Chapter 11.2

What is the motor pathway?

What is the nerve-muscle relationship?

What is the structure and function of the neural muscular junction?

What is the significance of the sliding filament theory?

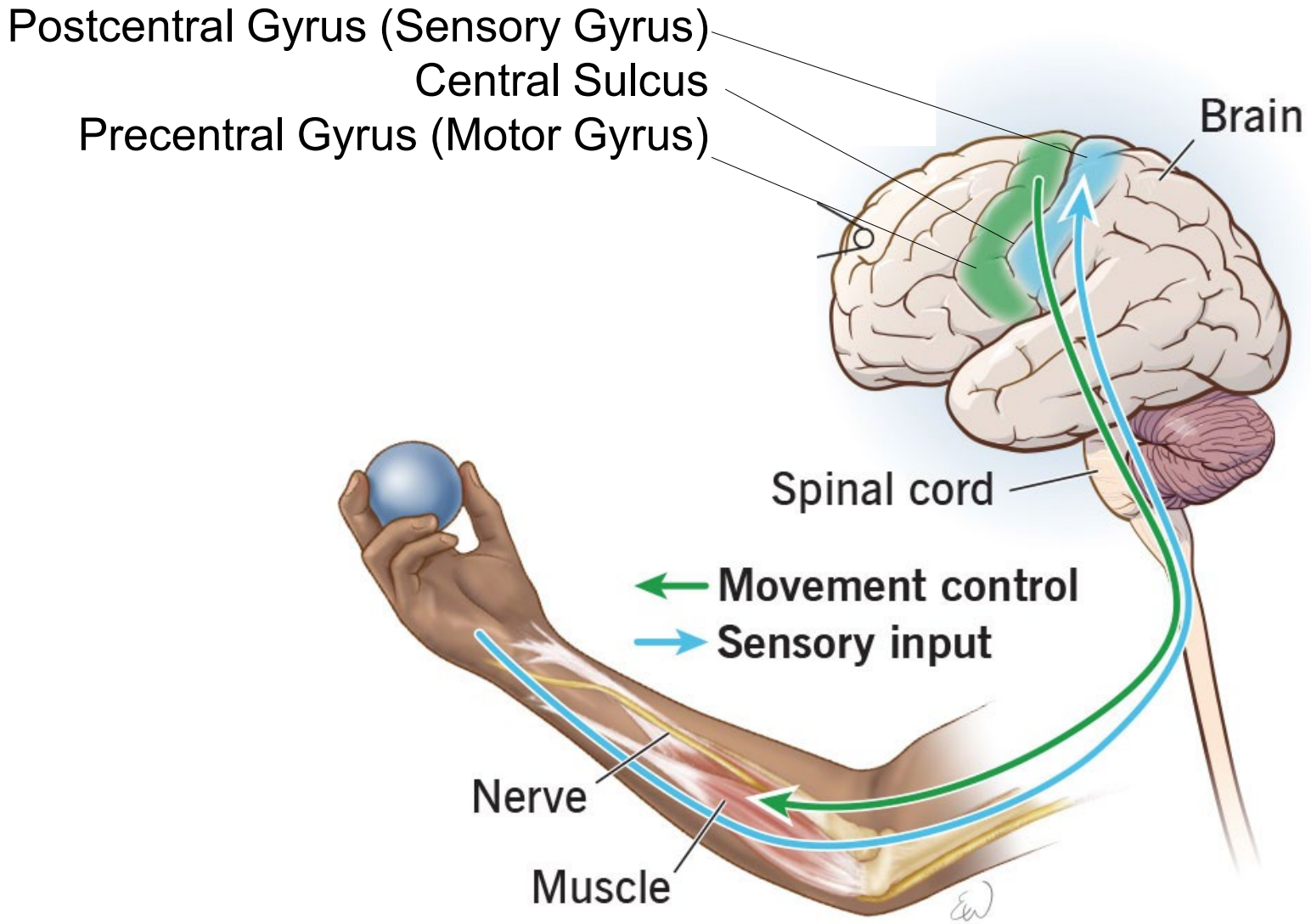
What is the "sequence" of steps in a skeletal muscle contraction cycle?

What is the structure and function of a motor unit?

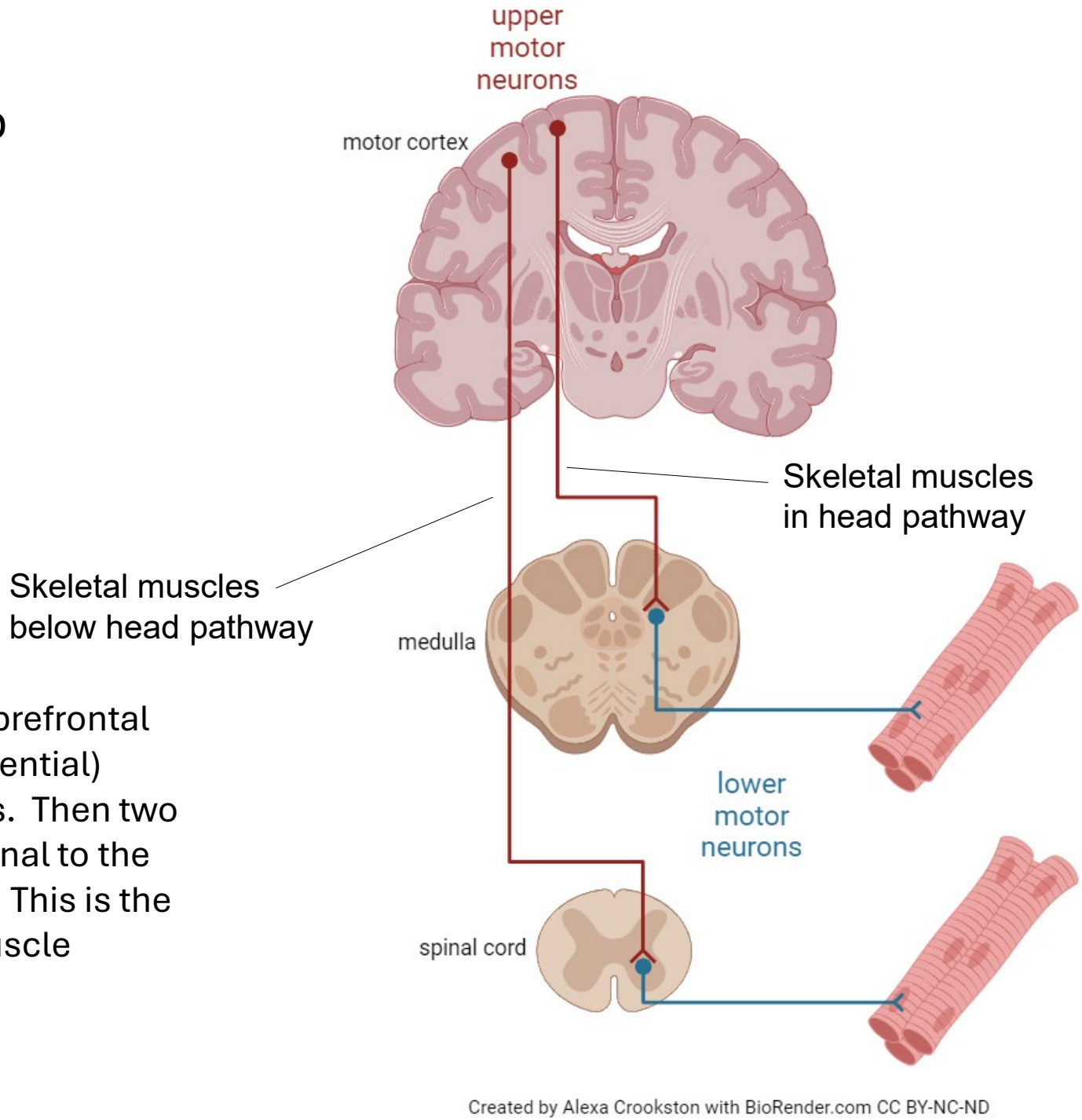
Somatic Nervous System

Skeletal Muscle
Motor Pathway

(This is a voluntary pathway)



Upper and Lower Motor Neurons From Motor Strip to Skeletal Muscles



The voluntary pathway starts in the prefrontal cortex and the signal (the action potential) makes its way to the precental gyrus. Then two neurons are used to transmit the signal to the surface of the skeletal muscle fiber. This is the "excitement phase" of a skeletal muscle contraction.

The Nerve-Muscle Relationship

To contract a skeletal muscle, voluntary command is sent to the motor strip (i.e. precentral gyrus) // there is a point to point relationship between a location on the motor strip and every skeletal muscle in the body muscle (called somatotopy).

- There are two neurons between the motor strip and the skeletal muscle, an upper motor neuron and lower motor neuron.

- Upper Motor Neurons connect the precentral gyrus to a lower motor neuron in the brainstem or in the spinal cord's anterior horn // UMN run in the “spinal bulbar or spinal cortical tracts”

The Nerve-Muscle Relationship

The lower motor neuron (second neuron to the skeletal muscle) is either a cranial nerve(exit through cranial foramen for the UMN corticobulbar nerves) or a spinal nerve that exit from the spinal cord (for UMN in spinal cortical tract).

Spinal nerves and cranial nerves are both LMN

LMN's “somas” are in the brain-stem (if cranial nerves) or in spinal cord (if spinal nerve)

The terminal knobs of LMN's nerves synapse (“connect to”) skeletal muscles

A single axon of the LMN may form many branches at the distal end of the axon – each branch “synapse” with individual muscle fibers (terminal knobs)

All the muscle fibers controlled by a single nerve pathway is call a motor unit (more later on this topic)

The Nerve-Muscle Relationship

If this nerve connection to the muscle fiber is cut, then the muscle is paralyzed (can not contract muscle)

Denervation atrophy – occurs when a somatic motor nerve to a skeletal muscle is cut. The muscle is paralyzed and over time the muscle will atrophy (reduced sarcoplasm volume because myofibils break apart and they are not replaced)

Loss of sacroplasmic volume (loss of contractile proteins) results in less strength /// What is disuse atrophy?

- Muscle fibers are innervated by a unique motor unit. A single muscle fiber can not be innervated by two different motor units.

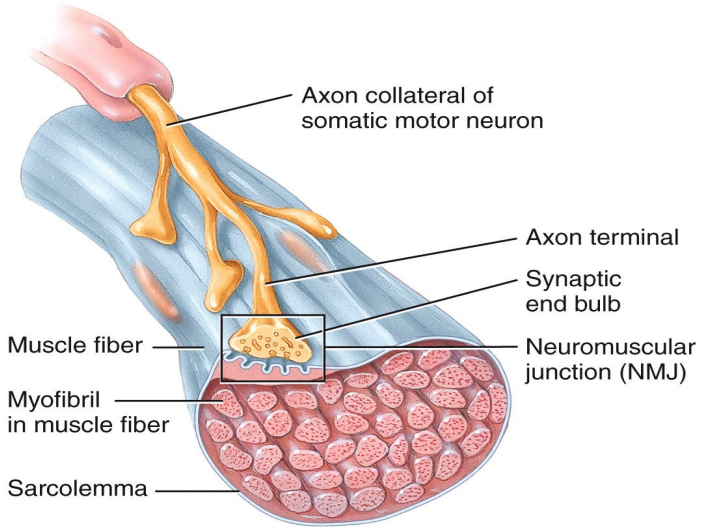
- The number of muscle fibers in a motor unit may vary. Motor units in the fingers are very small but in the gastrocnemius are very large.

