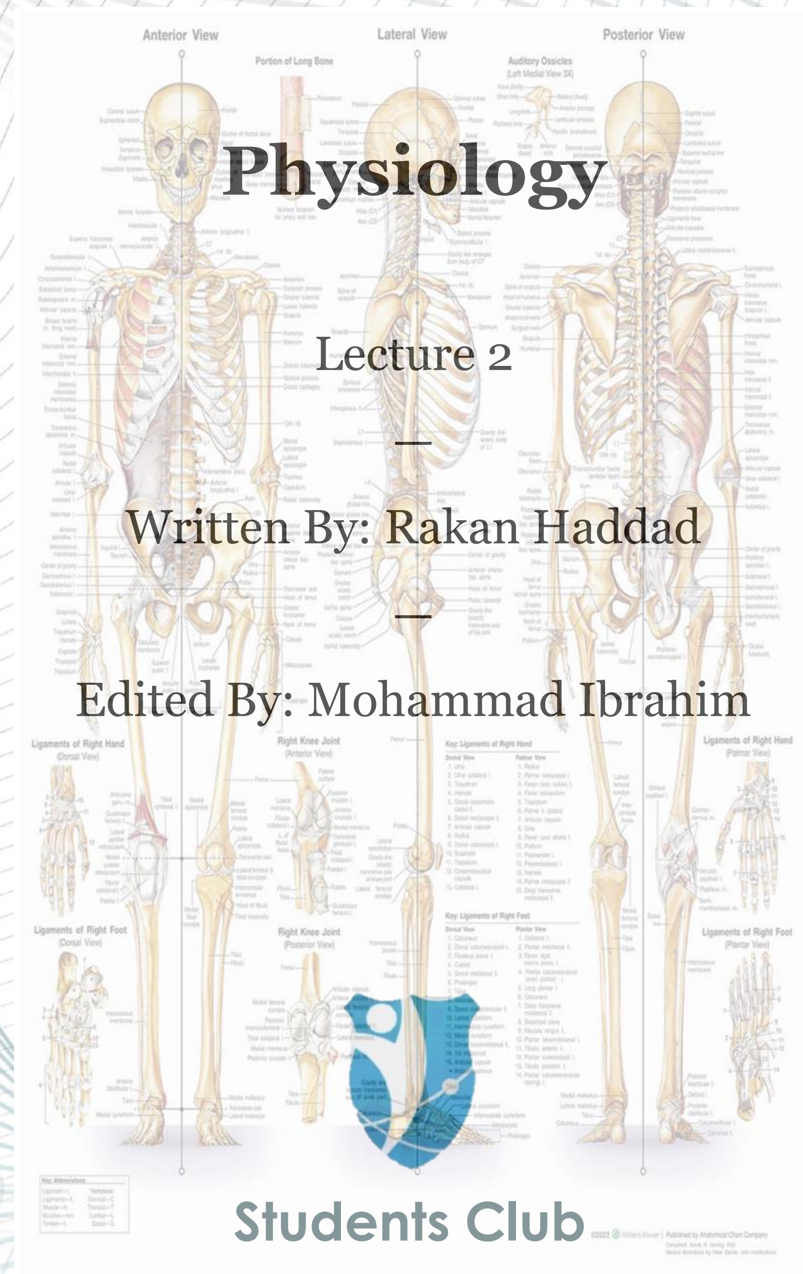
MUSCULOSKELETAL SYSTEM



Physiology

Lecture 2

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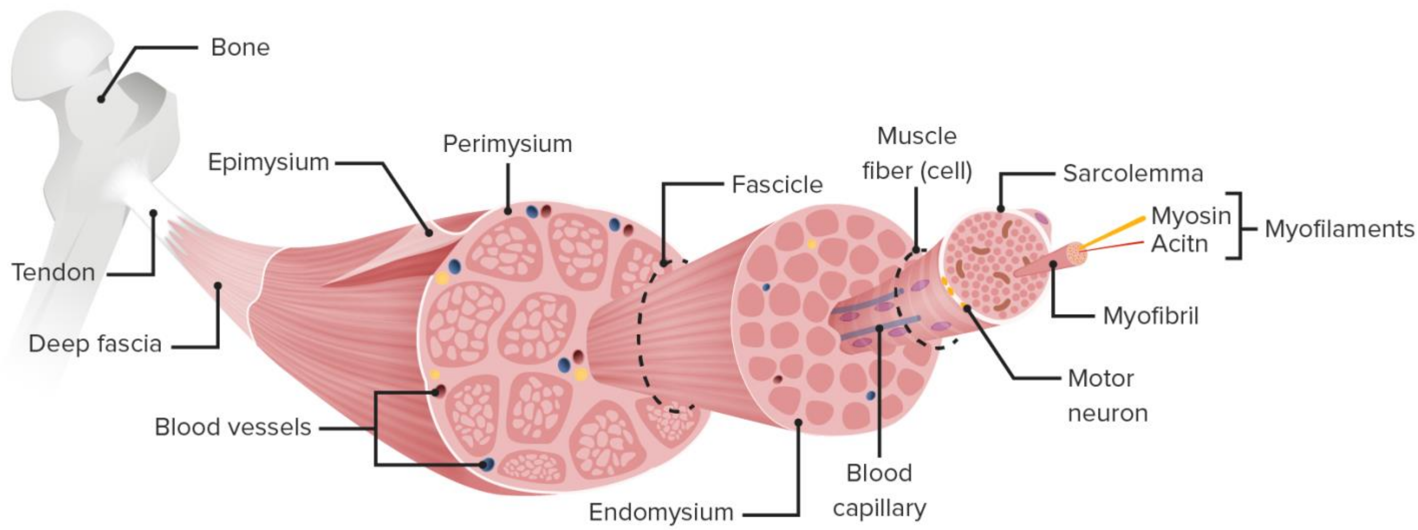
Students Club

