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Muscular system

Muscle is a tissue specialized for contraction and transmission of impulses.

Muscle is classified based on the appearance of its cells. The two principal types of muscle include striated and smooth muscle. Striated muscle appears to have cross striations when viewed under the light microscope, whereas smooth muscle lacks such striations.

Striated muscle can be further subdivided into two types: skeletal muscle that is attached to bone and responsible for the movements of the axial and appendicular skeleton, and cardiac muscle that makes up the heart. Skeletal muscle and cardiac muscle are sometimes referred to as voluntary striated and involuntary striated muscles, respectively. The prefixes *myo* and *sarco* refer to muscle. Therefore, terms such as *myofibril* or *myofilament* reference structures within a muscle. For example, the plasma membrane of a muscle cell is called the sarcolemma, the cytoplasm the sarcoplasm, and the endoplasmic reticulum the sarcoplasmic reticulum (SR). In addition, a single skeletal muscle cell is also called a muscle fiber

Properties of muscles

Four properties of muscles enable them to perform their functions. These properties include

- Contractility. When stimulated, the electrical impulse spreading across a muscle cell can cause the cell to contract.
- Excitability. Sometimes called irritability. Muscle cells maintain a membrane potential and are able to respond to a stimulus such as a neurotransmitter by developing an electrical impulse. The stimulus is usually neurochemical, but can also be mechanical or chemical. The electrical impulse can migrate across the sarcolemma
- Extensibility. In addition to contraction, muscle cells can lengthen in response to stretch. This is more evident in smooth muscle compared to skeletal muscle.
- Elasticity. Once stretched, muscle fibers can recoil to their original resting length due to the elastic elements within the muscle.

Functions of muscles

Muscles serve four major functions, including production of movement, maintenance of posture, stabilization of joints, and generation of heat.

Sarcoplasmic reticulum

Similar to the endoplasmic reticulum in non-muscle cells, the sarcoplasmic reticulum (SR) forms a tubular network surrounding each myofibril (Fig. 7.3). The terminal cisternae (end sacs) of the SR are always found in pairs, with an intervening T tubule. The combination of a terminal cisterna, a T tubule, and the adjacent terminal cisterna form a triad. Note that the T tubule communicates with the extracellular space while the SR is intracellular. The terminal cisternae have an active calcium pump that pumps calcium from the sarcoplasm into the SR. This maintains a low concentration of free calcium within the sarcoplasm, whereas the free calcium concentration inside the SR may be 1000 times greater. The terminal cisternae of the SR are the source of calcium for skeletal muscle contraction.

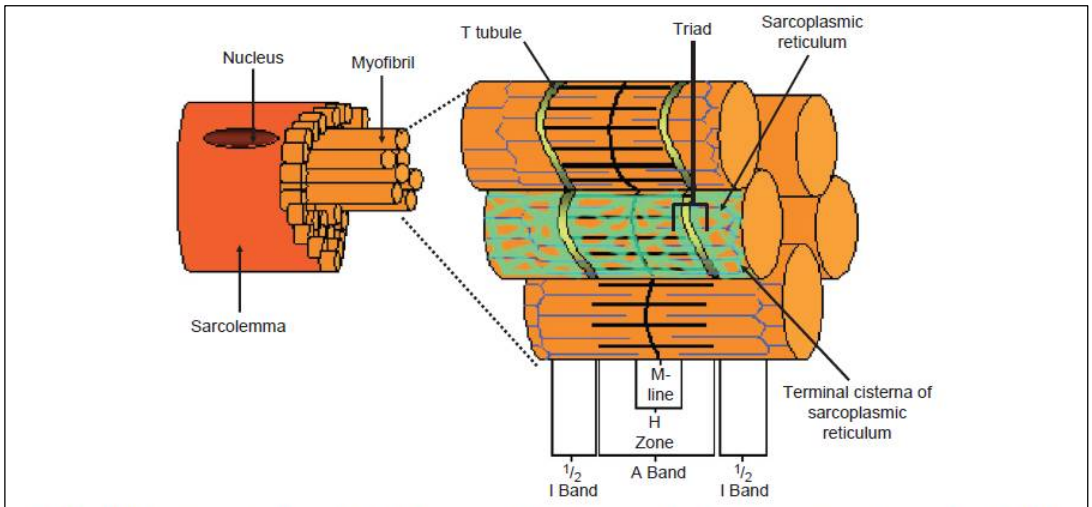

Fig. 7.3. T tubule and sarcoplasmic reticulum. The transverse, or T tubules are inwardly directed invaginations of the sarcolemma found near the junction of the A and I bands. The sarcoplasmic reticulum is a network of tubules found inside the cell and which have terminal cisternae near the T tubules. Two terminal cisterna and the intervening T tubule make a triad.

Myofibrils

Muscle fibers are composed of functional subunits called myofibrils. Each muscle fiber contains hundreds to thousands of myofibrils that run longitudinally the length of the fiber. The myofibrils consist of bundles of myofilaments that are protein filaments composed primarily of actin and myosin, the two contractile proteins in muscle. Actin forms the bulk of the thin filaments, and myosin forms the bulk of the thick filaments.

