MSS

Physiology

|Modified slides

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Skeletal muscle physiology for medical students 2022

Skeletal muscle contraction-1

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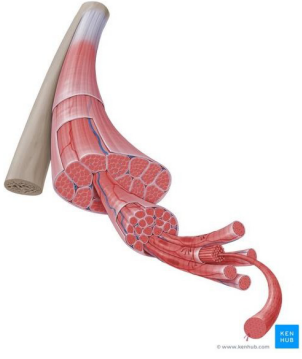
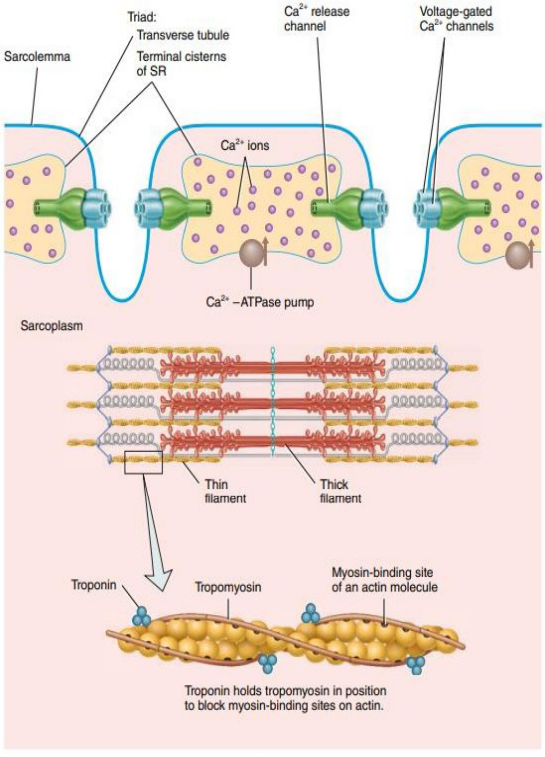


Outline

- Calcium role in contraction
- Sliding filament/ walk-along theory
- ATP sources in muscle fiber
- Types of skeletal muscle fibers

Relaxation



(a) Relaxation

Remember what we said about relaxation or resting state of skeletal muscle fibers :

- We have resting membrane potential
- The channels are deactivated
- Calcium ions are sequestered in the sarcoplasmic reticulum (Whenever there is no high concentration of calcium in the sarcoplasm, there is no binding, no contractions between the actin and myosin…… the binding sites of myosin on actin are covered by tropomyosin)

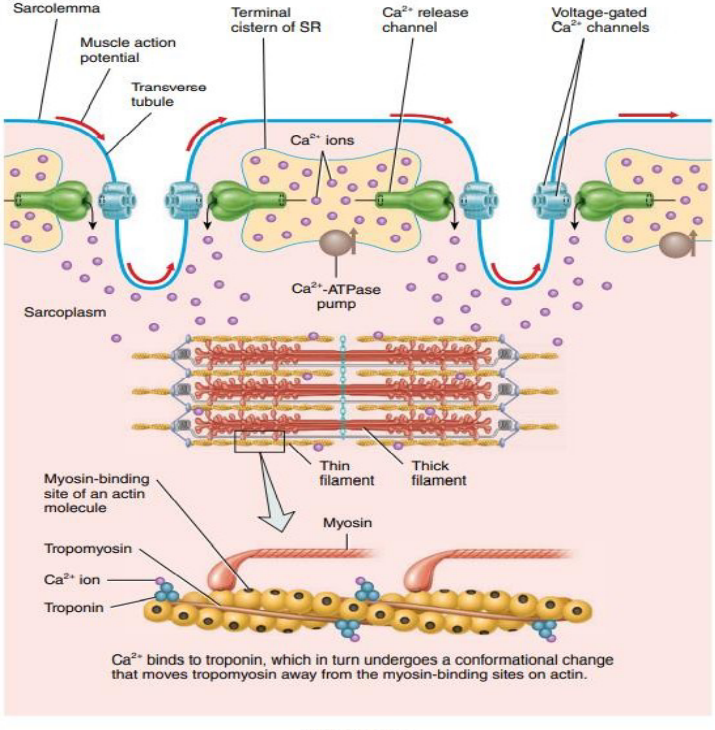
In the normal case if the binding sites are exposed they have high affinity for the myosin, so in the resting state the are covered to prevent the contractions all the time .

