Skeletal muscle physiology for medical students 2022

NMJ and excitation-contraction coupling

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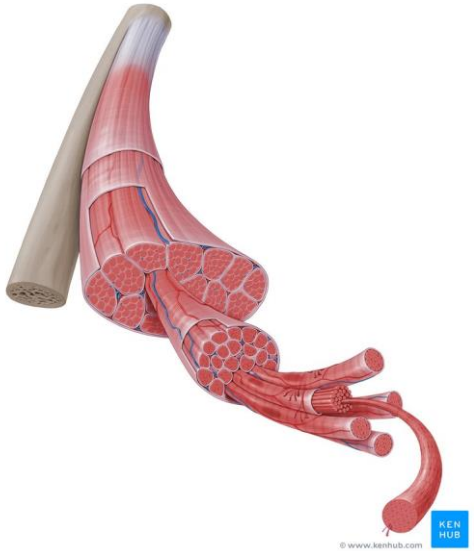
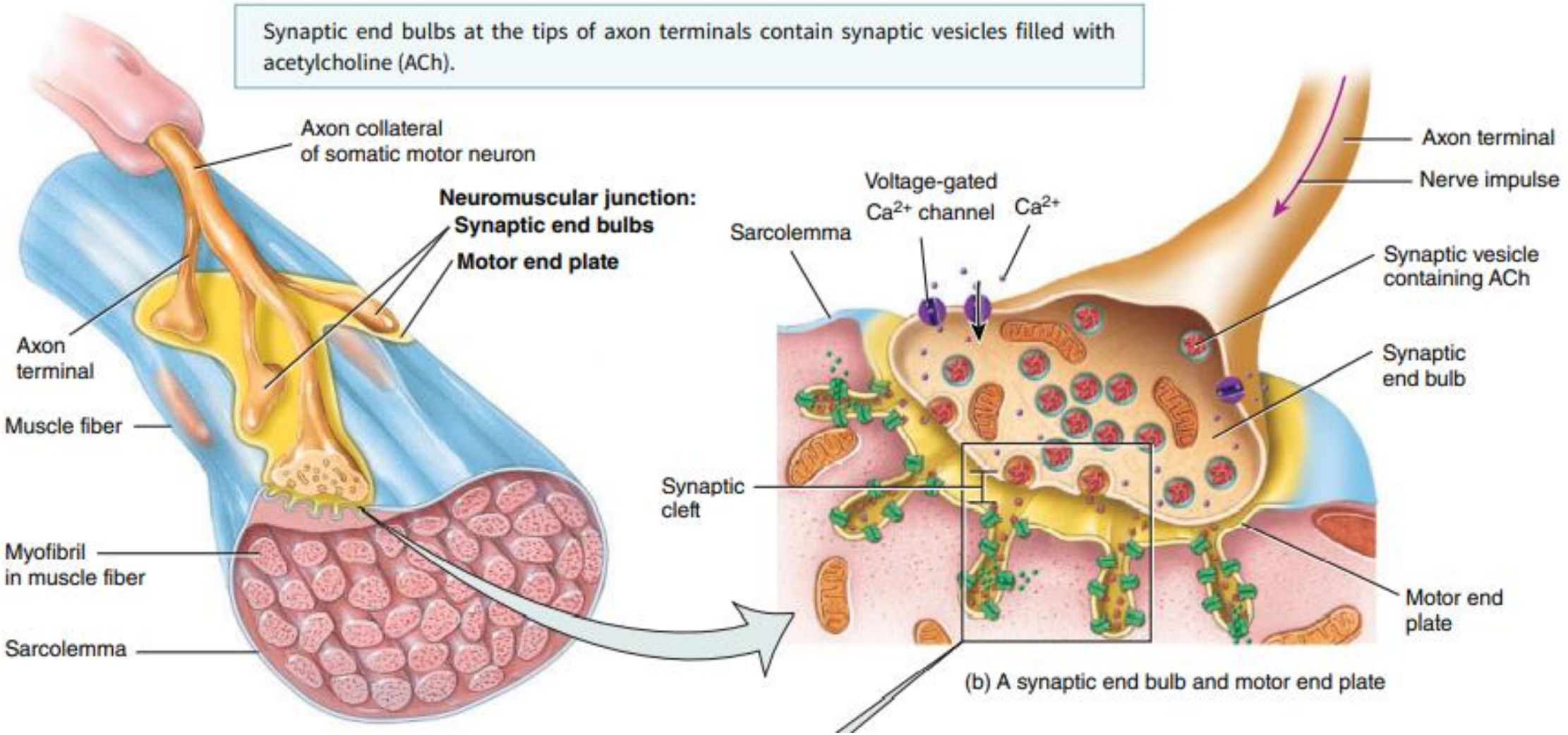


Outline

- NMJ
- Acetylcholine: synthesis and release
- Acetylcholine receptor
- Acetylcholine esterase
- Excitation of skeletal muscle
- Physiological anatomy of skeletal muscle

Neuromuscular junction (NMJ)



NMJ

- 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.

NMJ

- 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.