The Neuromuscular Junction

Synapse = the location where the terminal end of a nerve (synaptic end bulb) reaches the target tissue

Three components of a synapse

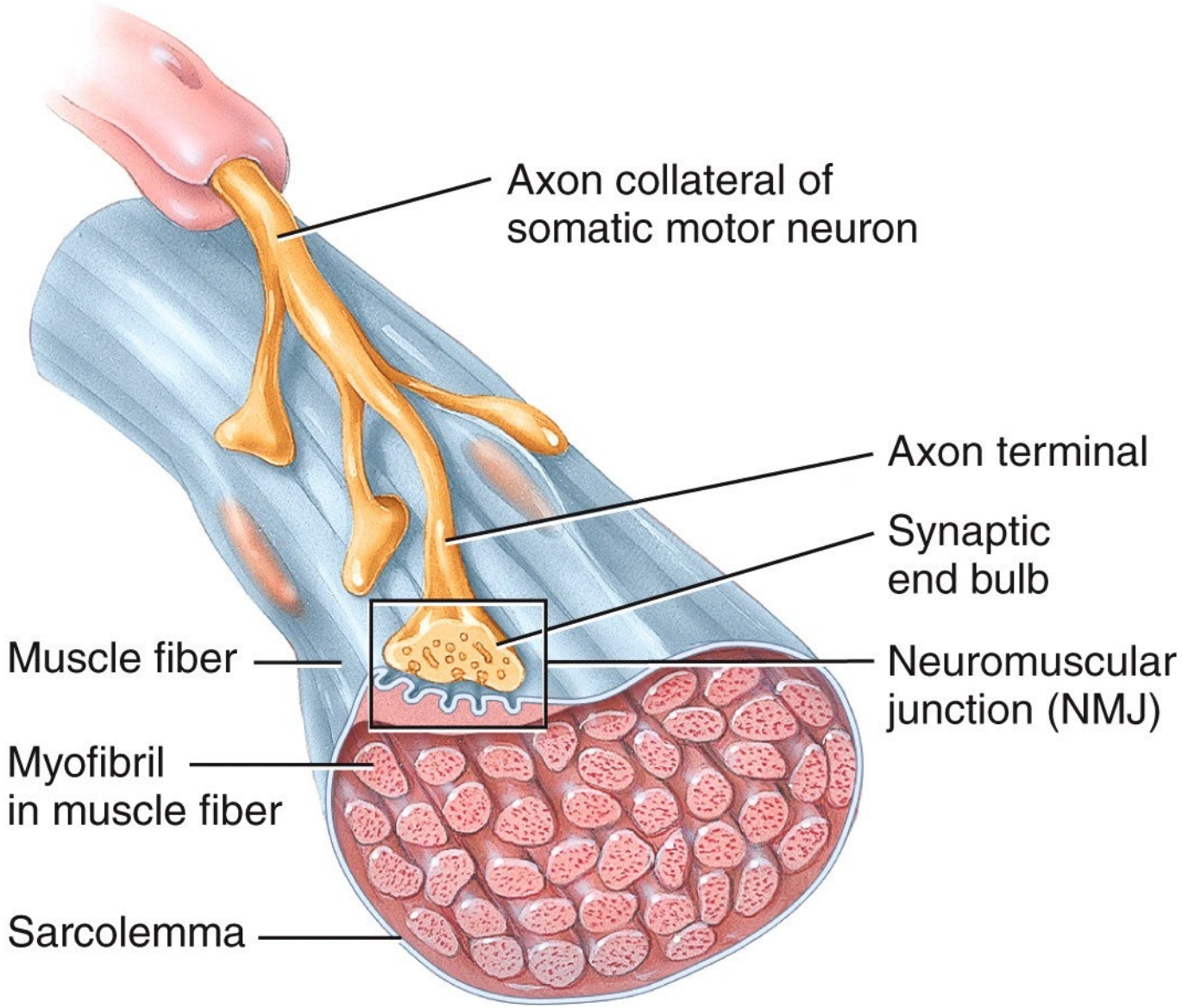
- pre-synaptic membrane
- synaptic cleft
- post-synaptic membrane



(a) Neuromuscular junction

Neuromuscular junction (NMJ) describes a special type of synapse /// This occurs when a spinal nerve "targets" a muscle fiber

The synaptic end bulb releases a neurotransmitter.



(a) Neuromuscular junction

Neurotransmitter starts an action potential on the sarcolemma at the neuromuscular junction.
(This will result in a muscle contraction.)

Components of Neuromuscular Junction

Synaptic end bulb (knob) - swollen end of terminal end of the nerve fiber

Synaptic knob contains synaptic vesicles filled with acetylcholine (ACh)

Synaptic vesicles undergo exocytosis to release ACh into synaptic cleft

Acetylcholine (the ligand) will diffuse to the post synaptic membrane and dock to a ligand regulated sodium channel. What happens next???

Synaptic cleft - tiny gap between synaptic knobs and muscle sarcolemma

Schwann cell - envelops & isolates all of the NMJ from surrounding tissue fluid

Components of Neuromuscular Junction

ACh receptors – 50 million protein receptors are built into muscle cell plasma membrane at synaptic junction

Junctional folds of sarcolemma beneath synaptic knob // increases surface area holding ACh receptors

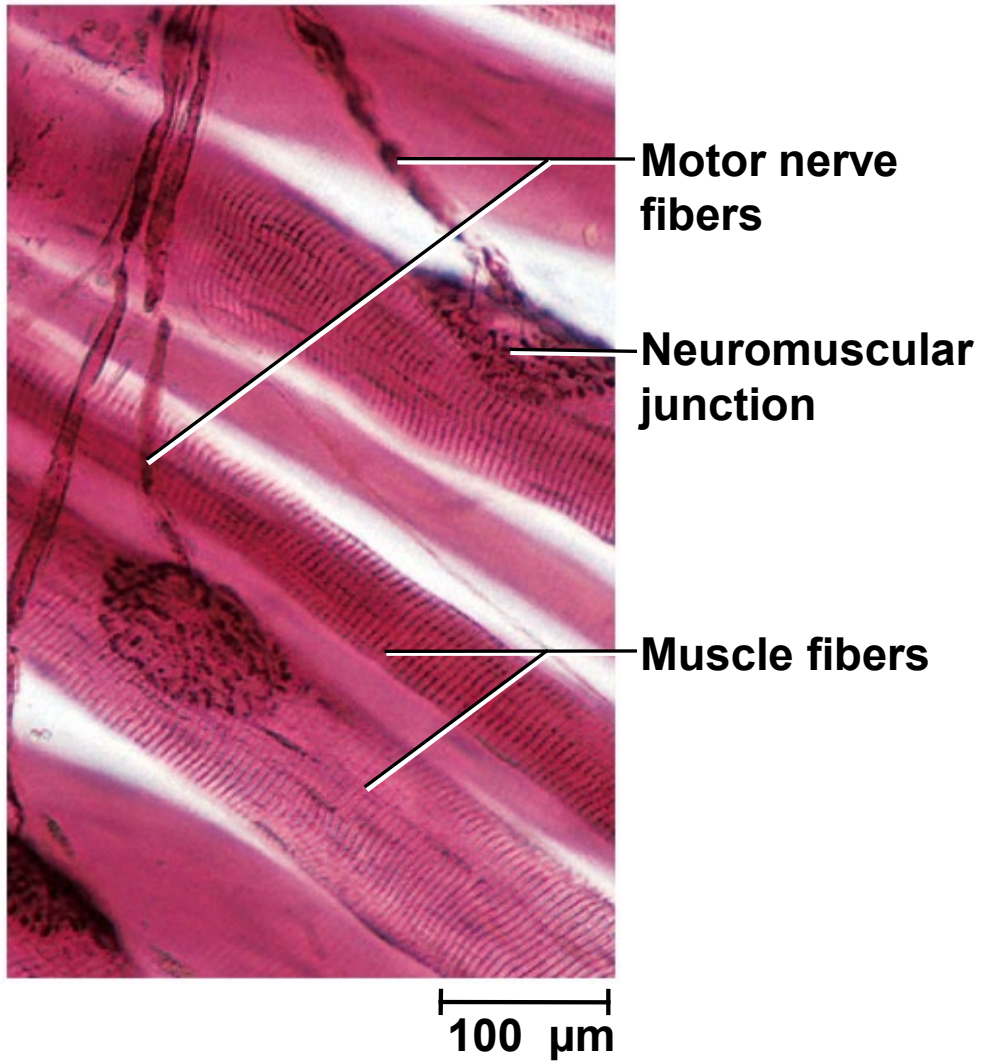
Lack of receptors leads to paralysis in disease like myasthenia gravis

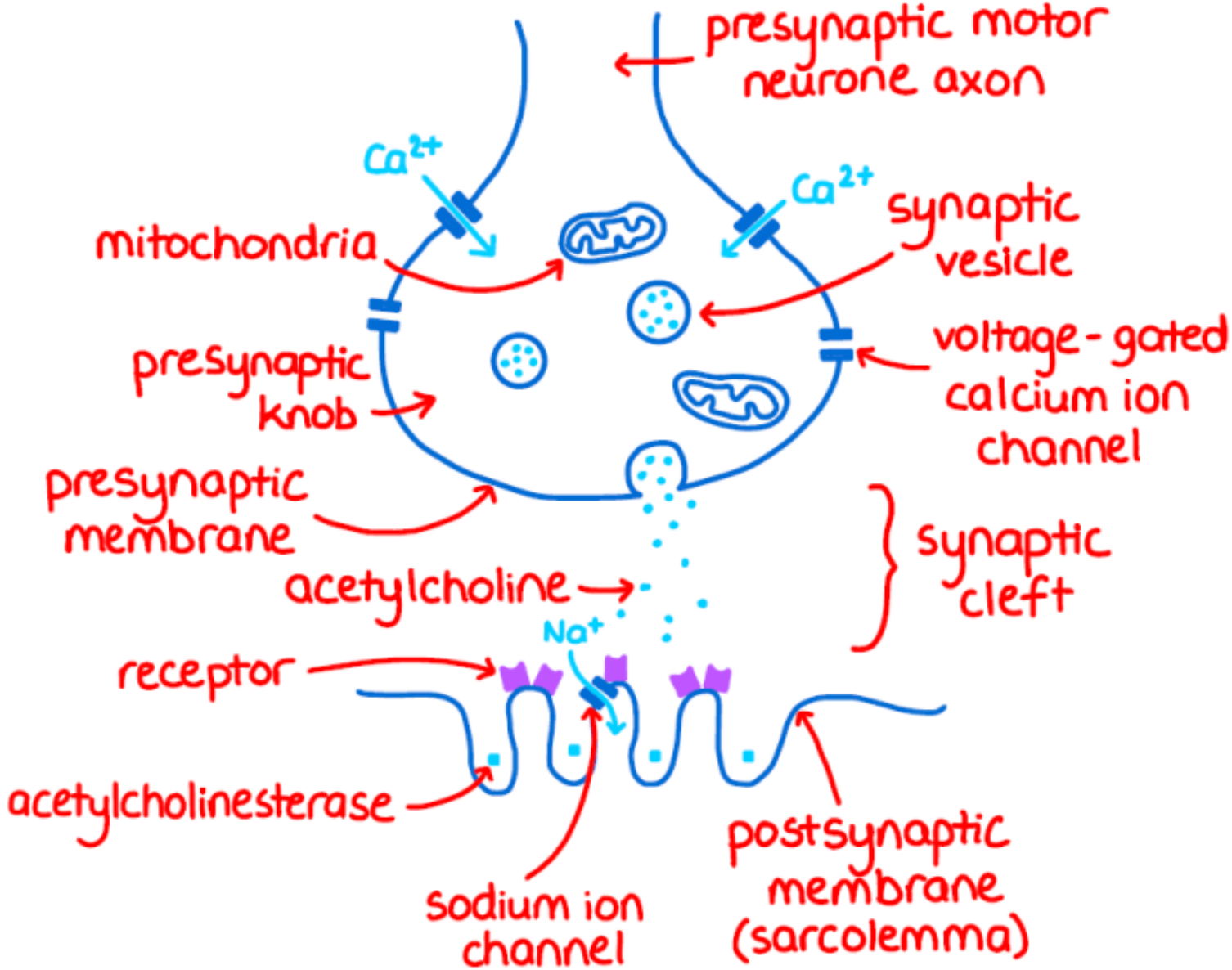
Basal lamina - thin layer of collagen and glycoprotein separates Schwann cell and entire muscle cell from surrounding tissues

