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Excitable Tissue: Muscle

Muscle cells, like neurons, can be excited chemically, electrically, and mechanically to produce an action potential that is transmitted along their cell membranes. Unlike neurons, they respond to stimuli by activating a contractile mechanism. The contractile protein myosin and the cytoskeletal protein actin are abundant in muscle, where they are the primary structural components that bring about contraction.

Muscle is generally divided into three types: **skeletal, cardiac,** and **smooth,** although smooth muscle is not a homogeneous single category. Skeletal muscle makes up the great mass of the somatic musculature. It has well-developed cross-striations, does not normally contract in the absence of nervous stimulation, and is generally under voluntary control. Cardiac muscle also has cross-striations, but it is functionally syncytial and, although it can be modulated via the autonomic nervous system, it can contract rhythmically in the absence of external innervation owing to the presence in the myocardium of pacemaker cells that discharge spontaneously. Smooth muscle lacks cross-striations and can be further subdivided into two broad types: **unitary (or visceral)** smooth muscle and **multiunit** smooth muscle. The type found in most hollow viscera is functionally syncytial and contains pacemakers that discharge irregularly. The multiunit type found in the eye and in some other locations is not spontaneously active and resembles skeletal muscle in graded contractile ability.

SKELETAL MUSCLE MORPHOLOGY

Skeletal muscle is made up of individual muscle fibers that are the "building blocks" of the muscular system in the same sense that the neurons are the building blocks of the nervous system. Most skeletal muscles begin and end in tendons, and the muscle fibers are arranged in parallel between the tendinous ends.

The term **muscle** refers to a number of muscle fibers bound together by connective tissue (**Figure 1**). The most striking feature seen when viewing **skeletal muscle** through a microscope is a distinct series of alternating light and dark bands perpendicular to the long axis. Because **cardiac** muscle shares this characteristic striped pattern, these two types are both referred to as **striated muscle.** The third basic muscle type, **smooth muscle,** derives its name from the fact that it lacks this striated appearance.

Each muscle fiber is a single cell that is multinucleated, long, cylindrical, and surrounded by a cell membrane, the **sarcolemma**. The muscle fibers are made up of myofibrils, which are divisible into individual filaments. These myofilaments contain several proteins that together make up the contractile machinery of the skeletal muscle.

