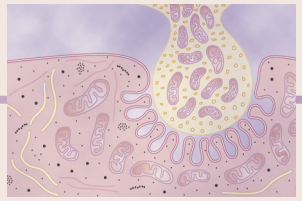

CHAPTER 7

Excitation of Skeletal Muscle: Neuromuscular Transmission and Excitation-Contraction Coupling

NEUROMUSCULAR JUNCTION AND TRANSMISSION OF IMPULSES FROM NERVE ENDINGS TO SKELETAL MUSCLE FIBERS

Skeletal muscle fibers are innervated by large myelinated nerve fibers that originate from large motoneurons in the anterior horns of the spinal cord. As discussed in Chapter 6, each nerve fiber, after entering the muscle belly, normally branches and stimulates from three to several hundred skeletal muscle fibers. Each nerve ending makes a junction, called the *neuromuscular junction*, with the muscle fiber near its midpoint. The action potential initiated in the muscle fiber by the nerve signal travels in both directions toward the muscle fiber ends. With the exception of about 2% of the muscle fibers, there is only one such junction per muscle fiber.

PHYSIOLOGIC ANATOMY OF THE NEUROMUSCULAR JUNCTION—THE MOTOR END PLATE

Figure 7-1*A* and ***B*** shows the neuromuscular junction from a large myelinated nerve fiber to a skeletal muscle fiber. The nerve fiber forms a complex of *branching nerve terminals* that invaginate into the surface of the muscle fiber but lie outside the muscle fiber plasma membrane. The entire structure is called the *motor end plate.* It is covered by one or more Schwann cells that insulate it from the surrounding fluids.

Figure 7-1*C* shows the junction between a single axon terminal and the muscle fiber membrane. The invaginated membrane is called the *synaptic gutter* or *synaptic trough*, and the space between the terminal and the fiber membrane is called the *synaptic space* or *synaptic cleft,* which is 20 to 30 nanometers wide. At the bottom of the gutter are numerous smaller *folds* of the muscle membrane called *subneural clefts*, which greatly increase the surface area at which the synaptic transmitter can act.

In the axon terminal are many mitochondria that supply adenosine triphosphate (ATP), the energy source used for synthesis of a transmitter, *acetylcholine,* which excites the muscle fiber membrane. Acetylcholine is synthesized in the cytoplasm of the terminal but is absorbed rapidly into many small *synaptic vesicles*, about 300,000 of which are normally in the terminals of a single end plate. In the synaptic space are large quantities of the enzyme *acetylcholinesterase*, which destroys acetylcholine a few milliseconds after it has been released from the synaptic vesicles.

SECRETION OF ACETYLCHOLINE BY THE NERVE TERMINALS

When a nerve impulse reaches the neuromuscular junction, about 125 vesicles of acetylcholine are released from the terminals into the synaptic space. Some of the details of this mechanism can be seen in **Figure 7-2**, which shows an expanded view of a synaptic space with the neural membrane above and the muscle membrane and its subneural clefts below.

On the inside surface of the neural membrane are linear *dense bars*, shown in cross section in **Figure 7-2**. To each side of each dense bar are protein particles that penetrate the neural membrane; these are *voltage-gated calcium channels*. When an action potential spreads over the terminal, these channels open and allow calcium ions to diffuse from the synaptic space to the interior of the nerve terminal. The calcium ions, in turn, are believed to activate *Ca^{2+}-calmodulin–dependent protein kinase*, which, in turn, phosphorylates *synapsin* proteins that anchor the acetylcholine vesicles to the cytoskeleton of the presynaptic terminal. This process frees the acetylcholine vesicles from the cytoskeleton and allows them to move to the *active zone* of the presynaptic neural membrane adjacent to the dense bars. The vesicles then dock at the release sites, fuse with the neural membrane, and empty their acetylcholine into the synaptic space by the process of *exocytosis*.

Although some of the aforementioned details are speculative, it is known that the effective stimulus for causing acetylcholine release from the vesicles is entry of calcium ions and that acetylcholine from the vesicles is then emptied through the neural membrane adjacent to the dense bars.