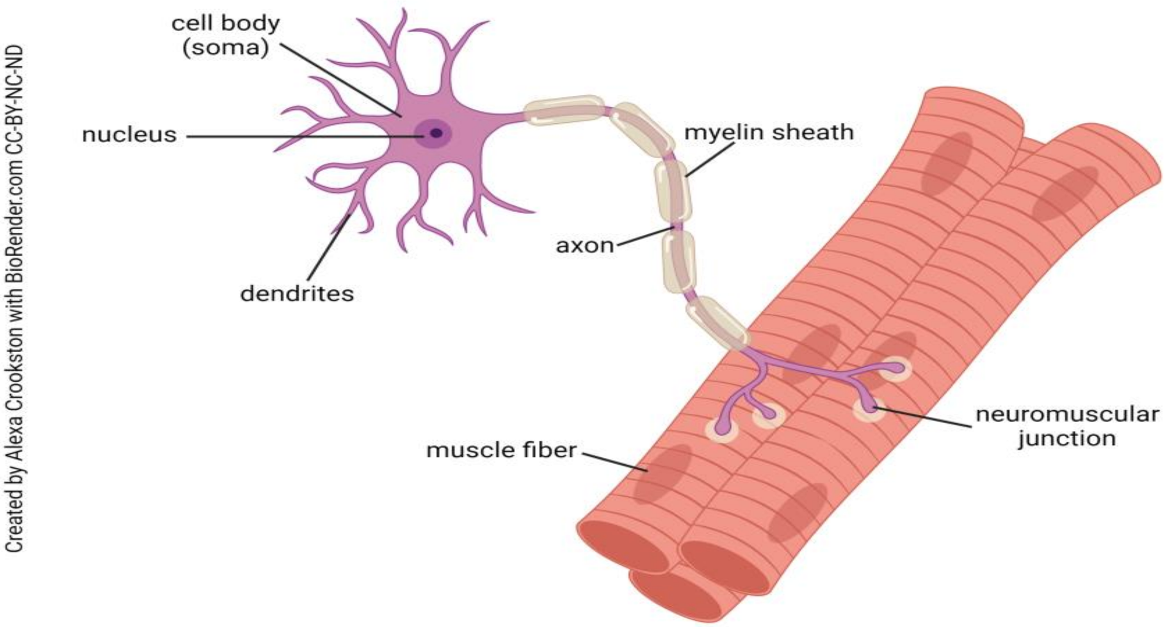
The Neuromuscular Junction

- The doctor began by explaining what muscles are so let's take a closer look at what muscles look like and understand that structure thoroughly!



- As we can see, the huge muscle structure we all know is in fact made of different building units that are really small!
- Actin & Myosin (Myofilaments) → Myofibril → Muscle Fiber → Muscle
- The basic building unit of muscles are actually called sarcomeres, they are the actin and myosin microfilaments in addition to other proteins that we will talk about later on.

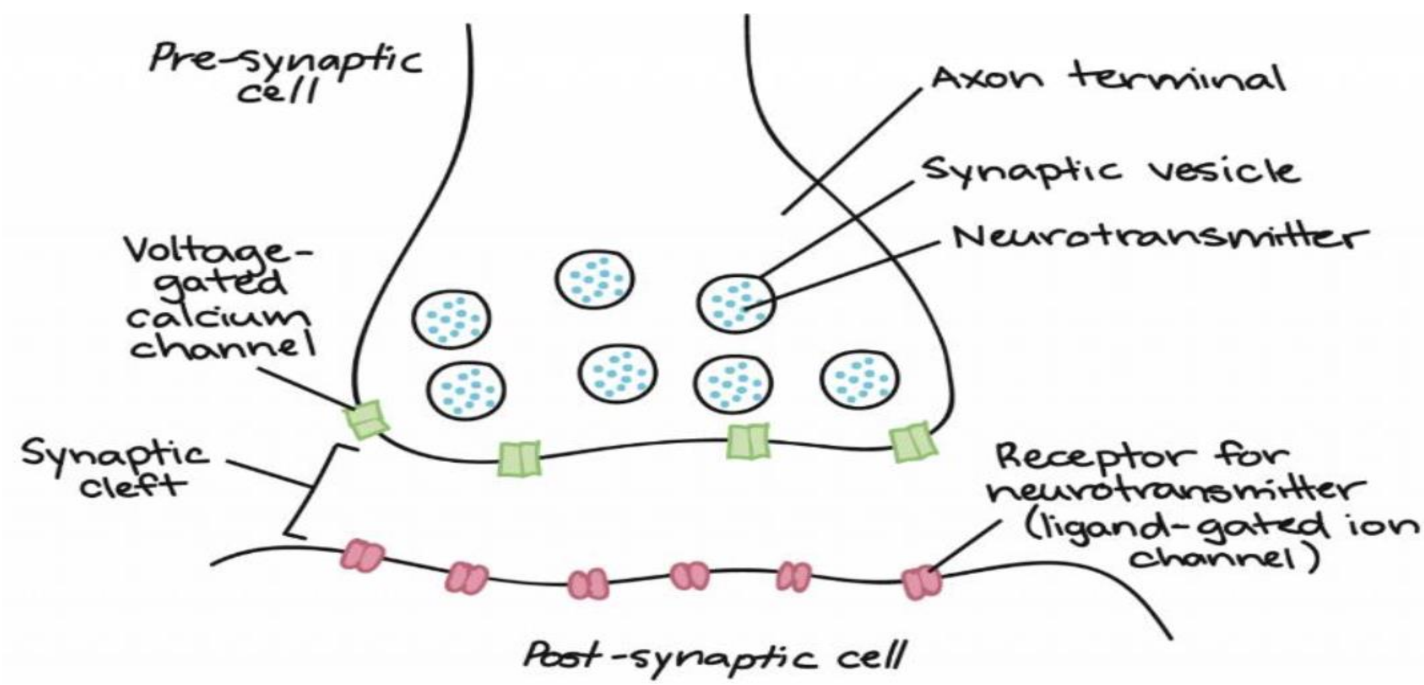
- So, in this lecture we will talk about what's called a neuromuscular junction (NMJ). It is simply the junction that arises from the synapse of a neuron with a muscle fiber, and usually this synapse occurs in the middle of the muscle fiber, so it allows the action potential to travel on all the muscle fiber with ease just as the picture below shows.