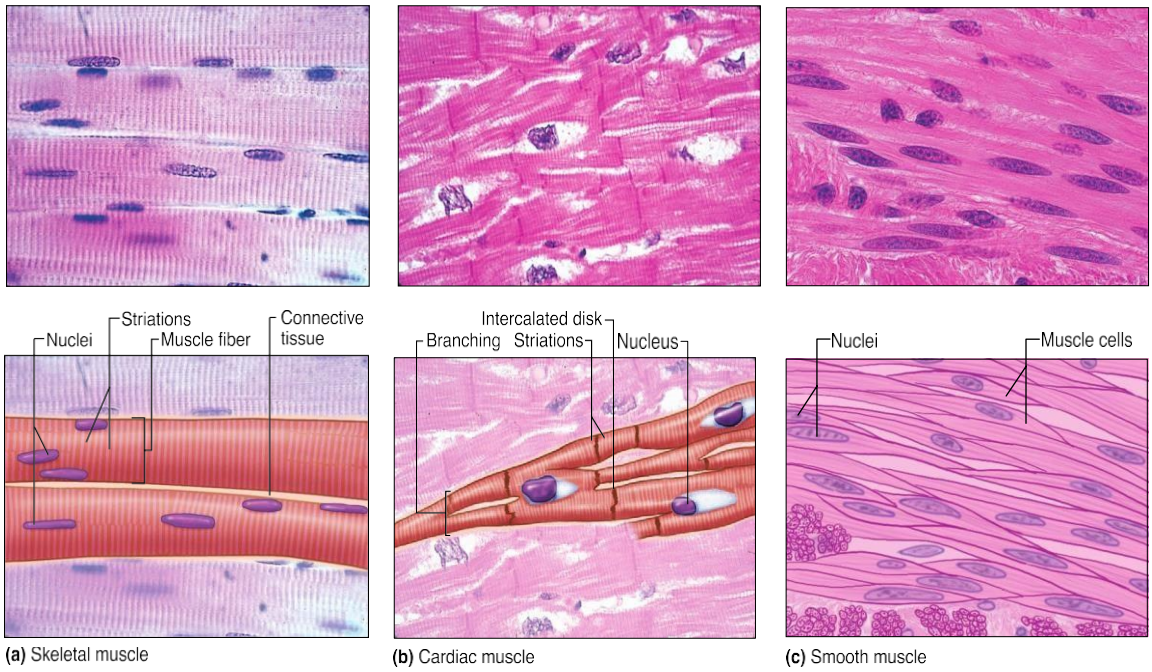


Figure 1: *Comparison of (a) skeletal muscle to (b) cardiac and (c) smooth muscle as seen with light microscopy (top panels) and in schematic form (bottom panels). Both skeletal and cardiac muscle have a striated appearance. Cardiac and smooth muscle cells generally have a single nucleus, but skeletal muscle fibers are multinucleated.*

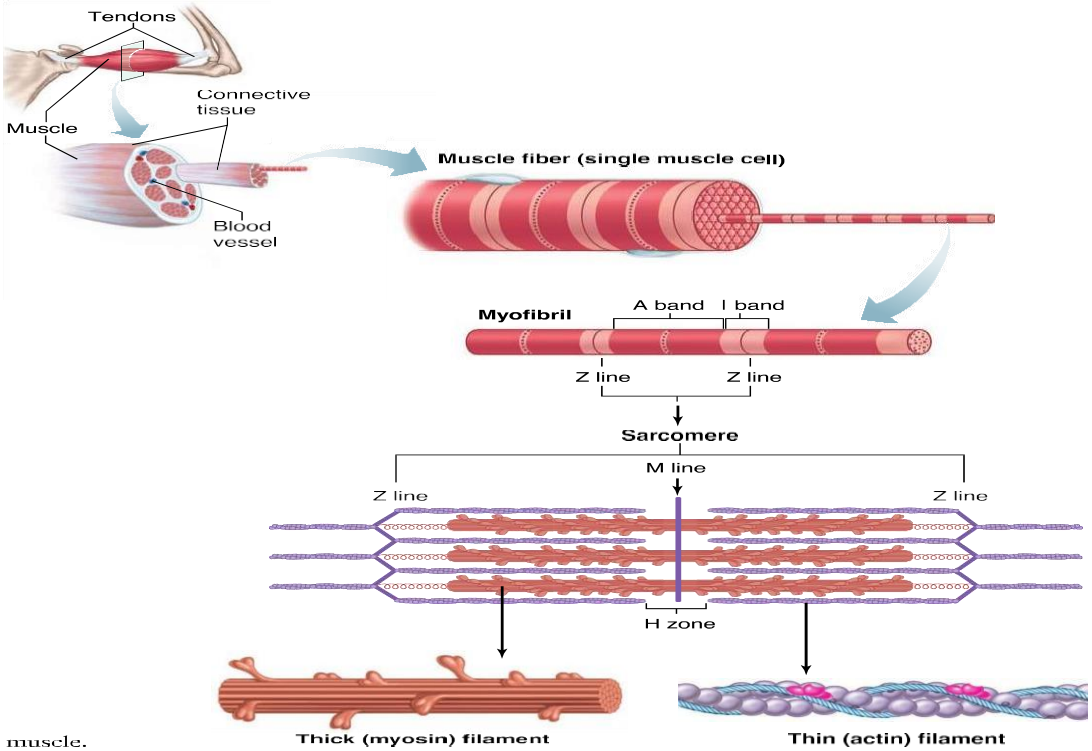
The Sarcolemma Is a Thin Membrane Enclosing a Skeletal Muscle Fiber.

