University of Anbar
College of science
Department of biotechnology

Lectures of human physiology

Lec. 3

Muscles

Mechanisms of Contraction and Neural Control

By
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Muscles are a means of converting chemical energy into kinetic energy

Vital activities depend on muscle contraction, such as heartbeat, dilatation or constriction of blood vessels, bowel movement, and others

There are three main types of muscles that differ from each other in the histological structure, location, physiological softness, and the type of nerve fibers connected to them.

SKELETAL MUSCLES

Skeletal muscles are composed of individual muscle fibers that contract when stimulated by a somatic motor neuron. Each motor neuron branches to innervate a number of muscle fibers. Activation of varying numbers of motor neurons results in gradations in the strength of contraction of the whole muscle.
Skeletal muscles are usually attached to bone on each end by tough connective tissue tendons. When a muscle contracts, it places tension on its tendons and attached bones. The muscle tension causes movement of the bones at a joint, the fibrous connective tissue proteins within the tendons extend around the muscle in an irregular arrangement, forming a sheath known as the epimysium (epi ═ above; my ═ muscle). Connective tissue from this outer sheath extends into the body of the muscle, subdividing it into columns, or fascicles (these are the “strings” in stringy meat). Each of these fascicles is thus surrounded by its own connective tissue sheath, which is known as the perimysium (peri ═ around).

Dissection of a muscle fascicle under a microscope reveals that it, in turn, is composed of many muscle fibers, or myo-fibers. Each is surrounded by a plasma membrane, or sarcolemma, enveloped by a thin connective tissue layer called an endomysium (fig.1). The endomysium is the basement membrane, or basal lamina, of the muscle fiber. Because the connective tissue of the tendons, epimysium, perimysium, and endomysium is continuous, muscle fibers do not normally pull out of the tendons when they contract.

Despite their unusual elongated shape, muscle fibers have the same organelles that are present in other cells: mitochondria, endoplasmic reticulum, glycogen granules, and others. Unlike most other cells in the body, skeletal muscle fibers are multinucleate— they contain multiple nuclei.

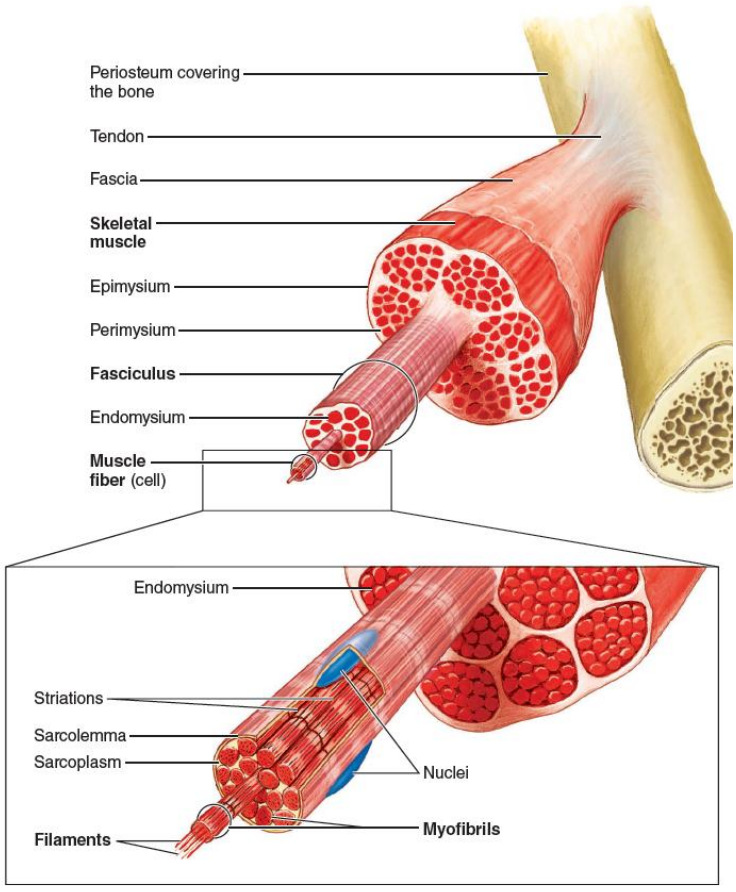

Fig.1 The structure of a skeletal muscle.

The most distinctive feature of skeletal muscle fibers, however, is their **striated** appearance when viewed microscopically (fig. 2). The striations (stripes) are produced by alternating dark and light bands that appear to span the width of the fiber.