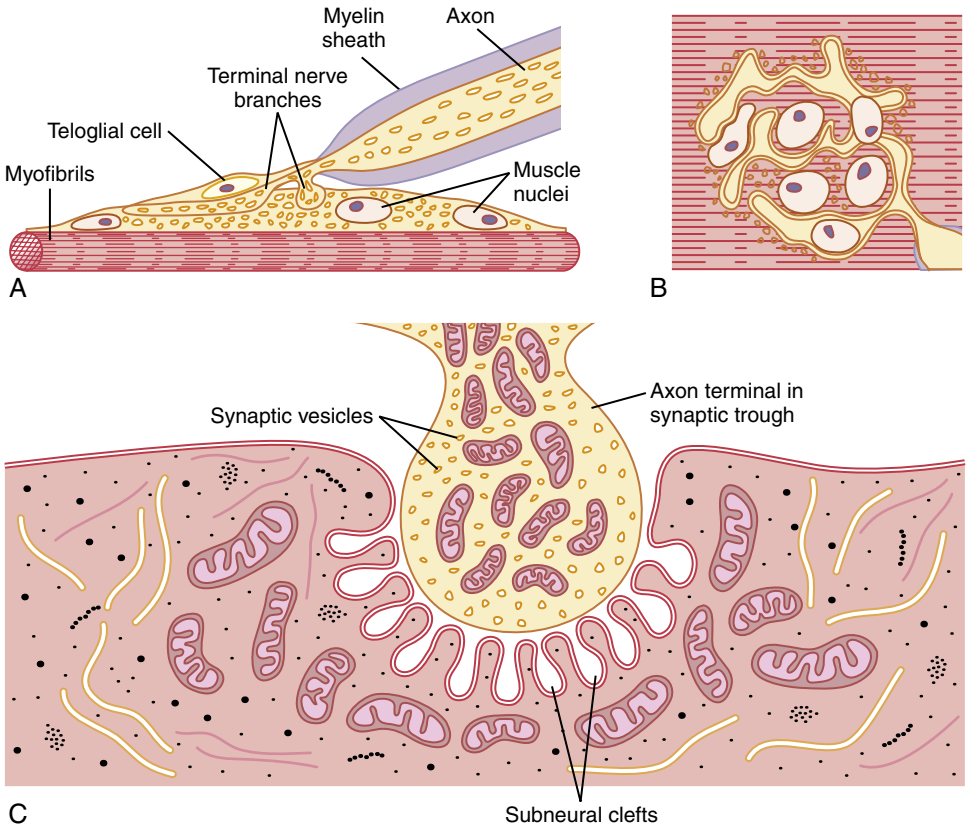

Figure 7-1. Different views of the motor end plate. **A,** Longitudinal section through the end plate. **B,** Surface view of the end plate. **C,** Electron micrographic appearance of the contact point between a single axon terminal and the muscle fiber membrane.

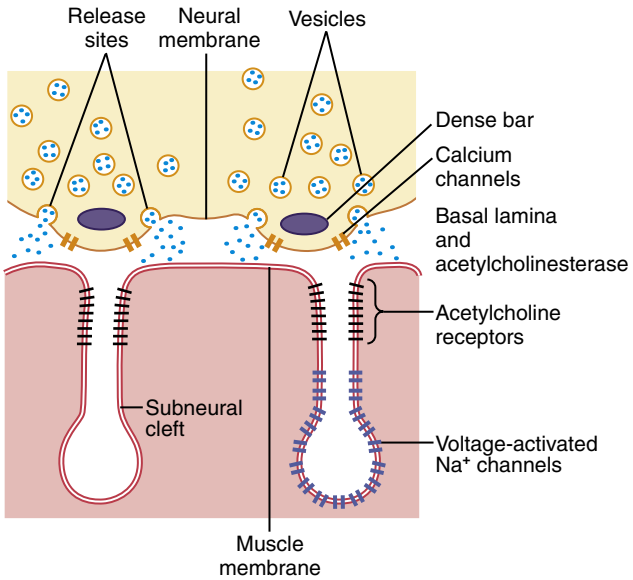

Figure 7-2. Release of acetylcholine from synaptic vesicles at the neural membrane of the neuromuscular junction. Note the proximity of the release sites in the neural membrane to the acetylcholine receptors in the muscle membrane at the mouths of the subneural clefts.

Acetylcholine Opens Ion Channels on Postsynaptic Membranes. Figure 7-2 also shows many small *acetylcholine receptors* and *voltage-gated sodium channels* in the muscle fiber membrane. The *acetylcholine-gated ion channels* are located almost entirely near the mouths of the subneural clefts lying immediately below the dense bar areas, where the acetylcholine is emptied into the synaptic space. The voltage-gated sodium channels also line the subneural clefts.

Each acetylcholine receptor is a protein complex that has a total molecular weight of approximately 275,000. The fetal acetylcholine receptor complex is composed of five subunit proteins, two *alpha* proteins and one each of *beta, delta*, and *gamma* proteins. In the adult, an *epsilon* protein substitutes for the gamma protein in this receptor complex. These protein molecules penetrate all the way through the membrane, lying side by side in a circle to form a tubular channel, illustrated in Figure 7-3. The channel remains constricted, as shown in part A of the figure, until two acetylcholine molecules attach respectively to the two *alpha* subunit proteins. This attachment causes a conformational change that opens the channel, as shown in part B of the figure.