- Skeletal muscle fibers are innervated by large, myelinated nerve fibers that originate from large motoneurons in the anterior horns of the spinal cord.
- Each nerve fiber, after entering the muscle belly, normally branches and stimulates from three to several hundred skeletal muscle fibers.
- Each nerve ending makes a junction, called the neuromuscular junction, with the muscle fiber near its midpoint.
- The action potential initiated in the muscle fiber by the nerve signal travels in both directions toward the muscle fiber ends.

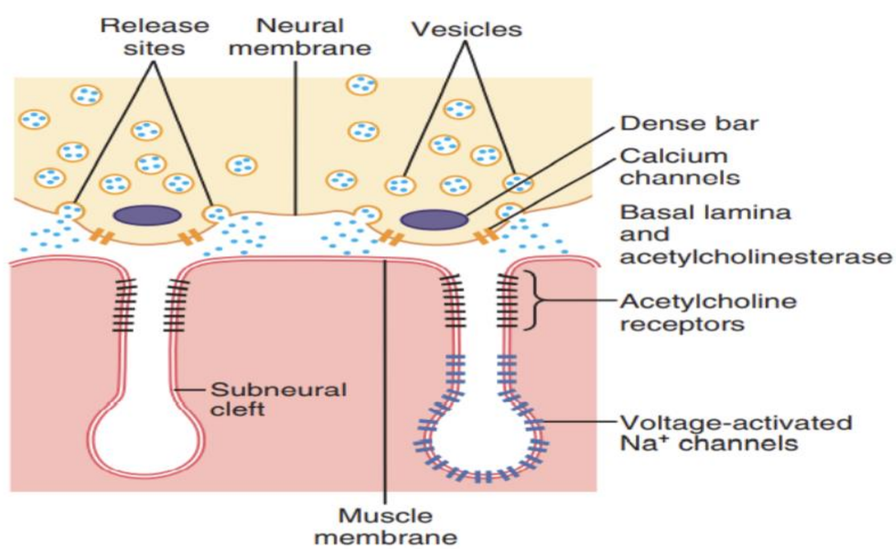
- But how does this signal manage to travel from a neuron to these muscles? There definetely must be neurotransmitters that have the ability to convey the signal that starts in the neuron to the muscle so it either contracts or relaxes depending on the stimulus.

- The main neurotransmitter that causes the action potential to reach our muscle fibers is Acetylcholine. This neurotransmitter is really important as it has the ability to bind to special ion channels on the muscle fiber membrane called Ligand-Gated ion channels.
- In the axon terminal are many mitochondria that supply ATP, the energy source that is used for synthesis of an excitatory transmitter, acetylcholine.
- The acetylcholine in turn excites the muscle fiber membrane.
- Acetylcholine is synthesized in the cytoplasm of the terminal, but it is absorbed rapidly into many small synaptic vesicles which are normally in the terminals of a single end plate.
- This excitation is really important as it allows the membrane voltage to stray away from the resting potential by allowing for sodium ions to enter making the muscle fiber membrane potential change from (-80 to -90mv) to 0 mv which allows for voltage-gated sodium ion channels to open which allows for the full depolarization of the muscle fiber and for the

