CONTRACTION OF SKELETAL MUSCLE

About 40 percent of the body mass is skeletal muscle, and perhaps another 10 percent is smooth muscle and cardiac muscle. Many of the principles of contraction apply to all three types of muscle.

ANATOMY OF SKELETAL MUSCLE:

Skeletal Muscle Fiber

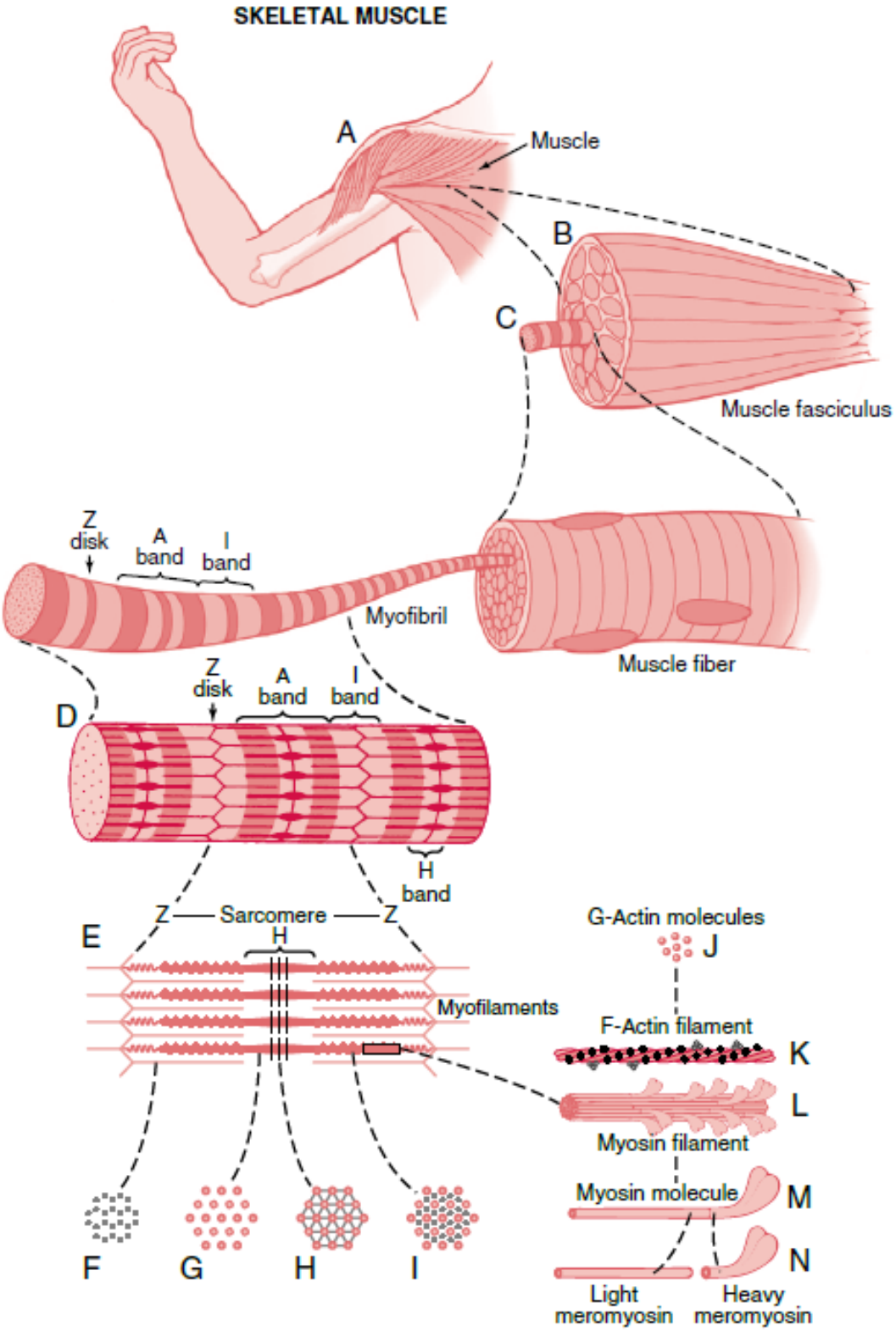
In most muscles, the fibers extend the entire length of the muscle. Each fiber is innervated by only one nerve ending. Myofibrils Are Composed of Actin and Myosin Filaments.