The myofibrils contain three types of proteins.

1. Contractile proteins. Contractile proteins generate the force during contraction. These proteins include myosin and actin.
2. Regulatory protein. Regulatory proteins help initiate and terminate the contraction process and include tropomyosin and troponin found on the thin filaments.
3. Structural proteins. Structural proteins help maintain the alignment of the thin and thick filaments, provide elasticity and extensibility, and attach the myofibrils to the sarcolemma. These proteins include titin, myomesin, and dystrophin

Sarcoplasmic reticulum

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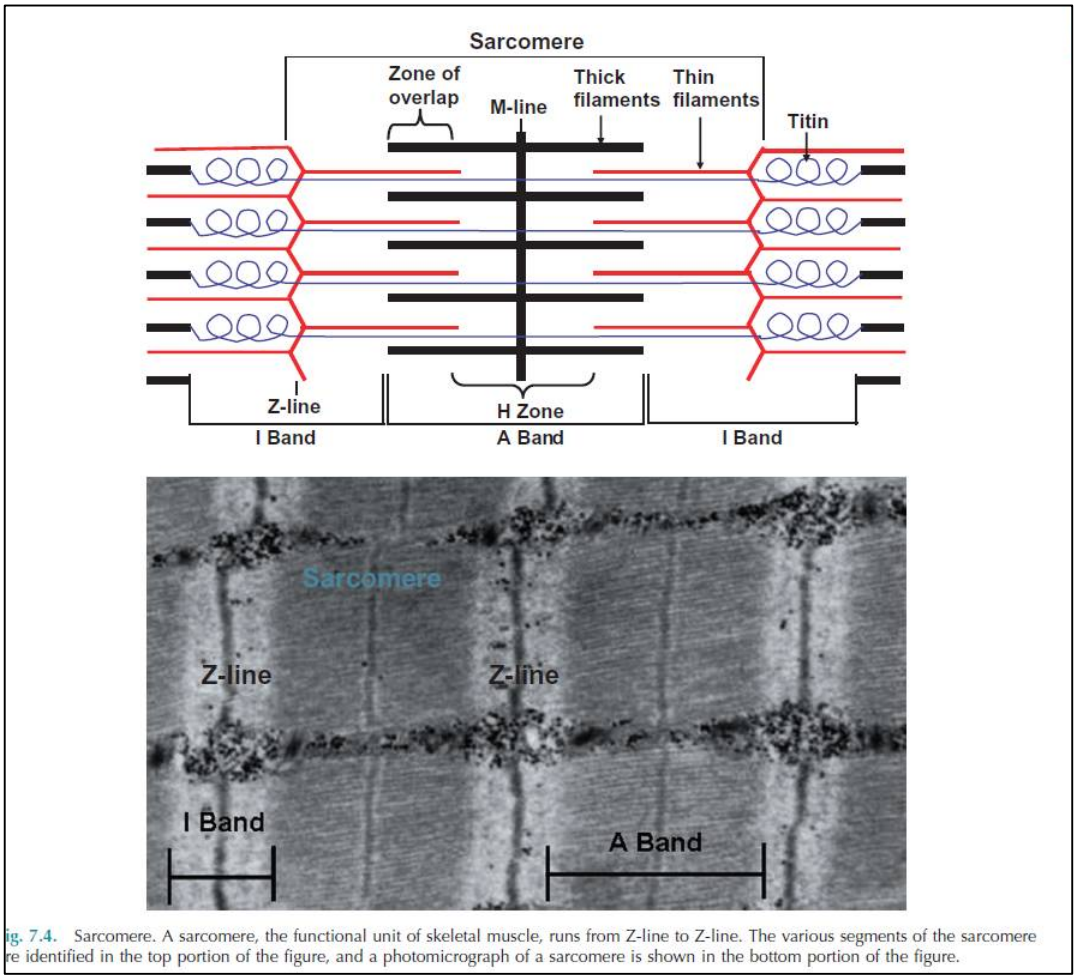
Sarcomeres

Definition: The functional unit of skeletal muscle is the sarcomere. A myofibril consists of thousands of sarcomeres.

Structure: The sarcomere is composed of thick and thin filaments, proteins that stabilize those filaments, and proteins that regulate the interactions between thick and thin filaments. As shown in Figure 7.4, a sarcomere is the region between two adjacent Z discs (or Z-lines). It consists of one-half I band, A band, and one half I band. The A band is the length of the thick filament, and can contain both thick and thin filaments. In a muscle at rest, a lighter region can be found in the center of the A band called the H zone (from *helle*, meaning bright), which contains only myosin. This region disappears as skeletal muscle contracts and the actin filaments overlap, thus entering this area. The M-line, named for being in the middle of the sarcomere, transects the H zone and is composed of proteins that stabilize the position of the thick filaments. Near the ends of the A band there are zones of overlap where thin and thick filaments are found side by side. The I band, located between each intervening A band, contains thin filaments. The I band is bisected by the Z-line that consists of proteins called actinins, which interconnect adjacent thin filaments



ig. 7.4. Sarcomere. A sarcomere, the functional unit of skeletal muscle, runs from Z-line to Z-line. The various segments of the sarcomere re identified in the top portion of the figure, and a photomicrograph of a sarcomere is shown in the bottom portion of the figure.