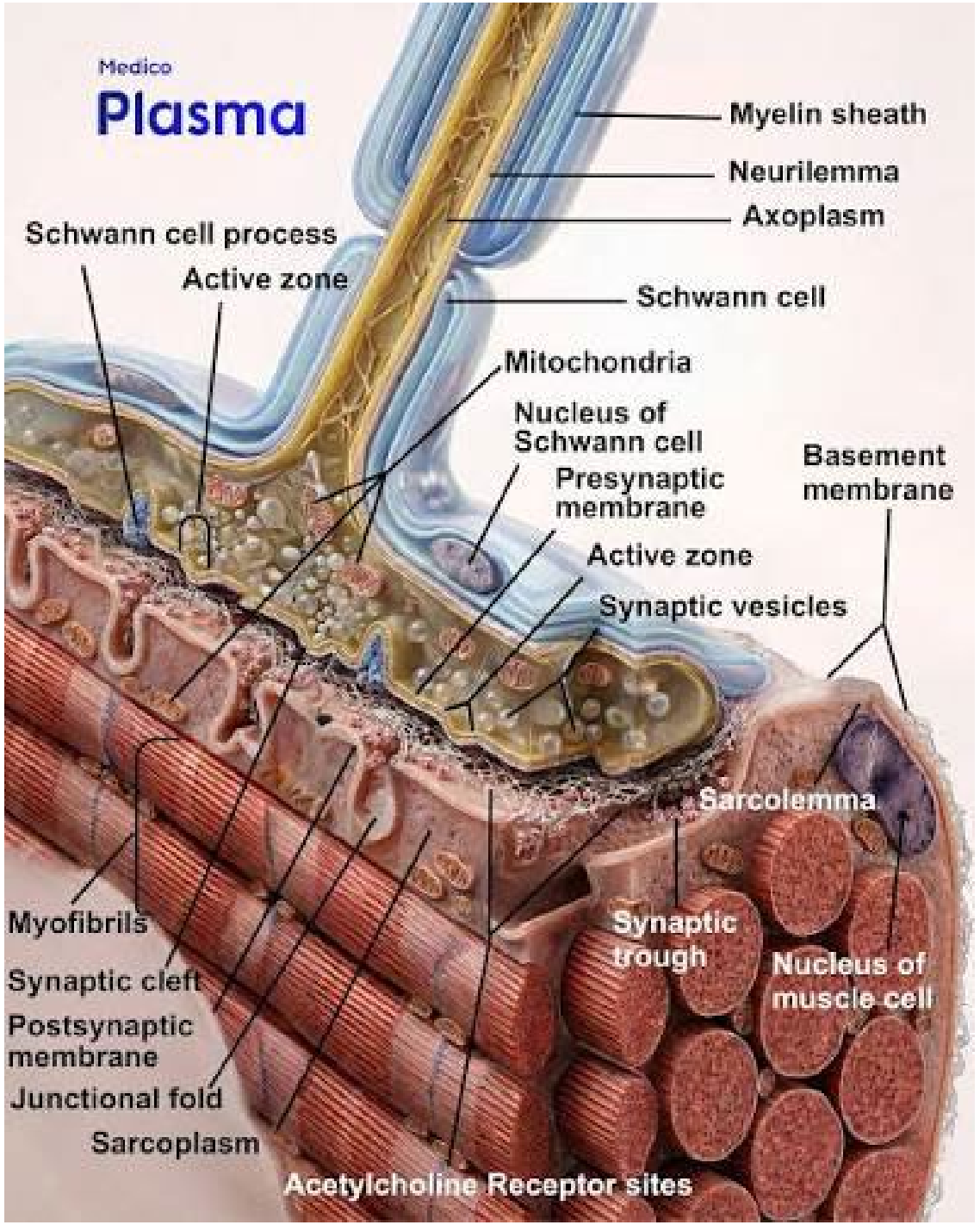
The enzyme acetylcholinesterase (AchE) is within the synaptic cleft. This enzyme degrades ACh in a sequence of events to stop muscle contraction and allows the muscle to relax.

Neuromuscular Junction

(scanning electron microscope)




presynaptic motor neurone axon
Ca^{2+}
Ca^{2+}
mitochondria
synaptic vesicle
presynaptic knob
voltage-gated calcium ion channel
presynaptic membrane
synaptic cleft
acetylcholine
Na^{+}
receptor
acetylcholinesterase
sodium ion channel
postsynaptic membrane (sarcolemma)


Medico
Plasma
Myelin sheath
Neurilemma
Axoplasm
Schwann cell process
Active zone
Schwann cell
Mitochondria
Nucleus of Schwann cell
Presynaptic membrane
Basement membrane
Active zone
Synaptic vesicles
Sarcolemma
Myofibrils
Synaptic cleft
Postsynaptic membrane
Junctional fold
Sarcoplasm
Synaptic trough
Nucleus of muscle cell
Acetylcholine Receptor sites

What does it mean if a cell is excitable?

Electro-physiology is the study of the electrical activity of cells

Voltage = a separation of charge across the plasma membrane /// electrical potential = separation of charge

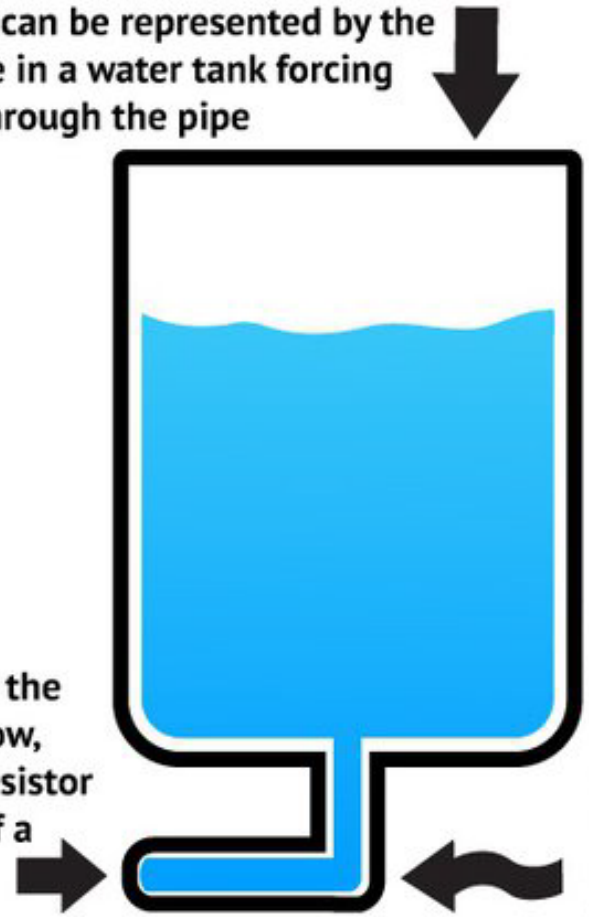
In a cells the negative charge is inside the cell and the positive charge is outside the cell. All cells have a voltage difference across their plasma membrane. It is called the resting membrane potential.

All living cells maintain a "resting membrane potential" which is about -70mV. To maintain a resting membrane potential the cell needs sodium channels, potassium channels, and the sodium-potassium ATP-ase pump.

Current is the movement of a negative charge across a membrane. This is like the flow of electrons in a wire. We call current in human physiology the "action potential".

Voltage

Voltage can be represented by the pressure in a water tank forcing water through the pipe