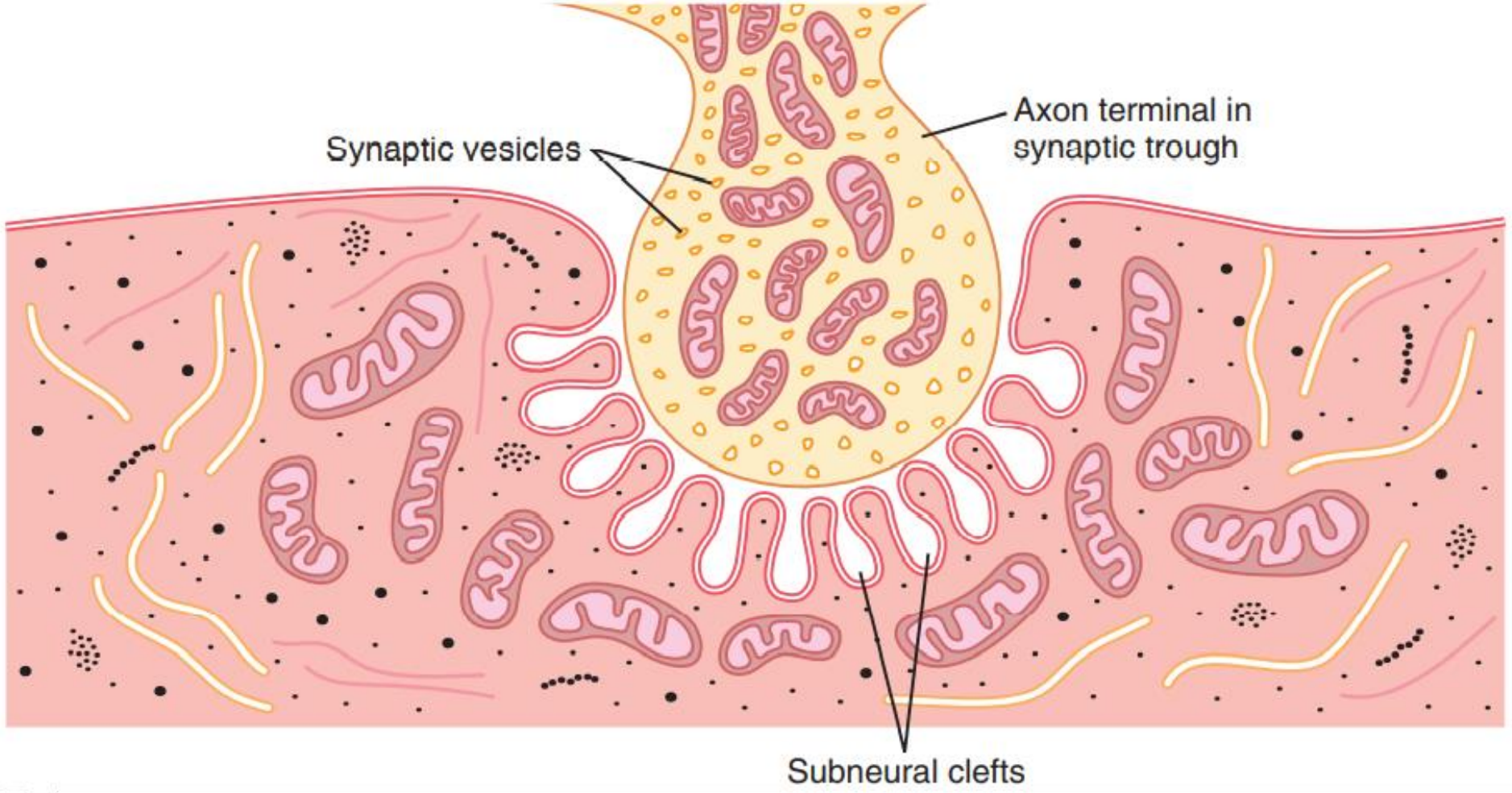
Acetylcholine

- 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.

Excitation of skeletal muscles



Release of Acetylcholine

- 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.

- The calcium ions are believed to activate Ca2+-calmodulin dependent protein kinase, which, in turn, phosphorylates synapsin proteins that anchor the acetylcholine vesicles to the cytoskeleton of the presynaptic terminal.

Release of Acetylcholine

- This process frees the acetylcholine vesicles from the cytoskeleton and allows them to move to the active zone of the presynaptic neural membrane adjacent to the dense bars.

- The vesicles then dock at the release sites, fuse with the neural membrane, and empty their acetylcholine into the synaptic space by the process of exocytosis.

Acetylcholine-gated channels

- Acetylcholine receptors in the muscle fiber membrane are acetylcholine-gated ion channels.

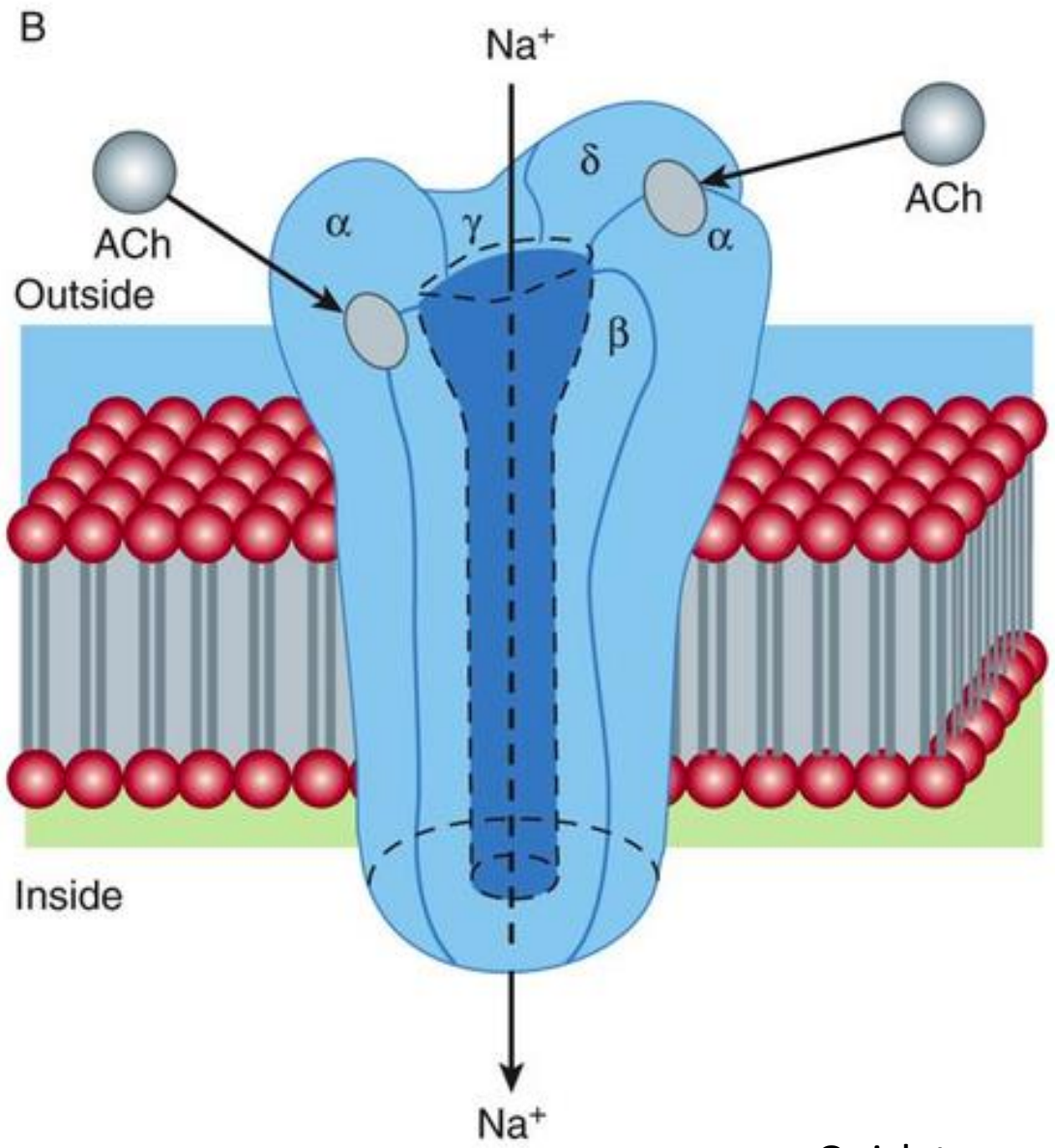
- They are located almost entirely near the mouths of the sub-neural clefts lying immediately below the dense bar areas, where the acetylcholine is emptied into the synaptic space.

Acetylcholine-gated channels

- Each receptor is a protein complex. The fetal acetylcholine receptor complex is composed of five subunit proteins, two alpha proteins and one each of beta, delta, and gamma proteins.

- In the adult, an epsilon protein substitutes for the gamma protein in this receptor complex.

Acetylcholine-gated channels



Quizlet.com

Acetylcholine-gated channels

- The channel remains constricted until two acetylcholine molecules attach respectively to the two alpha subunit proteins.