Each muscle fiber contains hundreds to thousands of myofibrils; in turn, each myofibril is composed of about 1500 myosin filaments and 3000 actin filaments lying side by side. These filaments are large polymerized protein molecules that are responsible for muscle contraction. The thick filaments are myosin, and the thin filaments are actin.

Note the following features:

- **Light and dark bands**. The myosin and actin filaments partially interdigitate and thus cause the myofibrils to have alternate light and dark bands. The light bands contain only actin filaments and are called I bands. The dark bands, called A bands, contain myosin filaments as well as the ends of the actin filaments. The length of the A band is the length of the myosin filament. The length of the I band changes with muscle contraction.
- **Cross-bridges**. The small projections from the sides of the myosin filaments are cross-bridges. They protrude from the surfaces of the myosin filament along its entire length except in the center. Myosin cross-bridges interact with actin filaments, causing contraction.
- **Z disk.** The ends of the actin filaments are attached to Z disks. The Z disk passes across the myofibril and from one to another, attaching and aligning the myofibrils across the muscle fiber. The entire muscle fiber therefore has light and dark bands, giving skeletal and cardiac muscle a striated appearance.
- **Sarcomere.** The portion of a myofibril that lies between two successive Z disks is called a sarcomere.

During rest, the actin filaments overlap the myosin filaments with an optimal amount of interdigitating in skeletal muscle and slightly shorter than optimal interdigitating in cardiac muscle.



GENERAL MECHANISM OF MUSCLE CONTRACTION:

The initiation and execution of muscle contraction occur in the following sequential steps:

1. An action potential travels along a motor neuron to its endings on muscle fibers, and each neuronal ending secretes a small amount of the neurotransmitter substance acetylcholine.
2. The acetylcholine diffuses to a local area of the muscle membrane, causing acetylcholine-gated cation channels to open. Sodium, potassium, and calcium ions move through the cation channels down their individual electrochemical gradients. The net effect is development of a local depolarization, called a generator potential or end-plate potential. The local depolarization in turn leads to opening of voltage gated sodium channels in the muscle membrane. A muscle fiber action potential follows.
3. The action potential travels along the muscle fiber membrane, causing the sarcoplasmic reticulum to release calcium ions into the sarcoplasm.
4. The calcium ions initiate attractive forces between the actin and myosin filaments of the myofibrils, causing them to slide together, which is the contractile process.
5. The calcium ions are continually pumped back into the sarcoplasmic reticulum where they remain stored until a muscle action potential arrives; this removal of calcium ions from the sarcoplasm causes muscle contraction to cease.

MOLECULAR MECHANISM OF MUSCLE CONTRACTION:

Muscle Contraction Occurs by a Sliding Filament Mechanism.

Mechanical forces generated by interactions between actin and myosin filaments cause the actin filaments to slide inward among the myosin filaments. Under resting conditions, these forces are inhibited, but when an action potential travels over the muscle fiber membrane, the sarcoplasmic reticulum releases large quantities of calcium ions, which activate the forces between the myosin and actin filaments, causing contraction to begin.

Myosin Filaments Are Composed of Multiple Myosin

Molecules. The tails of myosin molecules bundle together to form the body of the filament, whereas the myosin heads and part of each myosin molecule hang outward to the sides of the body, providing an arm that extends the head outward from the body. The protruding arms and heads together are called cross bridges. An important feature of the myosin head is that it functions as an adenosine triphosphatase enzyme, which allows it to cleave adenosine triphosphate (ATP) and thus energize the contraction process.