Myosin-Actin interaction

A pure actin filament without the presence of the troponin-tropomyosin complex (but in the presence of magnesium ions and ATP) binds instantly and strongly with the heads of the myosin molecules.

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. Before contraction can take place, the inhibitory effect of the troponin -tropomyosin complex must itself be inhibited.

Contraction

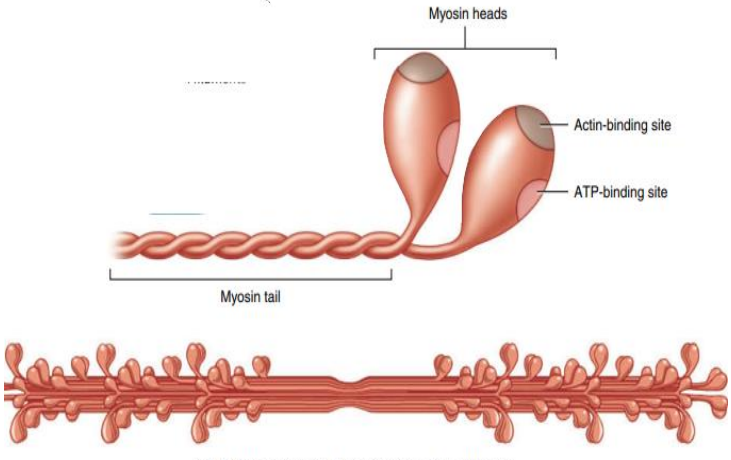


(b) Contraction

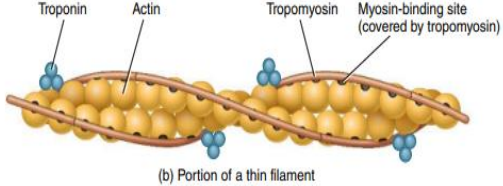
When the action potential has been achieved, it activated certain channels (dihydropyridine channels) which activate calcium release channels (ryanodine receptors) so calcium left the sarcoplasmic reticulum in high concentration.

Then calcium goes to bind with subunit c in troponin, conformational changes will take place, that Leads to uncovering of binding sites that are existing on the actin.

Thick and thin filaments



(a) Thick filament (below) and myosin molecule (above)



(b) Portion of a thin filament

Now we will talk about the structure of thick and thin filaments:

Thick filament are mainly composed from **myosin molecules.**

Myosin molecules : myosin tail and two heads, each head has actin binding site to attach with actin and ATP binding site which has ATPase characteristic so it can hydrolyze ATP into ADP and phosphate.

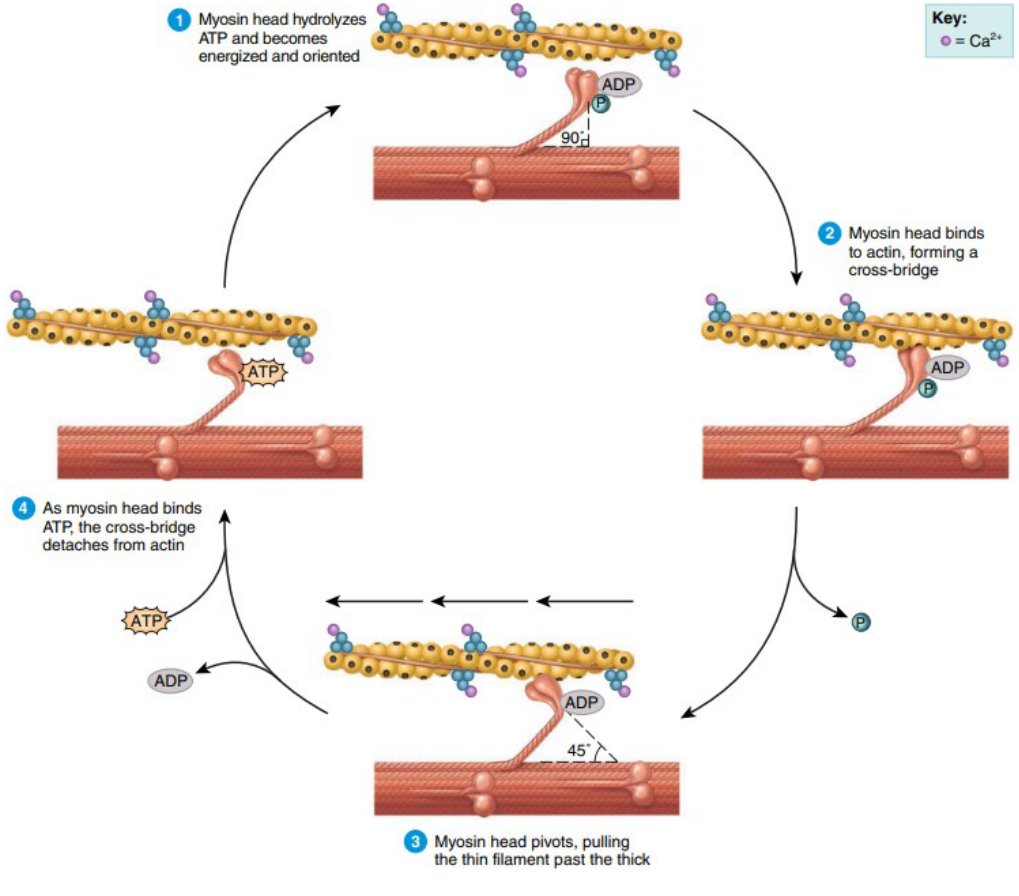
Notice the special orientation in the 3D, this aims to attach with multiple actins in multiple directions.

