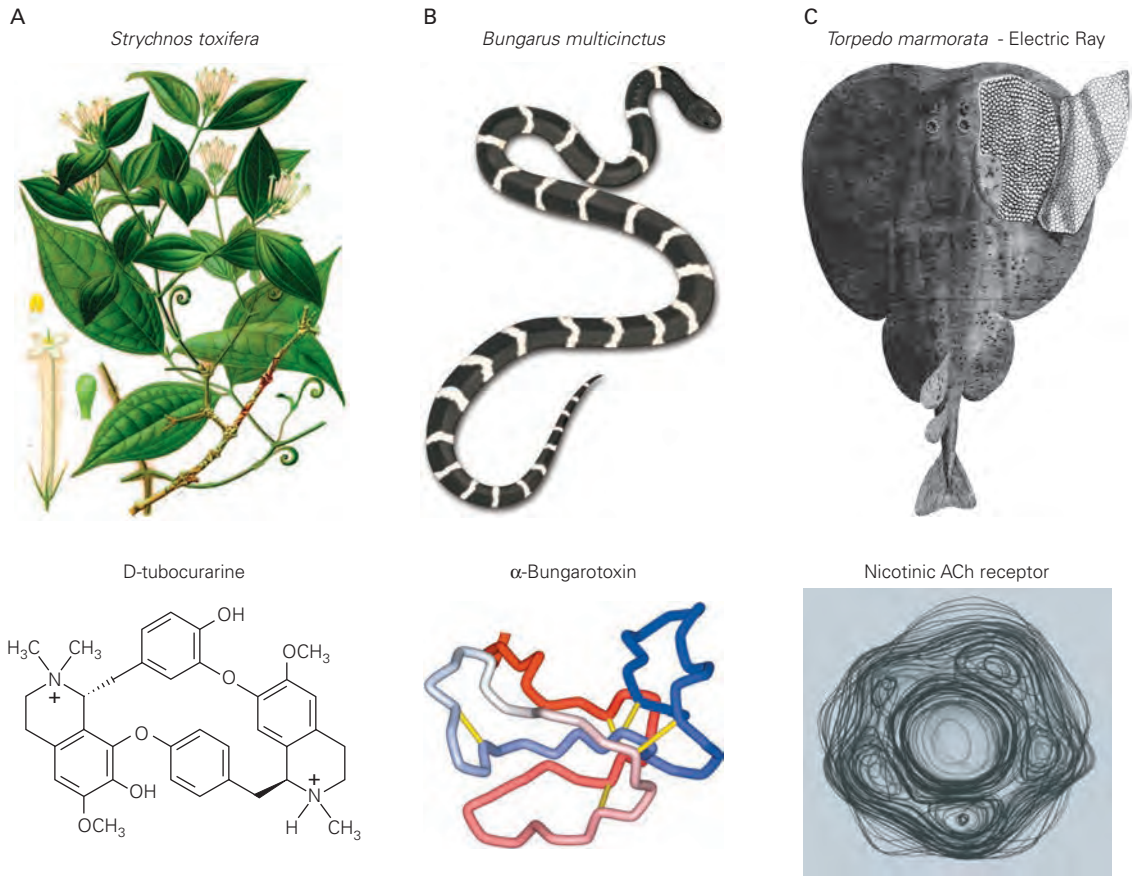

Figure 12–2 Poisons, venoms, and high-voltage electric fish help elucidate the structure and function of the nicotinic ACh receptor.

A. Curare is a mixture of toxins extracted from the leaves of *Strychnos toxifera* and is used by South American indigenous people on arrowheads to paralyze their quarry. The active compound, D-tubocurarine, is a complex multiring structure with positively charged amine groups that bear some similarity to ACh. It binds tightly to the ACh binding site on the nicotinic receptor, where it acts as a competitive antagonist for ACh. (Reproduced from Pabst, G (ed). 1898. *Köhler's Medizinal-Pflanzen*, Vol. 3, Plate 45. Gera-Untermhaus, Germany: Franz Eugen Köhler.)