Thin filaments

Thin filaments are 5–6 nm in diameter and 1 μm in length (Fig. 7.5). Each thin filament is composed of four proteins:

1. F actin. Thin filaments are composed of two strands of F actin, also called filamentous actin, arranged in a double-stranded helix. Each strand of F actin is composed of polymers of G actin, or globular actin. Therefore, the F actin appears as two twisted strands of pearls, with each pearl being analogous to a molecule of G actin.

2. Tropomyosin. Strands of tropomyosin (*trope* = turning) wrap around the length of the F actin. Each tropomyosin molecule is a double-stranded protein that, at rest, covers seven myosin-binding sites on the actin filament.

3. Troponin. A globular protein, troponin consists of three subunits. One binds to tropomyosin (TnT), one to G actin (TnI), and the other to calcium ions (TnC). Therefore, troponin controls the structural relationship between tropomyosin and F actin.

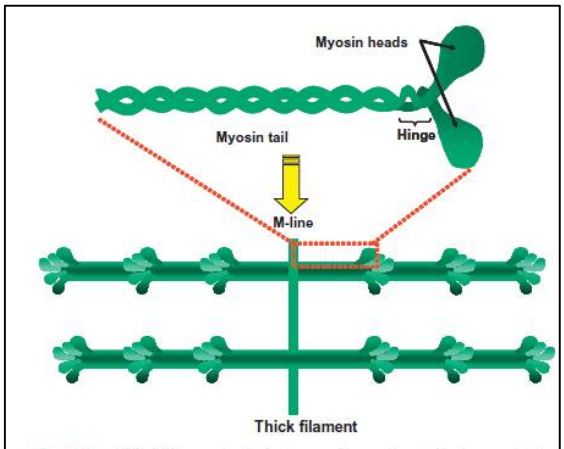


Fig. 7.6. Thick filament. A single myosin molecule is shown at the top. It contains a pair of intertwined subunits each consisting of a tail, a hinge region, and a globular head. The thick filaments contain approximately 500 myosin molecules in which the tails are lined up so that the heads project away from the M-line.

Thick filaments

Thick filaments are 10–12 nm in diameter and 1.6 μm in length (Fig. 7.6). Thick filaments consist of approximately 500 myosin molecules, each composed of two myosin subunits wrapped around each other. The long tails of the myosin molecules line up forming the thick filament, and the heads of the myosin molecules project off the filament toward the adjacent thin filaments.

The head of the myosin molecule consists of two globular proteins, has ATPase activity, and is able to bind to the actin filament. A cross bridge is formed when the head of the myosin binds to the actin filament.

There is a hinge between the head and the tail of the myosin molecule that allows the head to pivot

toward or away from the M-line. The myosin molecules are arranged so that their

tails point toward the M-line. In the H zone, there are no myosin heads, only tails. Also within each thick

filament is a molecule of titin extending from the M-line to the Z-line.