Actin structure: double stranded of f actin and each molecule has myosin binding site, these sites are usually covered with another type of protein (tropomyosin), troponin has essential role also (calcium binding leads to uncovering of myosin binding sites ….. Regulation of contraction)

Excitation-contraction coupling

- The series of events occurring from the generation of the action potential (AP) in the skeletal muscle fibres to the beginning of muscle tension (binding of myosin with actin) ….. The definition of ***Excitation-contraction coupling*** . (Sandow, 1950)

Contraction cycle



Contraction cycle The cycle and contraction are just theories

- 1. In order to achieve the contraction, the binding of myosin with actin should take place, Before contraction begins, the heads of the cross-bridges bind with ATP. The ATPase activity of the myosin head immediately cleaves the ATP but leaves the cleavage products, ADP plus phosphate ion, bound to the head. In this state, the conformation of the head is such that it extends perpendicularly toward the actin filament but is not yet attached to the actin (the head is energized and oriented in place to bind with actin)
- 2. When the troponin-tropomyosin complex binds with calcium ions (calcium binds with troponin c, then the tropomyosin will have conformational change, active sites on the actin filament are uncovered and the myosin heads then bind with these sites.

Contraction cycle

- 3. The bond between the head of the cross-bridge and the active site of the actin filament causes a conformational change in the head, prompting the head to tilt toward the arm (mid line) of the cross-bridge and providing the power stroke for pulling the actin filament.
- The conformational change enables the filaments to move, the tilting can take place, so myosin filaments can pull the actin with them and that's why it is called sliding filaments mechanism or walk along theory, this mechanism is power stroke because of the pulling of actin.
- The energy that activates the power stroke is the energy already stored, like a "cocked" spring, by the conformational change that occurred in the head when the ATP molecule was cleaved earlier.

Contraction cycle

- 4. Once the head of the cross-bridge tilts, release of the ADP and phosphate ion that were previously attached to the head is allowed. At the site of release of the ADP, a new molecule of ATP binds. This binding of new ATP causes detachment of the head from the actin.
- 5. After the head has detached from the actin, the new molecule of ATP is cleaved to begin the next cycle, leading to a new power stroke. That is, the energy again "cocks" the head back to its perpendicular condition, ready to begin the new power stroke cycle.

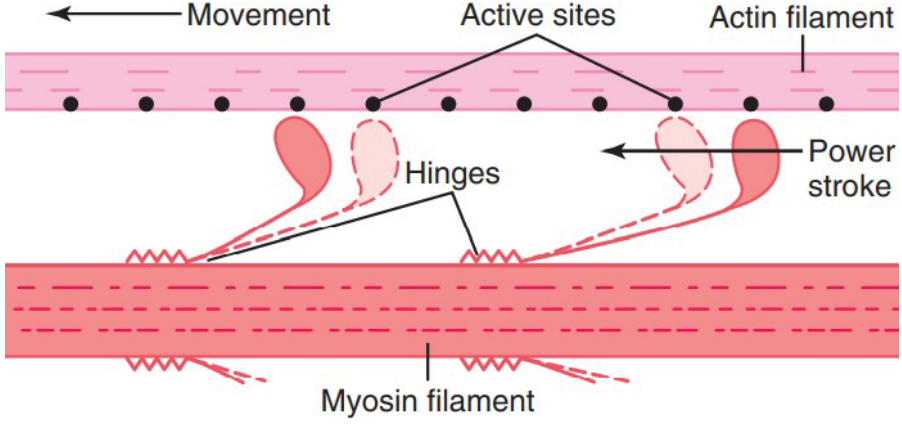
To maintain the contraction, calcium should be available, which will be available when action potential takes place, when the action potential is terminated the calcium will go back to its store in sarcoplasmic reticulum, we need active transport because the conc. Of calcium inside is high (we need calcium pump) and we need ATP for binding and detachment

Clinical connection

- Rigor mortis

Few hours after death, the body gets stiff due to the lack of ATP needed for detachment of myosin head from actin.