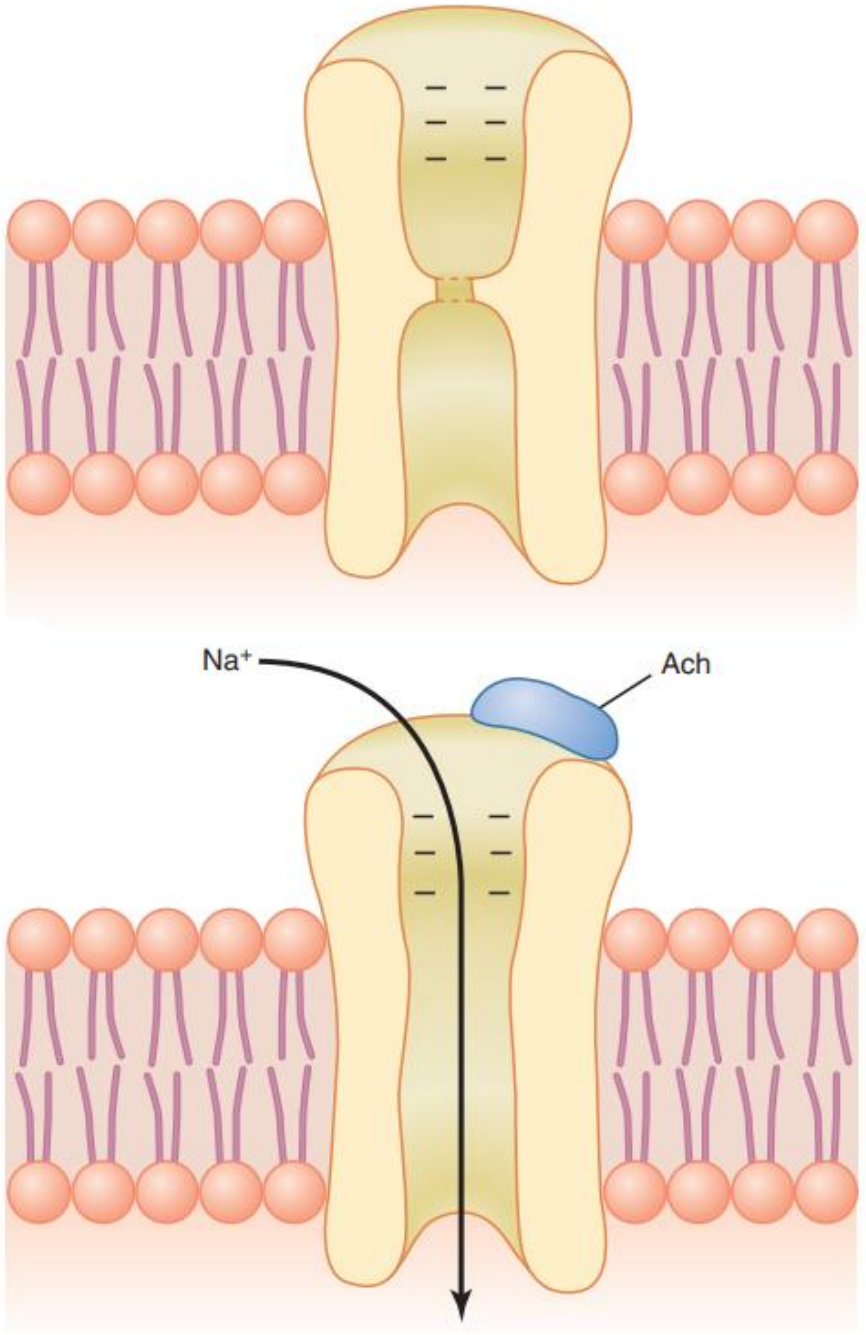
- This attachment causes a conformational change that opens the channel.

Acetylcholine-gated channels

- The acetylcholine-gated channel allow the important positive ions: Na+, K+, and Ca++ to move easily through the opening.

- Conversely, negative ions, such as Cl-, do not pass through because of strong negative charges in the mouth of the channel that repel these negative ions.

Acetylcholine-gated ion channel



Acetylcholine-gated channels

- In practice, far more sodium ions flow through the acetylcholine-gated channels than any other ions, for two reasons:

- First, there are only two positive ions in large concentration: Na+ in the ECF and K+ in the ICF.

- Second, the negative potential on the inside of the muscle membrane, −80 to −90 millivolts, pulls the positively charged sodium ions to the inside of the fiber.

End plate potential

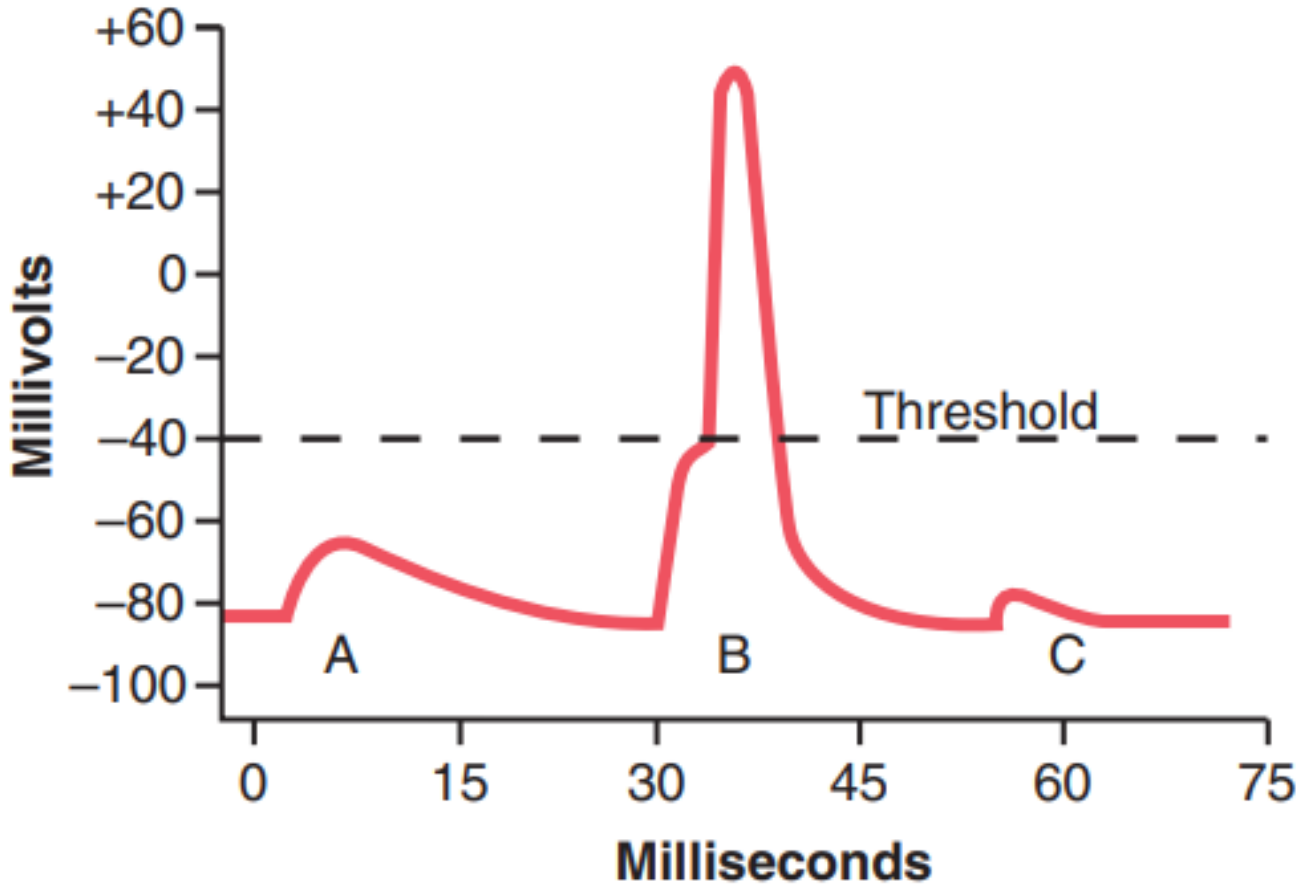
- The principal effect of opening the acetylcholine-gated channels is to allow large numbers of sodium ions to pour to the inside of the fiber, carrying with them large numbers of positive charges.

- This action creates a local positive potential change inside the muscle fiber membrane, called the end plate potential.

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



Clinical connection

- Botulinum toxin (Botox): blockage of the presynaptic release of acetylcholine at the neuromuscular junction.

Skeletal muscle action 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.

Skeletal muscle action potential

- 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

Acetylcholine esterase

- 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.

Acetylcholine esterase

- (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.