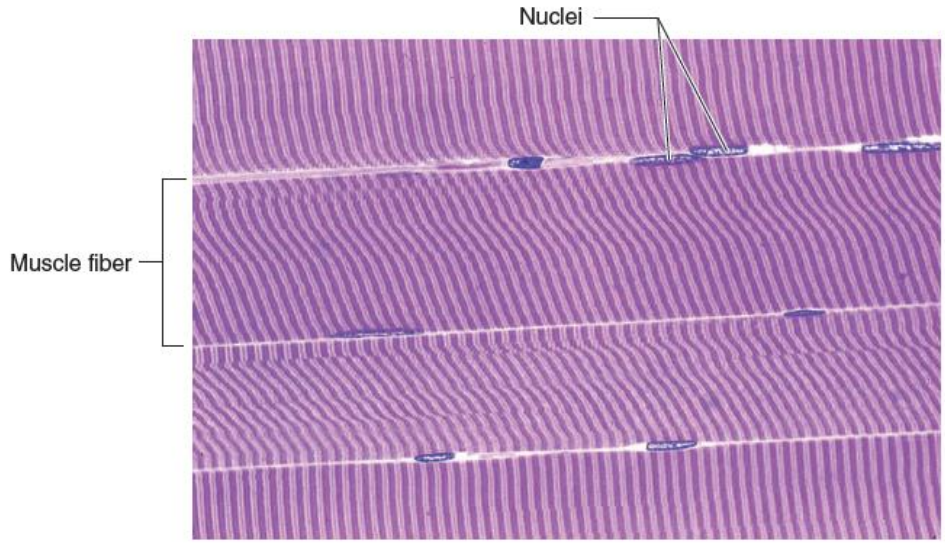

Fig.2 The appearance of skeletal muscle fibers through the light microscope.

Motor End Plates and Motor Units

In vivo, each muscle fiber receives a single axon terminal from a somatic motor neuron. The motor neuron stimulates the muscle fiber to contract by liberating acetylcholine at the neuromuscular junction. The specialized region of the sarcolemma of the muscle fiber at the neuromuscular junction is known as a **motor end plate**. Contraction of a skeletal muscle rapidly follows its stimulation by somatic motor axons. Depolarization of a motor axon terminal by an action potential causes the exocytosis of acetylcholine (ACh) from about 100 synaptic vesicles, in a process. These ACh molecules rapidly diffuse across the narrow 100 nm synaptic cleft that separates the axon terminal from the motor end plate, where they bind to several thousand nicotinic

ACh receptors. This binding causes the ACh receptor ion channels to open, producing a depolarization known as an **end plate potential** that stimulates action potentials. Action potentials lead to muscle contraction.

Each axon, however, can produce a number of collateral branches to innervate an equal number of muscle fibers. Each somatic motor neuron, together with all of the muscle fibers that it innervates, is known as a **motor unit**. Fig.3 .

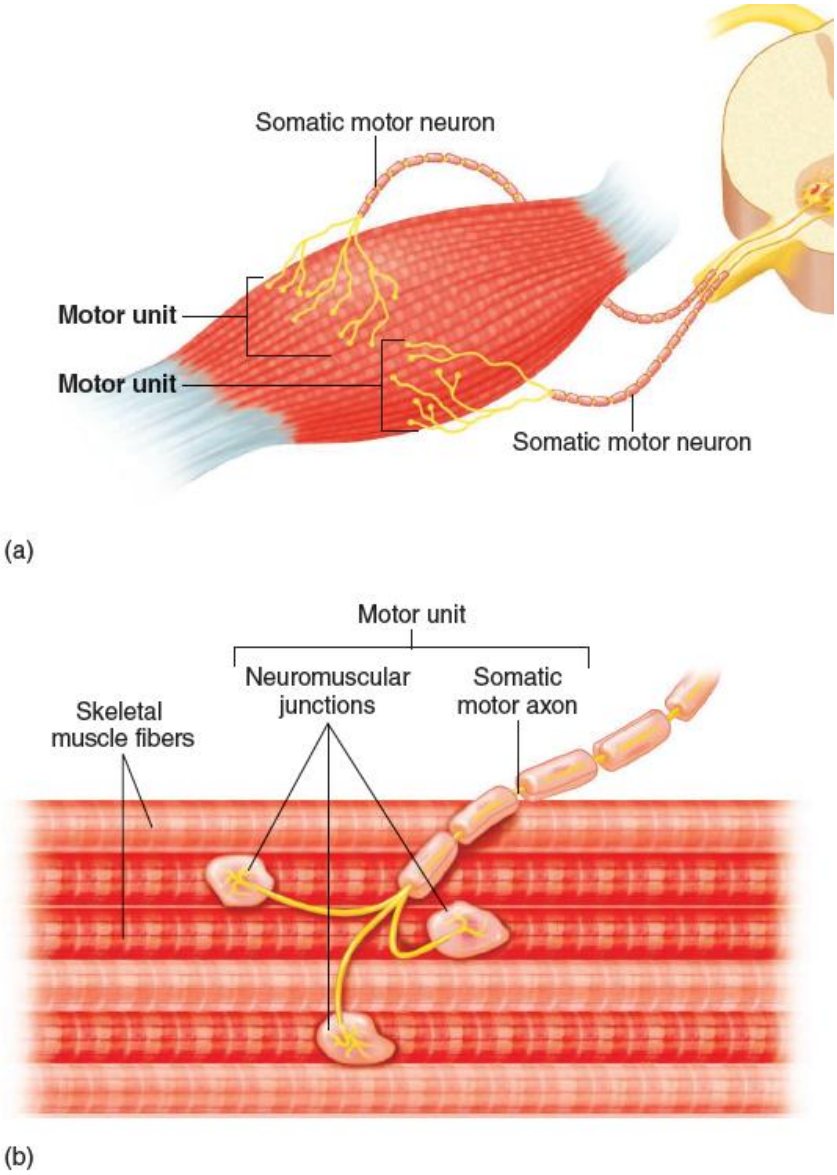

Fig.3 Motor units

MECHANISMS OF CONTRACTION

Muscle cell under electron microscope seen to be of many subunits known as myofibrils, these myofibrils are approximately 1 micrometer (1 μ m) in diameter and extend in parallel rows from one end of the muscle fiber to the other.