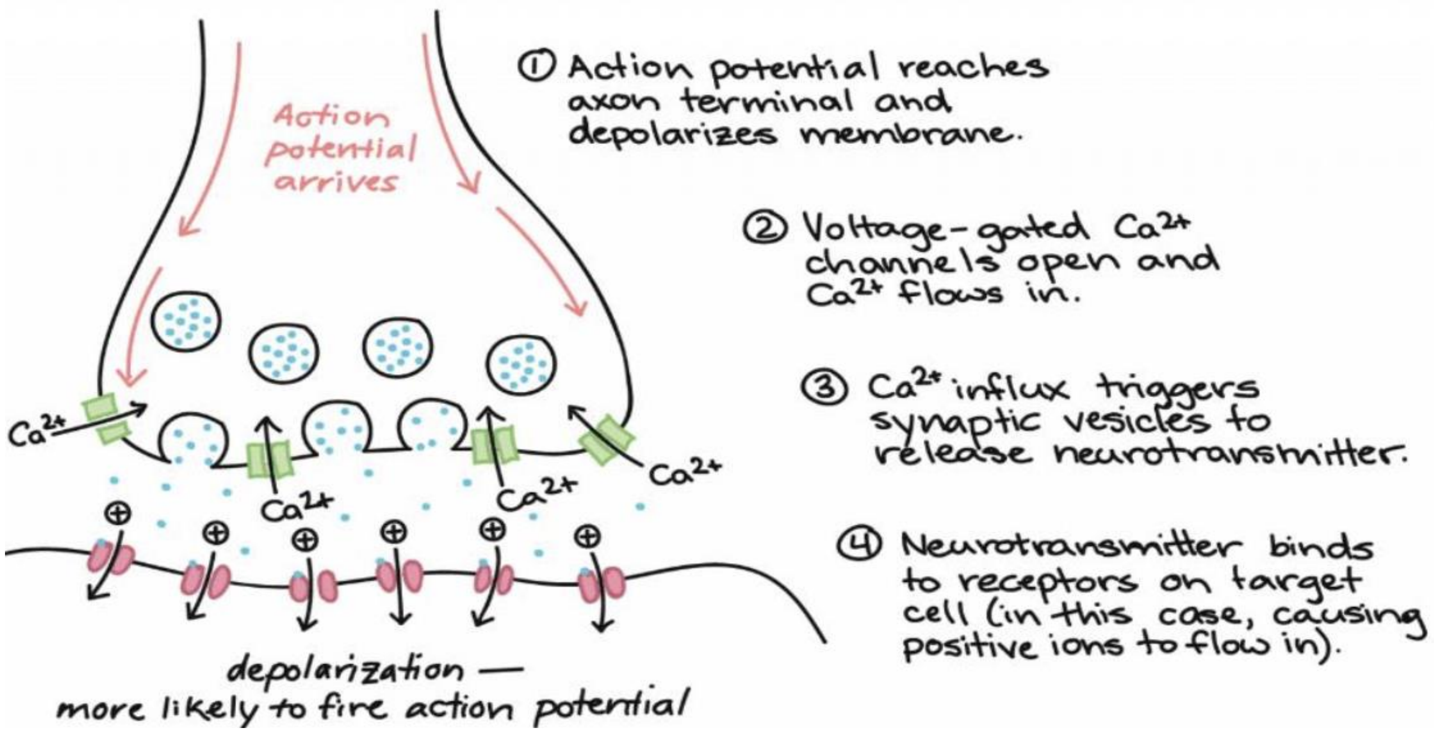


action potential to take place.

- Let's further explain this process, how does the neurotransmitter (Ach) exit the neuron terminals? We can't forget the presence of voltage gated calcium channels, when they open they allow for ACh to exit from the presynaptic neuron and bind to their receptors. Now, there are structures knows as linear dense bars which are structures on the inside of the presynaptic terminal where the actual ACh vesicles are brought to so they leave.
- To each side of each dense bar are protein particles that penetrate the neural membrane; these are voltage-gated calcium channels.
- When an action potential spreads over the terminal, these channels open and allow calcium ions to diffuse from the synaptic space to the interior of the nerve terminal.
- Usually the ACh vesicles are anchored to the cytoskeleton in the presynaptic terminal via proteins called synapsin. The calcium ions are believed to activate Ca++/Calmodulin dependent protein kinase which phosphorylates synapsin proteins which causes the vesicles to be freed from the cytoskeleton and move to the active zone of the presynaptic neural membrane adjacent to the dense bars. The vesicles then dock at release sites, fuse with neural membrane, and empty Ach into the synaptic space via exocytosis.

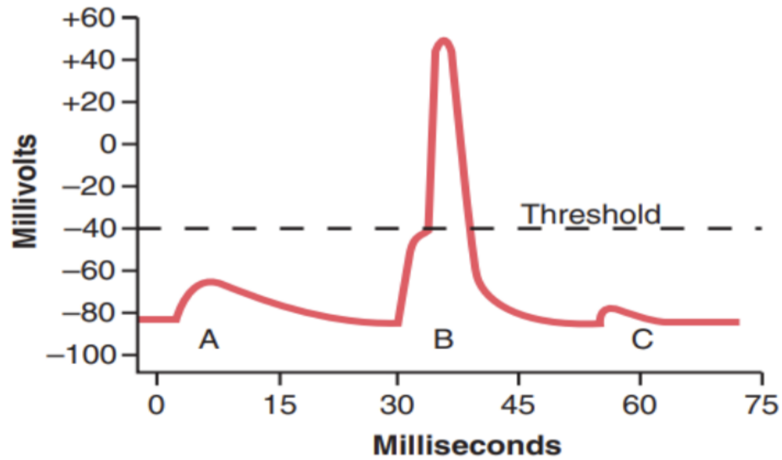


- Now returning to the postsynaptic membrane, Acetylcholine receptors in the muscle fiber membrane are acetylcholine-gated ion channels.
- They are located almost entirely near the mouths of the sub-neural clefts lying immediately below the dense bar areas, where the acetylcholine is emptied into the synaptic space.