The sarcolemma consists of a true cell membrane, called the *plasma membrane*, and an outer coat made up of a thin layer of polysaccharide material that contains numerous thin collagen fibrils. At each end of the muscle fiber, this surface layer of the sarcolemma fuses with a tendon fiber. The tendon fibers in turn collect into bundles to form the muscle tendons that then insert into the bones.

Myofibrils Are Composed of Actin and Myosin Filaments

Each muscle fiber contains several hundred to several thousand *myofibrils*. Each myofibril (Figure 2) is composed of about 1500 adjacent *myosin filaments* and 3000 *actin filaments*, which are large polymerized protein molecules that are responsible for the actual muscle contraction. The thick filaments in the diagrams are *myosin*, and the thin filaments are *actin.*

The molecular structure of thick and thin filaments is shown in **Figure 2**. The thick filaments are composed almost entirely of the protein **myosin.** The myosin molecule is composed of two large polypeptide **heavy chains** and four smaller **light chains.** These polypeptides combine to form a molecule that consists of two globular heads extend out to the sides, forming **cross-bridges,** which make contact with the thin filament and exert force during muscle contraction.



muscle.

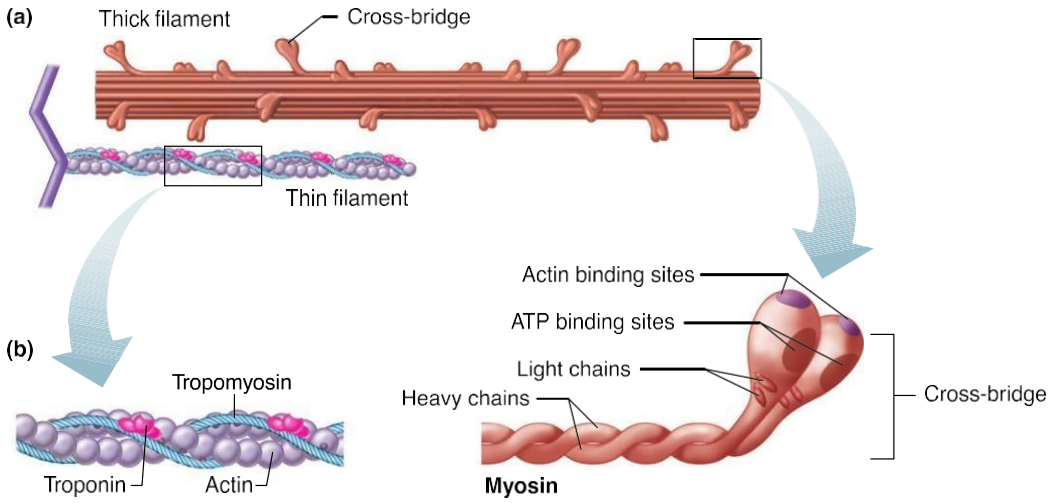


Figure 2: *Structure of skeletal muscle.*

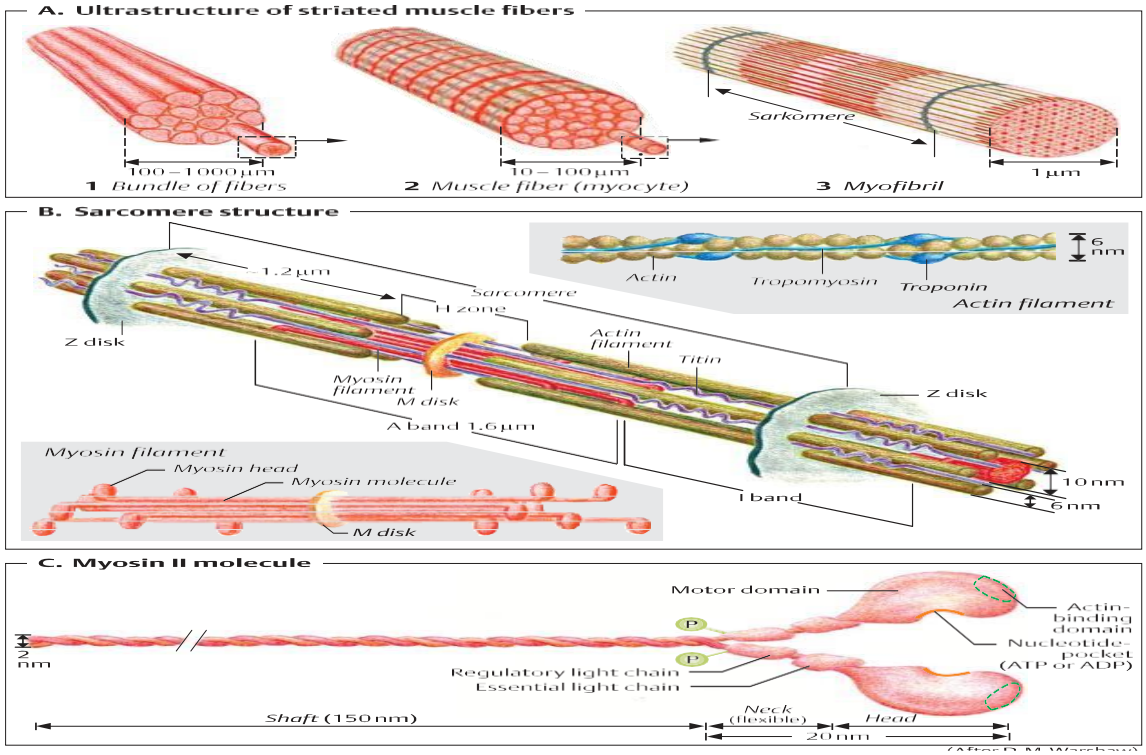


Figure 3: *Structure of skeletal muscle.*