Each myofibril contains even smaller structures called myofilaments. When a myofibril is observed at high magnification in longitudinal section (side view), the A bands are seen to contain thick filaments. These are about 110 angstroms thick (110 Å, where 1 Å 5 10 2 10 m) and are stacked in register. It is these thick filaments that give the A band its dark appearance. The lighter I band, by contrast, contains thin filaments (from 50 to 60 Å thick). The thick filaments are primarily composed of the protein myosin, and the thin filaments are primarily composed of the protein actin. The thin filaments, however, do not end at the edges of the I band. Instead, each thin filament extends partway into the A bands on each side (between the stack of thick filaments on each side of an I band). Because thick and thin filaments overlap at the edges of each A band, the edges of the A band are darker in appearance than the central region. These central lighter regions of the A bands are called the H bands (for helle, a German word meaning “bright”). The central H bands thus contain only thick filaments that are not overlapped by thin filaments.

In the center of each I band is a thin dark Z line. The arrangement of thick and thin filaments between a pair of Z lines forms a repeating pattern that serves as the basic subunit of striated muscle contraction. These subunits, from Z to Z, are known as sarcomeres (fig.4)

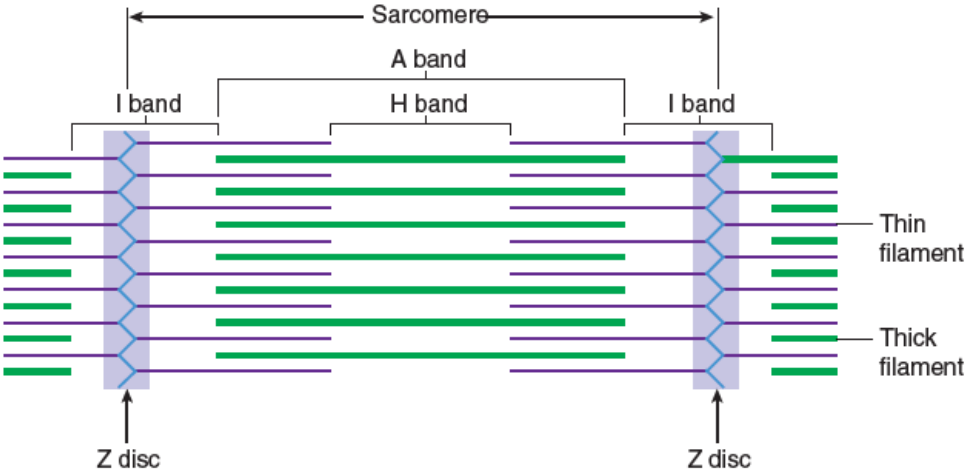

Fig.4 Arrangement of thick and thin filaments in a striated muscle fiber

Sliding Filament Theory of Contraction

When a muscle contracts it decreases in length as a result of the shortening of its individual fibers. Shortening of the muscle fibers, in turn, is produced by shortening of their myofibrils, which occurs as a result of the shortening of the distance from Z disc to Z disc. As the sarcomeres shorten in length, however, the A bands do not shorten but instead move closer together. The I bands—which represent the distance between A bands of successive sarcomeres—decrease in length.

The thin filaments composing the I band, however, do not shorten. Close examination reveals that the thick and thin filaments remain the same length during muscle contraction. Shortening of the sarcomeres is produced not by shortening of the filaments, but rather by the sliding of thin filaments over and between the thick filaments. In the process of contraction, the thin filaments on either side of each A band slide deeper and deeper toward the center, producing increasing amounts of overlap with the thick filaments. The I bands (containing only thin filaments) and H bands (containing only thick filaments) thus get shorter during contraction. (fig.5).

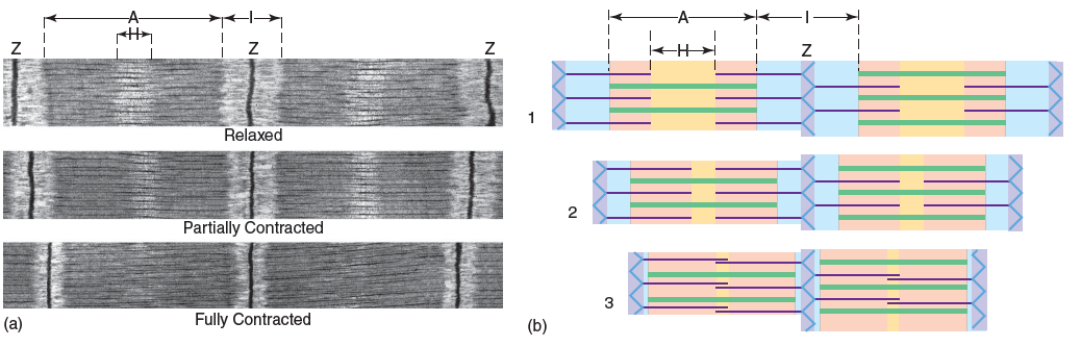

Fig.5 The sliding filament model of muscle contraction. *(a)* The upper image is an electron micrograph of sarcomeres in a relaxed muscle. The lower two images are photo illustrations of the changes that occur during contraction. *(b)* An illustration of the sliding filament model of striated muscle contraction as a relaxed muscle fiber (1) partially contracts (2) and then contracts fully (3). Although the sarcomeres shorten, the filaments slide rather than shorten.