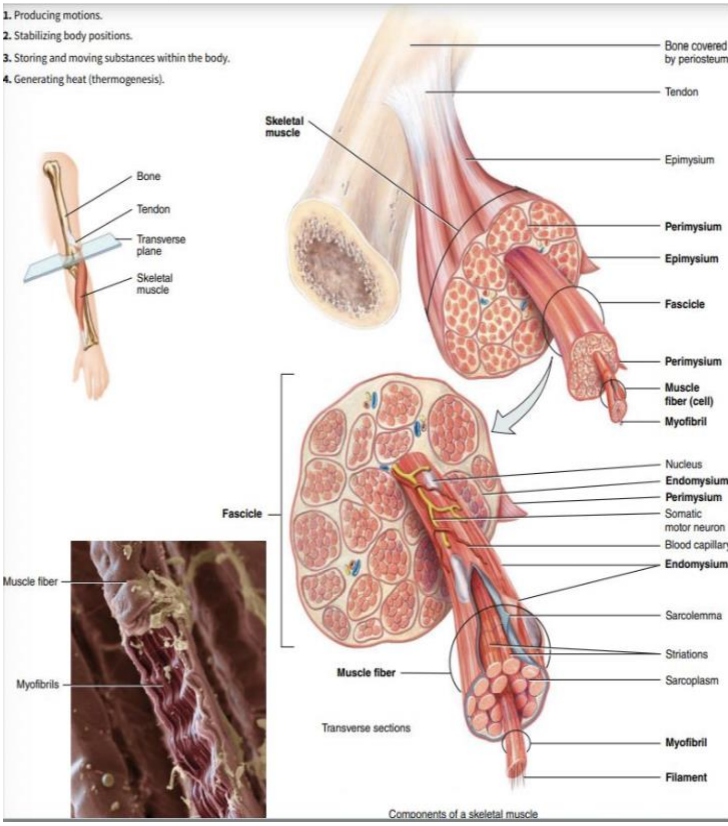


- The principal effect of opening the acetylcholine-gated channels is to allow large numbers of sodium ions to pour to the inside of the fiber, carrying with them large numbers of positive charges.
- This action creates a local positive potential change inside the muscle fiber membrane, called the **end plate potential.**
- A sudden increase in nerve membrane potential of more than 20 to 30 millivolts is normally sufficient to initiate more and more sodium channel opening, thus initiating an action potential at the muscle fiber membrane.

End-plate potential



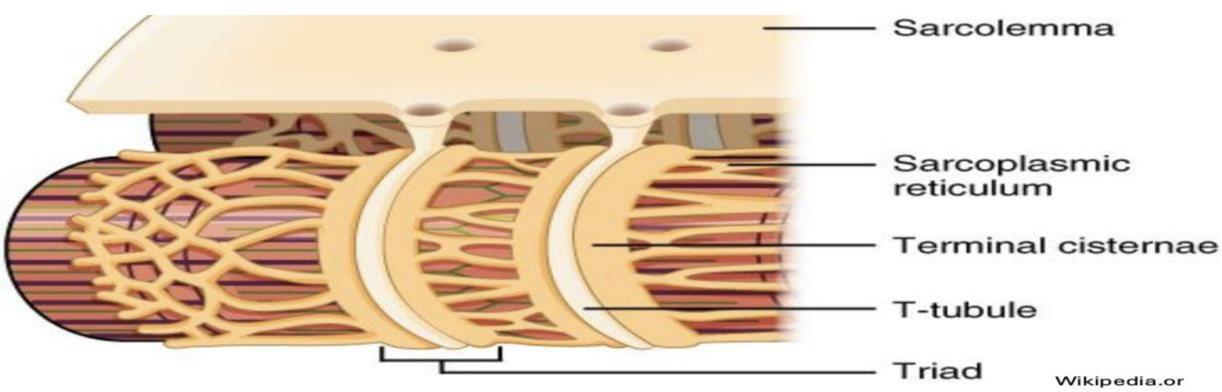
- Initiation and conduction of action potentials in nerve fibers applies equally to skeletal muscle fibers, except for quantitative differences. Some of the quantitative aspects of muscle potentials are as follows:
- 1. Resting membrane potential is about −80 to −90 millivolts in skeletal fibers—the same as in large myelinated nerve fibers. (Usually nerves have. -70mv).
- 2. Duration of action potential is 1 to 5 milliseconds in skeletal muscle—about five times as long as in large myelinated nerves.
- 3. Velocity of conduction is 3 to 5 m/sec—about 1/13 the velocity of conduction in the large myelinated nerve fibers that excite skeletal muscle
- The acetylcholine, once released into the synaptic space, continues to activate the acetylcholine receptors as long as the acetylcholine persists in the space. However, it is removed rapidly by two means:
- (1) Most of the acetylcholine is destroyed by the enzyme acetylcholinesterase, which is in the synaptic space. It destroys acetylcholine a few milliseconds after it has been released from the synaptic vesicles.
- (2) a small amount of acetylcholine diffuses out of the synaptic space and is then no longer available to act on the muscle fiber membrane.
- The short time that the acetylcholine remains in the synaptic space—a few milliseconds at most—normally is sufficient to excite the muscle fiber. Then the rapid removal of the acetylcholine prevents continued muscle re-excitation.



Skeletal muscle

- The Physiological anatomy of skeletal muscles

- In 98%of muscle fibers in skeletal muscles, each fiber is innervated by one nerve ending, located near the middle of the fiber.
- Each muscle fiber contains several hundred to several thousand **myofibrils**.
- Each myofibril is composed of thousands of **myosin and actin filaments.**



Wikipedia.org

- The **sarcoplasm** contains large quantities of potassium, magnesium, and phosphate, plus multiple protein enzymes. Also present are tremendous numbers of mitochondria that lie parallel to the myofibrils.
- The **sarcoplasmic reticulum** has a special organization that is extremely important in regulating calcium storage, release, and reuptake and therefore muscle contraction.

• The skeletal muscle fiber is so large that action potentials spreading along its surface membrane cause almost no current flow deep within the fiber.

•Maximum muscle contraction, however, requires the current to penetrate deeply into the muscle fiber to the vicinity of the separate myofibrils.

- This penetration is achieved by transmission of action potentials along transverse tubules (T tubules) that penetrate all the way through the muscle fiber from one side of the fiber to the other.
- The T tubule action potentials cause release of calcium ions inside the muscle fiber in the immediate vicinity of the myofibrils, and these calcium ions then cause contraction. This overall process is called excitation- contraction coupling.
- Also, where the T tubules originate from the cell membrane, they are open to the exterior of the muscle fiber. Therefore, they communicate with the extracellular fluid surrounding the muscle fiber and contain extracellular fluid in their lumens.