The acetylcholine-gated channel has a diameter of about 0.65 nanometer, which is large enough to allow the important positive ions—sodium (Na^+), potassium (K^+), and calcium (Ca^{2+})—to move easily through the opening. Patch clamp studies have shown that one of these channels, when opened by acetylcholine, can transmit 15,000 to 30,000 sodium ions in 1 millisecond. Conversely, negative ions, such as chloride ions, do not pass through because of strong negative charges in the mouth of the channel that repel these negative ions.

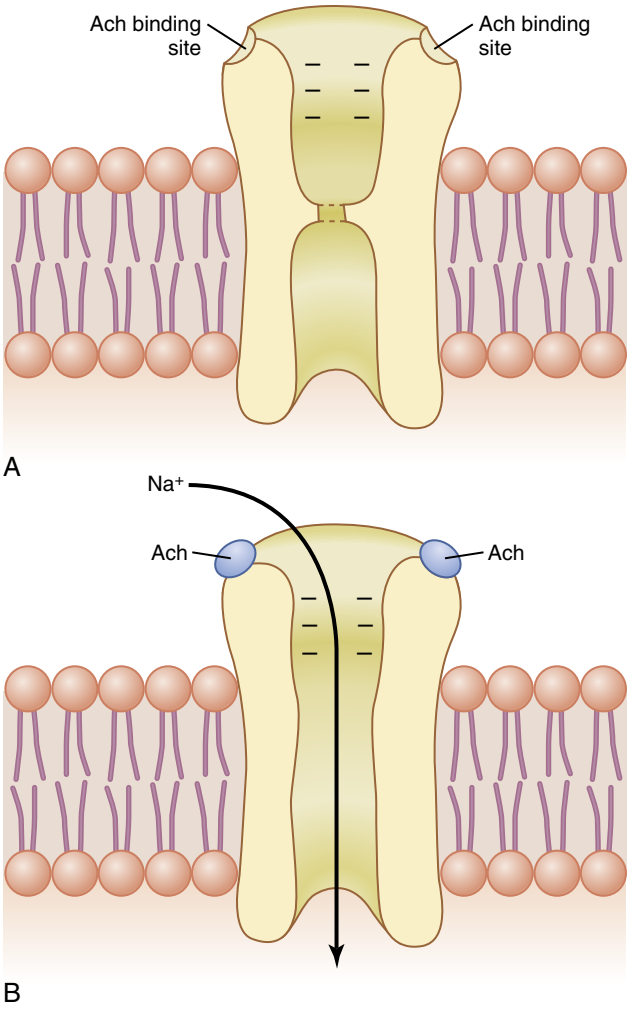

Figure 7-3. Acetylcholine-gated channel. **A,** Closed state. **B,** After acetylcholine (Ach) has become attached and a conformational change has opened the channel, allowing sodium ions to enter the muscle fiber and excite contraction. Note the negative charges at the channel mouth that prevent passage of negative ions such as chloride ions.

In practice, far more sodium ions flow through the acetylcholine-gated channels than any other ions for two reasons. First, there are only two positive ions present in large concentrations—sodium ions in the extracellular fluid and potassium ions in the intracellular fluid. Second, the negative potential on the inside of the muscle membrane, −80 to −90 millivolts, pulls the positively charged sodium ions to the inside of the fiber while simultaneously preventing efflux of the positively charged potassium ions when they attempt to pass outward.

As shown in **Figure 7-3*B***, the principal effect of opening the acetylcholine-gated channels is to allow sodium ions to flow to the inside of the fiber, carrying positive charges with them. This action creates a local positive potential change inside the muscle fiber membrane, called the *end plate potential.* This end plate potential normally causes sufficient depolarization to open neighboring voltage-gated sodium channels, allowing even greater sodium ion inflow and initiating an action potential that

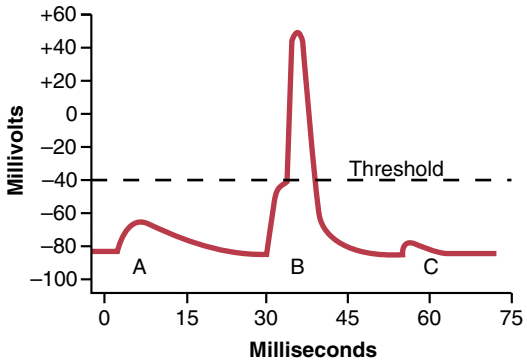

Figure 7-4. End plate potentials (in millivolts). **A,** Weakened end plate potential recorded in a curarized muscle that is too weak to elicit an action potential. **B,** Normal end plate potential eliciting a muscle action potential. **C,** Weakened end plate potential caused by botulinum toxin that decreases end plate release of acetylcholine, again too weak to elicit a muscle action potential.

spreads along the muscle membrane and causes muscle contraction.