Cross Bridges

Sliding of the filaments is produced by the action of numerous **cross bridges** that extend out from the myosin toward the actin. These cross bridges are part of the myosin proteins that extend from the axis of the thick filaments to form "arms" that terminate in globular "heads" (fig. 6). A myosin protein has globular heads that serve as cross bridges. The orientation of the myosin heads on one side of a sarcomere is opposite to that of the other side, so that, when the myosin heads form cross bridges by attaching to actin on each side of the sarcomere, they can pull the actin from each side toward the center.

Isolated muscles are easily stretched, demonstrating that the myosin heads are not attached to actin when the muscle is at rest. Each globular myosin head of a cross bridge contains an *ATP-binding site* closely associated with an *actin-binding site* (fig. 6). The globular heads function as **myosin ATPase** enzymes, splitting ATP into ADP and P i .

This reaction must occur *before* the myosin heads can bind to actin. When ATP is hydrolyzed to ADP and P i , the phosphate binds to the myosin head, phosphorylating it and causing it to change its conformation so that it becomes "cocked" (by analogy to the hammer of a gun). The position of the myosin head has

changed and it now has the potential energy required for contraction. Perhaps a more apt analogy is with a bow and arrow: The energized myosin head is like a pulled bowstring; it is now in position to bind to actin (fig. 6) so that its stored energy can be released in the next step.

Once the myosin head binds to actin, forming a cross bridge, the bound Pi is released (the myosin head becomes dephosphorylated). This results in a conformational change in the myosin, causing the cross bridge to produce a **power stroke** (fig. 7). This is the force that pulls the thin filaments toward the center of the A band.

After the power stroke, with the myosin head now in its flexed position, the bound ADP is released as a new ATP molecule binds to the myosin head. This release of ADP and binding to a new ATP is required for the myosin head to break its bond with actin after the power stroke is completed. The myosin head will then split ATP to ADP and P i , and—if nothing prevents the binding of the myosin head to the actin—a new cross-bridge cycle will occur.

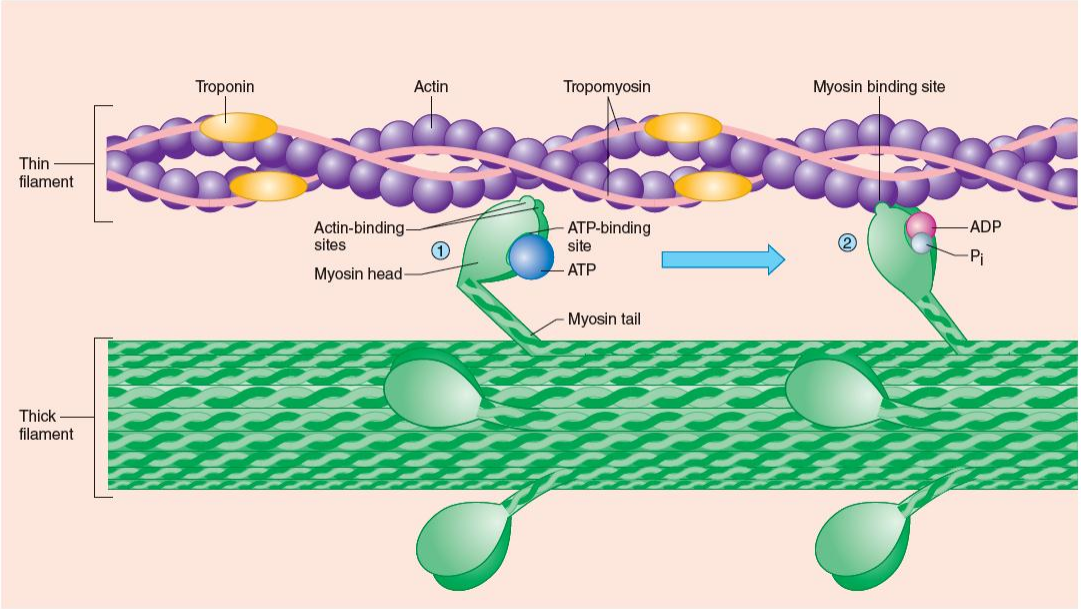

Fig.6 Activation of the myosin head. (1) The myosin head has an actin-binding site and an ATP-binding site, which serves as an ATPase to hydrolyze ATP. (2) When ATP is hydrolyzed into ADP and P i , the myosin head becomes activated and changes its orientation .

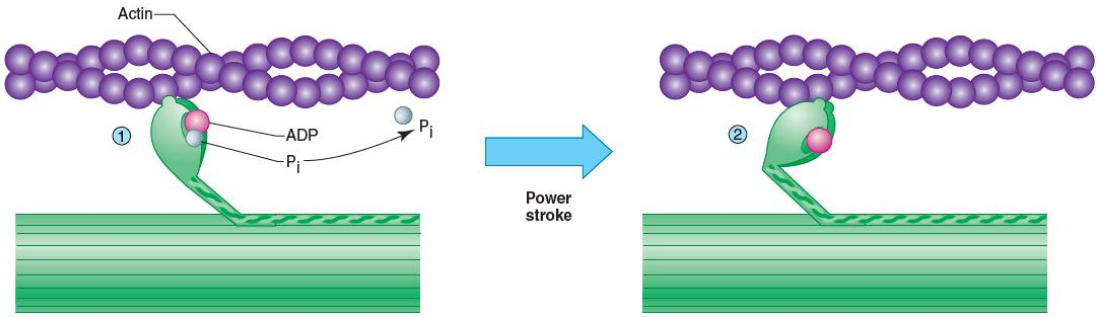

Figure 7 **The cross-bridge power stroke. (1) The myosin head has been activated by the splitting of ATP into ADP and P_i, which remain bound. At this point, the myosin head has bonded to the actin, forming a cross bridge between the thick and thin filaments. (2) After the P_i group leaves the cross bridge, the myosin head changes its orientation, producing the power stroke that moves the actin filament.**