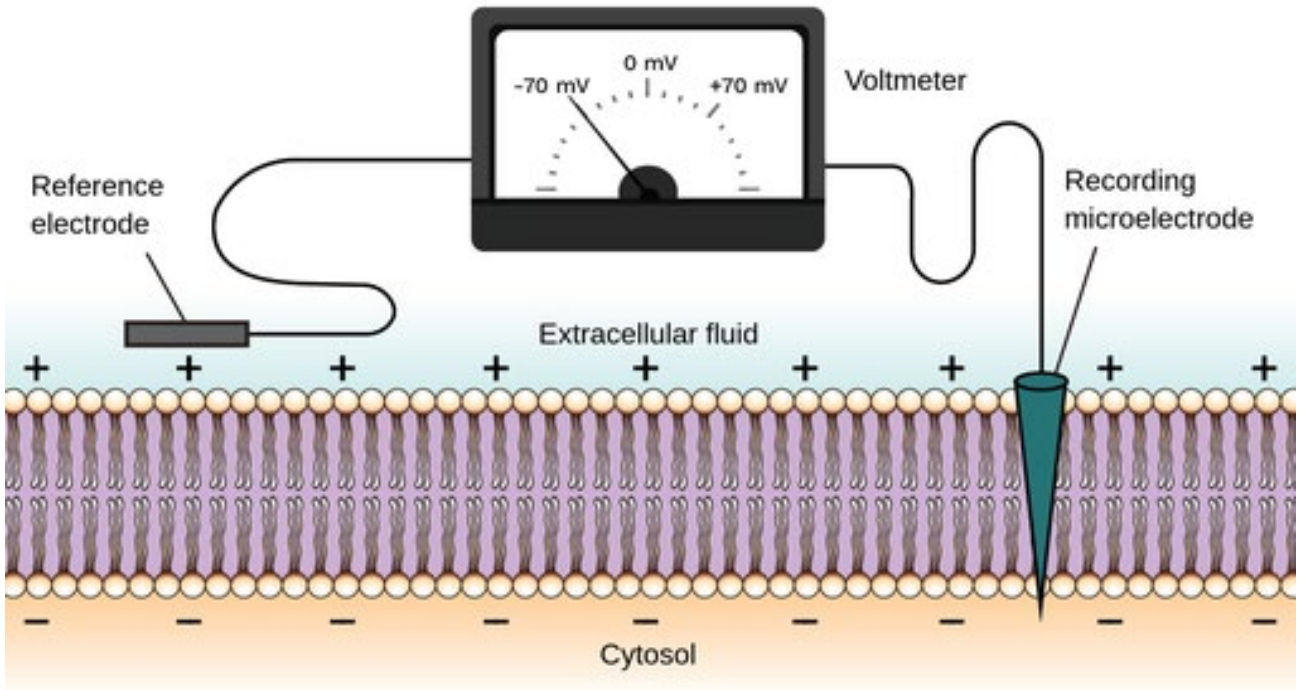


Resistor

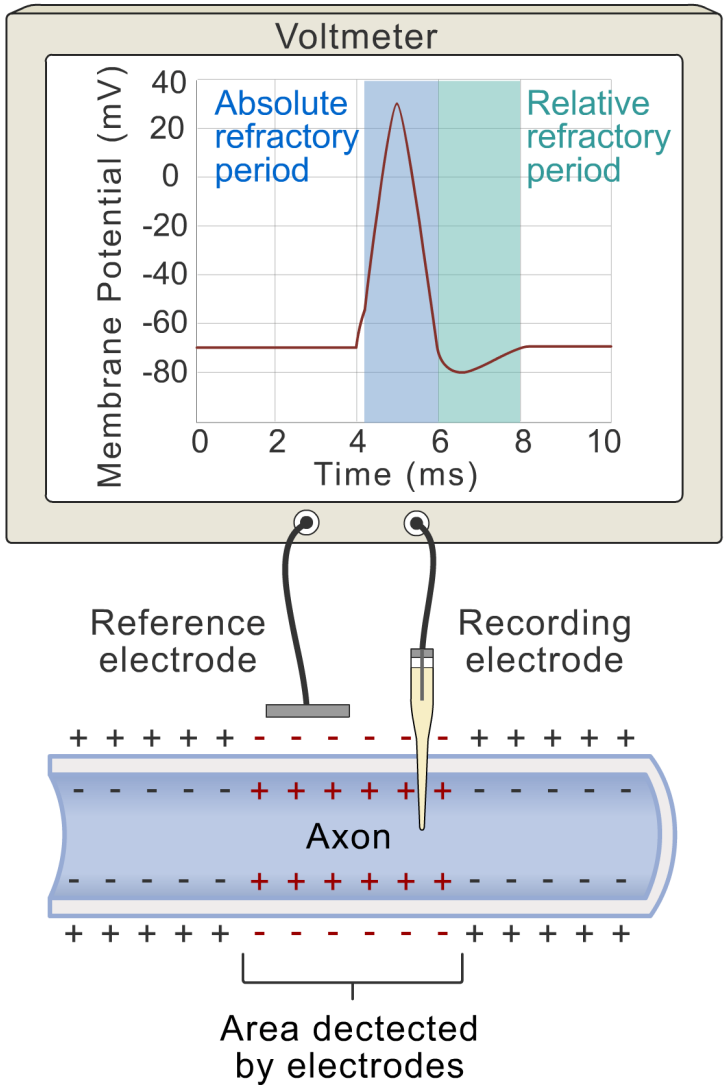
The small diameter of the pipe restricts water flow, similar to the way a resistor restricts the current of a circuit

Current

The water flowing through the pipe represents the electrical current, the more pressure there is the more current you get



Voltage = separation of charge



Current = action potential = reversal of charge across membrane that then moves in one direction across the membrane

What does it mean if a cell is excitable?

- Muscle (skeletal, cardiac, smooth) and neurons are excitable cells. This means these cells are able to create an action potential (movement of current). In nerve and muscle cells the resting membrane potential voltage is reversed at the origin of the action potential. Now the positive charge is inside the cell and the negative charge is outside the cell. The action potential moves only in one direction from its origin across the plasma membrane.

- As the current moves across the plasma membrane, the current opens transmembrane "gates" to propragates the action potential across the plasma membrane. As the action potential moves, the resting membrane potential is restored behind the action potential.

- Action Potentials = Current = movement of electrical charge across surface of plasma membrane /// once an action potential is created the action potential will "flow" in one direction across the surface of the membrane.

Excitable Cells

An excitable cell if not stimulated will maintain a resting membrane potential

Ther are more anions (negative ions) right next to the inside of the plasma membrane than on the outside // highly negatively charge cytoplasmic proteins contribute to this phenomena

In the intra-cellular fluid, there are anions such as proteins, nucleic acids, and phosphates that cannot leave the cell /// these anions help to make the inside of the plasma membrane negatively charged by comparison to its outer surface

Sodium ions (Na^+) is the major extracellular fluid (ECF) cation /// there are excess potassium ions (K^+) in the intracellular fluid (ICF)

The net effect of all these ions is to create a voltage difference across the plasma membrane

Facilitated gated diffusion for sodium and potassium ions contribute to maintaining the resting membrane potential.

Electrically Excitable Cells

Muscle and nerve cells at a resting membrane potential state maybe stimulated to generate an action potential

Voltage shift from the negative RMP to a positive value, and back to the negative value again occurs during an action potential.

An action potential at one point on a plasma membrane will cause another one to happen immediately in front of the first action potential.

This then triggers another one a little farther along and so forth (appropriates a wave of negativity “now on the outer surface” moving across the plasma membrane) – this propagates the action potential across surface

RMP (resting membrane potential) is a stable voltage potential seen in all cells but only in muscle and nerve cell may the RMP be changed into an action potential

What steps occur to change a resting potential into an action potential in excitable cells?

Sodium ion gates open in the plasma membrane (these are voltage regulated gates!) Remember, sodium concentration is higher outside of the cell!

Sodium ion diffuses instantly down their concentration gradient into the cell

These cations override the negative charges in the cytosol

This causes “depolarization” - inside of the plasma membrane becomes briefly positive

Now, the Na^+ gates close and K^+ gates open. Remember, potassium ion concentration is higher inside the cell.

Now K^+ to rush out of cell – making interior once again more negative (i.e. repolarize cytosol to restore negative state) /// repelled by the positive sodium charge and partly because of its concentration gradient

The sodium-potasium-ATPase pump moves ions (Na and K) across the membrane to readjust the concentration of sodium and potassium across the plasma membrane and restore the resting membrane potential

The Skeletal Muscle's Sliding Filament Theory

In the early 1950s, a hypothesis to explain skeletal muscle contractions was to think of proteins folding like an accordion

With the discovery of the electron microscope, scientist could “see” the thin and thick proteins inside the skeletal muscle.

These proteins did not shorten during contraction (no accordion like action)

Therefore, the original hypothesis was wrong!

A new hypothesis suggested the muscle fibers shortened by having the proteins sliding across each other.

This hypothesis was proven to be “true” and is now called the sliding filament theory.

Four phases of a skeletal muscle contraction cycle

Excitation > the process in which the action potential from the motor strip reaches the neuromuscular junction. Acetylcholine is released into the synaptic cleft.

Excitation-contraction coupling > Acetylcholine initiates a local potential and if there is enough acetylcholine then an action potential is created on the sarcolemma. The action potential is propagated to the sarcoplasmic reticulum /// now the AP opens voltage regulated gates on the sarcoplasmic reticulum to allow calcium to diffuse out of the SR // calcium binds to regulatory proteins

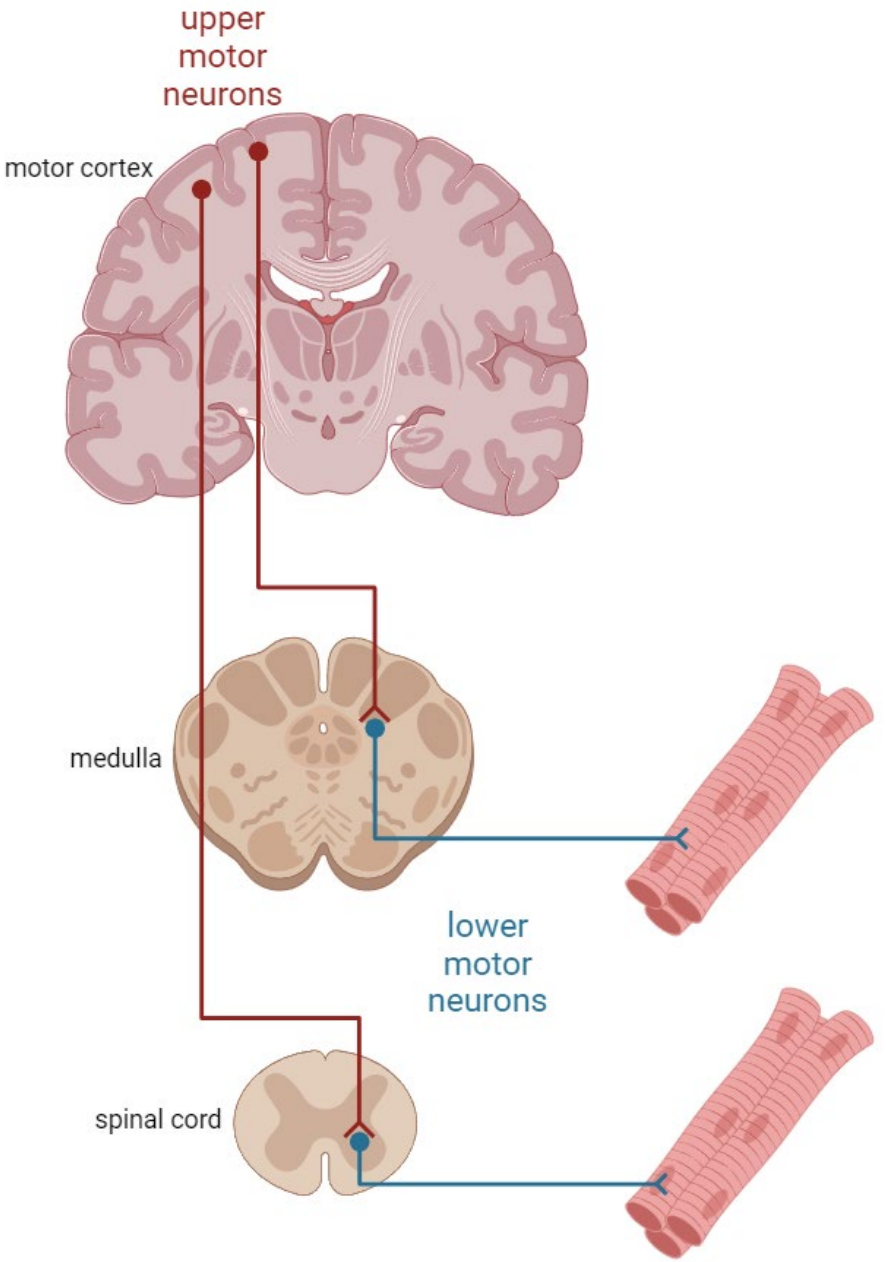
Contraction (the power stroke) > myosin head (pre-charged with energy) and actin are now able to form a cross “bridge” // step in which the muscle fiber develops tension and the contractile proteins “slide” across each other

Relaxation > after tension is created, events occur to allow a muscle fiber to lose tension and return to its resting length // this occurs at the synapse when acetylcholine is removed from the synaptic junction // then all downstream events are reversed!!!!!