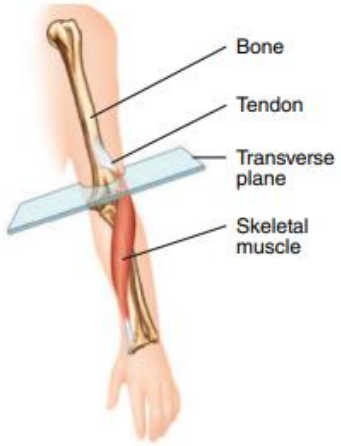
Clinical connection

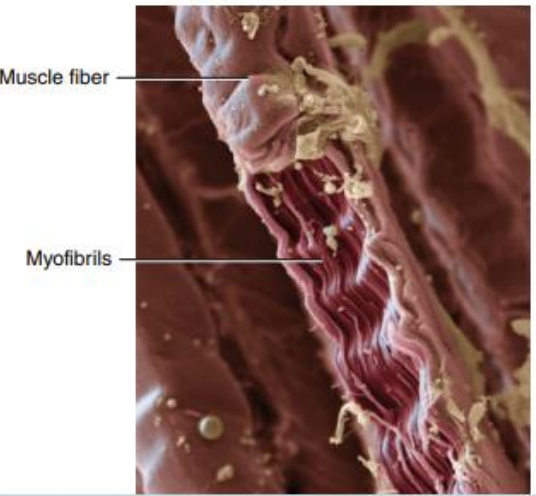
Myasthenia gravis:

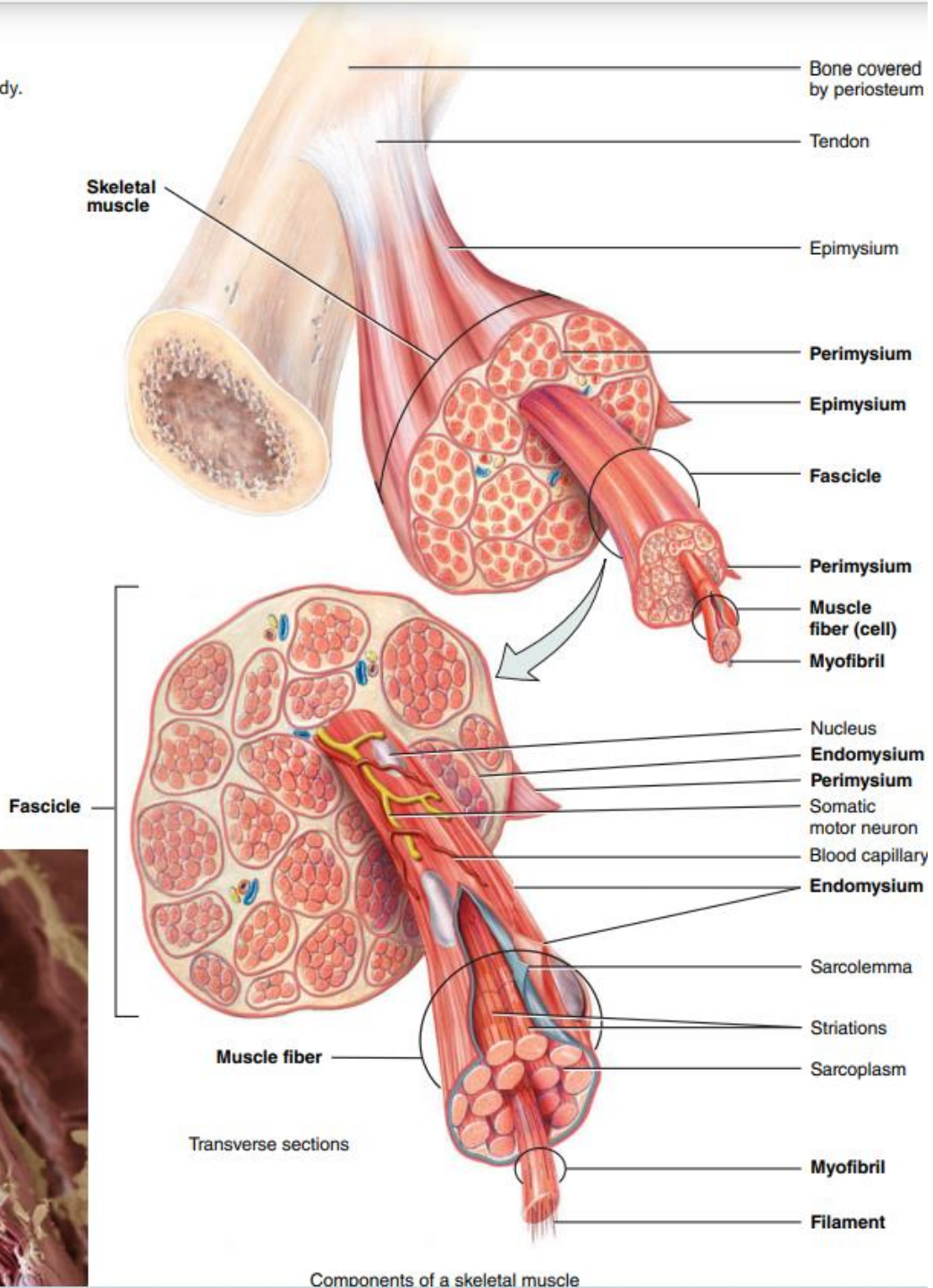
- The most common autoimmune disorder that affects the neuromuscular junction.
- MG is largely a treatable disease but can result in significant morbidity and even mortality.
- Neuromuscular junction disorders such as MG disrupt the cascade of events that lead to reliable muscle contraction.
- In addition, there is a reduction in the number of AChRs and voltage-gated sodium channels as the result of complement-related injury to the postsynaptic membrane in MG.
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8196750/