Actin Filaments Are Composed of Actin, Tropomyosin, and Troponin.

Each actin filament is about 1 micrometer long. The bases of the actin filaments are inserted strongly into the Z disks, whereas the other ends protrude in both directions into the adjacent sarcomeres where they lie in the spaces between the myosin molecules.

Interaction of One Myosin Filament, Two Actin Filaments, and Calcium Ions to Cause Contraction.

The actin filament is inhibited by the troponin-tropomyosin complex. Activation is stimulated by calcium ions.

- Inhibition by the troponin-tropomyosin complex. The active sites on the normal actin filament of the relaxed muscle are inhibited or physically covered by the troponin-tropomyosin complex. Consequently, the sites cannot attach to the heads of the myosin filaments to cause contraction until the inhibitory effect of the troponin-tropomyosin complex is itself inhibited.
- Activation by calcium ions. The inhibitory effect of the troponin-tropomyosin complex on the actin filaments is inhibited in the presence of calcium ions.

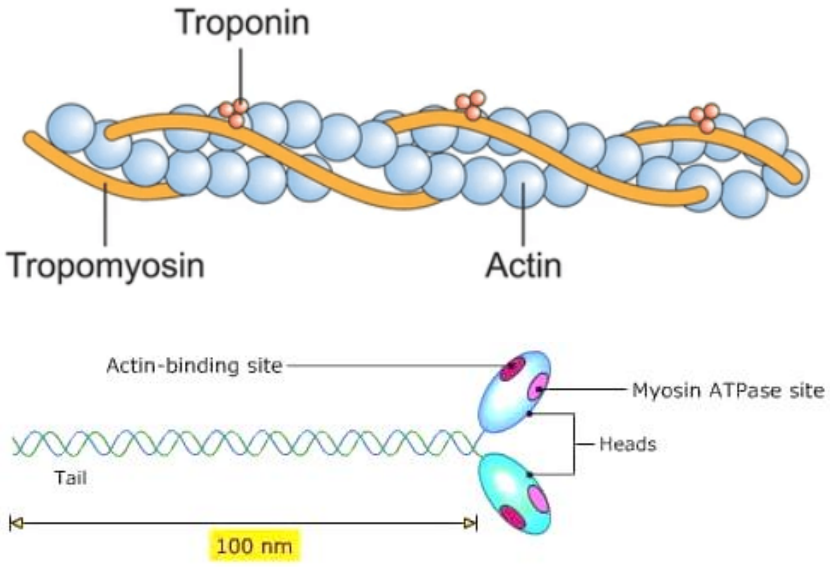
Calcium ions combine with troponin C, causing the troponin complex to tug on the tropomyosin molecule. This action “uncovers” the active sites of the actin, allowing myosin heads to attach and contraction to proceed.

A “Walk-Along” Theory Can Explain How the Activated Actin Filament and the Myosin Cross-Bridges Interact to Cause Contraction. When a myosin head attaches to an active site, the head tilts automatically toward the arm that is dragging along the actin filament. This tilt of the head is called the power stroke. Immediately after tilting, the head automatically breaks away from the active site.

The head then returns to its normal perpendicular direction. In this position, it combines with a new active site farther along the actin filament. Thus, the heads of the cross-bridges bend back and forth and, step by step, walk along the actin filament, pulling the ends of the actin filaments toward the center of the myosin filament.

The Amount of Actin and Myosin Filament Overlap Determines Tension Developed by the Contracting Muscle. The Strength of Contraction Is Maximal When There Is Optimal Overlap

Between Actin Filaments and the Cross-Bridges of the Myosin Filaments. A muscle cannot develop tension at very long, non-physiological sarcomere lengths because there is no overlap between actin and myosin filaments. As the sarcomere shortens and actin and myosin filaments begin to overlap, the tension increases progressively. Full tension is maintained at a sarcomere length of about 2.0 micrometers because the actin filament has overlapped all of the cross-bridges of the myosin filament. Upon further shortening, the ends of the two actin filaments begin to overlap (in addition to overlapping the myosin filaments), causing muscle tension to decrease. When the sarcomere length decreases to about 1.65 micrometers, the two Z disks of the sarcomere abut the ends of the myosin filaments, and the strength of contraction decreases greatly.