Once an action potential starts, you can not stop it.
The action potential goes only in one direction!

Excitement

Moves action potential to sarcolemma.



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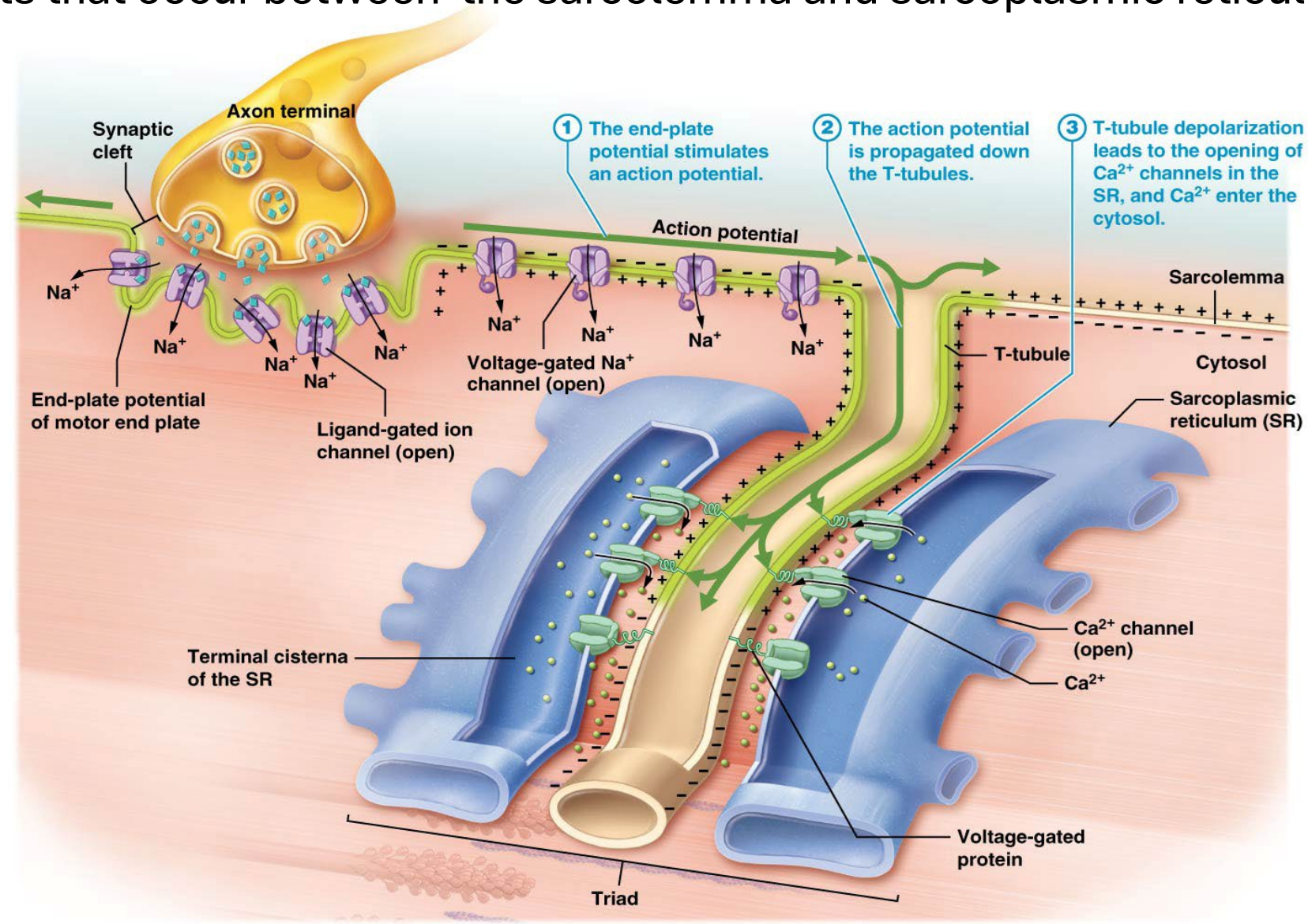
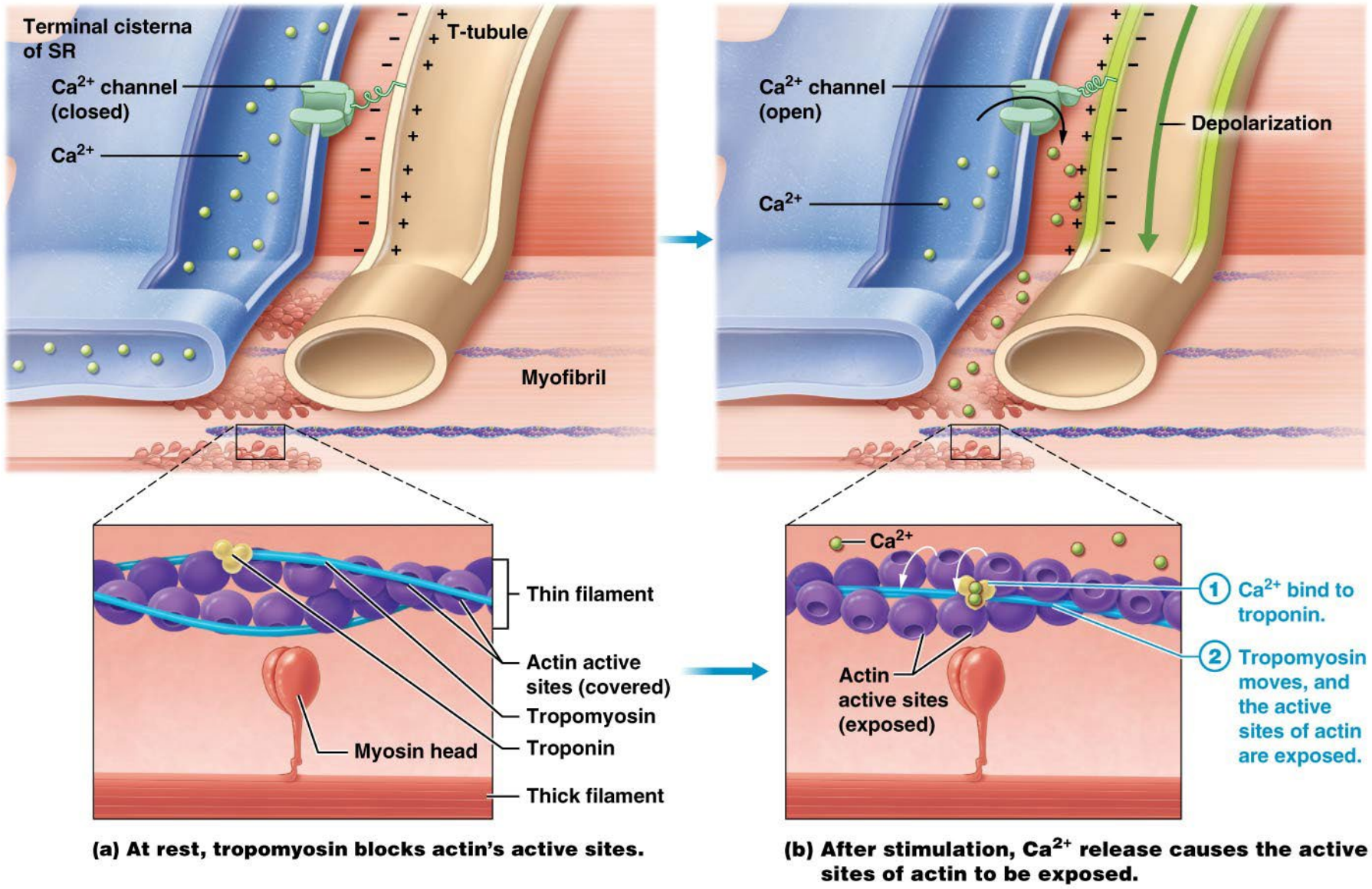
Excitation-contraction coupling.

Events that occur between the sarcolemma and sarcoplasmic reticulum.



Excitation-contraction coupling.
Events before contraction.



(a) At rest, tropomyosin blocks actin's active sites.

(b) After stimulation, Ca^{2+} release causes the active sites of actin to be exposed.

Contraction = Power Stroke

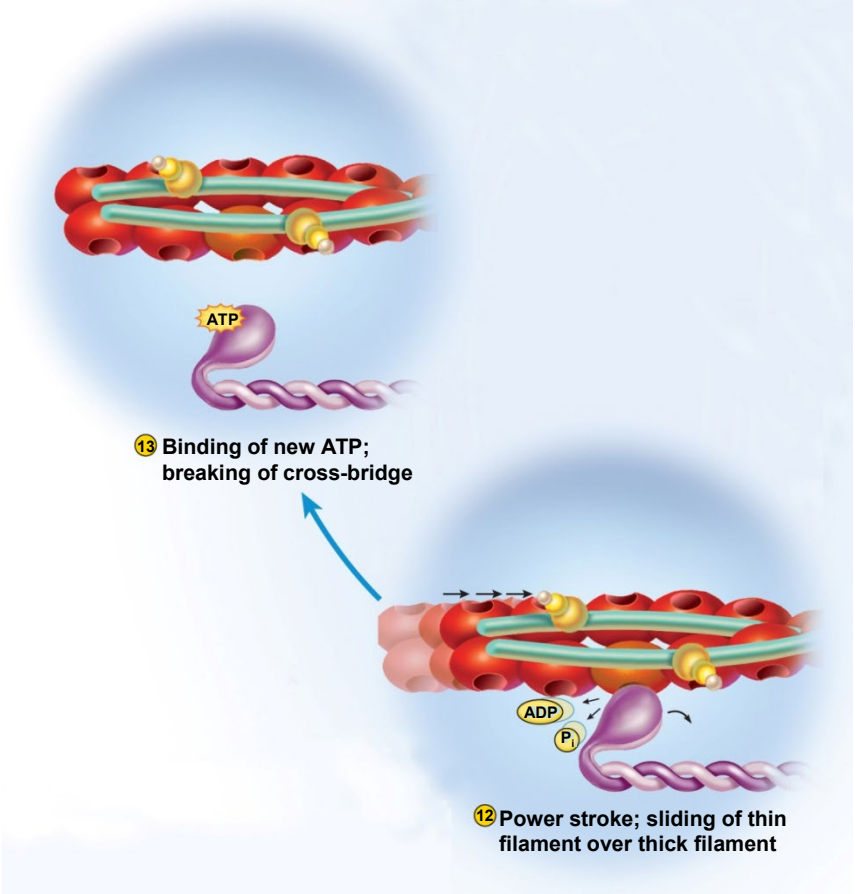
The Power Stroke

When the “precocked myosin head” is allowed to bind to the actin receptor for myosin – the stored energy in the cocked myosin head is released