Destruction of the Released Acetylcholine by Acetylcholinesterase. The acetylcholine, once released into the synaptic space, continues to activate acetylcholine receptors as long as the acetylcholine persists in the space. However, it is rapidly destroyed by the enzyme *acetylcholinesterase*, which is attached mainly to the spongy layer of fine connective tissue that fills the synaptic space between the presynaptic nerve terminal and the postsynaptic muscle membrane. A small amount of acetylcholine diffuses out of the synaptic space and is then no longer available to act on the muscle fiber membrane.

The short time that the acetylcholine remains in the synaptic space—a few milliseconds at most—normally is sufficient to excite the muscle fiber. Then the rapid removal of the acetylcholine prevents continued muscle re-excitation after the muscle fiber has recovered from its initial action potential.

End Plate Potential and Excitation of the Skeletal Muscle Fiber. The sudden insurgence of sodium ions into the muscle fiber when the acetylcholine-gated channels open causes the electrical potential inside the fiber at the *local area of the end plate* to increase in the positive direction as much as 50 to 75 millivolts, creating a *local potential* called the *end plate potential.* Recall from Chapter 5 that a sudden increase in nerve membrane potential of more than 20 to 30 millivolts is normally sufficient to initiate more and more sodium channel opening, thus initiating an action potential at the muscle fiber membrane.

Figure 7-4 illustrates an end plate potential initiating the action potential. This figure shows three separate end plate potentials. End plate potentials A and C are too weak to elicit an action potential, but they do produce weak local end plate voltage changes, as recorded in the figure. By contrast, end plate potential B is much stronger and causes enough sodium channels to open

so that the self-regenerative effect of more and more sodium ions flowing to the interior of the fiber initiates an action potential. The weakness of the end plate potential at point A was caused by poisoning of the muscle fiber with *curare*, a drug that blocks the gating action of acetylcholine on the acetylcholine channels by competing for the acetylcholine receptor sites. The weakness of the end plate potential at point C resulted from the effect of *botulinum toxin*, a bacterial poison that decreases the quantity of acetylcholine release by the nerve terminals.

Safety Factor for Transmission at the Neuromuscular Junction—Fatigue of the Junction. Ordinarily, each impulse that arrives at the neuromuscular junction causes about three times as much end plate potential as that required to stimulate the muscle fiber. Therefore, the normal neuromuscular junction is said to have a high *safety factor*. However, stimulation of the nerve fiber at rates greater than 100 times per second for several minutes may diminish the number of acetylcholine vesicles so much that impulses fail to pass into the muscle fiber. This situation is called *fatigue* of the neuromuscular junction, and it is the same effect that causes fatigue of synapses in the central nervous system when the synapses are overexcited. Under normal functioning conditions, measurable fatigue of the neuromuscular junction occurs rarely and, even then, only at the most exhausting levels of muscle activity.

Acetylcholine Formation and Release

Acetylcholine formation and release at the neuromuscular junction occur in the following stages:

1. Small vesicles, about 40 nanometers in size, are formed by the Golgi apparatus in the cell body of the motoneuron in the spinal cord. These vesicles are then transported by axoplasm that streams through the core of the axon from the central cell body in the spinal cord all the way to the neuromuscular junction at the tips of the peripheral nerve fibers. About 300,000 of these small vesicles collect in the nerve terminals of a single skeletal muscle end plate.
2. Acetylcholine is synthesized in the cytosol of the nerve fiber terminal but is immediately transported through the membranes of the vesicles to their interior, where it is stored in highly concentrated form—about 10,000 molecules of acetylcholine in each vesicle.
3. When an action potential arrives at the nerve terminal, it opens many *calcium channels* in the membrane of the nerve terminal because this terminal has an abundance of voltage-gated calcium channels. As a result, the calcium ion concentration inside the terminal membrane increases about 100-fold, which in turn increases the rate of fusion of the acetylcholine vesicles with the terminal membrane about 10,000-fold. This fusion makes many of the vesicles rupture, allowing *exocytosis* of acetylcholine into the synaptic space. About 125 vesicles usually rupture with each action potential. Then, after a few milliseconds, the acetylcholine is split by acetylcholinesterase into acetate ion and choline, and the choline is actively reabsorbed into the neural terminal to be reused to form new acetylcholine. This sequence of events occurs within a period of 5 to 10 milliseconds.
4. The number of vesicles available in the nerve ending is sufficient to allow transmission of only a few thousand nerve to muscle impulses. Therefore, for continued function of the neuromuscular junction, new vesicles need to be re-formed rapidly. Within a few seconds after each action potential is over, coated pits appear in the terminal nerve membrane, caused by contractile proteins in the nerve ending, especially the protein *clathrin*, which is attached to the membrane in the areas of the original vesicles. Within about 20 seconds, the proteins contract and cause the pits to break away to the interior of the membrane, thus forming new vesicles. Within another few seconds, acetylcholine is transported to the interior of these vesicles, and they are then ready for a new cycle of acetylcholine release.