Skeletal muscle

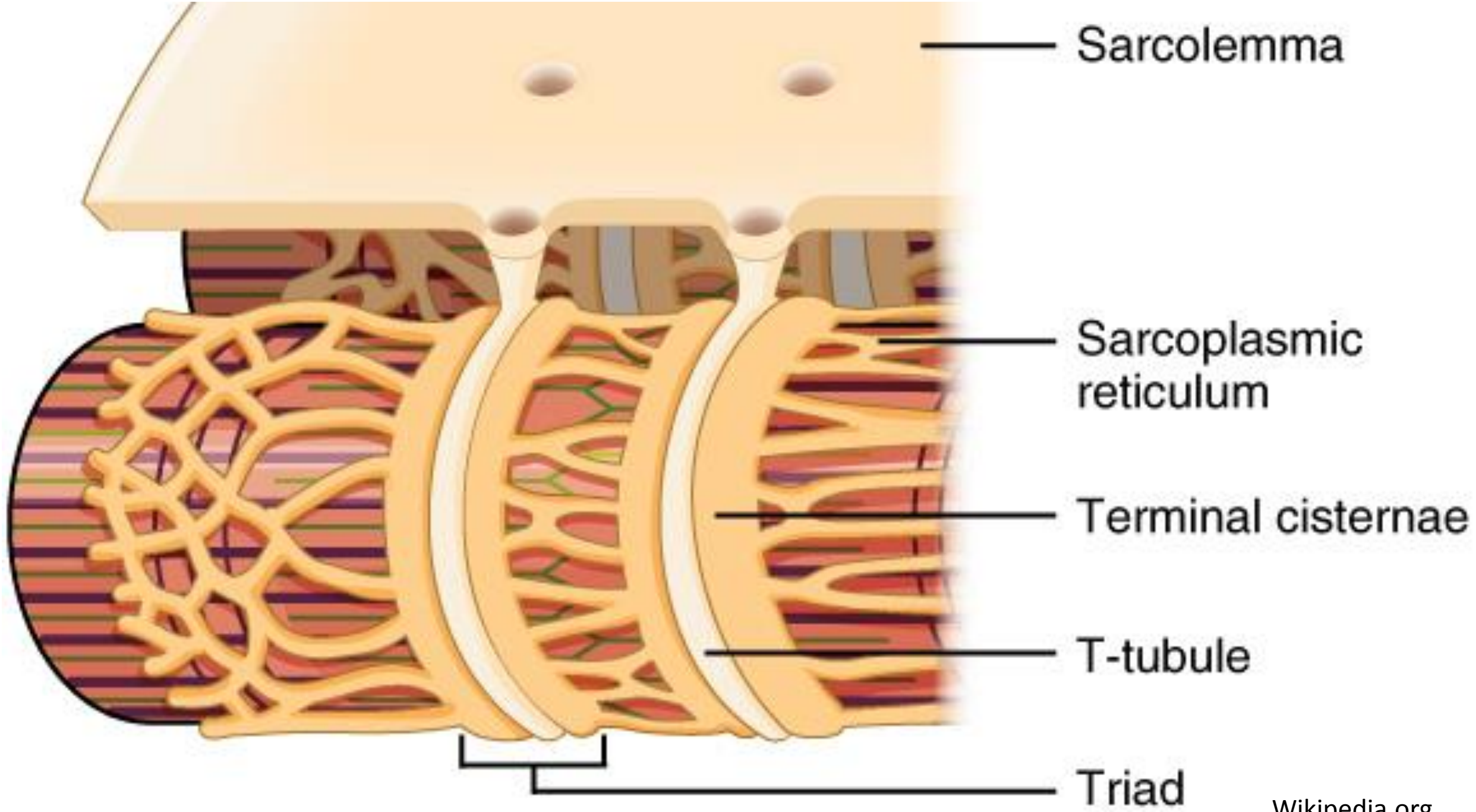
1. Producing motions.
2. Stabilizing body positions.
3. Storing and moving substances within the body.
4. Generating heat (thermogenesis).







Components of a skeletal muscle



Wikipedia.org

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.

Physiological anatomy of skeletal muscles

- 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.

T tubules

- 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.

T tubules

- 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.

T tubules

- 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.

The sarcoplasmic reticulum

- 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

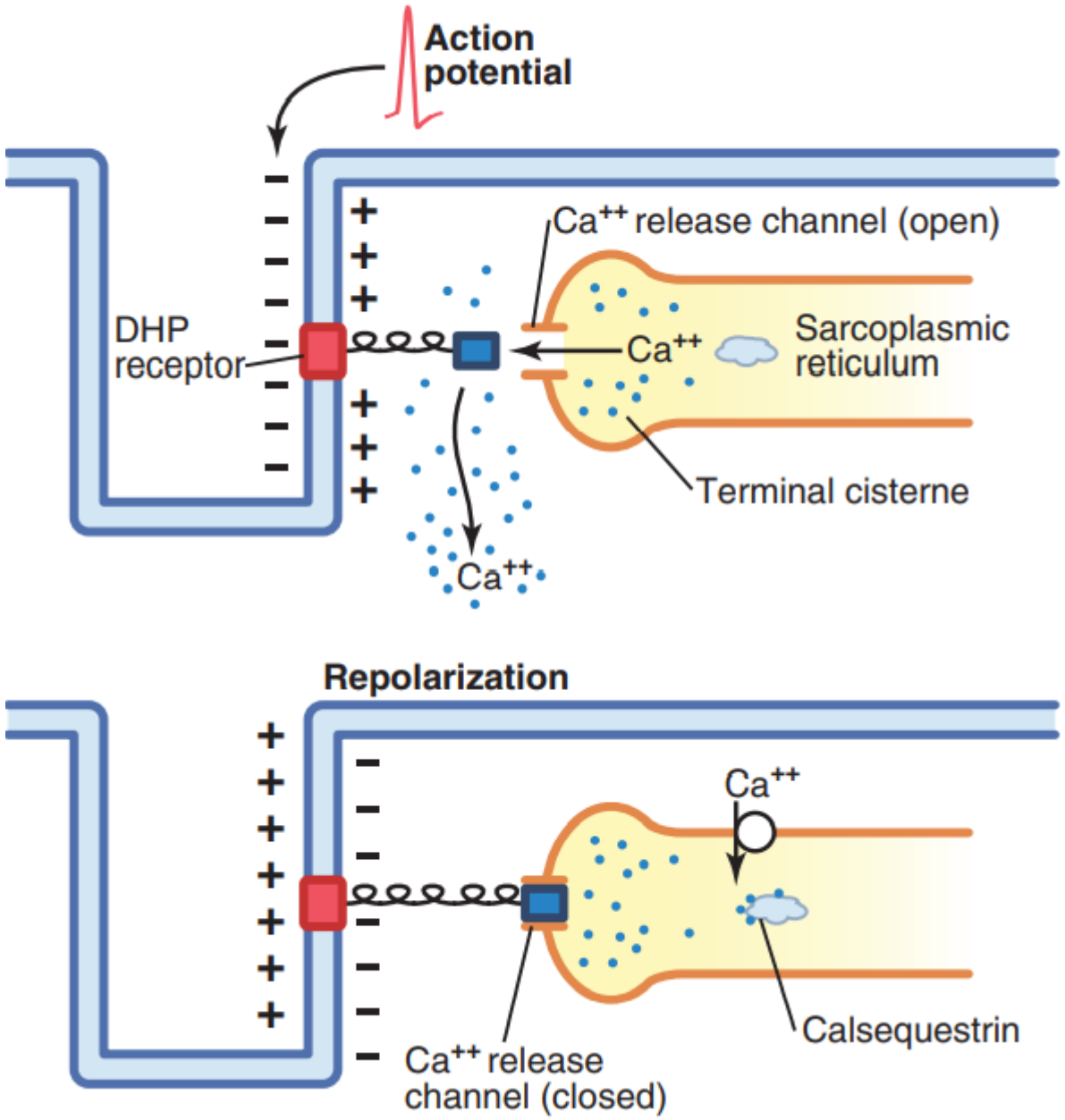
- The action potential of the T tubule causes current flow into the sarcoplasmic reticular cisternae where they abut the T tubule.