Walk-along theory of contraction



Walk-along theory of contraction

- Myosin head tilts toward the arm and to drag the actin filament along with it. This tilt of the head is called the **power stroke**.
- Immediately after tilting, the head then automatically breaks away from the active site (provided energy is available). Next, the head returns to its extended direction. In this position, it combines with a new active site farther down along the actin filament.

Calcium

- The normal resting state concentration (<10–7 molar) of calcium ions in the cytosol that bathes the myofibrils is too little to elicit contraction.
- Therefore, the troponin-tropomyosin complex keeps the actin filaments inhibited and maintains a relaxed state of the muscle.

Calcium

- Full excitation of the T tubule and sarcoplasmic reticulum system causes enough release of calcium ions to increase the concentration in the myofibrillar fluid to as high as 2 × 10–4 molar concentration, a 500-fold increase, which is about 10 times the level required to cause maximum muscle contraction.

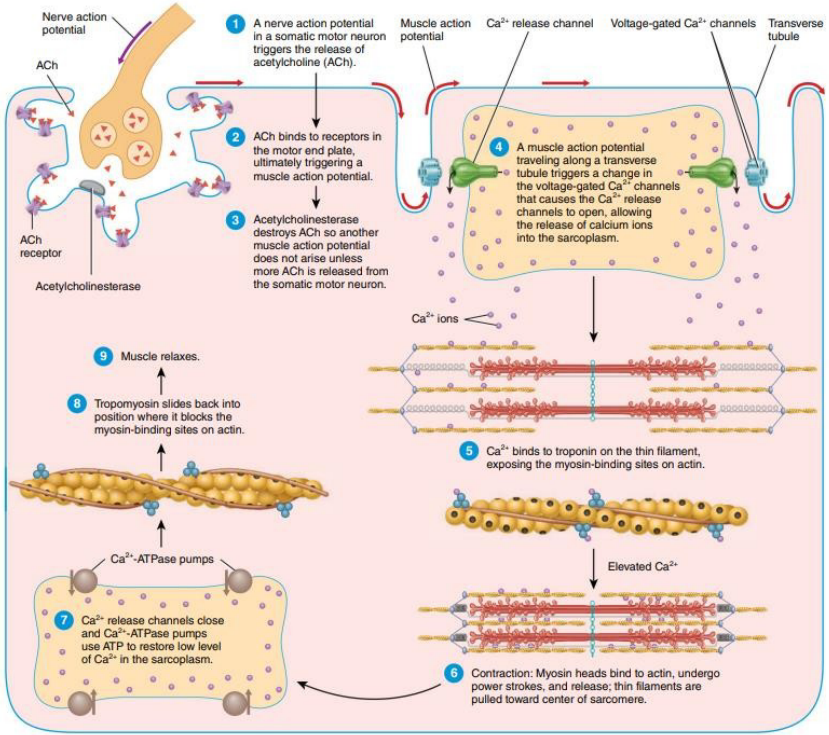
Calcium pump

- Once the calcium ions have been released from the sarcoplasmic tubules and have diffused among the myofibrils, muscle contraction continues as long as the calcium ion concentration remains high.

- However, a continually active calcium pump located in the walls of the sarcoplasmic reticulum pumps calcium ions away from the myofibrils back into the sarcoplasmic tubules.

Calcium pump

- This pump can concentrate the calcium ions about 10,000-fold inside the tubules. In addition, inside the reticulum is a protein called calsequestrin that can bind up to 40 times more calcium.
- The total duration of this calcium “pulse” in the usual skeletal muscle fiber lasts about 1/20 of a second, although it may last several times as long in some fibers and several times less in others.