ENERGETICS OF MUSCLE CONTRACTION:

Muscle Contraction Requires ATP to Perform Three Main Functions

• Most of the ATP is used to activate the walk-along mechanism of muscle contraction.

• Active transport of calcium ions back into the sarcoplasmic reticulum causes contraction to terminate.

• Active transport of sodium and potassium ions through the muscle fiber membrane maintains an appropriate ionic environment for the propagation of action potentials.

There Are Three Main Sources of Energy for Muscle Contraction. The concentration of ATP in the muscle fiber is sufficient to maintain full contraction for only 1 to 2 seconds. After the ATP is split

into adenosine diphosphate (ADP), the ADP is rephosphorylated to form a new ATP. There are several sources of energy for this rephosphorylation.

• Phosphocreatine carries a high-energy bond similar to that of ATP but has more free energy. The energy released from this bond causes bonding of a new inorganic phosphate ion to ADP to reconstitute the ATP. The combined energy of ATP and phosphocreatine is capable of causing maximal muscle contraction for only 5 to 8 seconds.

• The breakdown of glycogen to pyruvic acid and lactic acid liberates energy that is used to convert ADP to ATP. The glycolytic reactions can occur in the absence of oxygen. The rate of formation of ATP by the glycolytic process is about 2.5 times as rapid as ATP formation when the cellular foodstuffs react with oxygen.

Glycolysis alone can sustain maximum muscle contraction for only about 1 minute.

• Oxidative metabolism occurs when oxygen is combined with the various cellular foodstuffs to liberate ATP. More than 95 percent of all energy used by the muscles for sustained, long-term contraction is derived from this source. The foodstuffs consumed are carbohydrates, fats, and proteins.

CHARACTERISTICS OF WHOLE MUSCLE CONTRACTION

Isometric Contractions Do Not Shorten Muscle, Whereas Isotonic Contractions Shorten Muscle at a Constant Tension

• Isometric contraction occurs when the muscle does not shorten during contraction. True isometric contractions cannot be generated in the intact body because the so-called series elastic components stretch during the contraction, allowing some shortening of the muscle. These elastic elements include the tendons, sarcolemmal ends of muscle fibers, and perhaps the hinged arms of the myosin cross-bridges.

• Isotonic contraction occurs when the muscle shortens and the tension on the muscle remains constant. The characteristics of the isotonic contraction depend on the load against which the muscle contracts, as well as on the inertia of the load.

• Slow fibers (type I, red muscle) (1) are smaller muscle fibers, (2) have high capillarity and large numbers of mitochondria to support high levels of oxidative metabolism, and (3) contain large amounts of myoglobin, which gives the slow muscle a reddish appearance and the name “red muscle.” The deficit of red myoglobin in fast muscle provides the name “white muscle.”

- Fast fibers (type II, white muscle) (1) are larger for greater strength of contraction, (2) have extensive sarcoplasmic reticulum for rapid release of calcium ions, (3) have large amounts of glycolytic enzymes for rapid release of energy, and (4) have lower capillarity and fewer mitochondria because oxidative metabolism is of secondary importance.

Mechanics of Skeletal Muscle Contraction

Force Summation Is the Adding Together of Individual Twitch Contractions to Increase the Intensity of Overall Muscle Contraction. Summation occurs in two ways:

- Multiple motor unit summation. When the central nervous system sends a weak signal to contract a muscle, the motor units in the muscle that contain the smallest and fewest muscle fibers are stimulated in preference to the larger motor units. Then, as the strength of the signal increases, larger motor units also begin to be excited, with the largest motor units often having up to 50 times as much contractile force as the smallest units; this is called the size principle.
- Frequency summation and tetanization. As the frequency of muscle contraction increases, there comes a point at which each new contraction occurs before the preceding one has ended. As a result, the second contraction is added partially to the first, so the total strength of contraction rises progressively with increasing frequency. When the frequency reaches a critical level, the successive contractions fuse, and the action appears to be completely smooth; this is called tetanization.