Drugs That Enhance or Block Transmission at the Neuromuscular Junction

Drugs That Stimulate the Muscle Fiber by Acetylcholine-Like Action. Several compounds, including *methacholine, carbachol*, and *nicotine*, have nearly the same effect on the muscle fiber as acetylcholine. The main differences between these drugs and acetylcholine are that the drugs are not destroyed by cholinesterase or are destroyed so slowly that their action often persists for many minutes to several hours. The drugs work by causing localized areas of depolarization of the muscle fiber membrane at the motor end plate where the acetylcholine receptors are located. Then, every time the muscle fiber recovers from a previous contraction, these depolarized areas, by virtue of leaking ions, initiate a new action potential, thereby causing a state of muscle spasm.

Drugs That Stimulate the Neuromuscular Junction by Inactivating Acetylcholinesterase. Three particularly well-known drugs—*neostigmine, physostigmine*, and *diisopropyl fluorophosphate*—inactivate acetylcholinesterase in the synapses so that it no longer hydrolyzes acetylcholine. Therefore, with each successive nerve impulse, additional acetylcholine accumulates and stimulates the muscle fiber repetitively. This activity causes *muscle spasm* when even a few nerve impulses reach the muscle. Unfortunately, it can also cause death as a result of laryngeal spasm, which smothers a person.

Neostigmine and physostigmine combine with acetylcholinesterase to inactivate the acetylcholinesterase for up to several hours, after which these drugs are displaced from the acetylcholinesterase so that the esterase once again becomes active. Conversely, diisopropyl fluorophosphate, which is a powerful nerve gas poison, inactivates acetylcholinesterase for weeks, which makes this poison particularly lethal.

Drugs That Block Transmission at the Neuromuscular Junction. A group of drugs known as *curariform drugs* can prevent the passage of impulses from the nerve ending into the muscle. For example. D-tubocurarine blocks the action of acetylcholine on the muscle fiber acetylcholine receptors, thus preventing sufficient increase in permeability of the muscle membrane channels to initiate an action potential.

Myasthenia Gravis Causes Muscle Weakness

Myasthenia gravis, which occurs in about 1 in every 20,000 persons, causes muscle weakness because of the inability of the neuromuscular junctions to transmit enough signals from the nerve fibers to the muscle fibers. Antibodies that attack the acetylcholine receptors have been demonstrated in the blood of most patients with myasthenia gravis. Therefore, myasthenia gravis is believed to be an autoimmune disease in which the patients have developed antibodies that block or destroy their own acetylcholine receptors at the postsynaptic neuromuscular junction.

Regardless of the cause, the end plate potentials that occur in the muscle fibers are mostly too weak to initiate opening of the voltage-gated sodium channels, and muscle fiber depolarization does not occur. If the disease is intense enough, the patient may die of respiratory failure as a result of severe weakness of the respiratory muscles. The disease can usually be ameliorated for several hours by administering *neostigmine* or some other anticholinesterase drug, which allows larger than normal amounts of acetylcholine to accumulate in the synaptic space. Within minutes, some of those affected can begin to function almost normally until a new dose of neostigmine is required a few hours later.

MUSCLE ACTION POTENTIAL

Almost everything discussed in Chapter 5 regarding the initiation and conduction of action potentials in nerve fibers applies equally to skeletal muscle fibers, except for quantitative differences. Some of the quantitative aspects of muscle potentials are as follows:

1. The resting membrane potential is about −80 to −90 millivolts in skeletal fibers, about 10 to 20 millivolts more negative than in neurons.
2. The duration of the action potential is 1 to 5 milliseconds in skeletal muscle, about five times as long as in large myelinated nerves.
3. The velocity of conduction is 3 to 5 m/sec, about 1/13 the velocity of conduction in the large myelinated nerve fibers that excite skeletal muscle.

Action Potentials Spread to the Interior of the Muscle Fiber by Way of Transverse Tubules

The skeletal muscle fiber is so large that action potentials spreading along its surface membrane cause almost no current flow deep within the fiber. Maximum muscle contraction, however, requires the current to penetrate deeply into the muscle fiber to the vicinity of the separate myofibrils. This penetration is achieved by transmission of action potentials along *transverse tubules* (T tubules) that penetrate all the way through the muscle fiber, from one side of the fiber to the other, as illustrated in **Figure 7-5**. The T tubule action potentials cause release of calcium ions inside the muscle fiber in the immediate vicinity of the myofibrils, and these calcium ions then cause contraction. The overall process is called *excitation-contraction* coupling.