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

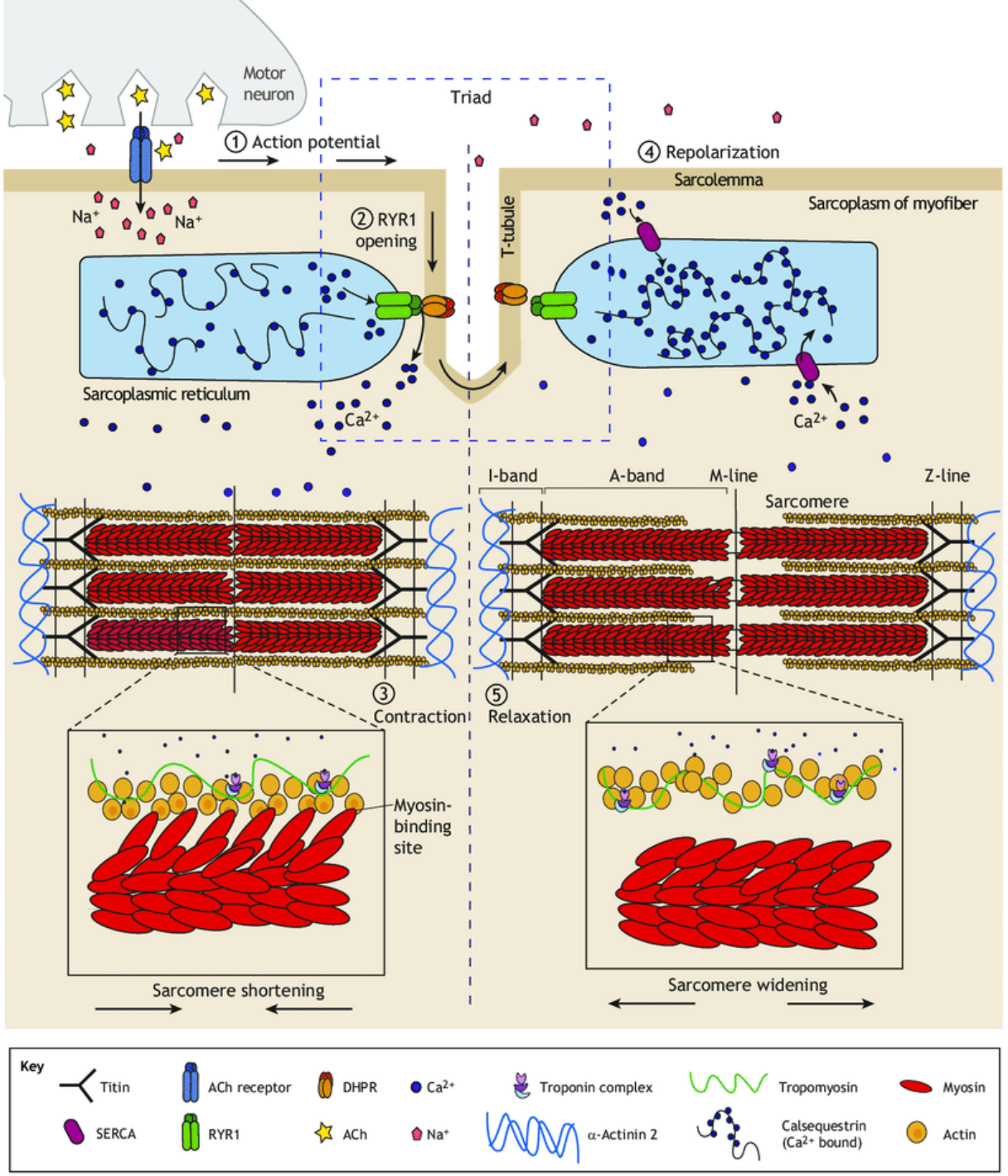
Calcium release from SR

- 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.