Regulation of Contraction

When the cross bridges attach to actin, they undergo power strokes and cause muscle contraction. In order for a muscle to relax, therefore, the attachment of myosin cross bridges to actin must be prevented. The regulation of cross-bridge attachment to actin is a function of two proteins that are associated with actin in the thin filaments.

The actin filament—or *F-actin* —is a polymer formed of 300 to 400 globular subunits (G-*actin)*, arranged in a double row and twisted to form a helix (fig. 8). A different type of protein, known as **tropomyosin,** lies within the groove between the double row of G-actin monomers. There are 40 to 60 tropomyosin molecules per thin filament, with each tropomyosin spanning a distance of approximately seven actin subunits.

Attached to the tropomyosin, rather than directly to the actin, is a third type of protein called **troponin.** Troponin is actually a complex of three proteins (fig. 8). These are *troponin I* (which inhibits the binding of the cross bridges to actin), *troponin T* (which binds to tropomyosin), and *troponin C* (which binds Ca^{2+}). Troponin and tropomyosin work together to regulate the attachment of cross bridges to actin, and thus serve as a switch for muscle contraction and relaxation. In a relaxed muscle, the position of the tropomyosin in the thin filaments is such that it

physically blocks the cross bridges from bonding to specific attachment sites in the actin. Thus, in order for the myosin cross bridges to attach to actin, the tropomyosin must be moved. This requires the interaction of troponin with Ca^{2+}.

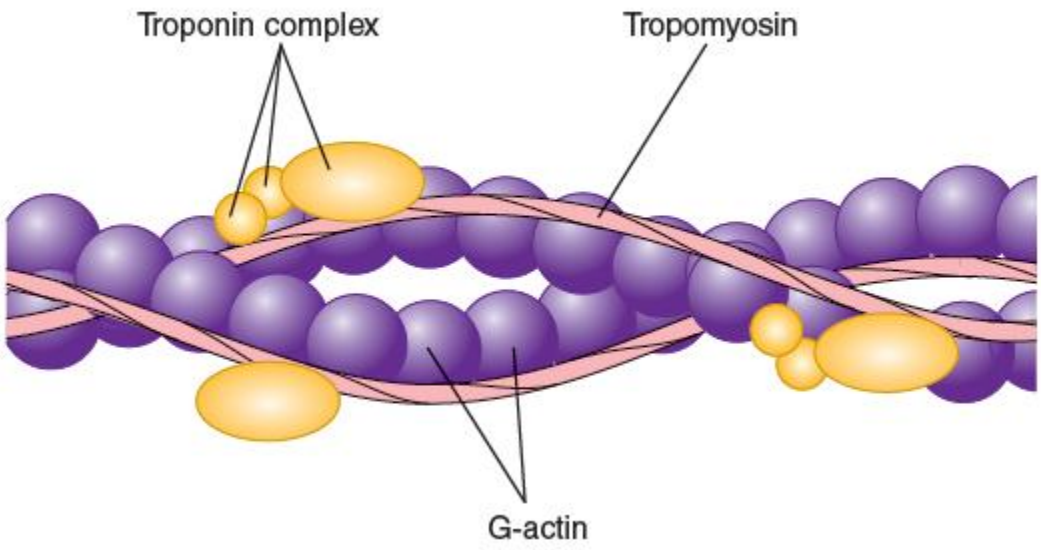

Figure 8 The structural relationship between troponin, tropomyosin, and actin. The tropomyosin is attached to actin, whereas the troponin complex of three subunits is attached to tropomyosin (not directly to actin).

Role of Ca^{2+} in Muscle Contraction

In a relaxed muscle, when tropomyosin blocks the attachment of cross bridges to actin, the concentration of Ca^{2+} in the sarcoplasm (cytoplasm of muscle cells) is very low. When the muscle cell is stimulated to contract. Some of this Ca^{2+} attaches to troponin, causing a conformational change that moves the troponin complex and its attached tropomyosin out of the way so that the cross bridges can attach to actin (fig. 9). Once the attachment sites on the actin are exposed, the cross bridges can bind to actin, undergo power strokes, and produce muscle contraction.

The position of the troponin-tropomyosin complexes in the thin filaments is thus adjustable. When Ca^{2+} is not attached to troponin, the tropomyosin is in a position that inhibits attachment of myosin heads to actin, preventing muscle contraction. When

Ca^{2+} attaches to troponin, the troponin-tropomyosin complexes shift position. The myosin heads can then attach to actin, produce a power stroke, and detach from actin. These contraction cycles can continue as long as Ca^{2+} is bonded to troponin.

