NERVE MUSCLE PHYSIOLOGY:

1.Nerve Action Potential (p. 60)

Nerve signals are transmitted by action potentials, which are rapid changes in the membrane potential. Each action potential begins with a sudden change from the normal resting negative potential to a positive membrane potential and then ends with an almost equally rapid change back to the resting negative potential. The successive stages of the action potential are as follows:

• Resting stage. This is the resting membrane potential before the action potential occurs.

• Depolarization stage. At this time, the membrane suddenly becomes permeable to sodium ions, allowing tremendous numbers of positively charged sodium ions to flow to the interior of the axon, and the potential rises rapidly in the positive direction.

• Repolarization stage. Within a few 10,000ths of a second after the membrane becomes highly permeable to sodium ions the sodium channels begin to close and the potassium channels open more than they normally do. Then rapid diffusion of potassium ions to the exterior re-establishes the normal negative resting membrane potential.

Voltage-Gated Sodium and Potassium Channels Are Activated and Inactivated during the Course of an Action Potential. The necessary factor for both depolarization and repolarization of the nerve membrane during the action potential is the voltage-gated sodium channel. The voltage-gated potassium channel also plays an important role in increasing the rapidity of repolarization of the membrane. These two voltage-gated channels are present in addition to the Naþ-Kþ pump and the Naþ-Kþ leak channels that establish the resting permeability of the membrane.

The Events That Cause the Action Potential Can Be Summarized as Follows

• During the resting state, before the action potential begins, the conductance for potassium ions about 100 times as great as the conductance for sodium ions. This is caused by much greater leakage of potassium ions than sodium ions through the leak channels.

• At the onset of the action potential, the sodium channels instantaneously become activated and allow up to a 5000-fold increase in sodium permeability (also called sodium conductance). Then the inactivation process closes the sodium channels within a few fractions of a millisecond. The onset of the action potential also causes voltage gating of the potassium channels, causing them to begin opening more slowly.

• At the end of the action potential, the return of the membrane potential to the negative state causes the potassium channels to close back to their original status but, again, only after a delay.

A Positive-Feedback, Vicious Circle Opens the Sodium Channels. If any event causes the membrane potential to rise from 90 millivolts toward the zero level, the rising voltage itself causes many voltage-

gated sodium channels to begin opening. This allows rapid inflow of sodium ions, which causes still further rise of the membrane potential, thus opening still more voltage- gated sodium channels. This process is a positive- feedback vicious circle that continues until all of the voltage-gated sodium channels have become activated (opened).

An Action Potential Does Not Occur until the Threshold Potential Has Been Reached. This happens when the number of sodium ions entering the nerve fiber becomes greater than the number of potassium ions leaving the fiber. A sudden increase in the membrane potential in a large nerve fiber from –90 millivolts to about –65 millivolts usually causes explosive develop- ment of the action potential. This level of –65 millivolts is said to be the threshold of the membrane for stimulation.

A New Action Potential Cannot Occur When the Membrane Is Still Depolarized from the Preceding Action Potential. Shortly after the action potential is initiated, the sodium channels become inactivated, and any amount of excitatory signal applied to these channels at this point does not open the inactivation gates. The only condition that can reopen them is when the membrane potential returns either to or almost to the original resting membrane potential level. Then, within another small fraction of a second, the inactivation gates of the channels open, and a new action potential can then be initiated.

• Absolute refractory period. An action potential cannot be elicited during the absolute refractory period, even with a strong stimulus. This period for large myelinated nerve fibers is about 1/2500 second, which means that a maximum of about 2500 impulses can be transmitted per second.

• Relative refractory period. This period follows the absolute refractory period. During this time, stronger than normal stimuli can excite the nerve fiber, and an action potential can be initiated.

2.Transmission of Impulses from Neurons to Skeletal Muscle Fibers: The Neuromuscular Junction

Skeletal muscle fibers are innervated by large, myelin- ated 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 neuromuscu- lar 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 (p. 83)

When a Nerve Impulse Reaches the Neuromuscular Junction, Vesicles Containing Acetylcholine Are Released into the Synaptic Space. On the inside surface of the neural 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 below the dense bar areas. 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 pour into the inside of 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. In turn, this end-plate potential normally leads to opening of voltage-gated sodium channels, which initiate an action potential at the muscle membrane and thus causes 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 acetylcho- line stimulation is normally far greater than that necessary to initiate an action potential in the muscle fiber. **Drugs That Enhance or Block Transmission at the Neuromuscular Junction (p. 86)**

Drugs Can Affect the Neuromuscular Junction by Having Acetylcholine-Like Actions, Blocking Neuromuscular Transmission, and Inactivating Acetylcholinesterase

• Drugs that have acetylcholine-like actions. Many compounds, including methacholine, carbachol, and nicotine, have the same effect on the muscle fiber as does acetylcholine. The difference between these drugs and acetylcholine is that they are not destroyed by cholinesterase, or they are destroyed slowly.