Sarcoplasmic reticulum is composed of two major parts:

• (1) large chambers called terminal cisternae that abut the T tubules.

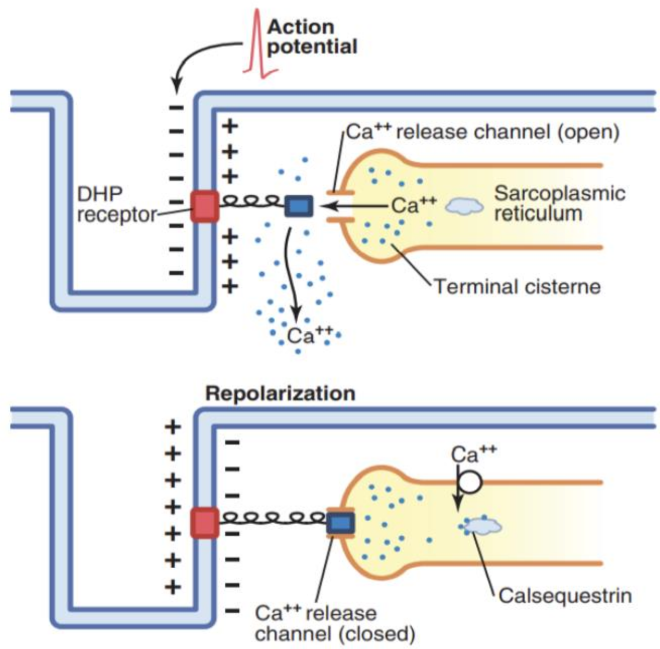
• (2) long longitudinal tubules that surround all surfaces of the actual contracting Myofibrils.

Excitation of skeletal muscle

- The action potential of the T tubule causes current flow into the sarcoplasmic reticular cisternae where they abut the T tubule.

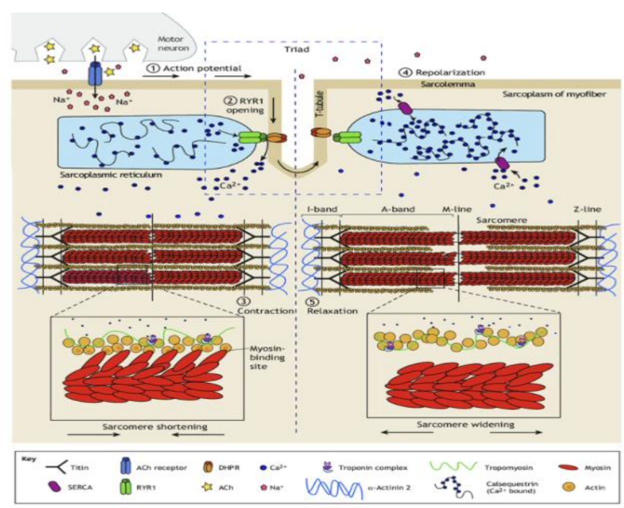
- As the action potential reaches the T tubule, the voltage change is sensed by **dihydropyridine receptors (DHP)** that are linked to calcium release channels, also called **ryanodine receptor channels (RYR)**, in the adjacent sarcoplasmic reticular cisternae.

Calcium release from SR



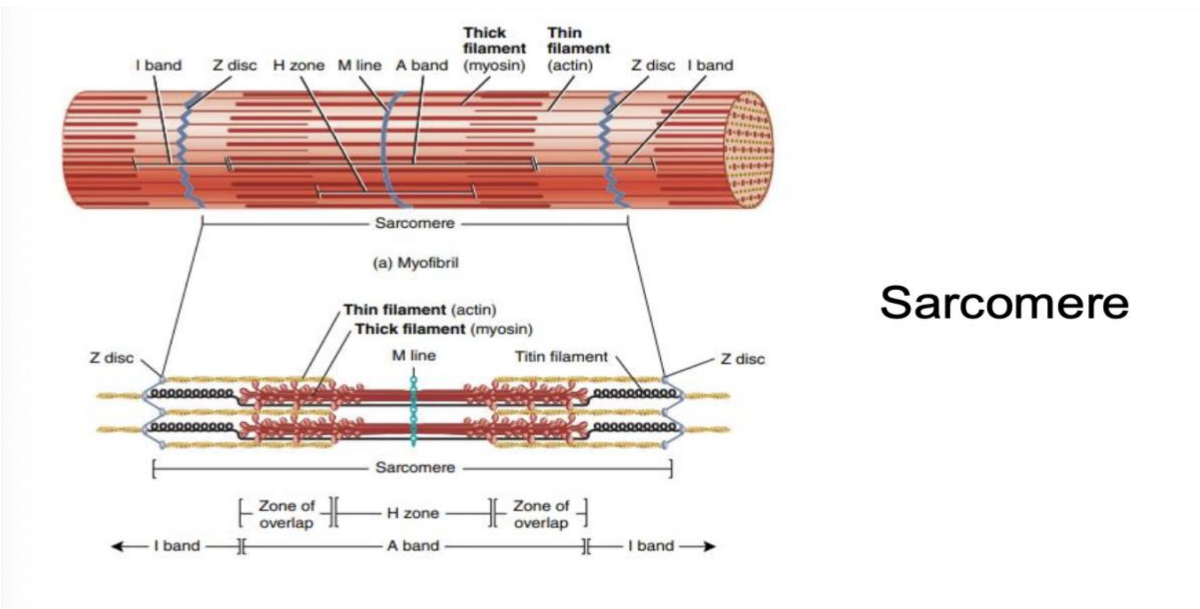
- Activation of dihydropyridine receptors triggers the opening of the calcium release channels in the cisternae, as well as in their attached longitudinal tubules. These channels remain open for a few milliseconds, releasing calcium ions into the sarcoplasm surrounding the myofibrils and causing contraction.