B. The toxin α-bungarotoxin is obtained from the venom of the banded krait, *Bungarus*. It is a 74-amino acid polypeptide that contains five disulfide bonds (**yellow lines**), producing a rigid structure (From https://en.wikipedia.org/wiki/Alpha-bungarotoxin. Adapted from Zeng et al. 2001.). The toxin binds extremely tightly to the ACh binding site and acts as an irreversible, noncompetitive antagonist of ACh.

C. The electric ray *Torpedo marmorata* has a specialized structure, the electric organ, which consists of a large number of small, flat, muscle-like cells, or electroplaques, arranged in series like a stack of batteries. When a motor nerve releases ACh, a large current is generated by the opening of a very large number of nicotinic ACh receptor-channels, which produces a very large voltage drop of up to 200 V outside the fish, thereby stunning nearby prey. The electroplaques provide a rich source of ACh receptors for biochemical purification and characterization. (From Walsh 1773.)

channels in the muscle membrane, converting the end-plate potential into an action potential, which then propagates along the muscle fiber. The threshold for generating an action potential in the muscle is particularly low at the end-plate, owing to a high density of voltage-gated Na^+ channels in the bottom of the junctional folds. The combination of a very large EPSP and low threshold results in a high safety factor for triggering an action potential in the muscle fiber. In contrast, in the central nervous system, most presynaptic neurons produce postsynaptic potentials less than 1 mV in amplitude, such that inputs from many presynaptic neurons are needed to generate an action potential in most central neurons.

The end-plate potential was first studied in detail in the 1950s by Paul Fatt and Bernard Katz using intracellular voltage recordings. Fatt and Katz were able to isolate the end-plate potential by applying the drug curare (Figure 12–2A) to reduce the amplitude of the postsynaptic potential below the threshold for the action potential (Figure 12–4). At the end-plate, the synaptic potential rises within 1 to 2 ms but decays more slowly.

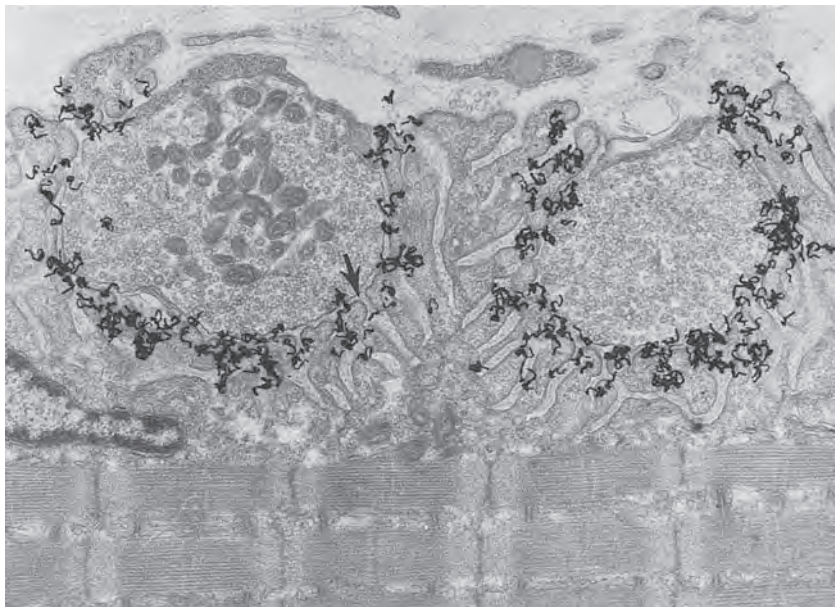

Figure 12–3 Acetylcholine receptors in the vertebrate neuromuscular junction are concentrated at the top one-third of the junctional folds. This receptor-rich region is characterized by an increased density of the postjunctional membrane (**arrow**). The autoradiograph shown here was made by first incubating the membrane with radiolabeled α-bungarotoxin, which binds to the ACh receptor. Radioactive decay results in the emittance of a particle that causes overlaid silver grains to become fixed along its trajectory (**black grains**). Magnification ×18,000. (Reproduced, with permission, from Salpeter 1987.)