For this to occur – regulatory proteins must move out of the way to expose the myosin binding site

After the “cross bridge” between the myosin and actin is formed – the energy released from the cocked myosin molecule pulls the thin filament over thick filament // the Z disc move closer together

Myosin head can not release the actin cross bridge until new ATP molecule binds to myosin // this “breaks the bridge”



Contraction

After power stroke the actin-myosin-cross bridge can not be “broken”

To break the cross bridge “new” ATP must bind to the myosin head

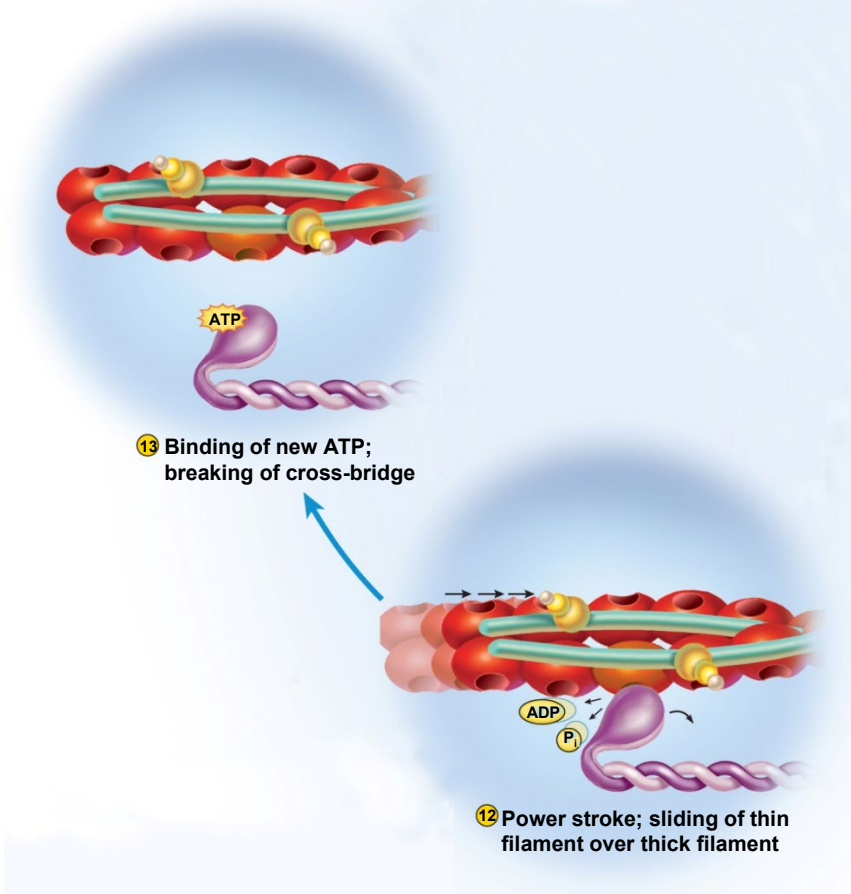
ATP now allows myosin head to release actin’s binding site.

At this moment, the myosin head is again “cocked” // it is again loaded with energy // now the power stroke may be repeated

each head performs 5 power strokes per second

each stroke utilizes one molecule of ATP

As one bridge is broken many more are formed which maintains tension in muscle // the myosin heads are wrapped around the axis of the myosin molecule and function like a “screw” as it finds new binding sites on the action molecule.



Power Stroke and the Sliding Filament

Review:

To start, lets assume that the myosin head pulled on the actin, but the myosin heads is still attached to the actin. The cross bridge can not be broken until new ATP binds to the myosin head. This will break the cross bridge, and re-cocks the myosin head.

1 - ATP docks on myosin head, hydrolysis of ATP to ADP, breaks cross bridge // this will cock myosin head (head is now loaded again with energy)

2 – Formation of myosin-actin cross bridge (myosin head binds to new receptor on actin molecule) – after the cross bridge forms then an enzyme will allow the energy of the myosin head to be released, next....

3- Power stroke, the myosin head pivots and now thin filament slides over thick filament // note: the cross bridge is still in attacked!

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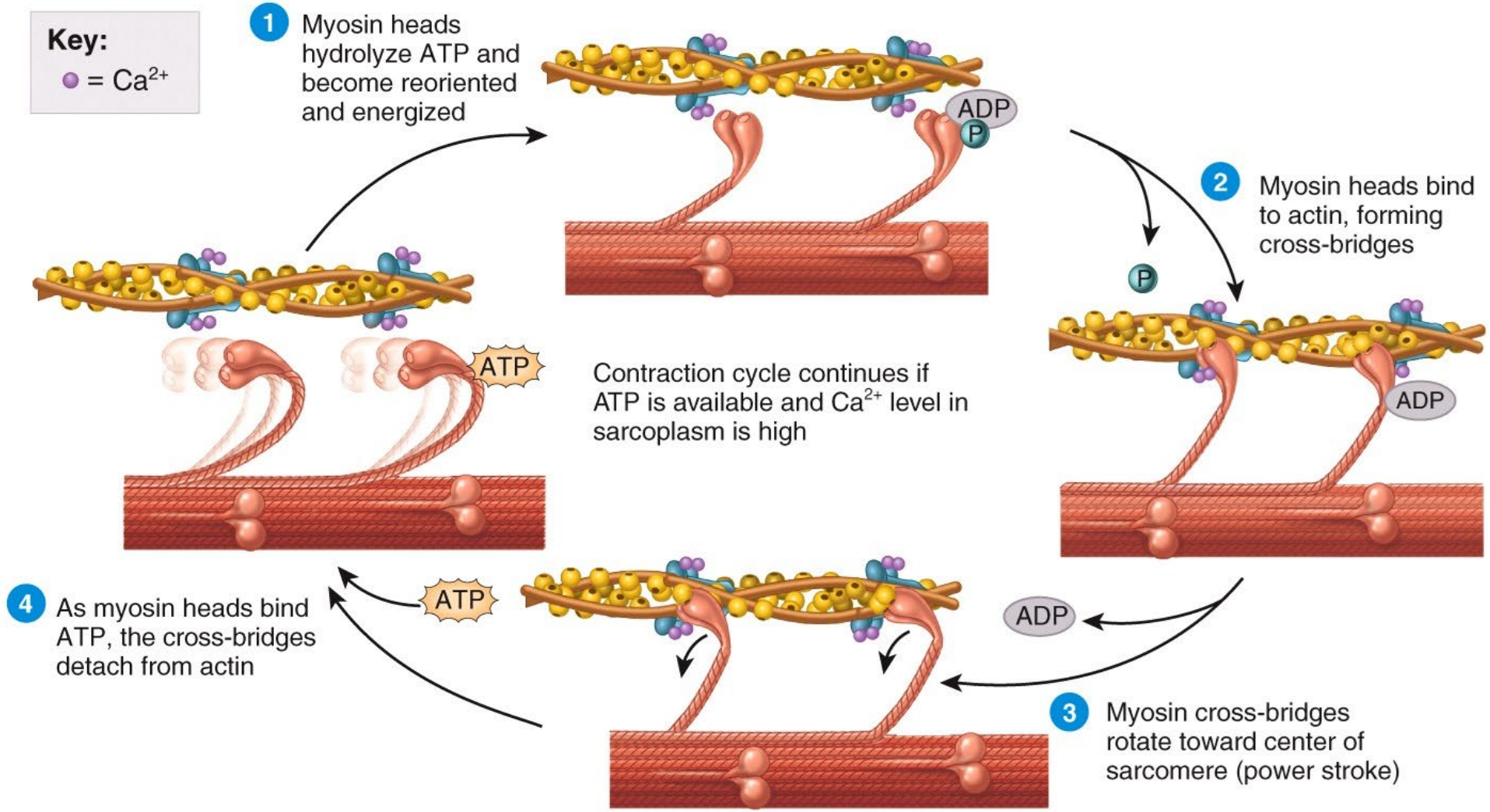
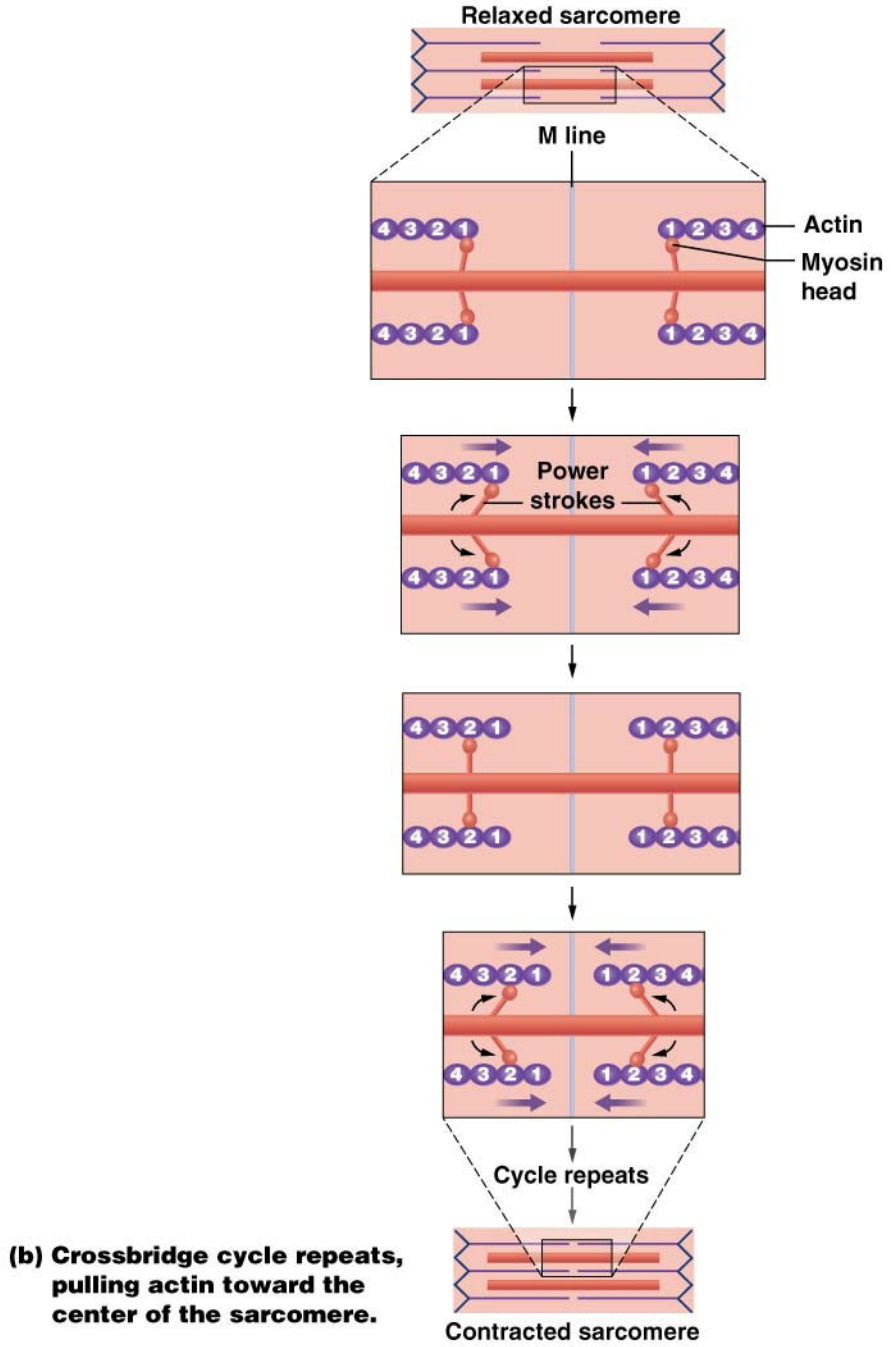
4 – Binding of another ATP to myosin head will break cross bridge and cock the myosin head with energy again /// if no ATP is available then the cross bridge may not be broken