Muscle Hypertrophy Is an Increase in the Total Mass of a Muscle; Muscle Atrophy Is a Decrease in the Mass.

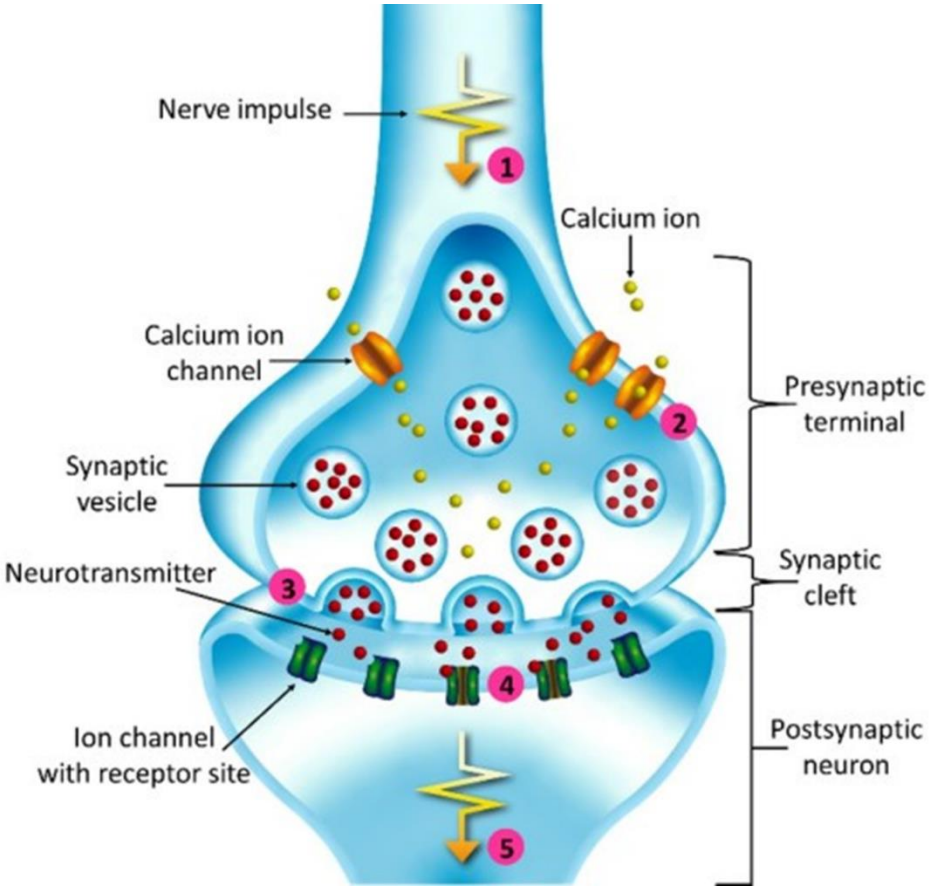
- Muscle hypertrophy results from an increase in the number of actin and myosin filaments in each muscle fiber. When the number of contractile proteins increases sufficiently, the myofibrils split within each muscle fiber to form new myofibrils. It is mainly this great increase in the number of additional myofibrils that causes muscle fibers to hypertrophy; however, under very intensive endurance training, the total number of muscle fibers can also increase.
- Muscle atrophy. When a muscle remains unused for a long period, the rate of decay of the contractile proteins occurs more rapidly than the rate of replacement; therefore, muscle atrophy occurs. Atrophy begins almost immediately when a muscle loses its nerve supply because it no longer receives the contractile signals that are required to maintain normal muscle size.