By recording at different points along the muscle fiber, Fatt and Katz found that the EPSP is maximal at the end-plate and decreases progressively with distance (Figure 12–5). In addition, the time course of the EPSP slows progressively with distance.

From this, Fatt and Katz concluded that the end-plate potential is generated by an inward ionic current that is confined to the end-plate and then spreads passively away. (An inward current corresponds to an influx of positive charge, which depolarizes the inside of the membrane.) Inward current is confined to the end-plate because the ACh receptors are concentrated there, opposite the presynaptic terminal from which transmitter is released. The decrease in amplitude and slowing of the EPSP as a function of distance is a result of the passive cable properties of the muscle fiber.

Electrophysiological evidence that the ACh receptors are localized to the end-plate was provided by Stephen Kuffler and his colleagues, who applied ACh to precise points on the muscle membrane

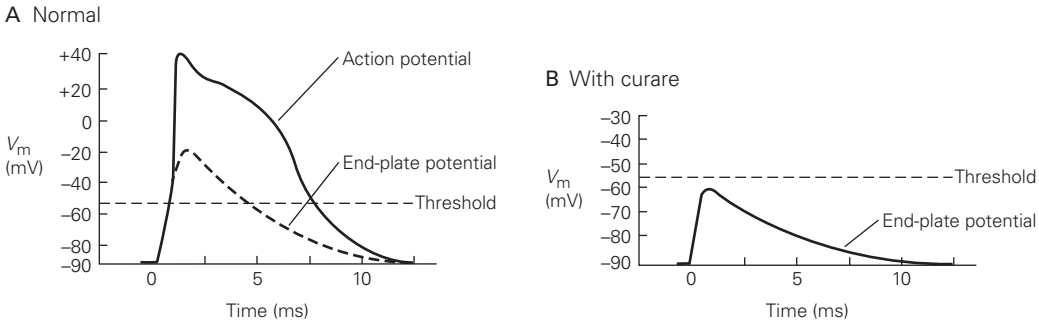

Figure 12–4 The end-plate potential can be isolated pharmacologically for study.

A. Under normal circumstances, stimulation of the motor axon produces an action potential in a skeletal muscle cell. The **dashed curve** in the plot shows the inferred time course of the end-plate potential that triggers the action potential. The lighter **dashed line** shows the action potential threshold.

B. Curare blocks the binding of ACh to its receptor and so prevents the end-plate potential from reaching the threshold for an action potential. In this way, the currents and channels that contribute to the end-plate potential, which are different from those producing an action potential, can be studied. The end-plate potential shown here was recorded in the presence of a low concentration of curare, which blocks only a fraction of the ACh receptors. The values for the resting potential (–90 mV), end-plate potential, and action potential in these intracellular recordings are typical of a vertebrate skeletal muscle.