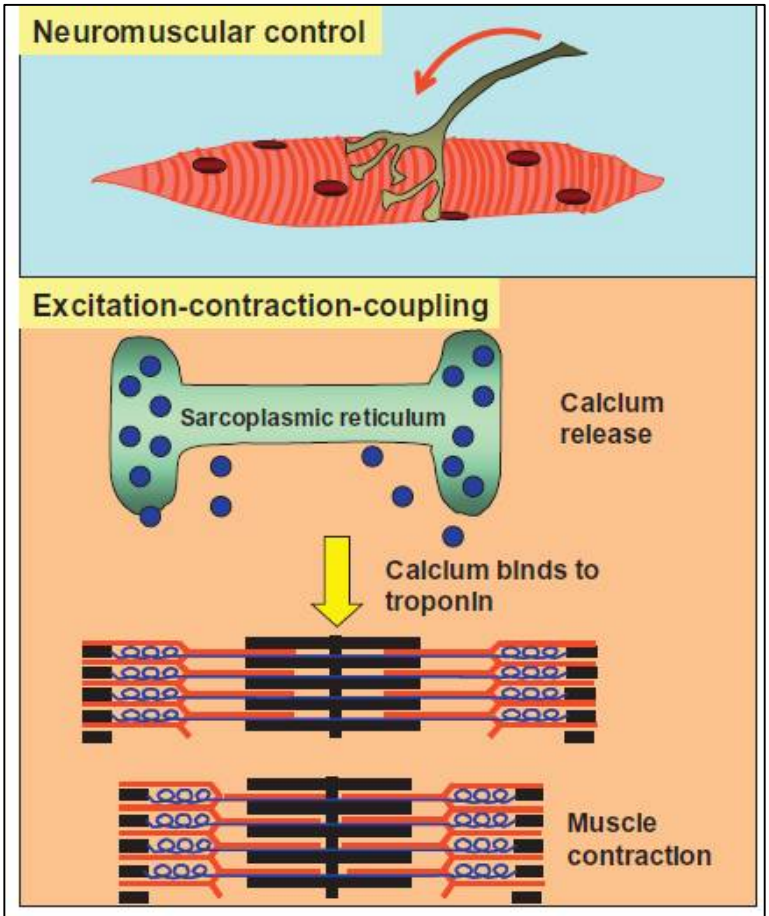


Fig. 7.7. Summary of skeletal muscle contraction. Stimulation of α-motor neurons going to skeletal muscle causes the release of acetylcholine at the neuromuscular junction. This causes the production of an action potential in the muscle fiber that spreads along the sarcolemma and down the T tubules where it causes the release of calcium ions from the sarcoplasmic reticulum. Calcium then diffuses to the thin filaments where it binds to troponin to initiate contraction.

Contraction of skeletal muscle

As summarized in Figure 7.7, control of skeletal muscle contraction involves the voluntary stimulation of motor neurons innervating the muscle. The release of the neurotransmitter from these motor neurons initiates excitation-coupling-contraction in which an action potential is generated within the skeletal muscle fiber. The action potential causes the release of calcium from the SR, which then causes muscle contraction.

Neuromuscular junction

Skeletal muscle is controlled by the somatic nervous system. The cell bodies of the α-motor neurons, that is, somatic motor neurons that innervate skeletal muscle reside in the central nervous system (CNS).

The axons of these neurons leave the CNS and innervate skeletal muscle fibers at a specialized junction called the neuromuscular junction (NMJ) or myoneural junction. Each muscle fiber is innervated by a neuron, although a single neuron may innervate multiple muscle fibers. The neuron branches as it enters the perimysium, and each branch ends in a synaptic terminal, sometimes called a synaptic bouton. The synapse is the region of contact between a neuron and its target cell, which in this case is a skeletal muscle fiber. The space between the neuron and the muscle fiber is the synaptic cleft. The sarcolemma in the region of the NMJ is called the motor end plate. Since an electrical signal cannot traverse the synaptic cleft, the signal from the motor neuron is communicated via the release of a neurotransmitter. The

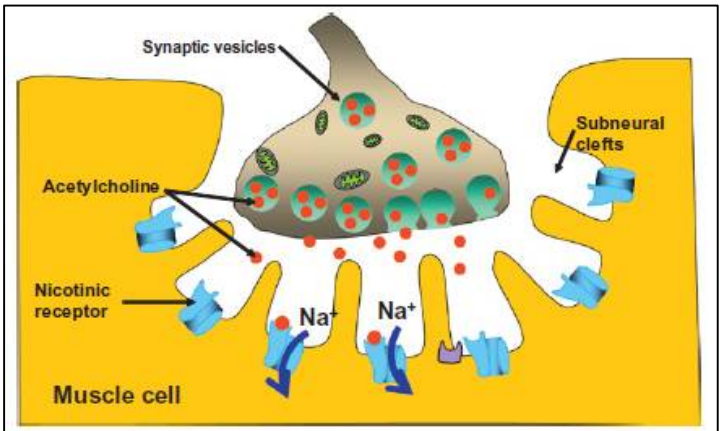


Fig. 7.8. Neuromuscular junction. The neuromuscular junction is a specialized synapse between an α-motor neuron and skeletal muscle fibers. The synaptic bouton is imbedded in the sarcolemma. At this site are subneural clefts that increase the surface area surrounding the synapse. Synaptic vesicles containing acetylcholine (ACh) are located in the nerve ending. Upon stimulation, the α-motor neuron releases ACh that can diffuse across the synaptic cleft and bind to nicotinic receptors on the skeletal muscle fiber. Upon binding to the receptor, ACh causes Na^+ ions to enter the skeletal muscle fiber, causing a postsynaptic potential. The postsynaptic potential is always large enough to induce an action potential in the skeletal muscle fiber.

neurotransmitter released from α-motor neurons is acetylcholine (ACh). ACh is contained in synaptic vesicles located in the synaptic bouton. When the action potential arrives at the synaptic bouton, it causes the release of ACh that then diffuses across the synapse and binds to a specialized cholinergic receptor located on the muscle fiber. This receptor is called a nicotinic receptor. This is a transmembrane protein that binds ACh, and can also be stimulated by the agonist Nicotine.

Excitation-contraction coupling

The process by which an action potential in skeletal muscle fibers induces contraction is called excitationcontraction coupling (Fig. 7.9). The action potential migrates along the sarcolemma and down the T tubules. At the triad, the action potential triggers the release of Ca^{2+} from the terminal cisterns of the SR.

Mechanism of muscle contraction-

Sliding theory: During muscle contraction, the actin and myosin filament sliding to each other and shorter. The Z lines come close together and the end of the actin filaments approach one another. At the maximal point of shortenings, the Z lines are close to the end of the myosin filaments and the end of the actin filaments overlap.