EXCITATION-CONTRACTION COUPLING

Transverse Tubule–Sarcoplasmic Reticulum System

Figure 7-5 shows myofibrils surrounded by the T tubule–sarcoplasmic reticulum system. The T tubules are small and run transverse to the myofibrils. They begin at the cell membrane and penetrate all the way from one side of the muscle fiber to the opposite side. Not shown in the figure is that these tubules branch among themselves and form entire *planes* of T tubules interlacing among all the separate myofibrils. Also, *where the T tubules originate from the cell membrane, they are open to the exterior of the muscle fiber.* Therefore, they communicate with the extracellular fluid surrounding the muscle fiber and contain extracellular fluid in their lumens. In other words, *the T tubules are actually internal extensions of the cell membrane.* Therefore, when an action potential spreads over a muscle fiber membrane, a potential change also spreads along the T tubules to the deep interior of the muscle fiber. The electrical currents surrounding these T tubules then elicit the muscle contraction.

Figure 7-5 also shows a sarcoplasmic *reticulum*, in yellow. This sarcoplasmic reticulum is composed of two major parts: (1) large chambers called *terminal cisternae* that abut the T tubules; and (2) long longitudinal tubules that surround all surfaces of the contracting myofibrils.

Release of Calcium Ions by the Sarcoplasmic Reticulum

One of the special features of the sarcoplasmic reticulum is that within its vesicular tubules is an excess of calcium ions in high concentration. Many of these ions are released from each vesicle when an action potential occurs in the adjacent T tubule.

Figures 7-6 and 7-7 show that the action potential of the T tubule causes current flow into the sarcoplasmic reticular cisternae where they abut the T tubule. As the action potential reaches the T tubule, the voltage change is sensed by dihydropyridine *receptors* linked to *calcium release channels*, also called *ryanodine receptor channels*, in the adjacent sarcoplasmic reticular cisternae (see **Figure 7-6**). Activation of dihydropyridine receptors triggers the opening of the calcium release channels in the cisternae, as well as in their attached longitudinal tubules. These channels remain open for a few milliseconds, releasing calcium ions into the sarcoplasm surrounding the myofibrils and causing contraction, as discussed in Chapter 6.

Calcium Pump Removes Calcium Ions from the Myofibrillar Fluid After Contraction Occurs. Once the calcium ions have been released from the sarcoplasmic tubules and have diffused among the myofibrils, muscle contraction continues as long as the calcium ion concentration remains high. However, a continually active calcium pump located in the walls of the sarcoplasmic reticulum