• Drugs that block neuromuscular transmission. A group of drugs known as the curariform drugs can prevent passage of impulses from the end-plate into the muscle. Thus d-tubocurarine competes with acetylcholine for the acetylcholine receptor sites, so the acetylcho- line generated by the end-plate cannot increase the permeability of the muscle membrane acetylcholine channels sufficiently to initiate an action potential.

• Drugs that inactivate acetylcholinesterase. Three par- ticularly well-known drugs—neostigmine, physostig- mine, and diisopropyl fluorophosphate—inactivate acetylcholinesterase. As a result, acetylcholine levels increase with successive nerve impulses, causing large amounts of acetylcholine to accumulate and then repetitively stimulate the muscle fiber.

Neostigmine and physostigmine last up to several hours. Diisopropyl fluorophosphate, which has potential military use as a powerful “nerve” gas poi- son, inactivates acetylcholinesterase for weeks.

Myasthenia Gravis Causes Muscle Paralysis

Paralysis Occurs Because of the Inability of the Neuro- muscular Junctions to Transmit Signals from the Nerve Fibers to the Muscle Fibers. Pathologically, myasthenia gravis is thought to be an autoimmune disease in which patients have developed antibodies against their own acetylcholine-gated ion channels. The end-plate potentials that occur in the muscle fibers are too weak to initiate opening of voltage-gated sodium channels so that muscle fiber depolarization does not occur. If the disease is sufficiently intense, the patient dies of paralysis—in particular, paralysis of the respiratory muscles. The disease usually can

be ameliorated by administration of neostigmine or another anticholinesterase drug. This treatment allows acetylcholine to accumulate in the synaptic cleft.

3.Muscle contraction:

About 40% of the body mass is skeletal muscle, and perhaps another 10% is smooth muscle and cardiac muscle. Many of the principles of contraction apply to all three types of muscle. In this chapter, the function of skeletal muscle is considered. The func- tions of smooth muscle are discussed in Chapter 8, and the functions of cardiac muscle are discussed in Chapter 9.

Physiologic Anatomy of Skeletal Muscle (p. 71)

Skeletal Muscle Fiber Figure 6–1 shows the organization of skeletal muscle. 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, and, in turn, each myofibril (see Fig. 6–1D) 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. In Figure 6–1 the thick filaments are myosin, and the thin filaments are actin; note the following features:

• Light and dark bands. The myosin and actin fila- ments 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 con- tain myosin filaments as well as the ends of the actin filaments. The length of the A band is the length of the myosin filament.

• 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 disc. The ends of the actin filaments are attached to Z discs (see Fig. 6–1E). The Z disc passes across the myofibril and from one to another, attaching and aligning the myofibrils across the muscle fiber.