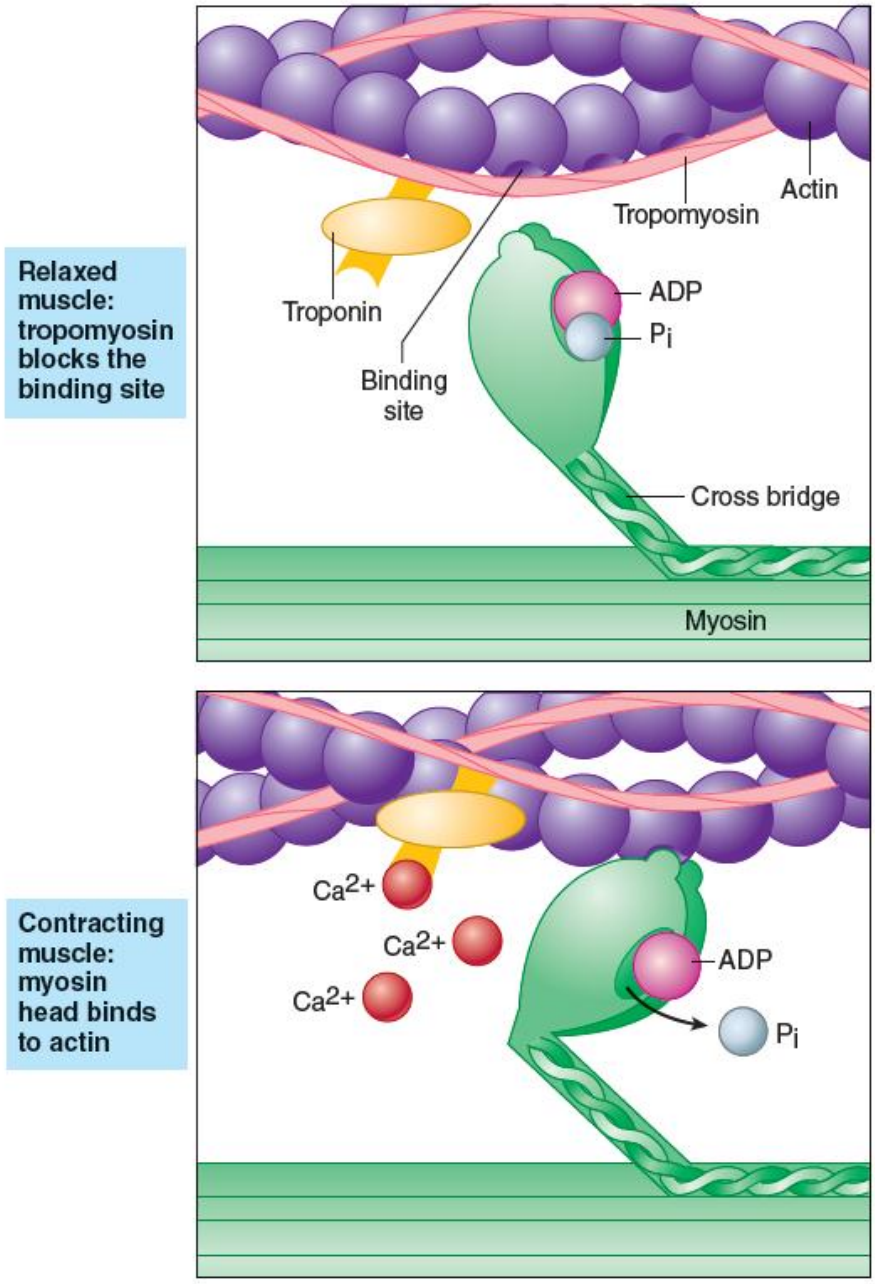

Figure 8 The role of Ca^{2+}in muscle contraction. The attachment of $Ca^{2+}$to troponin causes movement of the troponin-tropomyosin complex, which exposes binding sites on the actin. The myosin cross bridges can then attach to actin and undergo a power stroke.

Muscle Relaxation

As long as action potentials continue to be produced—which is as long as neural stimulation of the muscle is maintained— the calcium release channels in the sarcoplasmic reticulum will remain open, Ca^{2+}will passively diffuse out of the sarcoplasmic reticulum and the Ca^{2+}concentration of the sarcoplasm will remain high. Thus, Ca^{2+} will remain attached to troponin and the cross-bridge cycle will continue to maintain contraction.

To stop the cross-bridge cycle, the production of action potentials must cease. The calcium release channels will thereby close, so that Ca^{2+} can no longer passively diffuse out of the terminal cisternae. Ca^{2+} in the cytoplasm must then be moved against a concentration gradient back into the lumen of the sarcoplasmic reticulum. The active transport pumps for Ca^{2+} are in a family of sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase pumps (or SERCA pumps) that accumulate Ca^{2+} so that it is sequestered from the cytoplasm. This will prevent Ca^{2+} from binding to troponin, so that tropomyosin can resume its position that blocks the myosin heads from binding to actin. Because active transport pumps are powered by the hydrolysis of ATP, ATP is required for muscle relaxation as well as for muscle contraction.

Types of Muscle Contractions

There are two types of muscle contraction

1- Isometric contraction:

In it, there is no change in the length of the muscle, but rather the pressure or tension within it increases, and such a contraction occurs when the muscle fails to lift a certain weight.

2- Isotonic contraction:

In which there is a change in the length of the muscle while the pressure or tension remains the same inside it. Such a contraction occurs when it is possible for the muscle to lift a certain weight.