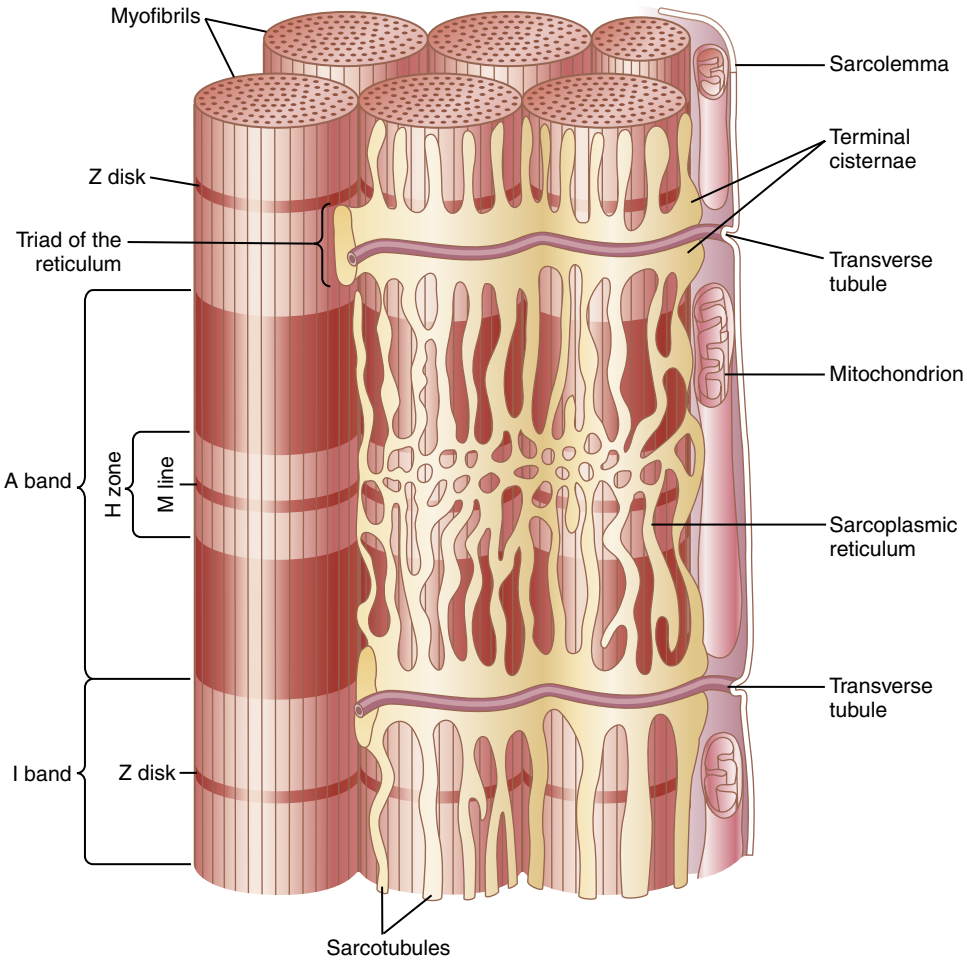

Figure 7-5. Transverse (T) tubule–sarcoplasmic reticulum system. Note that the T tubules communicate with the outside of the cell membrane and, deep in the muscle fiber, each T tubule lies adjacent to the ends of longitudinal sarcoplasmic reticulum tubules that surround all sides of the actual myofibrils that contract. This illustration was drawn from frog muscle, which has one T tubule per sarcomere, located at the Z disk. A similar arrangement is found in mammalian heart muscle, but mammalian skeletal muscle has two T tubules per sarcomere, located at the A-I band junctions.

pumps calcium ions away from the myofibrils back into the sarcoplasmic tubules (see **Figure 7-6**). This pump, called SERCA (***s***arcoplasmic ***r***eticulum ***C***a^{2+}-***A***TPase), can concentrate the calcium ions about 10,000-fold inside the tubules. In addition, inside the reticulum is a *calcium-binding protein* called *calsequestrin,* which can bind up to 40 calcium ions for each molecule of calsequestrin.

Excitatory Pulse of Calcium Ions. The normal resting state concentration (<10^{-7} molar) of calcium ions in the cytosol that bathes the myofibrils is too little to elicit contraction. Therefore, the troponin-tropomyosin complex keeps the actin filaments inhibited and maintains a relaxed state of the muscle.

Conversely, full excitation of the T tubule and sarcoplasmic reticulum system causes enough release of calcium ions to increase the concentration in the myofibrillar fluid to as high as 2×10^{-4} molar concentration, a 500-fold increase, which is about 10 times the level required to cause maximum muscle contraction. Immediately thereafter, the calcium pump depletes the calcium ions again. The total duration of this calcium pulse in the usual skeletal muscle fiber lasts about 1/20 of a second, although it may last several times as long in some fibers and several times less in others. In heart muscle, the calcium pulse lasts about one-third of a second because of the long duration of the cardiac action potential.

During this calcium pulse, muscle contraction occurs. If the contraction is to continue without interruption for long intervals, a series of calcium pulses must be initiated by a continuous series of repetitive action potentials, as discussed in Chapter 6.

Malignant Hyperthermia

In susceptible individuals, *malignant hyperthermia* and a *hypermetabolic crisis* may be triggered by exposure to certain types of anesthetics, including halothane and isoflurane, or succinylcholine. At least six genetic mutations, especially of the ryanodine receptor or dihydropyridine receptor genes, have been shown to increase susceptibility greatly to developing malignant hyperthermia during anesthesia. Little is known about the specific mechanisms