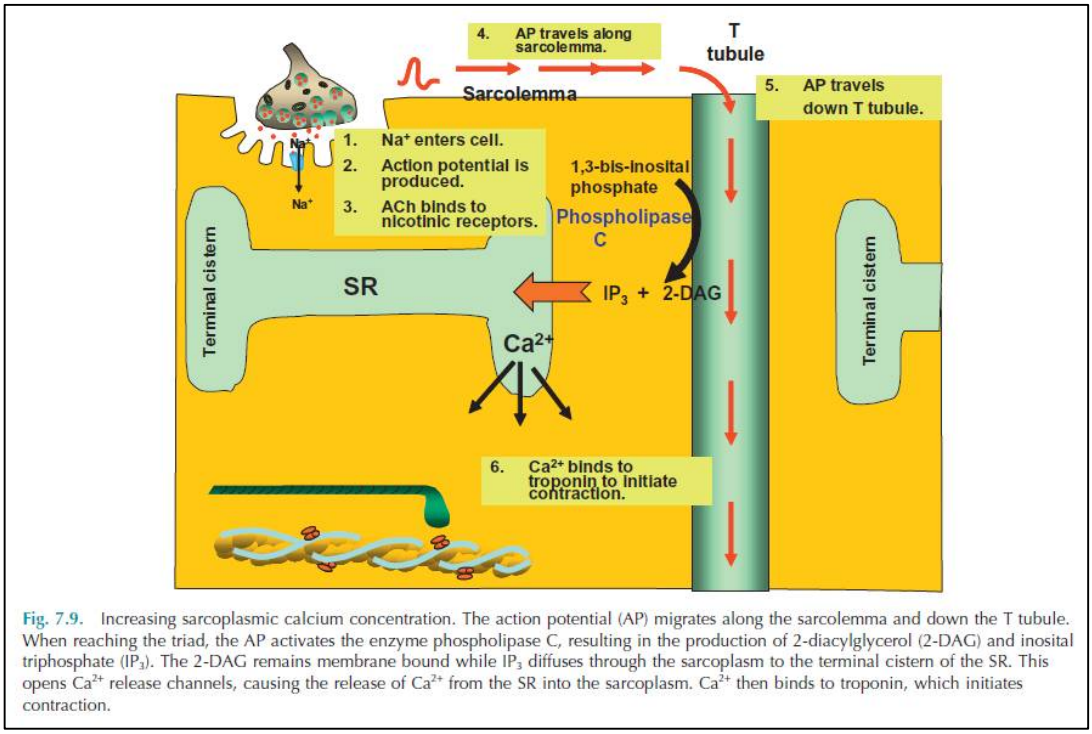


Fig. 7.9. Increasing sarcoplasmic calcium concentration. The action potential (AP) migrates along the sarcolemma and down the T tubule. When reaching the triad, the AP activates the enzyme phospholipase C, resulting in the production of 2-diacylglycerol (2-DAG) and inositol triphosphate (IP_3). The 2-DAG remains membrane bound while IP_3 diffuses through the sarcoplasm to the terminal cistern of the SR. This opens Ca^{2+} release channels, causing the release of Ca^{2+} from the SR into the sarcoplasm. Ca^{2+} then binds to troponin, which initiates contraction.

Molecular basis of skeletal muscle contraction-

The initiation and execution of muscle contraction occurs in the following sequential steps-

1. Stimulation of muscle fiber by nerve impulse
2. An action potential travels along a motor nerve to its ending on muscle fibers
3. An each ending, the nerve secrets a small amount of the neurotransmitter substances called acetylcholine (Ach).
4. The ACh acts on a local area of the muscle fiber membrane to open multiple acetylcholine gated protein channels in the muscle fiber membrane.
5. Opening of the ACh channels allows large quantities of sodium ions to flow to the interior of the muscle fiber membrane at the point of the nerve terminal. This initiates an action potential in the muscle fibers.
6. The action potential travels along the muscle fiber membrane in the same way that action potentials travel along nerve membranes.
7. The action potential depolarized the muscle fiber membrane and also travels deeply within the muscle fiber. Here it causes the SR to release large quantities of calcium ions into the myofibrils that have been stored within the SR.
8. The calcium ions initiate attractive forces between the actin and myosin filaments, causing them to slide together, which is the contraction process.

Molecular basis of muscle relaxation-

After a fraction of a second, the calcium ions are pumped back into the SR (sarcoplasmic reticulum) where they remain stored. It causes detachment of myosin from actin followed by relaxation of the muscle. The detachment of myosin from actin obtains energy from breakdown of ATP.

Types of contraction:

There are two types of contraction-

(1) Isotonic contraction: Isotonic contraction is that contraction when the muscle become shorter, thicker and physiologically but the tension on the muscle remain same. It is occur when one end of it is attached to a light weight which is lifted.

(2) Isometric contraction: Isometric contraction is that contraction of muscle when the length of the muscle fiber remains constant by making it contract against a strong spring but the tension increases.