Cardiac Muscle

Like skeletal muscle cells, cardiac (heart) muscle cells, or **myocardial cells,** are striated; they contain actin and myosin filaments arranged in the form of sarcomeres, and they contract by means of the sliding filament mechanism. The long, fibrous skeletal muscle cells, however, are structurally and functionally separated from each other, whereas the myocardial cells are short, branched, and interconnected. Each myocardial cell is tubular in structure and joined to adjacent myocardial cells by electrical synapses, or **gap junctions**.

The gap junctions are concentrated at the ends of each myocardial cell (fig. 9), which permits electrical impulses to be conducted primarily along the long axis from cell to cell. Gap junctions in cardiac muscle have an affinity for stain that makes them appear as dark lines between adjacent cells when viewed in the light microscope. These dark-staining lines are known as *intercalated discs.*

Action potentials that originate at any point in a mass of myocardial cells, called a myocardium, can spread to all cells in the mass that are joined by gap junctions. Because all cells in a myocardium are electrically joined, a myocardium behaves as a single functional unit. Thus, unlike skeletal muscles that produce contractions that are graded depending on the number of cells stimulated, a myocardium contracts to its full extent each time because all of its cells contribute to the contraction.

The ability of the myocardial cells to contract, however, can be increased by the hormone epinephrine and by stretching of the heart chambers.

Unlike skeletal muscles, which require external stimulation by somatic motor nerves before they can produce action potentials and contract, cardiac muscle is able to produce action potentials automatically. Cardiac action potentials normally originate in a specialized group of cells called the pacemaker. However, the rate

of this spontaneous depolarization, and thus the rate of the heartbeat, are regulated by autonomic innervation.

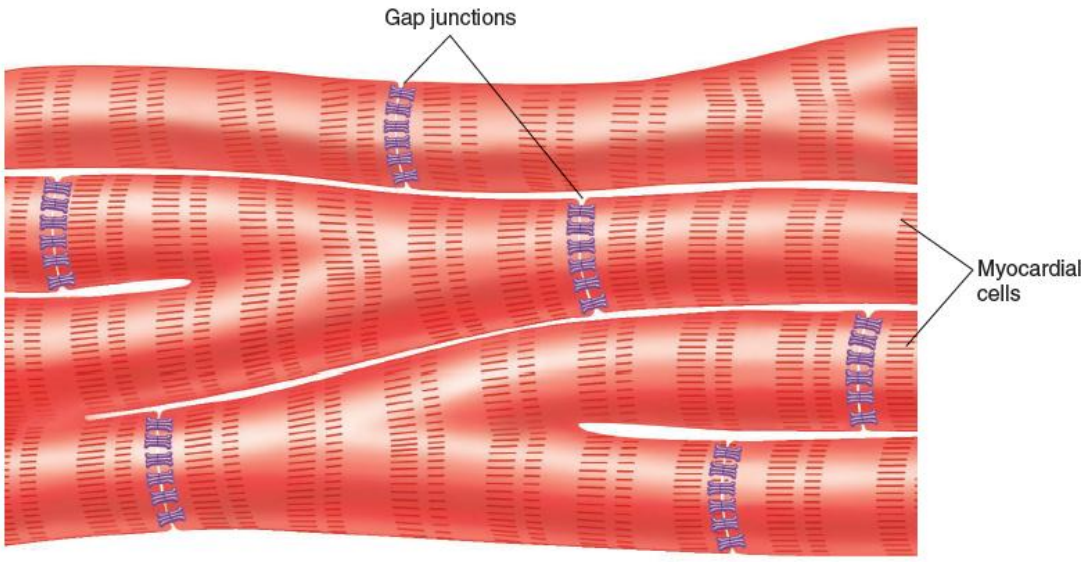

Figure 9 Myocardial cells are interconnected by gap junctions

Smooth Muscle

Smooth (visceral) muscles are arranged in circular layers in the walls of blood vessels and bronchioles (small air passages in the lungs). Both circular and longitudinal smooth muscle layers occur in the tubular digestive tract, the ureters (which transport urine), and the uterine tubes (which transport ova). The alternate contraction of circular and longitudinal smooth muscle layers in the intestine produces peristaltic waves, which propel the contents of these tubes in one direction.

Although smooth muscle cells do not contain sarcomeres (which produce striations in skeletal and cardiac muscle), they do contain a great deal of actin and some myosin, which produces a ratio of thin to thick filaments of about 16 to 1 (in striated muscles the ratio is 2 to 1). Unlike striated muscles, in which the thin filaments are relatively short (extending from a Z disc into a sarcomere), the thin filaments of smooth muscle cells are quite long. They attach either to regions of the plasma membrane of the smooth muscle cell or to cytoplasmic protein structures called

dense bodies, which are analogous to the Z discs of striated muscle (fig. 10 b). The myofilaments and dense bodies are so numerous that they occupy as much as 90% of the volume of a smooth muscle cell.

In smooth muscle, the myosin proteins of the thick filaments are stacked vertically so that their long axis is perpendicular to the long axis of the thick filament (fig. 10 c). In this way, the myosin heads can form cross bridges with actin all along the length of the thick filaments. This is different from the horizontal arrangement of myosin proteins in the thick filaments of striated muscles, which is required to cause the shortening of sarcomeres.