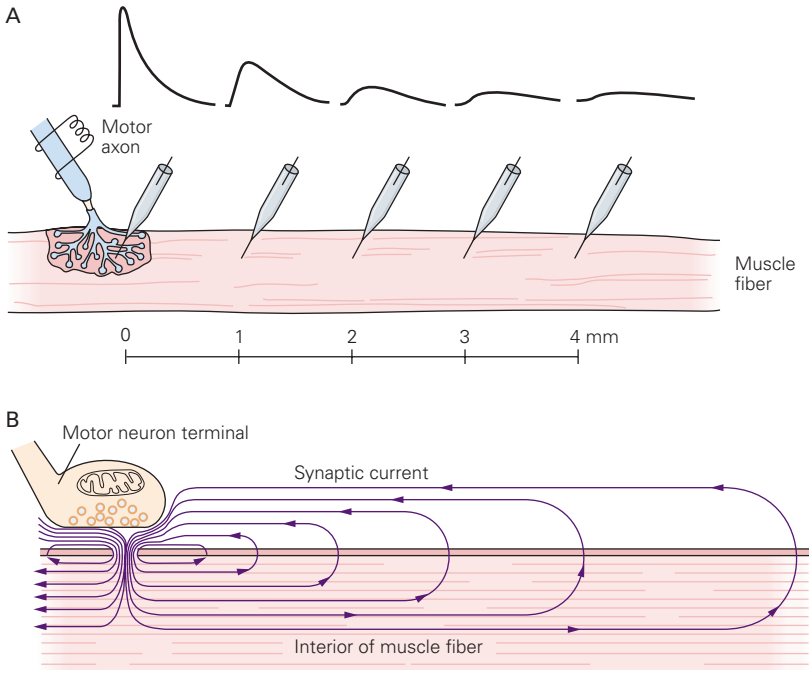

Figure 12–5 The end-plate potential decreases with distance as it passively propagates away from the end-plate. (Adapted, with permission, from Miles 1969.)

A. The amplitude of the postsynaptic potential decreases and the time course of the potential slows with distance from the site of initiation in the end-plate.

B. The decay results from leakiness of the muscle fiber membrane. Because charge must flow in a complete circuit, the inward synaptic current at the end-plate gives rise to a return outward current through resting channels and across the lipid bilayer (the capacitor). This return outward flow of positive charge depolarizes the membrane. Because current leaks out all along the membrane, the outward current and resulting depolarization decreases with distance from the end-plate.

using a technique called micro-iontophoresis. In this approach, the positively charged ACh is ejected from an ACh-filled extracellular microelectrode by applying a positive voltage to the inside of the electrode. Exposing the end-plate region to proteolytic enzymes allows the nerve terminal to be pulled away from the muscle surface and the ACh to be applied directly to the postsynaptic membrane directly under the tip of the small microelectrode. Using this technique, Kuffler found that the postsynaptic depolarizing response to ACh declined steeply within a few micrometers of the synaptic terminal.

Voltage-clamp experiments have revealed that the end-plate current rises and decays more rapidly than the resultant end-plate potential (Figure 12–6). The time course of the end-plate current is directly determined by the rapid opening and closing of the ACh receptor-channels. Because it takes time for an ionic

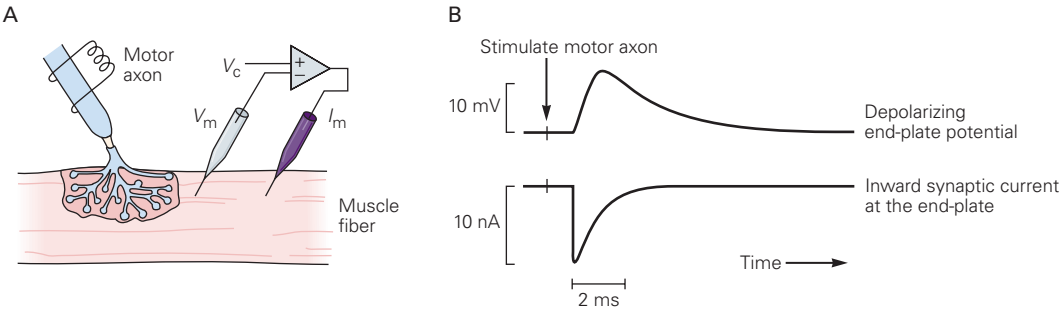

Figure 12–6 The end-plate current increases and decays more rapidly than the end-plate potential.

A. The membrane at the end-plate is voltage-clamped by inserting two microelectrodes into the muscle near the end-plate. One electrode measures membrane potential (V_m), and the second passes current (I_m). Both electrodes are connected to a negative feedback amplifier, which ensures that sufficient current (I_m) is delivered so that V_m will remain clamped at the command potential V_c. The synaptic current evoked by stimulating the motor nerve can then be measured at constant V_m, for example, –90 mV (see Box 10–1).

B. The end-plate potential (measured when V_m is not clamped) changes relatively slowly and lags behind the more rapid inward synaptic current (measured under voltage-clamp conditions). This is because synaptic current must first alter the charge on the muscle membrane capacitance before the muscle membrane can be depolarized.

current to charge or discharge the muscle membrane capacitance, and thus alter the membrane voltage, the EPSP lags behind the synaptic current (see Figure 9–10 and the Postscript at the end of this chapter).