The thin filaments (which are about half the diameter of the thick filaments) are principally composed of the protein **actin,** as well as two other proteins—**troponin** and **tropomyosin**—that play important roles in regulating contraction. An actin molecule is a globular protein composed of a single polypeptide (a monomer) that polymerizes with other actin monomers to form a polymer made up of two intertwined, helical chains. These chains make up the core of a thin filament. Each actin molecule contains a binding site for myosin.

Compositions of Myofibrils:

Figure 2 and 3 also shows that the ends of the actin filaments are attached to a so-called *Z disc*. From this disc, these filaments extend in both directions to interdigitate with the myosin filaments. The Z disc, which itself is composed of filamentous proteins different from the actin and myosin filaments, passes crosswise across the myofibril and also crosswise from myofibril to myofibril, attaching the myofibrils to one another all the way across the muscle fiber. Therefore, the entire muscle fiber has light and dark bands, as do the individual myofibrils. These bands give skeletal and cardiac muscle their striated appearance.

The portion of the myofibril (or of the whole muscle fiber) that lies between two successive Z discs is called a *sarcomere*. When the muscle fiber is contracted, as shown at the bottom of Figure 4, the length of the sarcomere is about 2 micrometers. At this length, the actin filaments completely overlap the myosin filaments, and the tips of the actin filaments are just beginning to overlap one another. At this length the muscle is capable of generating its greatest force of contraction.