The arrangement of the contractile apparatus in smooth muscle cells, and the fact that it is not organized into sarcomeres, is required for proper smooth muscle function. Smooth muscles must be able to contract even when greatly stretched— in the urinary bladder, for example, the smooth muscle cells may be stretched up to two and a half times their resting length. The smooth muscle cells of the uterus may be stretched up to eight times their original length by the end of pregnancy. Striated muscles, because of their structure, lose their ability to contract when the sarcomeres are stretched to the point where actin and myosin no longer overlap

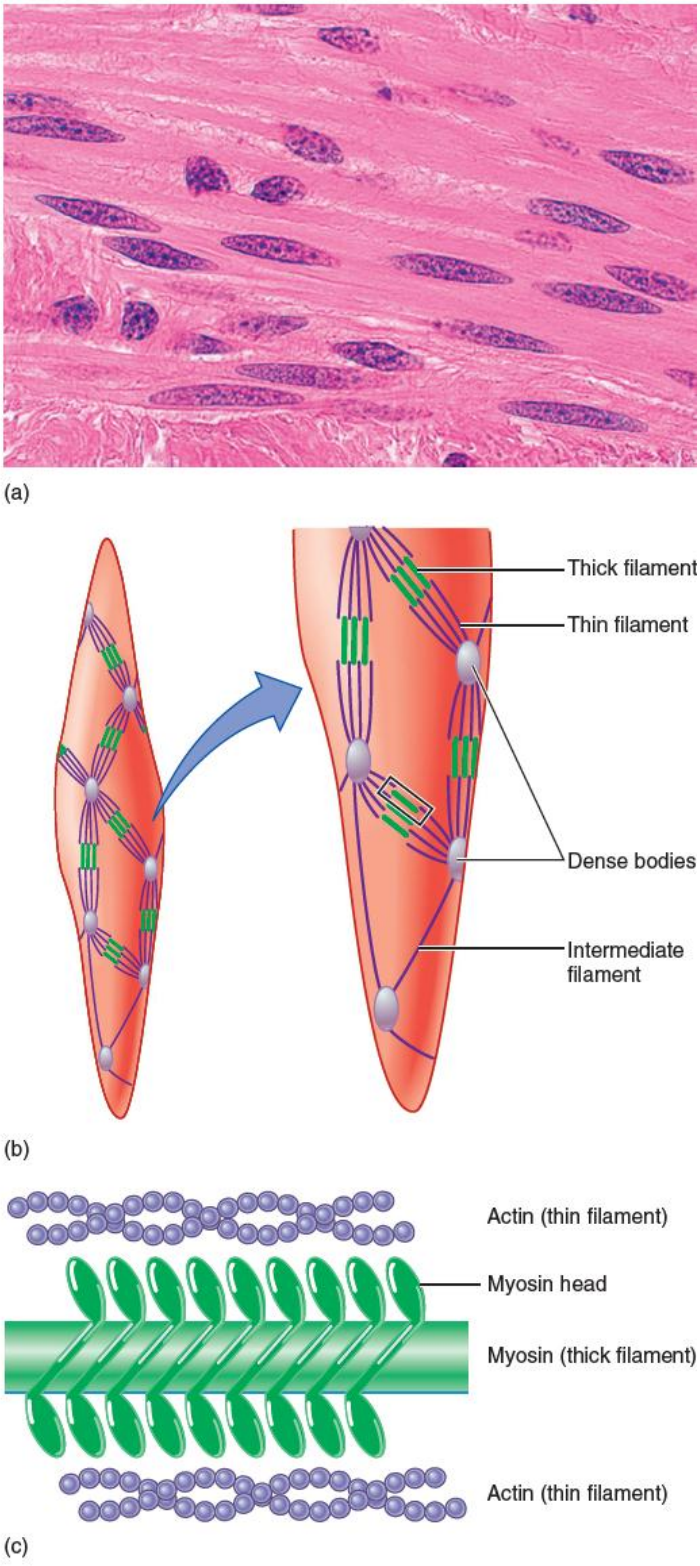

Figure 10 **Smooth muscle and its contractile apparatus**

Contraction of smooth muscles:

Sustained smooth muscle contractions are produced in response to extracellular Ca^{2+}that diffuses through the sarcolemma into the smooth muscle cells. This Ca^{2+}enters primarily through voltage-regulated Ca^{2+}channels in the plasma membrane. The opening of these channels is graded by the amount of depolarization; the greater the depolarization, the more Ca^{2+}will enter the cell and the stronger will be the smooth muscle contraction.

The events that follow the entry of Ca^{2+}into the cytoplasm are somewhat different in smooth muscles than in striated muscles. In striated muscles, Ca^{2+}combines with troponin. Troponin, however, is not present in smooth muscle cells. In smooth muscles, Ca^{2+}combines with a protein in the cytoplasm called **calmodulin,** which is structurally similar to troponin.

The calmodulin- Ca^{2+}complex thus formed combines with and activates **myosin light-chain kinase (MLCK),** an enzyme that catalyzes the phosphorylation (addition of phosphate groups) of *myosin light chains*, a component of the myosin cross bridges.

In smooth muscle (unlike striated muscle), the phosphorylation of myosin cross bridges is the regulatory event that permits them to bind to actin and thereby produce a contraction. The degree of phosphorylation of the myosin light chains largely determines the smooth muscle contraction strength and duration, allowing smooth muscles to produce graded contractions.

-Reference

Fox, S. I. (2014). Fox Human Physiology.