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

Skeletal muscle fibers are innervated by large, myelinated nerve fibers that originate in motoneurons of the spinal cord. Each nerve fiber normally stimulates three fibers to several hundred skeletal muscle fibers. The nerve ending makes a junction, called the neuromuscular junction, and the action potential in the muscle fiber travels in both directions toward the muscle fiber ends.

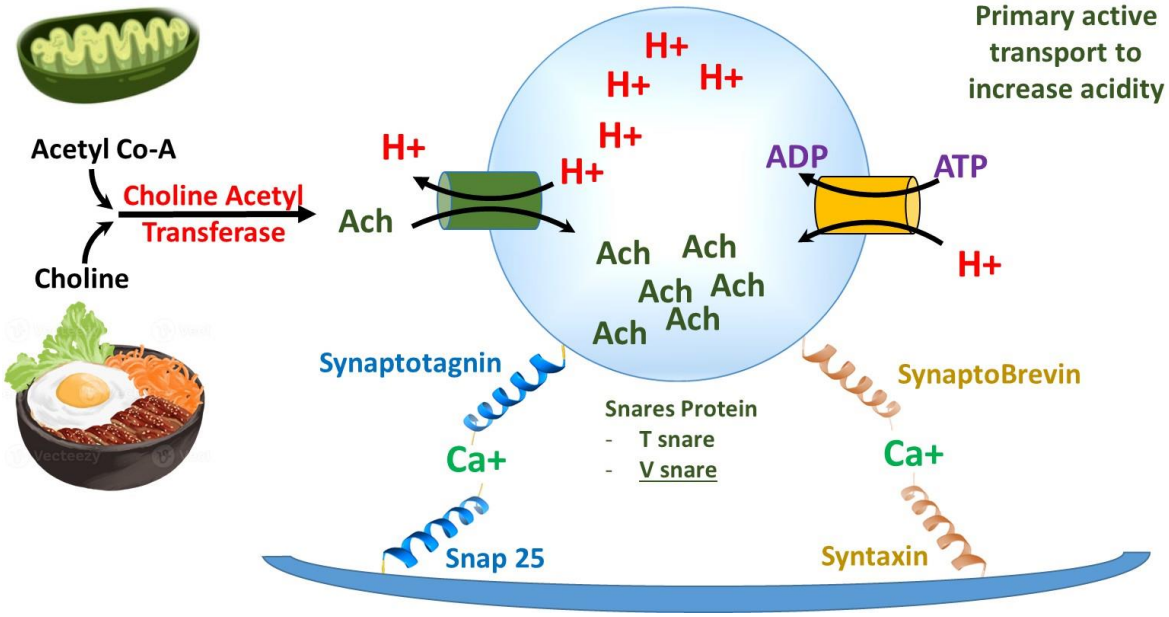
Secretion of Acetylcholine by the Nerve Terminals:

When a Nerve Impulse Reaches the Neuromuscular Junction, Vesicles Containing Acetylcholine Are Released Into the Synaptic Space. On the inside surface of the neuronal membrane are linear dense bars. To the side of each dense bar are voltage-gated calcium channels. When the action potential spreads over the nerve terminal, these channels open, allowing calcium ions to diffuse into the terminal. The calcium ions are believed to exert an attractive influence on the acetylcholine vesicles, drawing them adjacent to the dense bars. Some of the vesicles fuse with



the neural membrane and empty their acetylcholine into the synaptic space via the process of exocytosis.

Acetylcholine Opens Acetylcholine-Gated Ion Channels on the Postsynaptic Membrane. Acetylcholine-gated cation channels are located on the muscle membrane immediately adjacent to the dense bars. When two acetylcholine molecules attach to the channel receptors, a conformational change opens the channel. The principal effect of opening the acetylcholine-



gated channels is to allow large numbers of sodium ions to move into the muscle fiber, carrying with them large numbers of positive charges. This effect creates a local potential change at the muscle fiber membrane called the end-plate potential or generator potential. In turn, this end-plate potential normally leads to opening of voltage-gated sodium channels, which initiate an action potential at the muscle membrane, causing muscle contraction.