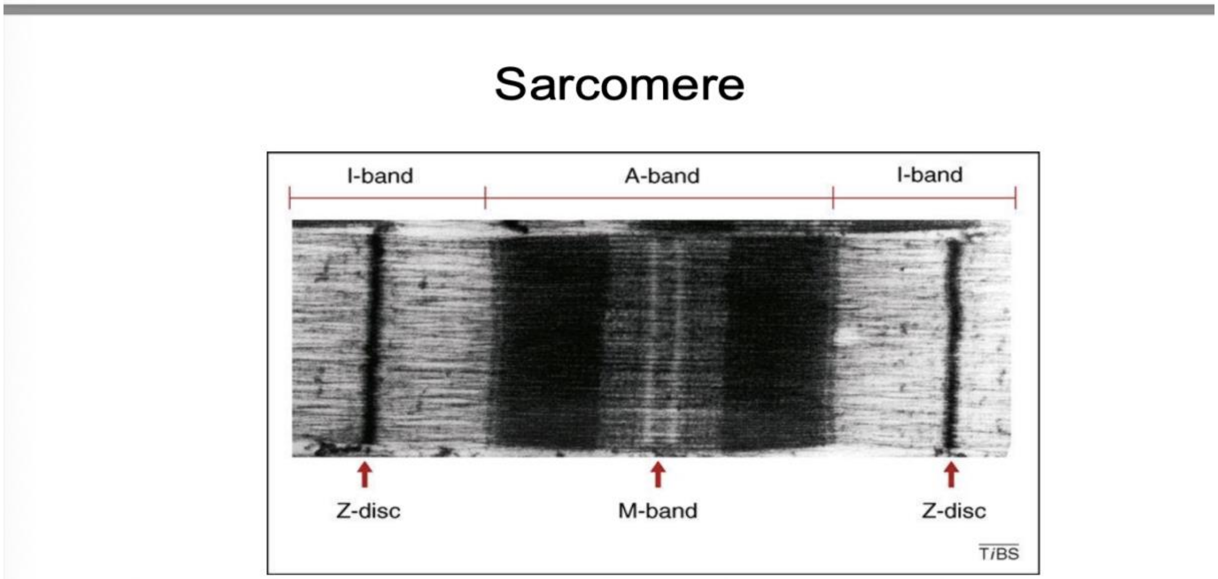
Calcium release from SR



Fusto et al. The use of models to understand core myopathies, 2019.

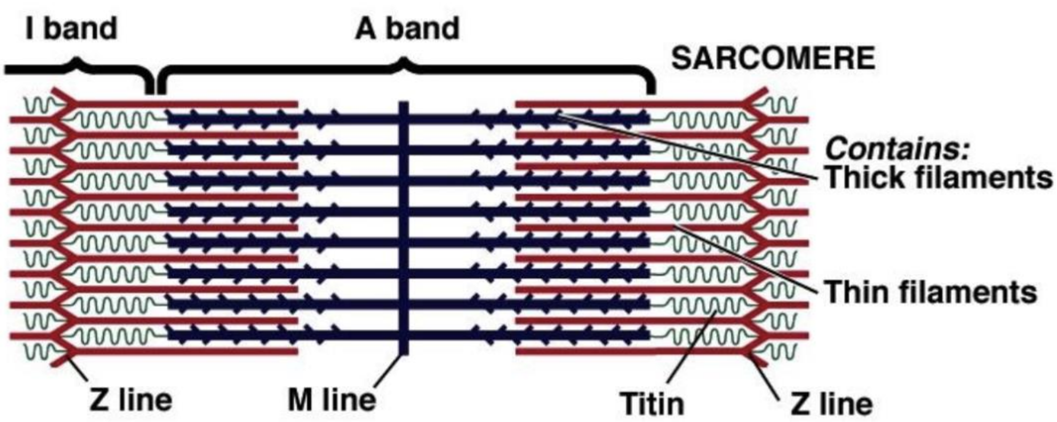
- Whats the deal with all this calcium being secreted? Wht is it doing? Here we will further understand but lets first look deeper at what muscles are,,, Remember the simplest unit we talked about… Sarcomeres! This is where I can see the contraction starting! So, lets understand how that happens.





Pinotsis et al. Terminal assembly of sarcomeric filaments by intermolecular beta-sheet formation, 2009.