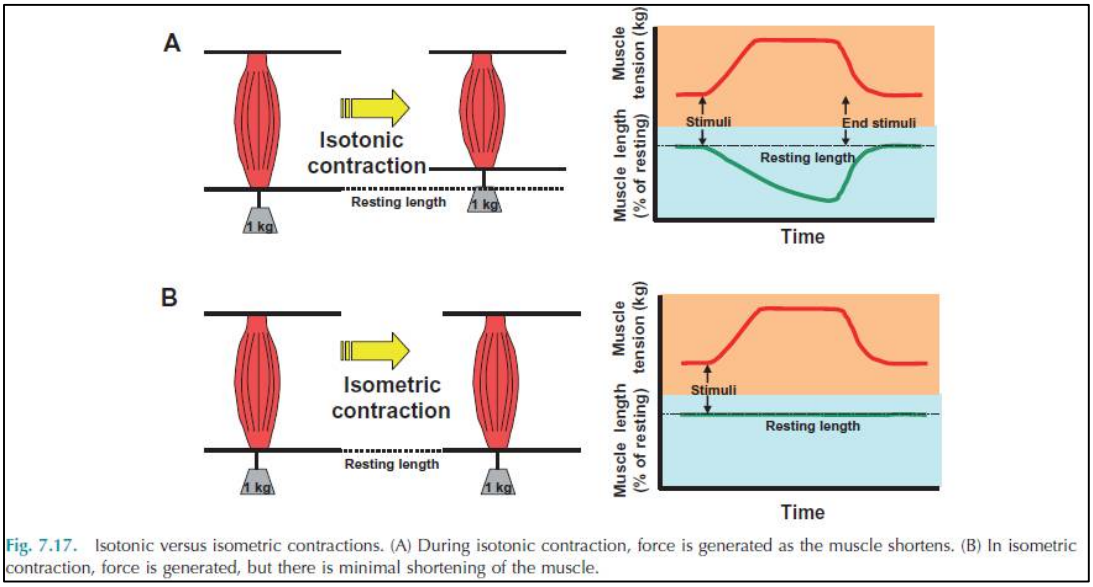


Fig. 7.17. Isotonic versus isometric contractions. (A) During isotonic contraction, force is generated as the muscle shortens. (B) In isometric contraction, force is generated, but there is minimal shortening of the muscle.

Muscle twitch

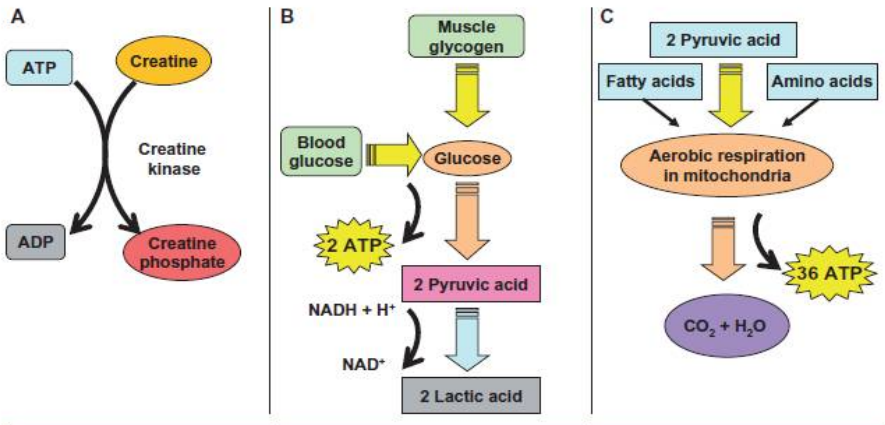
A single stimulation of a motor neuron results in a single contraction or twitch (Fig. 7.13). Although twitches can produce heat during shivering, they are not generally observed during normal muscle contraction. Instead, prolonged stimulation results in more tension being produced than caused by a single twitch. A recording of a single muscle twitch is called a myogram. A single twitch can last from 20 to 200 ms, depending on the type of muscle, temperature, stretch of the muscle, and so on.

Muscle tone

Skeletal muscle is seldom flaccid, but instead maintains a degree of tension called muscle tone. Since skeletal muscle contraction is controlled by motor neurons releasing ACh, muscle tone is established by the central nervous system. If these motor neurons are cut, skeletal muscle becomes flaccid. Muscle tone is due to the alternating stimulation of motor units by the central nervous system. Such tone helps keep an animal upright, keep the head held up, stabilize joints, and maintain posture.
Muscle tone is not unique to skeletal muscle, but it is also found in smooth muscle. For example, blood vessels generally maintain a vascular tone as does the gastrointestinal tract.

Metabolism of skeletal muscle

The major energy source for muscle metabolism is ATP. It is used for cross bridge formation, to actively pump calcium into the SR, and to pump Na^+ out of and K^+ into the muscle fiber. The endogenous stores of ATP are able to last only about 4–6 seconds. Therefore, there must be mechanisms to replenish this limited store. While at rest, skeletal muscle makes sufficient ATP to meet its metabolic needs, and to store surplus energy in the form of creatine phosphate and glycogen. Resting muscle can use fatty acids that are broken down in the mitochondria and the ATP used to make creatine phosphate.