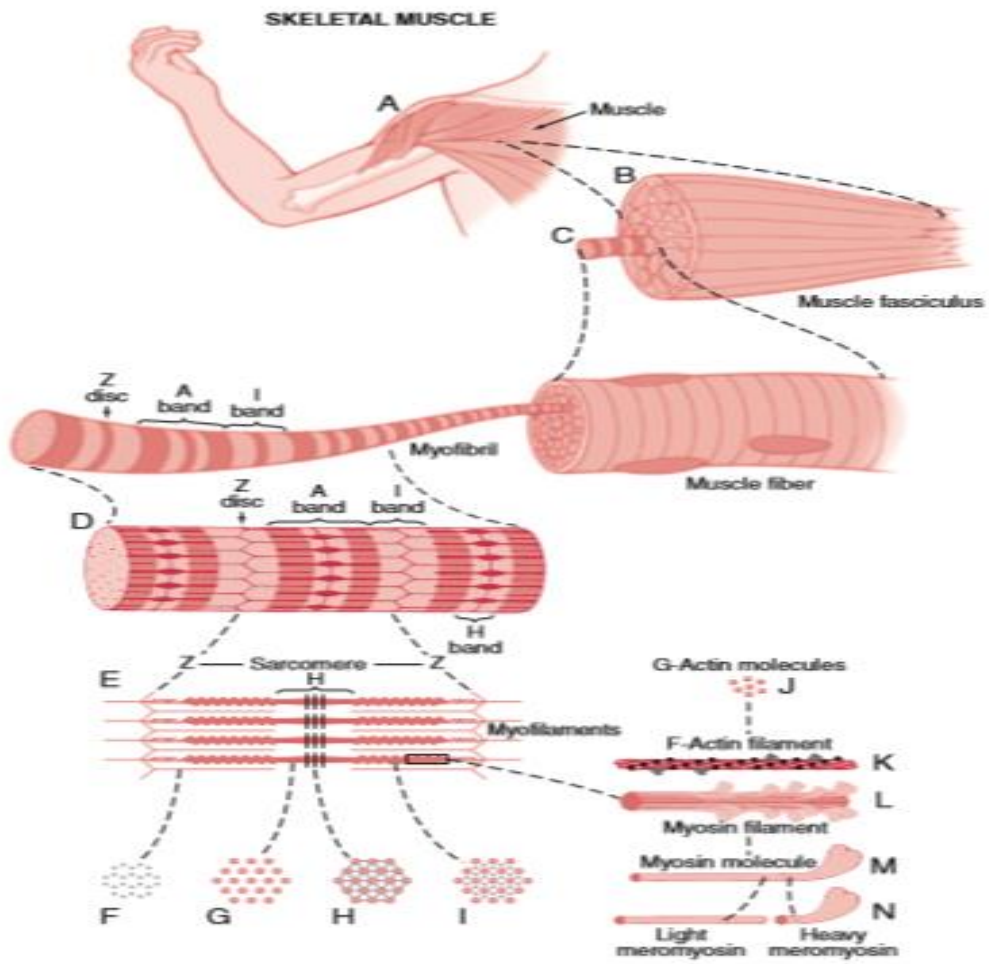

Figure 6–1. Organization of skeletal muscle, from the gross to the molecular level. *F, G, H,* and *I* are cross sections at the levels indicated.

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 discs is called a sarcomere. During rest, the actin filaments overlap the myosin filaments with an optimal amount of interdigitation in skeletal muscle and slightly shorter than optimal interdigitation in cardiac muscle.

General Mechanism of Muscle Contraction (p. 73) The initiation and execution of muscle contraction occur in the following sequential steps:

1. An action potential travels along a motor nerve to its endings on muscle fibers, and each nerve ending secretes a small amount of the neurotransmitter substance acetylcholine.

2. The acetylcholine acts on a local area of the muscle membrane to open acetylcholine-gated cation channels, which allows mainly sodium ions but also calcium ions to flow into the muscle fiber causing a local depolarization. The local depolarization in turn leads to opening of voltage-gated sodium channels resulting in an action potential.

3. The action potential travels along the muscle fiber membrane, causing the sarcoplasmic reticulum to release calcium ions into the myofibrils that have been stored in the sarcoplasmic reticulum.

4. The calcium ions initiate attractive forces between the actin and myosin filaments, causing them to slide together; this 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 the calcium ions from the myofibrils causes muscle contraction to cease.

Molecular Mechanism of Muscle Contraction (p. 74)

Muscle Contraction Occurs by a Sliding Filament Mechanism. Mechanical forces generated by the interaction of myosin cross-bridges with actin 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, and contraction begins.

The Myosin Filament Is 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 (ATPase) enzyme, which allows it to cleave adenosine triphosphate (ATP) and thus energize the contraction process.

The Actin Filament Is Composed of Actin, Tropo- myosin, and Troponin. Each actin filament is about 1 mm long. The bases of the actin filaments are inserted strongly into the Z discs, whereas the other ends pro- trude 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 fila- ments 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 “uncovers” the active sites of the actin, allowing 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 Dictates Tension Development by the Contracting Muscle (p. 77)

The Strength of Contraction Is Maximal When There Is Maximal Overlap between Actin Filaments and the Cross-Bridges of the Myosin Filaments. A muscle cannot develop tension at very long 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 mm because the actin filament has overlapped all of the cross-bridges of the myosin filament. On 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 mm, the two Z discs of the sarcomere abut the ends of the myosin filaments, and the strength of contraction decreases precipitously.

Energetics of Muscle Contraction (p. 78)

Muscle Contraction Requires ATP to Perform Three Main Functions

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

• Calcium is pumped back into the sarcoplasmic reticulum causing the contraction to terminate.

• Sodium and potassium ions are pumped through the muscle fiber membrane to maintain 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 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 com- bined with the various cellular foodstuffs to liberate ATP. More than 95% of all energy used by the mus- cles for sustained, long-term contraction is derived from this source. The foodstuffs consumed are car- bohydrates, fats, and proteins.

Characteristics of Whole Muscle Contraction (p. 79)

Isometric Contractions Do Not Shorten Muscle, Whereas Isotonic Contractions Do Shorten Muscle

• 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.

Fast Fibers Are Adapted for Powerful Muscle Contractions, Whereas Slow Fibers Are Adapted for Prolonged Muscle Activity. Each muscle is composed of a mixture of so-called fast and slow muscle fibers, with still other fibers that are between these two extremes. However, a given muscle may have predominantly fast muscle fibers (e.g., anterior tibialis), whereas other muscles may have predominantly slow muscle fibers (e.g., soleus).

• 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 (p. 80)

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.

• 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 ends. As a result ,the second contraction is added partially to the first, so the total strength of contraction rises progressively with increasing fre- quency. 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 special conditions, 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.