Nerve action potential
ACh
ACh receptor
Acetylcholinesterase
1 A nerve action potential in a somatic motor neuron triggers the release of acetylcholine (ACh).
2 ACh binds to receptors in the motor end plate, ultimately triggering a muscle action potential.
3 Acetylcholinesterase destroys ACh so another muscle action potential does not arise unless more ACh is released from the somatic motor neuron.
Muscle action potential
Ca2+ release channel
Voltage-gated Ca2+ channels
Transverse tubule
4 A muscle action potential traveling along a transverse tubule triggers a change in the voltage-gated Ca2+ channels that causes the Ca2+ release channels to open, allowing the release of calcium ions into the sarcoplasm.
Ca2+ ions
5 Ca2+ binds to troponin on the thin filament, exposing the myosin-binding sites on actin.
Elevated Ca2+
6 Contraction: Myosin heads bind to actin, undergo power strokes, and release; thin filaments are pulled toward center of sarcomere.
7 Ca2+ release channels close and Ca2+-ATPase pumps use ATP to restore low level of Ca2+ in the sarcoplasm.
Ca2+-ATPase pumps
8 Tropomyosin slides back into position where it blocks the myosin-binding sites on actin.
9 Muscle relaxes.

Mechanism of muscle contraction

- 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 “acetylcholine-gated” cation channels through protein molecules floating in the membrane.

Mechanism of muscle contraction

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

Mechanism of muscle contraction

- 6. The action potential depolarizes the muscle membrane, and much of 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.

Mechanism of muscle contraction

- 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.
- 8. After a fraction of a second, the calcium ions are pumped back into the sarcoplasmic reticulum by a Ca++ 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.

Processes require energy in muscle fiber

- 1. Most of the energy required for muscle contraction is used to actuate the walk-along mechanism by which the cross-bridges pull the actin filaments.
- 2. pumping calcium ions from the sarcoplasm into the sarcoplasmic reticulum after the contraction is over.
- 3. pumping sodium and potassium ions through the muscle fiber membrane to maintain an appropriate ionic action environment for propagation of muscle fiber potentials.

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. Before phosphocreatine we have very little amount of ATP stored in the cells in the sarcoplasm (1 or 2 seconds)
- Therefore, phosphocreatine is instantly cleaved, and its released energy causes bonding of a new phosphate ion to ADP to reconstitute the ATP. We need kinase for this process which is stimulated by high conc. Of ADP

Sources of energy for muscle contraction

- However, the total amount of phosphocreatine in the muscle fiber is also small—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.

Sources of energy for muscle contraction

- 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.

Sources of energy for muscle contraction

- The importance of this glycolysis mechanism is twofold:
- 1. 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.
- 2. 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.

Sources of energy for muscle contraction

- However, so many end products of glycolysis accumulate in the muscle cells that glycolysis also loses its capability to sustain maximum muscle contraction after about 1 minute.

- In the absence of oxygen, pyruvate will be converted to lactic acid the will accumulate in the muscles causing their fatigue.

Sources of energy for muscle contraction

- The third and final source of energy is **oxidative metabolism**, which means combining oxygen with the end products of glycolysis and with various other cellular foodstuffs to liberate ATP. Needing oxidative metabolism means needing a lot of mitochondria.
- More than 95 percent of all energy used by the muscles for sustained, long-term contraction is derived from oxidative metabolism. But it is slow process

Characteristics of slow fibers

- **Slow Fibers (Type 1, Red Muscle).**
- 1. Slow fibers are smaller than fast fibers.
- 2. Slow fibers are also innervated by smaller nerve fibers.
- 3. Compared with fast fibers, slow fibers have a more extensive blood vessel system and more capillaries to supply extra amounts of oxygen.

Characteristics of slow fibers

- 4. Slow fibers have greatly increased numbers of mitochondria to support high levels of oxidative metabolism.
- 5. Slow fibers contain large amounts of myoglobin, an iron-containing protein similar to hemoglobin in red blood cells. Myoglobin combines with oxygen and stores it until needed,which also greatly speeds oxygen transport to the mitochondria. The myoglobin gives the slow muscle a reddish appearance and hence the name red muscle.

Characteristics of fast fibers

- **Fast Fibers (Type II, White Muscle).**
- 1. Fast fibers are large for great strength of contraction.
- 2. Anextensive sarcoplasmic reticulum is present for rapid release of calcium ions to initiate contraction. Because the muscles and fibers are larger.
- 3. Large amounts of glycolytic enzymes are present for rapid release of energy by the glycolytic process.