Direct phosphorylation of creatine phosphate	Anaerobic metabolism	Aerobic metabolism
Energy substrate is creatine phosphate	Energy substrate is glucose	Energy substrates are glucose, pyruvate, and amino acids
Uses no O_2; produces 1 ATP	Uses no O_2; produces 2 ATP/glucose and 2 lactic acids	Uses O_2; produces 36 ATP/glucose, CO_2, and H_20

Fig. 7.18. ATP production in muscle. There are three mechanisms for generating ATP in muscle fibers. (A) During the direct phosphorylation of creatine phosphate, a phosphate group is moved from ATP to creatine producing creatine phosphate, an energy storage form in muscle. When ADP is plentiful, this reaction is reversed to produce ATP. (B) During glycolysis, glucose is anerobically broken down to two molecules of pyruvate, which are then converted to lactic acid in order to regenerate NAD^+. (C) In the presence of O_2, pyruvate is further metabolized to CO_2 and H_2O, plus ATP.

The glucose that is delivered through the bloodstream can be converted to glycogen.

Pathways of energy production: there are three pathways for generating ATP: (1) aerobic respiration, (2) ADP interacting with creatine phosphate, and (3) from stored glycogen through the anaerobic process of glycolysis (Fig. 7.18).

Aerobic mechanism

When O_2 is present, pyruvate enters the mitochondria where aerobic respiration occurs. This process produces 36 moles of ATP for every 1 mol of glucose. During aerobic respiration, the following reaction occurs:

Glucose $+O_2 \Rightarrow CO_2$ +water+ATP.

Since muscle is able to store glycogen, the breakdown of glycogen can yield glucose for aerobic metabolism. In addition, muscle can get energy from blood-borne glucose, pyruvic acid, free fatty acids, and some amino acids. During moderate exercise, aerobic metabolism is able to meet the energy demands of the muscle

Creatine phosphate

While at rest, muscles are able to produce more ATP than is utilized. This surplus energy is used to synthesize creatine phosphate, an energy storage form found exclusively in muscle. The enzyme creatine kinase catalyzes the transfer of a high-energy phosphate group from ATP to creatine. When ADP is present in the muscle, creatine kinase catalyzes the transfer of a high-energy phosphate group from creatine phosphate to ADP forming ATP. Creatine phosphate is three to six times more plentiful in muscle than ATP. These two compounds together can provide enough energy for muscles to contract for approximately 10–15 seconds. When energy is plentiful, creatine phosphate is replenished.

Anaerobic mechanism

Although ATP and creatine phosphate can provide energy for short periods of time, other mechanisms are needed to produce ATP. Glucose can be metabolized through glycolysis, the initial phase of glucose respiration. Glycolysis does not require oxygen, and therefore is termed an anerobic (without oxygen) process, anaerobic glycolyis. Therefore, this process is utilized when there is insufficient O_2 available for aerobic metabolism to sustain the energy needs of the muscle. During glycolysis, one molecule of glucose is metabolized to 2 molecules of pyruvic acid.

During this process, 2 ATPs are produced per molecule of glucose. Therefore, anaerobic glycolysis can produce only 5% of the amount of ATP from glucose as aerobic respiration whereas aerobic respiration produces 95% of the ATP.

In the process of breaking down glucose, NAD_+ is reduced to NADH + H_+. In order to continue glycolysis, the cell must be able to oxidize NADH back to NAD_+. When oxygen is not present, the cell can do this only by converting pyruvate to lactic acid, during which NAD_+ is regenerated. Lactic acid then diffuses out of the cells and goes to the liver, heart, or kidney. In the liver, it can be converted back to glycogen.

Muscle fatigue and oxygen consumption

Muscle fatigue is the inability of muscle to contract after prolonged activity. Several factors are responsible for muscle fatigue. These include inadequate release of Ca^{2+} from the SR, depletion of creatine phosphate, insufficient O_2, depletion of glycogen, buildup of lactic acid (decrease in pH) and ADP, or depletion of ACh from motor neurons. During prolonged exercise, muscles accumulate lactic acid. This lactic acid must be reconverted to pyruvic acid. In addition, the animal must replenish glycogen stores and replace creatine phosphate and ATP, and the liver must convert blood lactic acid to glycogen. These processes all require O_2, leading to what was termed the "oxygen debt," or the amount of extra O_2 that an animal must inspire to restore homeostasis.

Types of muscle fibers

There are three functional ways to classify skeletal muscle fibers: (1) speed of contraction, (2) metabolic pathways forming ATP, and (3) myoglobin content:

1. Speed of contraction. Based on rate of contraction, fibers can be classified as fast or slow. Speed is based on the rate at which the myosin ATPase splits ATP.

2. Metabolic pathways forming ATP. Fibers that rely on oxygen-requiring pathways for generating ATP are called oxidative, whereas those that rely on anaerobic glycolysis are called glycolytic.