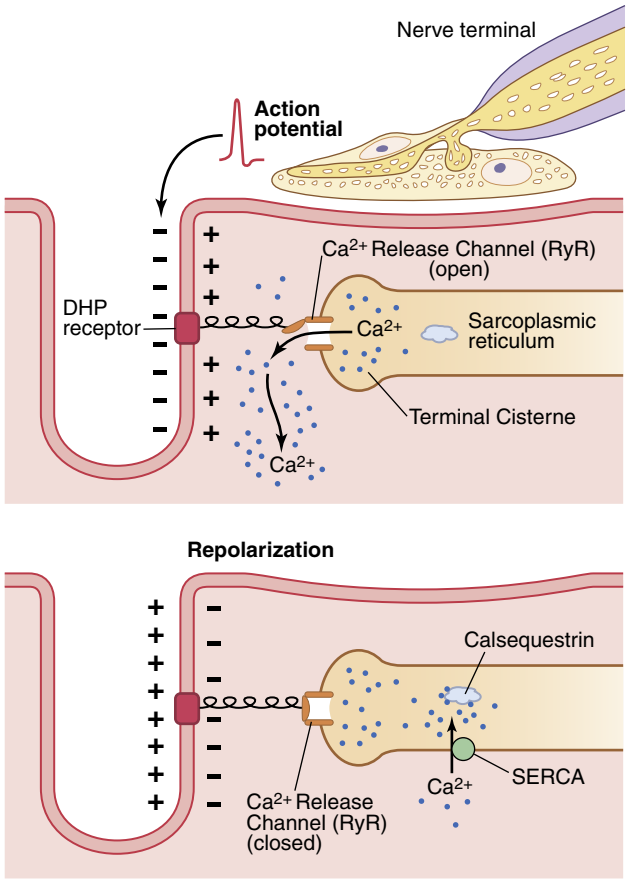

Figure 7-6. Excitation-contraction coupling in skeletal muscle. The *top panel* shows an action potential in the transverse tubule that causes a conformational change in the voltage-sensing dihydropyridine (DHP) receptors, opening the ryanodine (RyR) Ca^{2+} release channels in the terminal cisternae of the sarcoplasmic reticulum and permitting Ca^{2+} to diffuse rapidly into the sarcoplasm and initiate muscle contraction. During repolarization (*bottom panel*), the conformational change in the DHP receptor closes the Ca^{2+} release channels, and Ca^{2+} is transported from the sarcoplasm into the sarcoplasmic reticulum by an adenosine triphosphate–dependent calcium pump, called SERCA (*s*arcoplasmic *r*eticulum *C*a^{2+}-*A*TPase).

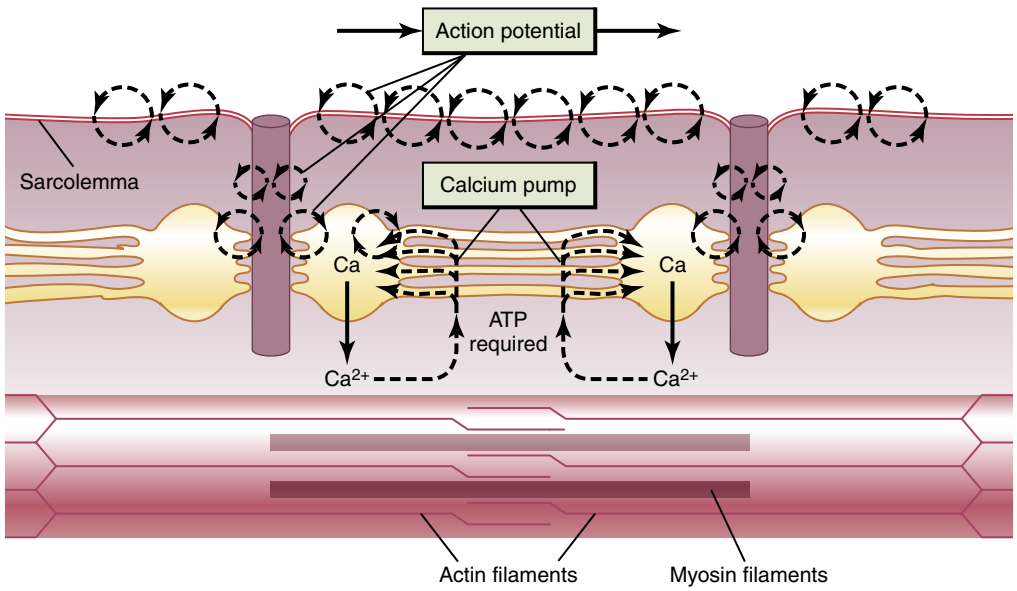

Figure 7-7. Excitation-contraction coupling in the muscle, showing (1) an action potential that causes release of calcium ions from the sarcoplasmic reticulum and then (2) re-uptake of the calcium ions by a calcium pump. ATP, Adenosine triphosphate.

whereby anesthetics interact with these abnormal receptors to trigger malignant hyperthermia. It is known, however, that these mutations cause unregulated passage of calcium from the sarcoplasmic reticulum into the intracellular spaces, which in turn causes the muscle fibers to contract excessively. These sustained muscled contractions greatly increase metabolic rate, generating large amounts of heat and causing cellular acidosis, as a well as depletion of energy stores.

Symptoms of malignant include muscle rigidity, high fever, and rapid heart rate. Additional complications in severe cases may include rapid breakdown of skeletal muscle (*rhabdomyolysis*) and a high plasma potassium level due to release of large amounts of potassium from damaged muscle cells. Treatment of malignant hyperthermia generally involves rapid cooling and the administration of *dantrolene*, a drug that antagonizes ryanodine receptors, which inhibits calcium ion release for the sarcoplasmic reticulum and thereby attenuating muscle contraction.

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