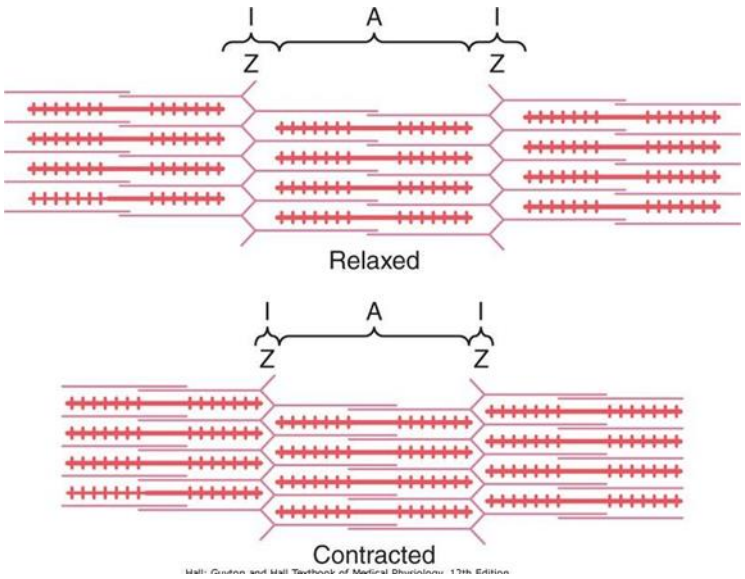


Figure 4: *Relaxed and contracted states of a myofibril showing (top) sliding of the actin filaments into the spaces between the myosin filaments and (bottom) pulling of the Z membranes toward each other.*

Molecular Mechanisms of Skeletal Muscle Contraction

The term **contraction,** as used in muscle physiology, does not necessarily mean "shortening."

The neurons whose axons innervate skeletal muscle fibers are known as **motor neurons** (or somatic efferent neurons), and their cell bodies are located in the brainstem and the spinal cord. The axons of motor neurons are myelinated and are the largest-diameter axons in the body. They are therefore able to propagate action potentials at high velocities, allowing signals from the central nervous system to travel to skeletal muscle fibers with minimal delay. Upon reaching a muscle, the axon of a motor neuron divides into many

branches, each branch forming a single junction with a muscle fiber. A single motor neuron innervates many muscle fibers, but each muscle fiber is controlled by a branch from only one motor neuron. A motor neuron plus the muscle fibers it innervates is called a **motor unit**

The axon terminals of a motor neuron contain vesicles similar to those found at synaptic junctions between two neurons. The vesicles contain the neurotransmitter **acetylcholine** (**Ach**). The region of the muscle fiber plasma membrane that lies directly under the terminal portion of the axon is known as the **motor end plate.** The junction of an axon terminal with the motor end plate is known as a **neuromuscular junction** (**Figure 5a**).