3. Myoglobin content. Some muscle fibers have a large amount of myoglobin, the red-colored protein that binds oxygen in muscle fibers. These fibers are termed red muscle fibers. In contrast, some fibers have low myoglobin content and are called white muscle fibers.

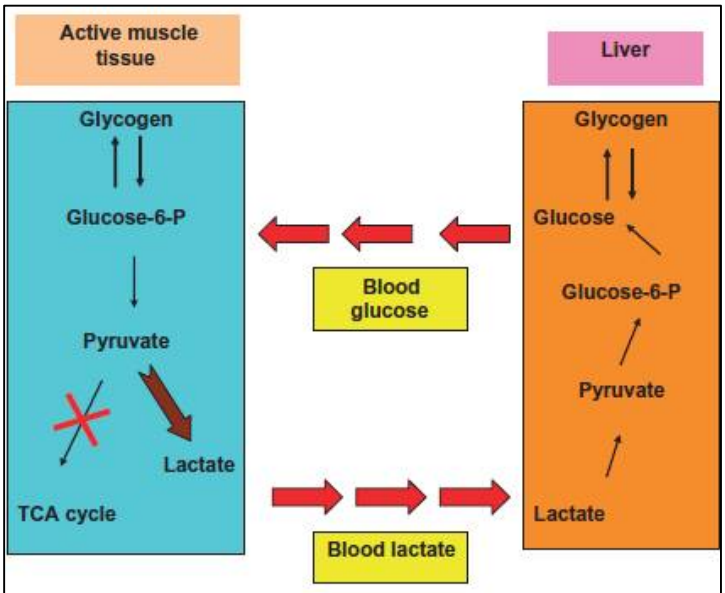


Fig. 3.6. The Cori cycle. In active muscle (e.g., with anaerobic conditions) the conversion of pyruvate into acetyl-CoA and processing via the TCA cycle is blocked (red X). This leads to lactate or lactic acid production. The lactate diffuses out of the muscle tissue into blood where the liver and kidney can convert lactate into glucose-6-phosphate for storage as glycogen or conversion to glucose-1-phosphate then glucose. Muscle or other tissues in the body can then use this regenerated glucose.

Based on these criteria, there are three major categories of muscle fibers, including slow oxidative fibers, fast oxidative-glycolytic fibers, and fast glycolytic fibers—sometimes called slow, intermediate, and fast fibers, respectively. Slow fibers allow for prolonged, sustained activities that are powered by aerobic metabolism and that fatigue slowly. Such fibers have a good blood supply, a high myoglobin content and many mitochondria. Conversely, fast glycolytic fibers are better suited for quick, powerful movements that occur over a short period of time and that fatigue quickly. Since these latter fibers contract quickly, they rely on endogenous glycogen stores rather than glucose delivered via the bloodstream, and they have fewer mitochondria and little myoglobin.

Cori cycle

Cycling of lactic acid from muscle to liver and the return of glucose is called the Cori cycle.

Molecular basis of smooth muscle contraction

The process of excitation and contraction is very slow in smooth muscles. It is because of poor development of sacroplasmic reticulum in smooth muscles fiber. So, the calcium ions, which are responsible for excitation contraction coupling, must be obtained from the extracellular fluid. It makes the process of excitation contraction coupling slow.

Calcium + Calmodulin

↓

Calcium- Calmodulin complex

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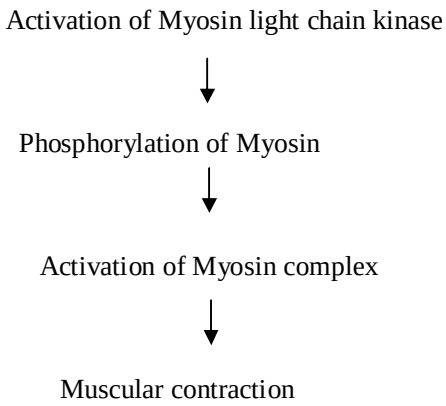

Fig. Molecular basis of smooth muscle contraction

RIGOR MORTIS (Rigidity of death):

It is characterized by a rigidity or stiffness of the sketetal muscle and immobilization of the joints after death. The time of onset in average is 2-4 hours after death, maximal rigor is activated in 24-48 hours and then it disappears due to autolysis.

The factors influences the time of onset and degree of rigor are the glycogen reserve, the pH of the muscle at time of death and the environment. It is slight or absence in cachectic animals but it is long delayed in well rested and well fed animals. It is hasten in onset and disappearance in warm environment and retarded in cold environment.

The chemicals event in rigor mortis must be a modification of those occurring in normal condition and they continue sometime after death. Immediately after death, glycogen is converted to lactic acid by anaerobic metabolism; creatine phosphate is broken down to produce creatinine. These two mechanisms are responsible for the resynthesis of ATP from ADP which determine the period of delay in the onset of rigor mortis.

The following changes of muscles take place at the time of rigor mortis-

- Loses of excitability
- Shorter in length
- Increases in thickness
- Become viscous
- Decrease pH level
- Gradually become stiff
- Glycogen disappearance
- The muscle give off carbolic acid