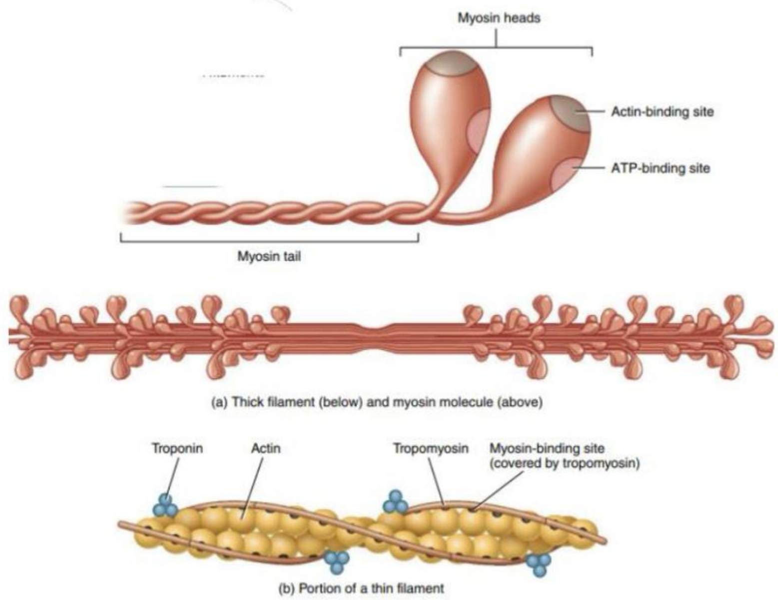
Organization of myofilaments



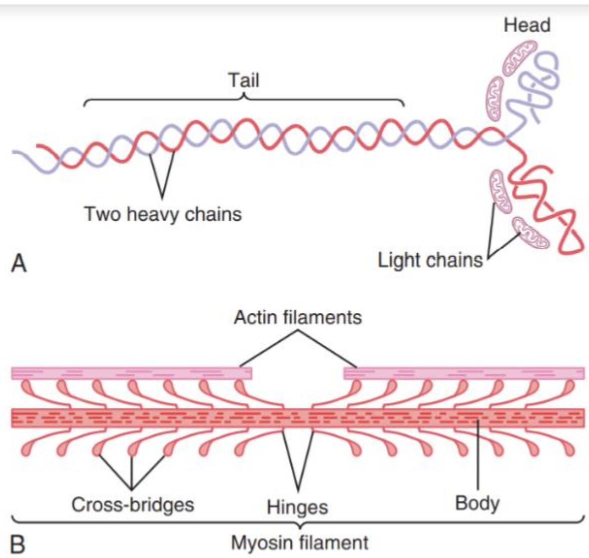
- What am I looking at?
  1. I band: ONLY has actin.
  2. A band: Has both fibers (Actin & Myosin).
  3. Z line/disc: Borders of one sarcomere.
  4. H zone: ONLY has myosin.
  5. M line: In the Middle.

- The side-by-side relationship between the myosin and actin filaments is maintained by a large number of filamentous molecules of a protein called **titin**.
- Springy titin molecules act as a framework that holds the myosin and actin filaments in place so that the contractile machinery of the sarcomere will work.

Thick and thin filaments



Myosin filament



- The protruding arms and heads together are called **cross-bridges.**

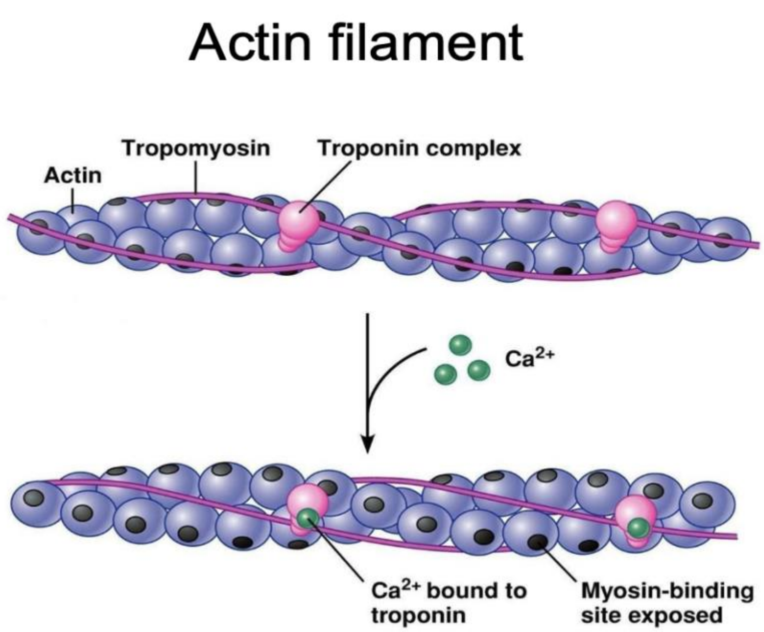
• Each cross-bridge is flexible at two points called **hinges**: one where the arm leaves the body of the myosin filament, and the other where the head attaches to the arm.

- The hinged arms allow the heads to be either extended far outward from the body of the myosin filament or brought close to the body.
- The hinged heads in turn participate in the actual contraction process.

- Another feature of the myosin head that is essential for muscle contraction is that it functions as an ATPase enzyme.
- This property allows the head to cleave ATP and use the energy derived from the ATP's high-energy phosphate bond to energize the contraction process.

- Actin filament:

- Actin Filaments Are Composed of Actin, Tropomyosin, and Troponin.
- The backbone of the actin filament is a double-stranded F-actin protein molecule.
- Each strand of the double F-actin helix is composed of polymerized G-actin molecules.



- Lets simplize this diagram, imagine this actin filament in the form of beads attatch together. These beads have special binding sites for myosin! But we know that in a relaxed state the myosin wouldn't be attatched to these sites. What happens is that another protein called tropomyosin is simply covering the actin "beads" and another protein called troponin can stabilize this bond.
- What happens when calcium enters is that it binds to the troponin causing the unveiling of the myosin binding sites on the actin beads, this here is the main idea for movement as the myosin heads will attach there and cause the movement of the muscle by the movement of the head and we will further clarify this later.
- The tropomyosin 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.

Troponin

• A complex of three loosely bound protein subunits, each of which plays a specific role in controlling muscle contraction:

• **Troponin I** has a strong affinity for actin,**troponin T** for tropomyosin, and **troponin C** for calcium ions.

• This complex is believed to attach the tropomyosin to the actin.

- Effect of Calcium on Myosin-Actin binding:

•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 inhibition is not known.


Good Luck Doctors!