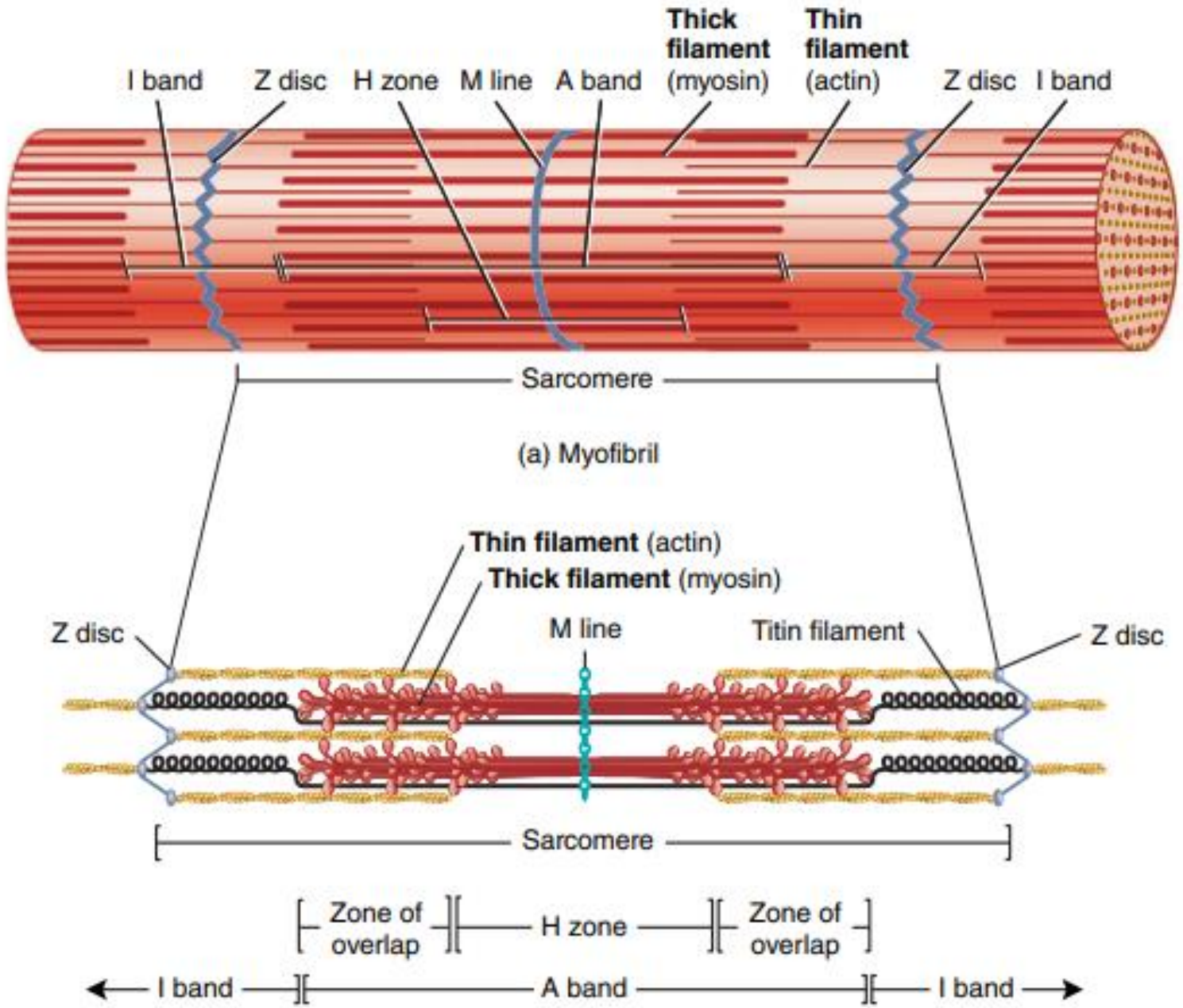
Calcium release from SR



Calcium release from SR

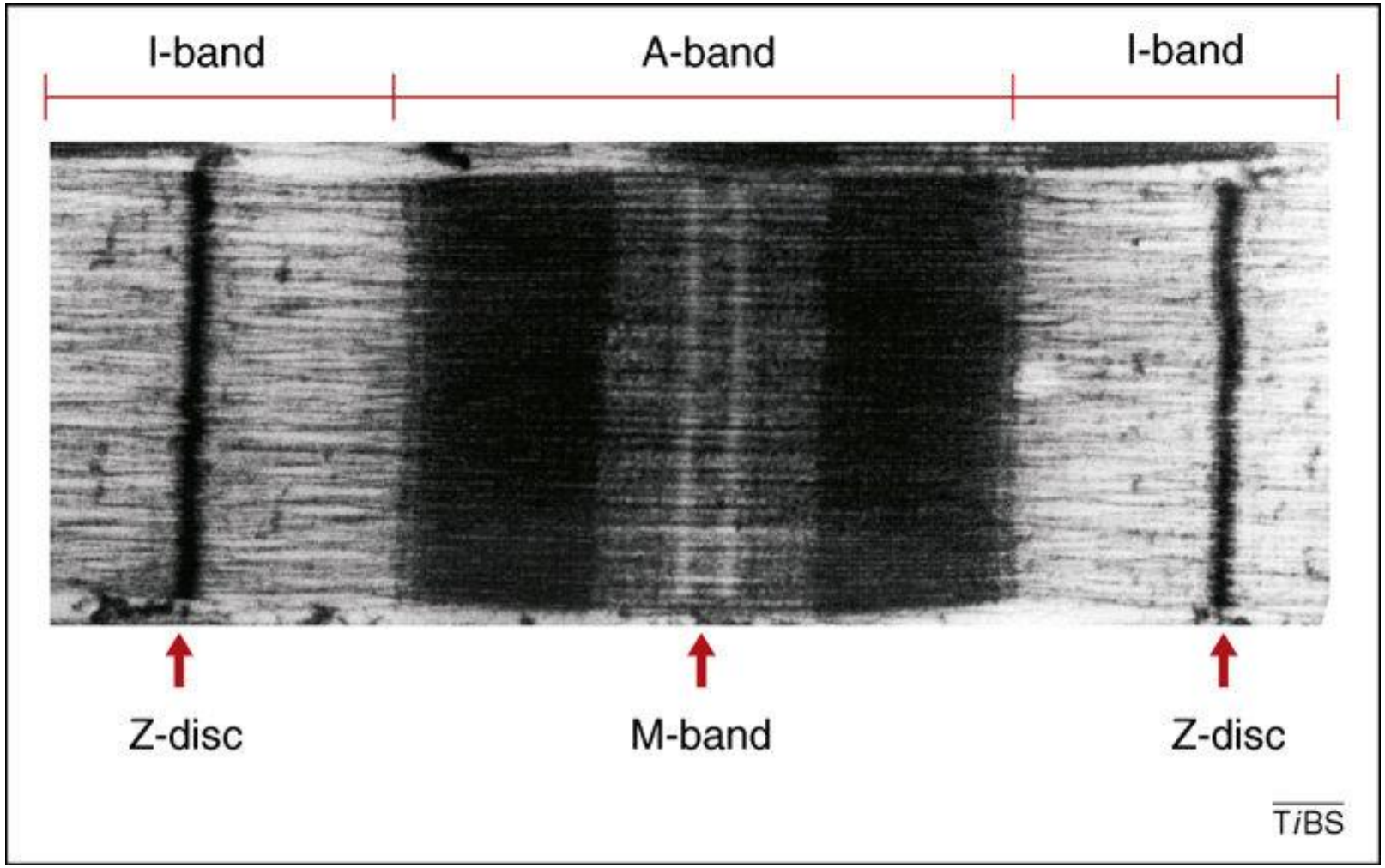


Fusto et al. The use of models to understand core myopathies, 2019.


Thick filament (myosin)
Thin filament (actin)
I band
Z disc
H zone
M line
A band
Z disc
I band
Sarcomere
(a) Myofibril
Thin filament (actin)
Thick filament (myosin)
Z disc
M line
Titin filament
Z disc
Sarcomere
Zone of overlap
H zone
Zone of overlap
I band
A band
I band

Sarcomere

Sarcomere



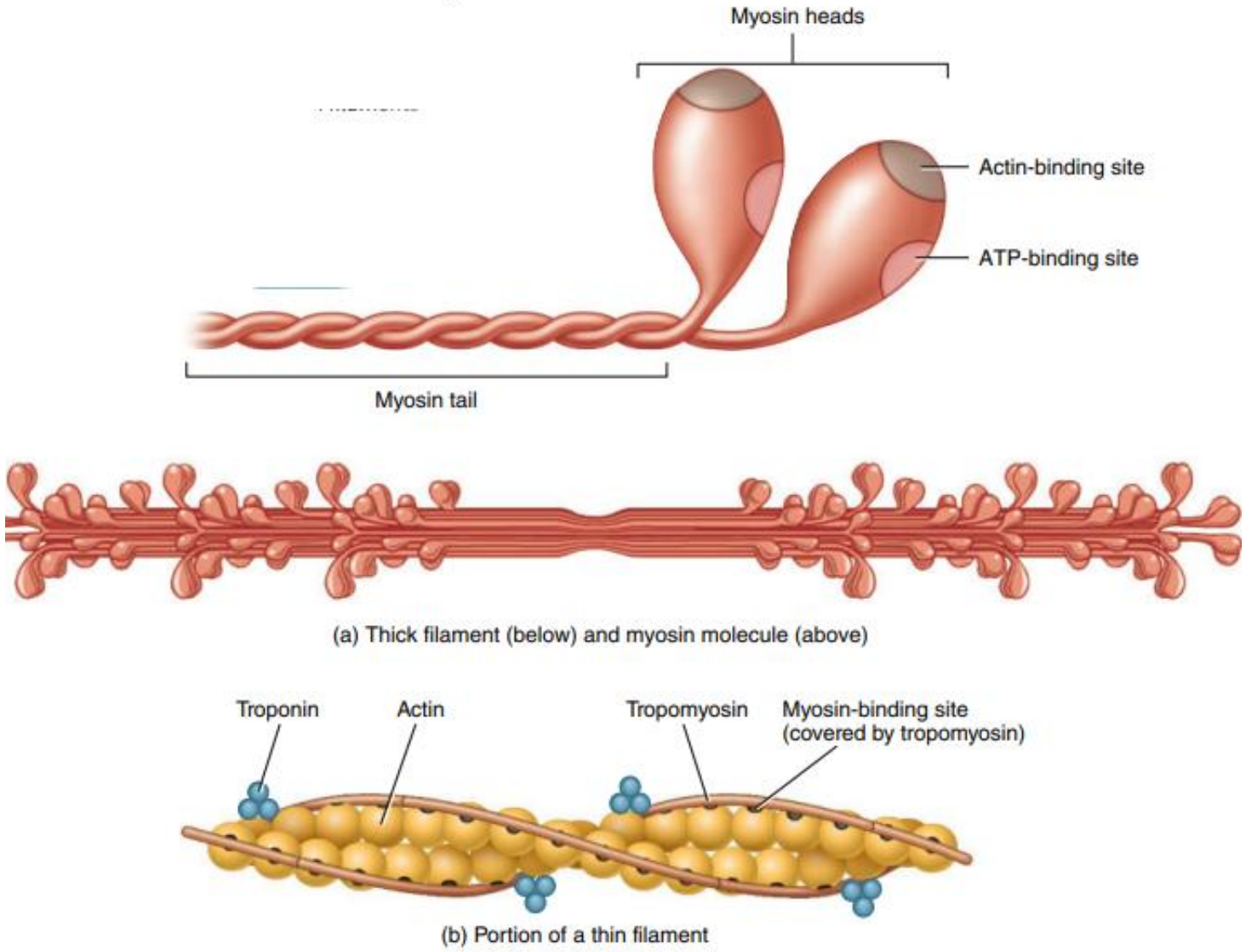
Pinotsis et al. Terminal assembly of sarcomeric filaments by intermolecular beta-sheet formation, 2009.