Characteristics of fast fibers

- 4. Fast fibers have a less extensive blood supply than do slow fibers because oxidative metabolism is of secondary importance.
- 5. Fast fibers have fewer mitochondria than do slow fibers, also because oxidative metabolism is secondary. A deficit of red myoglobin in fast muscle gives it the name white muscle.

Types of muscle fibers

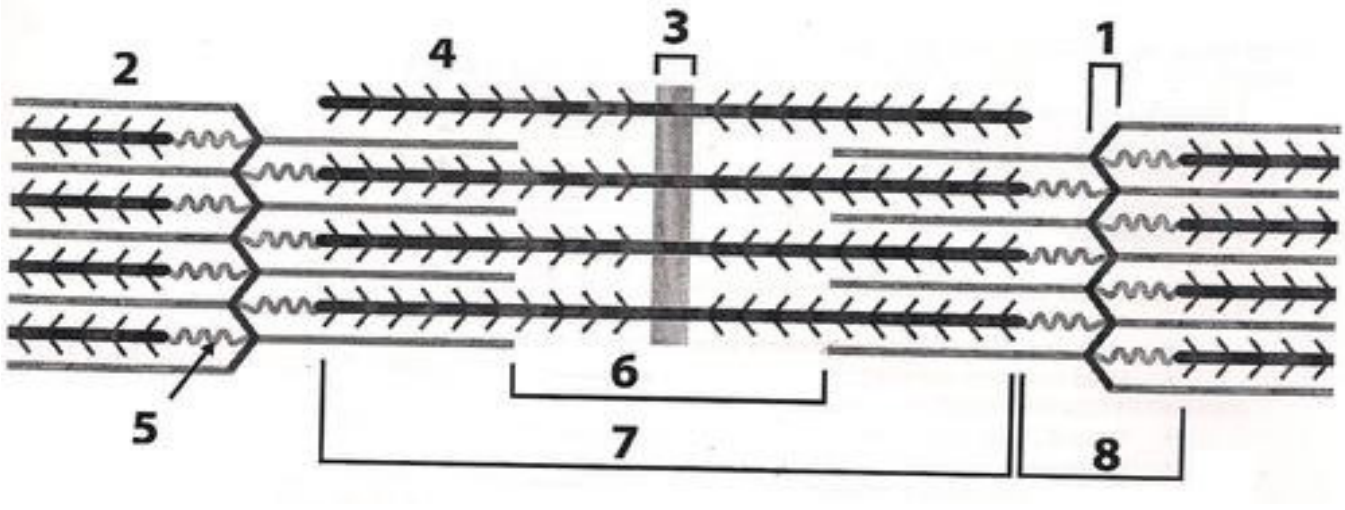
there are many classifications for muscle fiber types, this table is from Tortora textbook, let's focus on fast vs slow fibers only as per Gyton.

	SLOW OXIDATIVE (SO) FIBERS	FAST OXIDATIVE–GLYCOLYTIC (FOG) FIBERS	FAST GLYCOLYTIC (FG) FIBERS
STRUCTURAL CHARACTERISTIC			
Myoglobin content	Large amount.	Large amount.	Small amount.
Mitochondria	Many.	Many.	Few.
Capillaries	Many.	Many.	Few.
Color	Red.	Red-pink.	White (pale).
FUNCTIONAL CHARACTERISTIC			
Capacity for generating ATP and method used	High, by aerobic respiration.	Intermediate, by both aerobic respiration and anaerobic glycolysis.	Low, by anaerobic glycolysis.
Rate of ATP hydrolysis by myosin ATPase	Slow.	Fast.	Fast.
Contraction velocity	Slow.	Fast.	Fast.
Fatigue resistance	High.	Intermediate.	Low.
Creatine kinase	Lowest amount.	Intermediate amount.	Highest amount.
Glycogen stores	Low.	Intermediate.	High.
Order of recruitment	First.	Second.	Third.
Location where fibers are abundant	Postural muscles such as those of neck.	Lower limb muscles.	Extraocular muscles.
Primary functions of fibers	Maintaining posture and aerobic endurance activities.	Walking, sprinting.	Rapid, intense movements of short duration.