Key:
= Ca^{2+}
1 Myosin heads hydrolyze ATP and become reoriented and energized
ADP
P
2 Myosin heads bind to actin, forming cross-bridges
P
ADP
3 Myosin cross-bridges rotate toward center of sarcomere (power stroke)
ADP
ATP
4 As myosin heads bind ATP, the cross-bridges detach from actin
ATP
Contraction cycle continues if ATP is available and Ca^{2+} level in sarcoplasm is high

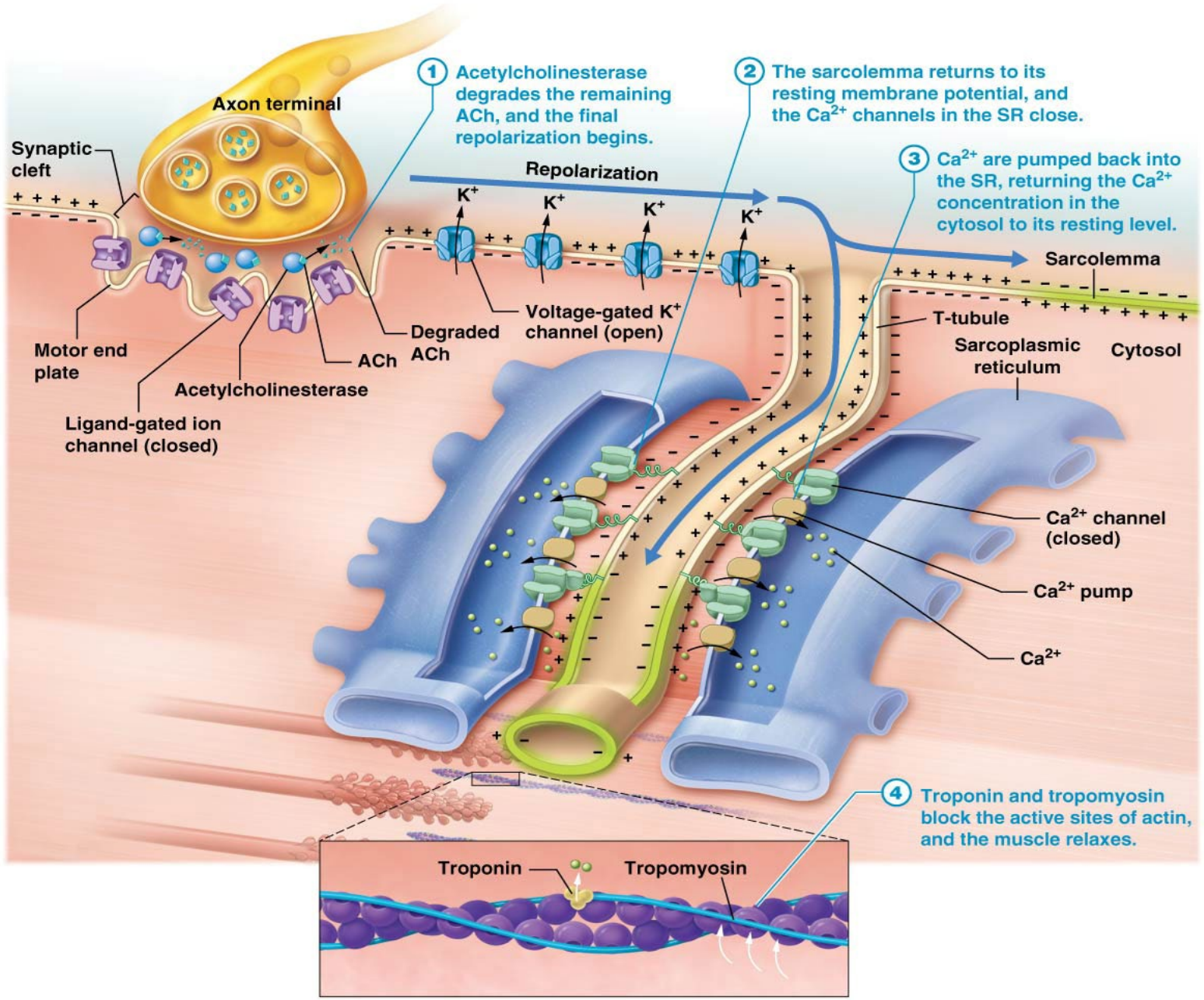
The Contraction Phase

A cross-bridge cycle brings the thin filaments closer to the center



(b) Crossbridge cycle repeats, pulling actin toward the center of the sarcomere.

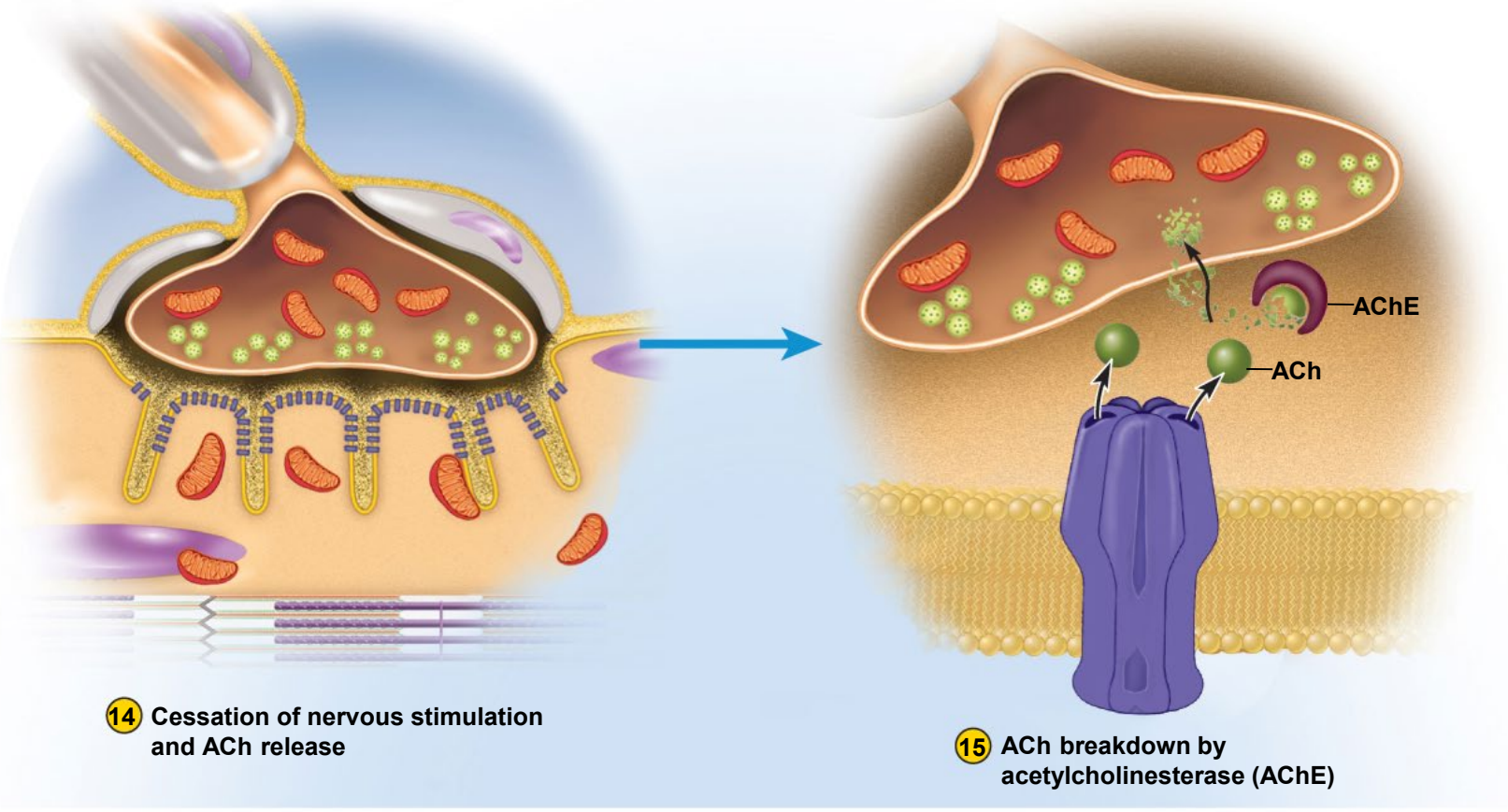
Relaxation Phase – calcium “pumped” back into sarcoplasmic reticulum.



What happens to the regulatory proteins when calcium is removed from the cytosol?

What must occur at the neuromuscular junction before calcium maybe pumped back into the sarcoplasmic reticulum?

Relaxation



If you stop new nerve action potentials, then this will close voltage regulated calcium channel at synaptic knob.