Titin

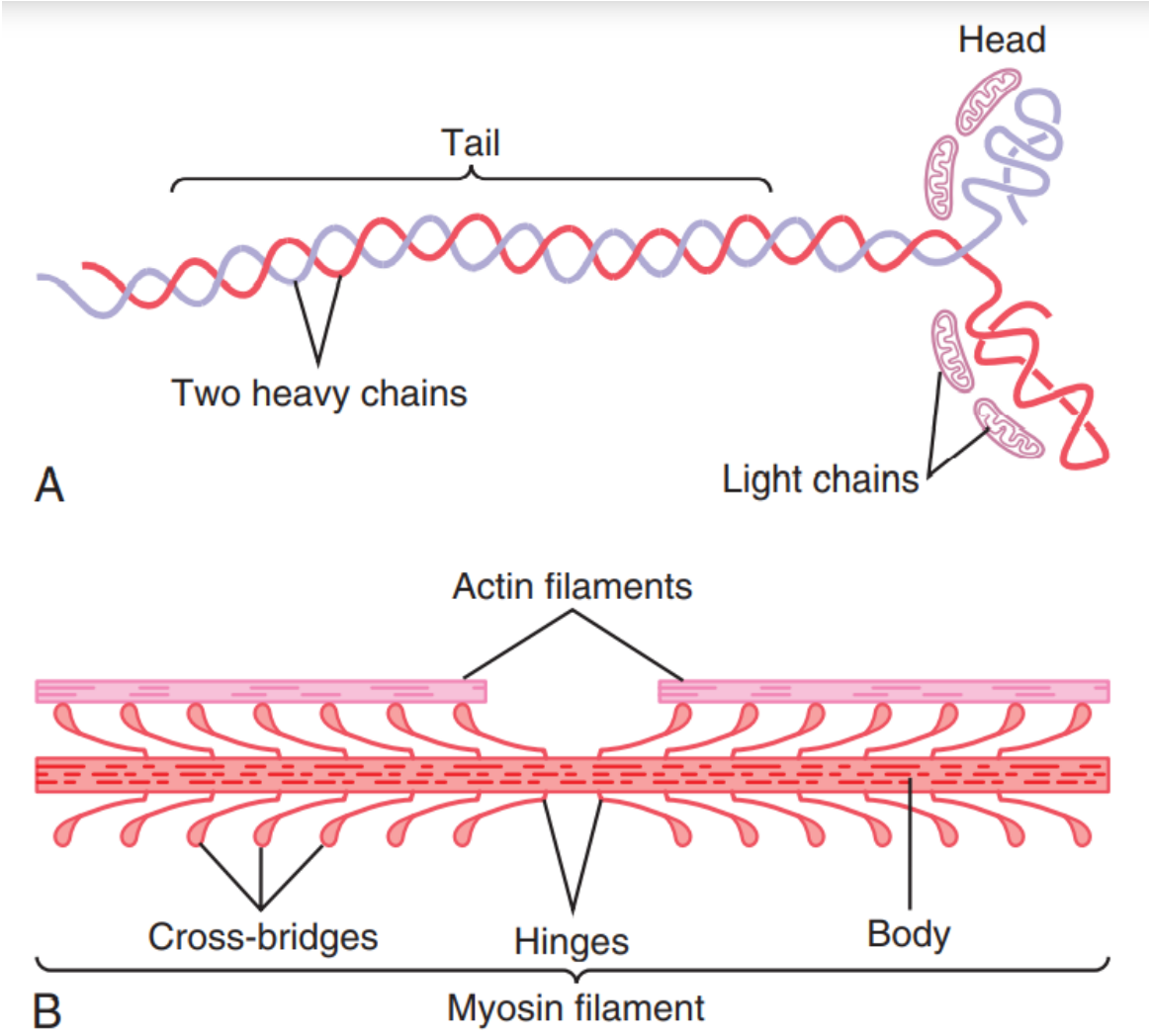
- The side-by-side relationship between the myosin and actin filaments is maintained by a large number of filamentous molecules of a protein called **titin**.

- 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



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.

Myosin head

- Another feature of the myosin head that is essential for muscle contraction is that it functions as an ATPase enzyme.

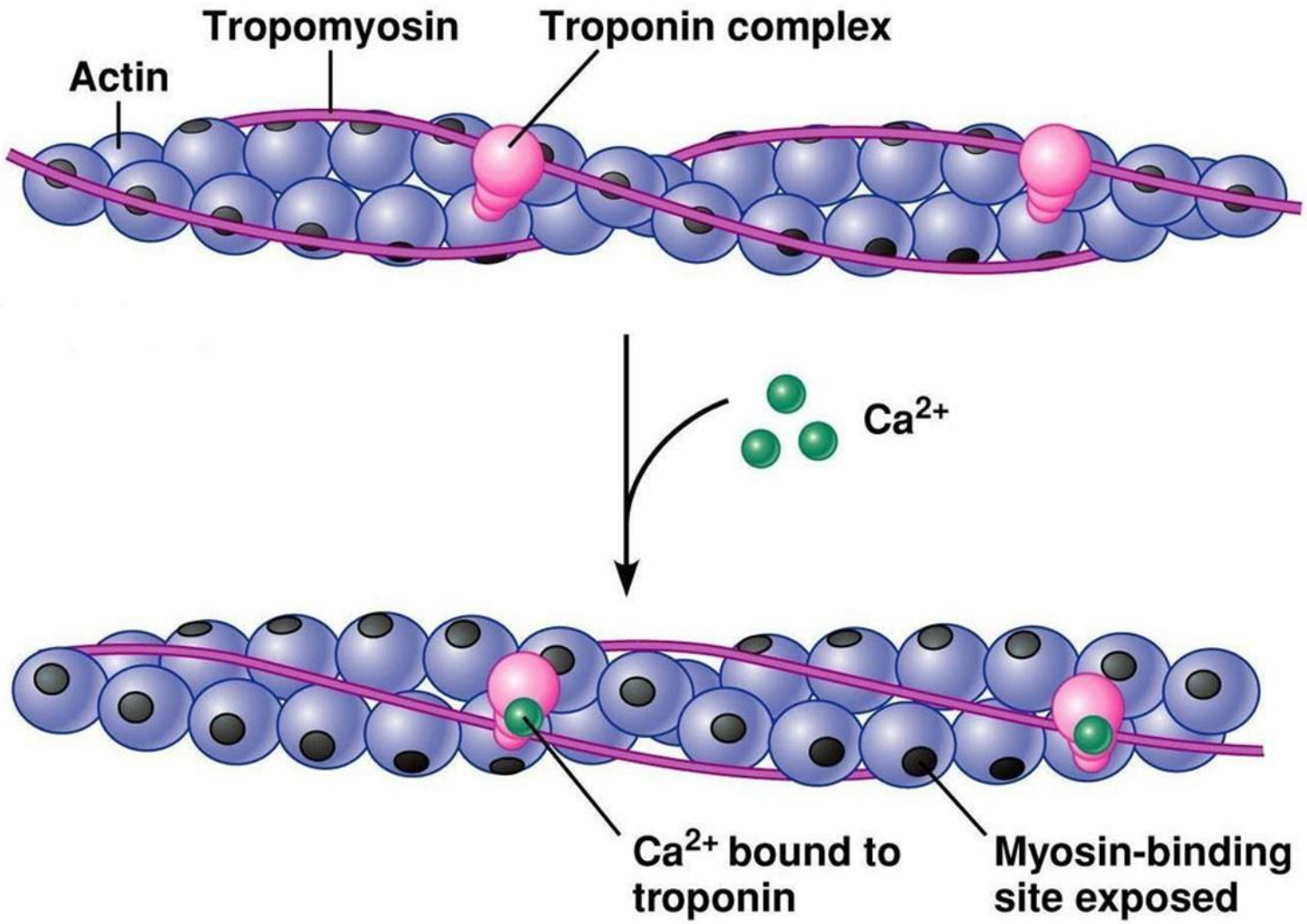
- This property allows the head to cleave ATP and use the energy derived from the ATP’s high-energy phosphate bond to energize the contraction process.

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.

Actin filament



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.

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.

Thank you