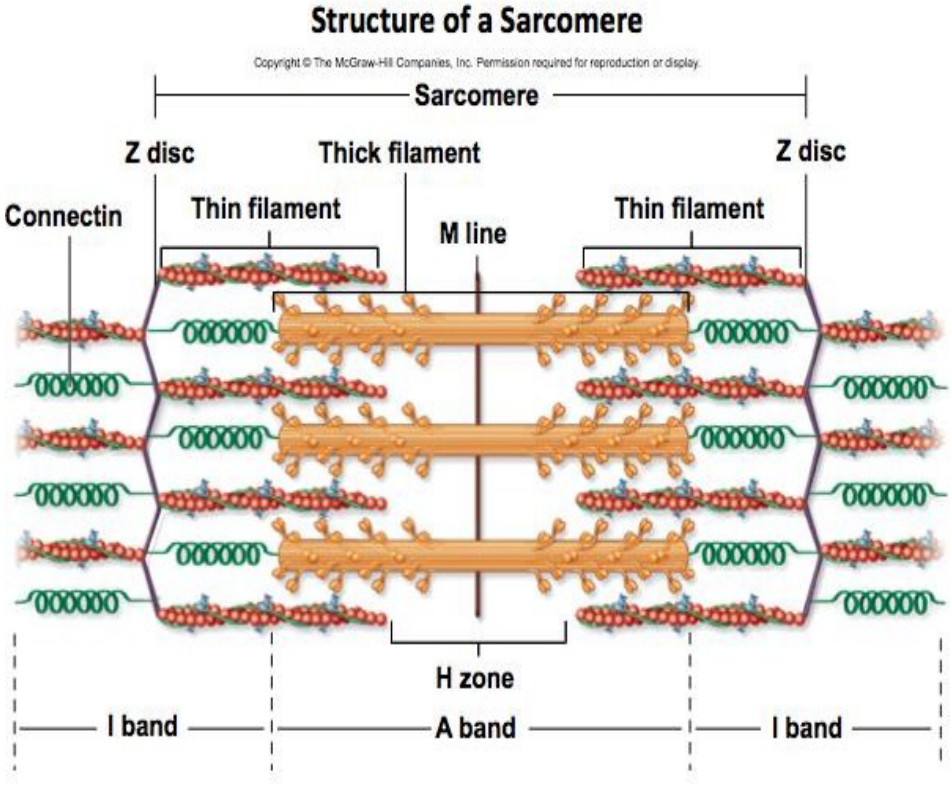
Types of muscle fibers

- Every muscle of the body is composed of a mixture of fast and slow muscle fibers, with still other fibers gradated between these two extremes.
- Muscles that react rapidly, including the anterior tibialis, are composed mainly of "**fast**" **fibers** with only small numbers of the slow variety. Like in ocular muscles.
- Conversely, muscles such as soleus that respond slowly but with prolonged contraction are composed mainly of "**slow**" **fibers**. Muscles of balance.

Name it!



Sarcomeres which is the structural basic unit of muscles, use the photo in the following slide to ensure what the numbers refer to ;)



There are proteins that are very important in fixing actin and myosin in their places and ensuring the contraction as a whole unit at a time.

The borders of sarcomeres are the z lines

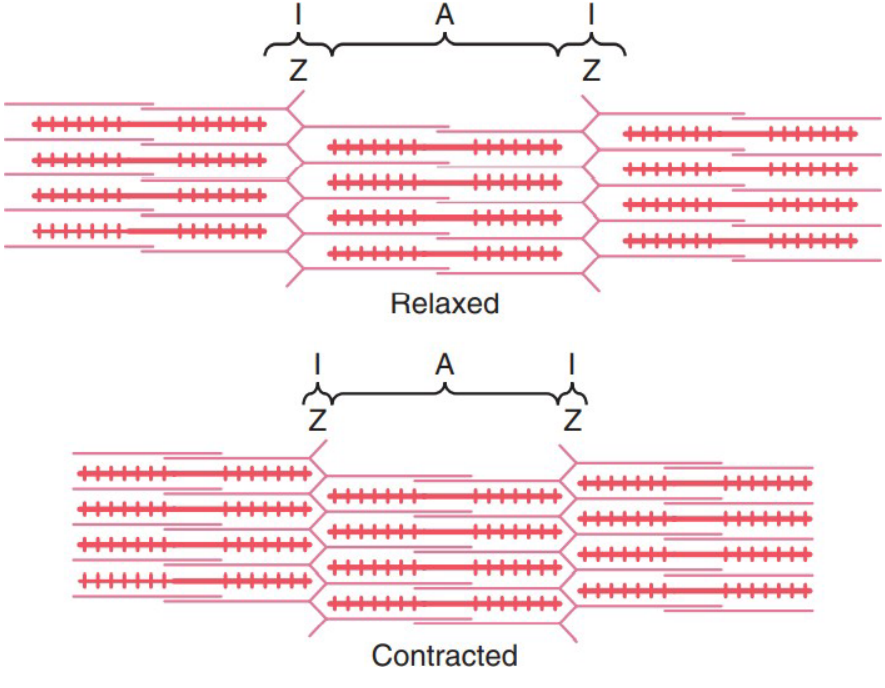
I band contain actin filaments only.