The Neurotransmitter Acetylcholine Is Released in Discrete Packets

During their first microelectrode recordings at frog motor end-plates in the 1950s, Fatt and Katz observed small spontaneous depolarizing potentials (0.5–1.0 mV) that occurred at an average rate of about 1/s. Such spontaneous potentials were restricted to the end-plate, exhibited the same time course as stimulus-evoked EPSPs, and were blocked by curare. Hence, they were named "miniature" end-plate potentials (mEPPs, or mEPSPs in our current terminology).

What could account for the small, fixed size of the miniature end-plate potential? Del Castillo and Katz tested the possibility that an mEPSP represents the action of a *single* ACh molecule. This hypothesis was quickly dismissed, because applying very small amounts of ACh to the end-plate could elicit depolarizing responses that were much smaller than the 1.0-mV mEPSP. The low doses of ACh did produce an increase in baseline fluctuations or "noise." Later analysis of the statistical components of this noise led to estimates that the underlying unitary postsynaptic response was a depolarization of 0.3 μV in amplitude and 1.0 ms in duration. This was the first hint of the electrical signaling properties of a single ACh receptor-channel (described later).

Del Castillo and Katz concluded that each mEPSP must represent the action of a multimolecular packet or "quantum" of transmitter. Further, they suggested that the large, stimulus-evoked EPSP was made up of an integral number of quanta. Evidence for this quantal hypothesis is presented in Chapter 15.

Individual Acetylcholine Receptor-Channels Conduct All-or-None Currents

What are the properties of the ACh receptor-channels that produce the inward current that generates the depolarizing end-plate potential? Which ions move through the channels to produce this inward current? And what does the current carried by a single ACh receptor-channel look like?

In 1976, Erwin Neher and Bert Sakmann obtained key insights into the biophysical nature of ACh receptor-channel function from recordings of the current conducted by single ACh receptor-channels in skeletal muscle cells, the unitary or elementary current. They found that the opening of an individual channel generates a very small rectangular step of ionic current (Figure 12–7A). At a given resting potential, each channel opening generates the same-size current pulse. At –90 mV, the current steps are approximately –2.7 pA in amplitude. Although this is a very small current, it corresponds to a flow of approximately 17 million ions per second!

Whereas the amplitude of the current through a single ACh receptor-channel is constant for every opening, the duration of each opening and the time between openings vary considerably. These variations occur because channel openings and closings are stochastic; they obey the same statistical law that describes the exponential time course of radioactive decay. Because channels and ACh undergo random thermal motions and fluctuations, it is impossible to predict exactly how long it will take any one channel to bind ACh or how long that channel will stay open before the ACh dissociates and the channel closes. However, the average length of time a particular type of channel stays open is a well-defined property of that channel, just as the half-life of radioactive decay is an invariant property of a particular isotope. The mean open time for ACh receptor-channels is approximately 1 ms. Thus, each channel opening permits the movement of approximately 17,000 ions. Once a channel closes, the ACh molecules dissociate and the channel remains closed until it binds ACh again.

The Ion Channel at the End-Plate Is Permeable to Both Sodium and Potassium Ions

Once a receptor-channel opens, which ions flow through the channel, and how does this lead to depolarization of the muscle membrane? One important means of identifying the ion (or ions) responsible for the synaptic current is to measure the value of the chemical driving force (the chemical battery) propelling ions through the channel. Remember, the current through a single open channel is given by the product of the single-channel conductance and the electrochemical driving force on the ions conducted through the channel (Chapter 9). Thus, the current generated by a single ACh receptor-channel is given by:

$$I_{EPSP} = \gamma_{EPSP} \times (V_m - E_{EPSP}), \qquad \textbf{(12–1)}$$

where I_{EPSP} is the amplitude of current through one channel, γ_{EPSP} is the conductance of a single open channel, E_{EPSP} is membrane potential at which the net flux of ions through the channel is zero, and $V_m - E_{EPSP}$ is the electrochemical driving force for ion flux. The current steps change in