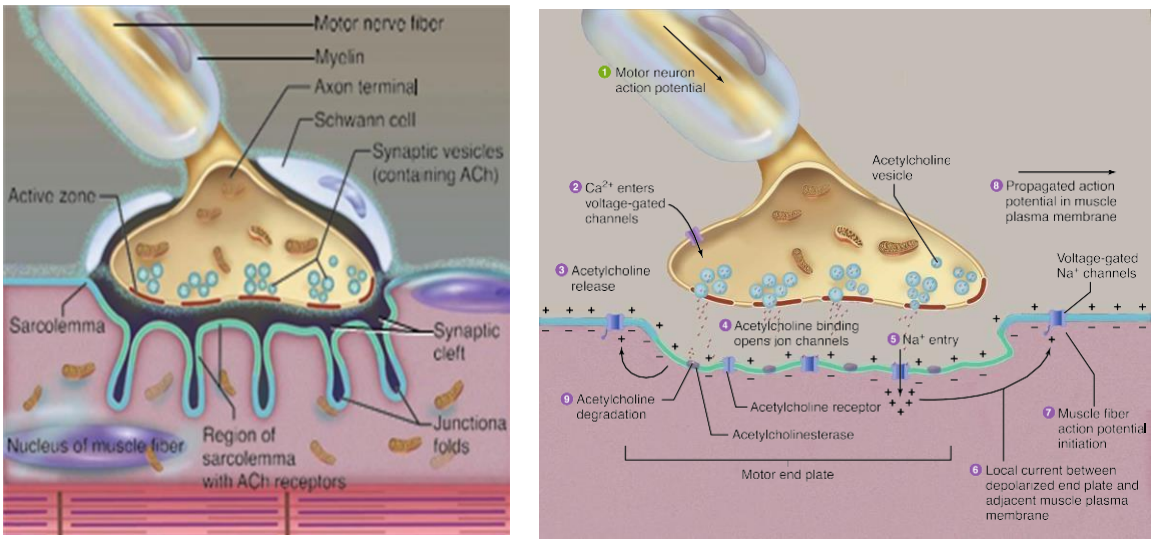


Figure 5 shows the events occurring at the neuromuscular junction. When an action potential in a motor neuron arrives at the axon terminal, it depolarizes the plasma membrane, opening voltage-sensitive Ca^{2+} channels and allowing calcium ions to diffuse into the axon terminal from the extracellular fluid. This Ca^{2+} binds to proteins that enable the membranes of acetylcholine-containing vesicles to fuse with the neuronal plasma membrane, thereby releasing acetylcholine into the extracellular cleft separating the axon terminal and the motor end plate.

ACh diffuses from the axon terminal to the motor end plate where it binds to ionotropic receptors of the nicotinic type. The binding of ACh opens an ion channel in each receptor protein; both sodium and potassium ions can pass through these channels. Because of the differences in electrochemical gradients across the plasma membrane, more Na^+ moves in than K^+ out, producing a local depolarization of the motor end plate known as an **end-plate potential** (**EPP**). Thus, an EPP is analogous to an EPSP (excitatory postsynaptic potential) at a neuron–neuron synapse.

Every action potential in a motor neuron normally produces an action potential in each muscle fiber in its motor unit. This is quite different from synaptic junctions between neurons, where multiple EPSPs must occur in order for threshold to be reached and an action potential elicited in the postsynaptic membrane.

There is another difference between inter-neuronal synapses and neuromuscular junctions, the IPSPs (inhibitory postsynaptic potentials) are produced at some synaptic junctions. They hyperpolarize or stabilize the postsynaptic membrane and decrease the probability of its firing an action potential. In contrast, inhibitory potentials do not occur in human skeletal muscle; *all neuromuscular junctions are excitatory.*

In addition to receptors for ACh, the synaptic junction contains the enzyme **acetylcholinesterase,** which breaks down ACh, just as it does at ACh-mediated synapses in the nervous system. Choline is then transported back into the axon terminals, where it is reused in the synthesis of new ACh.

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 nerve to its endings on muscle fibers.

2. At each ending, the nerve secretes a small amount of the neurotransmitter substance *acetylcholine.*

3. The acetylcholine acts on a local area of the muscle fiber membrane to open multiple "acetylcholine-gated" cation channels through protein molecules floating in the membrane.

4. Opening of the acetylcholine-gated channels allows large quantities of sodium ions to diffuse to the interior of the muscle fiber membrane. This causes a local depolarization that in turn leads to opening of voltage-gated sodium channels. This initiates an action potential at the membrane.

5. The action potential travels along the muscle fiber membrane in the same way that action potentials travel along nerve fiber membranes.

6. The action potential depolarizes the muscle membrane, and much of the action potential electricity flows through the center of the muscle fiber. Here it causes the sarcoplasmic reticulum to release large quantities of calcium ions that have been stored within this reticulum.

7. The calcium ions initiate attractive forces between the actin and myosin filaments, causing them to slide alongside each other, which is the contractile process (figure 4).

8. After a fraction of a second, the calcium ions are pumped back into the sarcoplasmic reticulum by a Ca^{++} membrane pump and remain stored in the reticulum until a new muscle action potential comes along; this removal of calcium ions from the myofibrils causes the muscle contraction to cease.