Acetylcholine Released Into the Synaptic Space Is Destroyed by Acetylcholinesterase or Simply Diffuses Away.

The acetylcholine, once released into the synaptic space, continues to activate the acetylcholine receptors for as long as it remains in the space. Most of the acetylcholine is destroyed by the enzyme acetylcholinesterase. A small amount diffuses out of the synaptic space. The short period during which the acetylcholine remains in the synaptic space—a few milliseconds at most—is always sufficient to excite the muscle fiber under normal conditions.

Acetylcholine Produces an End-Plate Potential That Excites the Skeletal Muscle Fiber. The movement of sodium ions into the muscle fiber causes the internal membrane potential in 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. The end plate potential created by acetylcholine stimulation is normally far greater than that necessary to initiate an action potential in the muscle fiber. Thus, every action potential in a motor neuron leads to contraction of muscle fibers.

MUSCLE ACTION POTENTIAL:

The Conduction of Action Potentials in Nerve Fibers Is Qualitatively but not Quantitatively Similar to That in Skeletal Muscle Fibers. Some of the quantitative differences and similarities include the following:

- The resting membrane potential is about −80 to −90 millivolts in skeletal muscle fibers, which is similar to that of large myelinated nerve fibers.
- The duration of the action potential is 1 to 5 milliseconds in skeletal muscle, which is about five times longer than in large myelinated nerves.
- The velocity of conduction is 3 to 5 m/sec in skeletal muscle, which is about 1/18 the velocity of conduction in the large myelinated nerve fibers that excite skeletal muscle.

EXCITATION-CONTRACTION COUPLING

Transverse Tubules Are Internal Extensions of the Cell Membrane. The transverse tubules (T tubules) run transverse to the myofibrils. They begin at the cell membrane and penetrate from one side of the muscle fiber to the opposite side. At the point where T tubules originate from the cell membrane, they are open to the exterior and thus contain extracellular fluid in their lumens. Because the T tubules are internal extensions of the cell membrane, when an action potential spreads over a muscle fiber membrane, it also spreads along the T tubules to the interior of the muscle fiber.

The Sarcoplasmic Reticulum Is Composed of Longitudinal Tubules and Terminal Cisternae. The longitudinal tubules run parallel to the myofibrils and terminate in large chambers called terminal cisternae. The cisternae abut the T tubules. In cardiac muscle, a single T tubule network for each sarcomere is located at the level of the Z disk. In mammalian skeletal muscle, there are two T

tubule networks for each sarcomere located near the two ends of the myosin filaments, which are the points at which the mechanical forces of muscle contraction are created. Thus mammalian skeletal muscle is optimally organized for rapid excitation of muscle contraction.

Calcium Ions Are Released From the Terminal Cisternae of the Sarcoplasmic Reticulum. Calcium ions located in the sarcoplasmic reticulum are released when an action potential occurs in the adjacent T tubule. The action potential itself is thought to cause rapid opening of calcium channels through the membranes of the terminal cisternae of the sarcoplasmic reticulum. These channels remain open for a few milliseconds; during this time the calcium ions responsible for muscle contraction are released into the sarcoplasm surrounding the myofibrils.

A Calcium Pump Removes Calcium Ions from the Sarcoplasmic Fluid. A continually active calcium pump located in the walls of the longitudinal tubules of the sarcoplasmic reticulum pumps calcium ions away from the myofibrils back into the sarcoplasmic tubules. This pump can concentrate the calcium ions about 10,000-fold inside the tubules. In addition, inside the reticulum is a calcium-binding protein called calsequestrin that can provide another 40-fold increase in the storage of calcium. This transfer of calcium into the sarcoplasmic reticulum depletes calcium ions in the sarcoplasmic fluid, thereby terminating the muscle contraction.