Contraction doesn't affect the length of A band

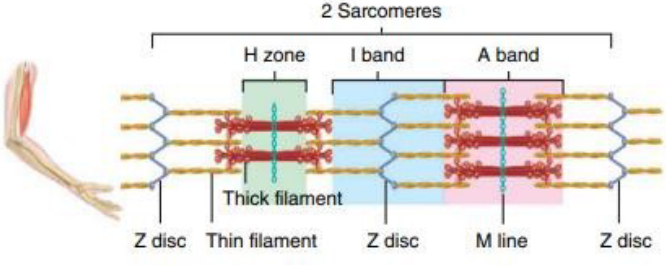
I band will be shorter, H zone will do that also

Sarcomere as whole will be shortened

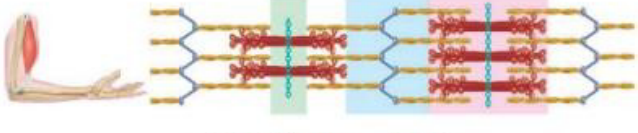
The sliding filament mechanism



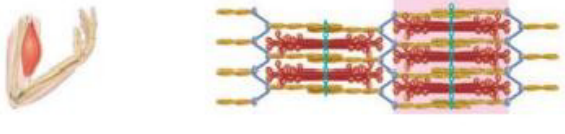
Sarcomere changes during contraction



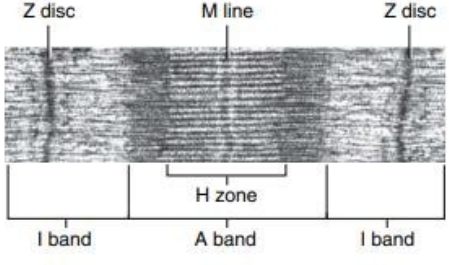
(a) Relaxed muscle



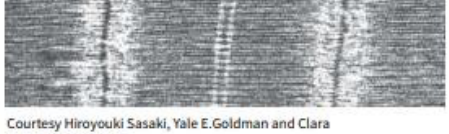
(b) Partially contracted muscle



(c) Maximally contracted muscle



E microscope



Courtesy Hiroyouki Sasaki, Yale E.Goldman and Clara Franzini-Armstrong

- The greater the number of cross-bridges in contact with the actin filament at any given time, the greater the force of contraction.

Characteristics of whole muscle contraction

- The human body has many sizes of skeletal muscles, from stapedius muscle in the middle ear up to quadriceps.
- The energetics of muscle contraction vary considerably from one muscle to another. Therefore, mechanical characteristics of muscle contraction differ among muscles.

Guyton listed quadriceps as the largest muscle, however, other resources consider Gluteus Maximus. After consulting Dr Heba Kalbouneh, she kindly explained that quadriceps is the largest surface area wise, and Gluteus Maximus thickness wis. Anyway, this will never e a physiology question, just because few asked about it.

#physiology

Skeletal Muscle Contraction

Test your self

One of the following processes require energy in the muscle fiber:

a. Release of the Ca ions from the sarcoplasmic reticulum.
b. Pulling the actin filament toward the M line by myosin Head.
c. Require for entering of Na to the cell.
d. Uncovering the myosin binding site in the actin filament.

ANSWER: B

The first source of energy that reconstitute the ATP is:

a. Oxidative phosphorylation
b. Aerobic glycolysis
c. Anaerobic glycolysis
d. Phosphocreatine

ANSWER:D

Which of the following is a characteristic of fast fibers:

a. Contain less blood supply compared with the slow fibers.
b. Depending on the oxidative phosphorylation as source of energy.
c. Have low rate of ATP hydrolysis.
d. Have high resistant to fatigue.

ANSWER: A

Regarding type 1 and type 2 fibers, which one is wrong:

a. Type 1 fibers contain larger amount of iron-containing proteins than type 2 fibers.
b. Type 2 fibers depend on glycolysis as source of energy.
c. Type 2 fibers contain large amount of glycolytic enzymes.
d. All of the following are true

ANSWER: D

Thank you