From this we found the following:

The actin filament also contains another protein, tropomyosin. Each molecule of tropomyosin. These molecules are wrapped spirally around the sides of the F-actin helix. In the resting state, the tropomyosin molecules lie on top of the active sites of the actin strands so that attraction cannot occur between the actin and myosin filaments to cause contraction.

Attached intermittently along the sides of the tropomyosin molecules are still other protein molecules called troponin. These are actually complexes of three loosely bound protein subunits, each of which plays a specific role in controlling muscle contraction. One of the subunits (troponin I) has a strong affinity for actin, another (troponin T) for tropomyosin, and a third (troponin C) for calcium ions. This complex is believed to attach the tropomyosin to the actin. The strong affinity of the troponin for calcium ions is believed to initiate the contraction process.

In the presence of large amounts of calcium ions, the inhibitory effect of the troponin-tropomyosin on the actin filaments is itself inhibited. The mechanism

of this is not known, but one suggestion is the following: When calcium ions combine with troponin C, each molecule of which can bind strongly with up to four calcium ions, the troponin complex supposedly undergoes a conformational change that in some way tugs on the tropomyosin molecule and moves it deeper into the groove between the two actin strands. This "uncovers" the active sites of the actin, thus allowing these to attract the myosin cross-bridge heads and cause contraction to proceed. Although this is a hypothetical mechanism, it does emphasize that the normal relation between the troponin-tropomyosin complex and actin is altered by calcium ions, producing a new condition that leads to contraction.

Sources of Energy for Muscle Contraction

The first source of energy that is used to reconstitute the ATP is the substance ***phosphocreatine,*** which carries a high-energy phosphate bond similar to the bonds of ATP. The high-energy phosphate bond of phosphocreatine has a slightly higher amount of free energy than that of each ATP bond. Therefore, phosphocreatine is instantly cleaved, and its released energy causes bonding of a new phosphate ion to ADP to reconstitute the ATP. However, the total amount of phosphocreatine in the muscle fiber is also very little-only about five times as great as the ATP. Therefore, the combined energy of both the stored ATP and the phosphocreatine in the muscle is capable of causing maximal muscle contraction for only 5 to 8 seconds.

The second important source of energy, which is used to reconstitute both ATP and phosphocreatine, is "glycolysis" of *glycogen* previously stored in the

muscle cells. Rapid enzymatic breakdown of the glycogen to pyruvic acid and lactic acid liberates energy that is used to convert ADP to ATP; the ATP can then be used directly to energize additional muscle contraction and also to re-form the stores of phosphocreatine.

The importance of this glycolysis mechanism is twofold. ***First,*** the glycolytic reactions can occur even in the absence of oxygen, so muscle contraction can be sustained for many seconds and sometimes up to more than a minute, even when oxygen delivery from the blood is not available. ***Second,*** the rate of formation of ATP by the glycolytic process is about 2.5 times as rapid as ATP formation in response to cellular foodstuffs reacting with oxygen.

The third and final source of energy is *oxidative metabolism.* This means combining oxygen with the end products of glycolysis and with various other 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 that are consumed are carbohydrates, fats, and protein. For extremely long-term maximal muscle activity-over a period of many hours-by far the greatest proportion of energy comes from fats, but for periods of 2 to 4 hours, as much as one half of the energy can come from stored carbohydrates.

Muscle Fatigue

Prolonged and strong contraction of a muscle leads to the well-known state of muscle fatigue. Studies in athletes have shown that muscle fatigue increases in almost direct proportion to the rate of depletion of muscle glycogen.

Therefore, fatigue results mainly from inability of the contractile and metabolic processes of the muscle fibers to continue supplying the same work output. However, experiments have also shown that transmission of the nerve signal through the neuromuscular junction, can diminish at least a small amount after intense prolonged muscle activity, thus further diminishing muscle contraction. Interruption of blood flow through a contracting muscle leads to almost complete muscle fatigue within 1 or 2 minutes because of the loss of nutrient supply, especially loss of oxygen.