This stops exocytosis of more ACh into synaptic cleft

ACh-Esterase breaks down Ach already in synaptic cleft // fragments reabsorbed into synaptic knob

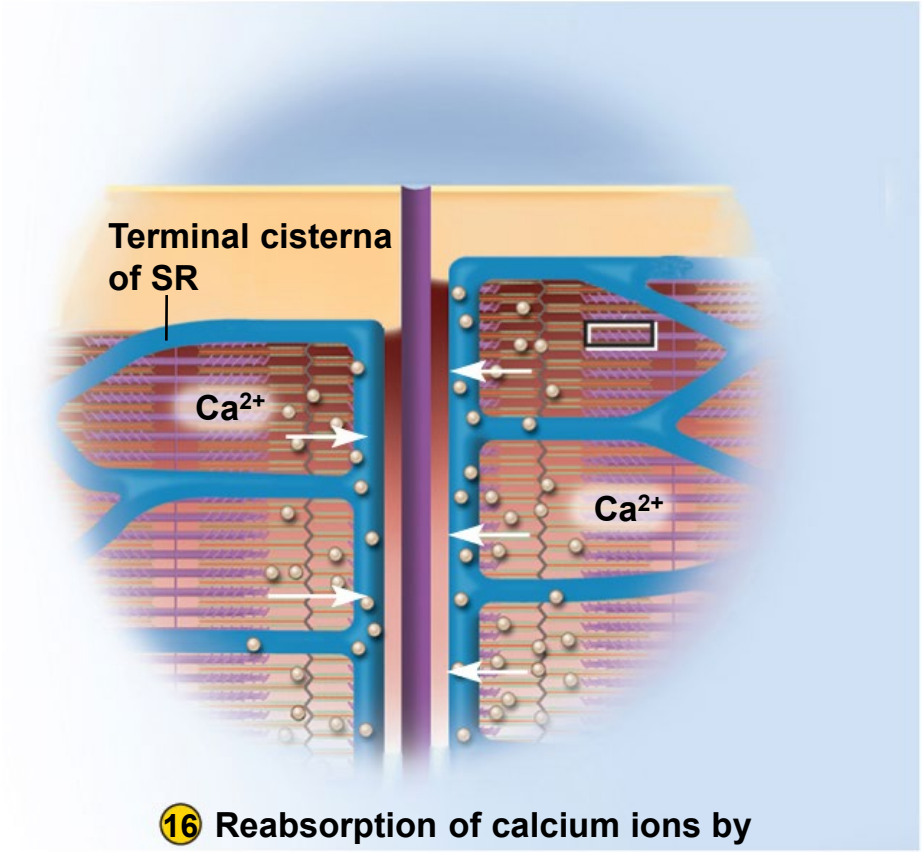
This prevents excitation by ACh and all the “downstream” events are reversed

Relaxation

- Ca^{+2} is pumped back into SR by active transport. // Why is this is active transport?

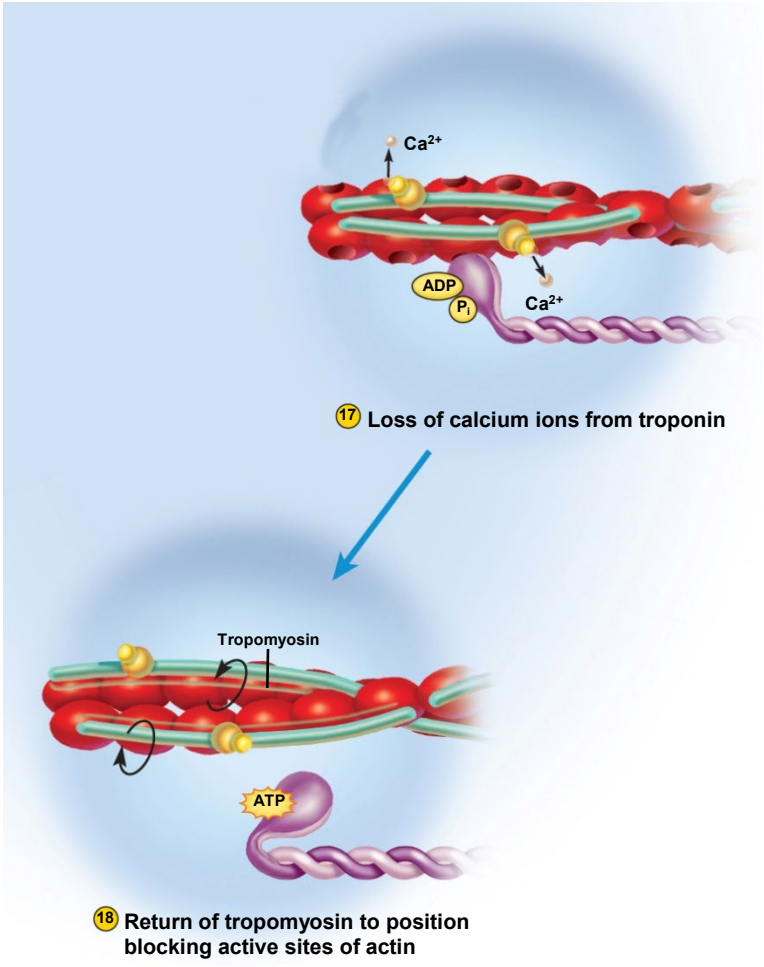
- Ca^{+2} binds to calsequestrin while in storage in SR

- <u>Muscle function requires a lot of ATP because ATP is required for both muscle contraction and muscle relaxation.</u>

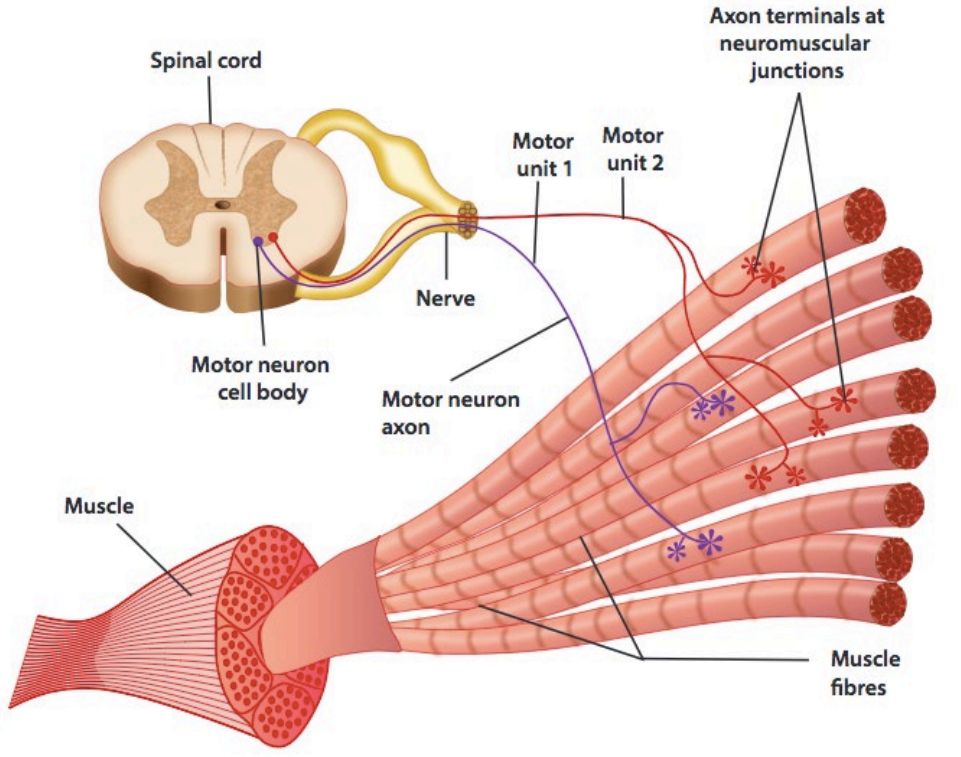


Relaxation

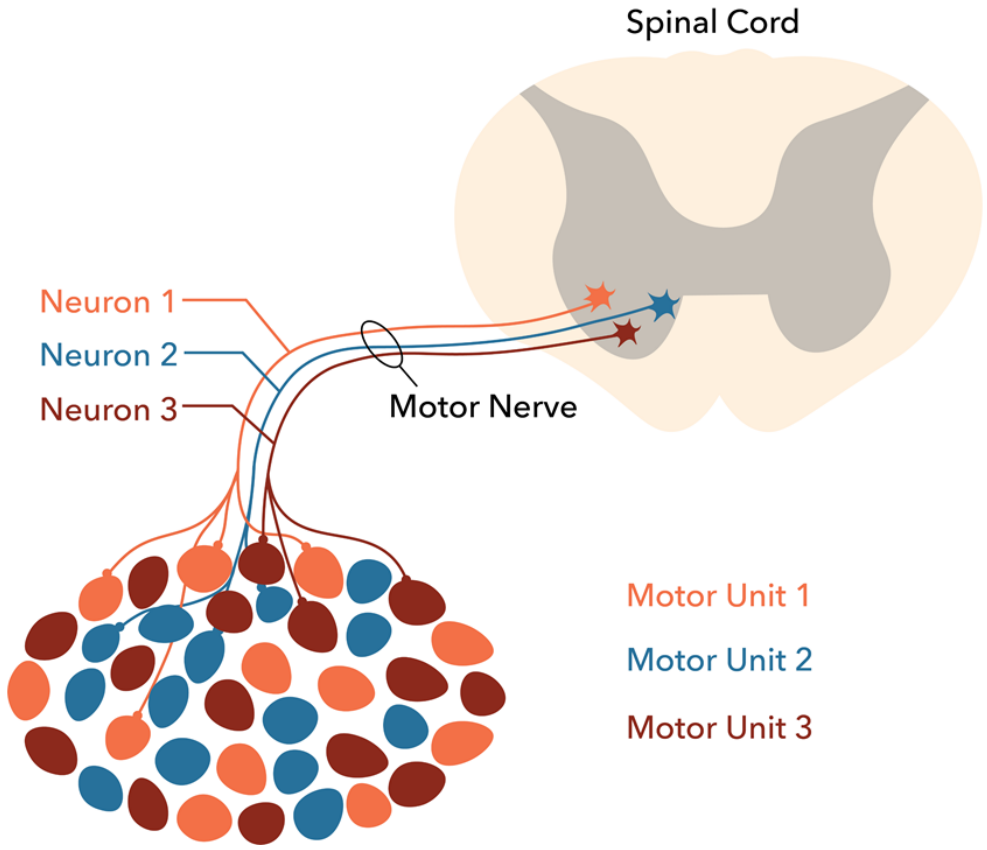
- Ca^{+2} removed from troponin as calcium is pumped back into SR
- Now tropomyosin moves back to block the myosin binding sites
- Muscle fiber ceases to produce or maintain tension
- Note: in relaxation more ATP is used to cox myosin heads for future contractions
- Muscle fiber returns to its resting length due to recoil of elastic components & contraction of antagonistic muscles



Motor Unit



Axon of motor neurons extend from the spinal cord to the muscle. There each axon divides into a number of axon terminals that form neromuscular junctions with muscle fibers scattered throughout the muscle.



A skeletal muscle motor unit is the basic functional unit of contraction, consisting of a single somatic motor neuron and all the muscle fibers it innervates. When the neuron fires, all associated fibers contract simultaneously. Motor units vary in size—from a few fibers (precise, small muscles) to over 1,000 (powerful, large muscles)—and are recruited based on required force, with smaller, fatigue-resistant units activated before larger, fast-fatiguing ones.

Characteristics of Muscle Contraction

- Innervation ratio
  - Measures of size of motor unit
    - $Innervation\ Ratio = \frac{\#\ of\ muscle\ fibers}{\#\ of\ axons}$
  - Varies across muscle
    - Ocular muscles ~ 10-15 fibers per axon
    - First dorsal interosseous ~ 340 fibers per axon
    - Biceps branchii ~ 750 fibers per axon
    - Gastrocnemius ~ 2000 fibers per axon

The Physiology of Rigor Mortis

Why may a deceased person roll over or sit up in a bed?

Rigor mortis is the hardening of muscles and stiffening of body that occurs after death.

Rigor mortis begins 3 to 4 hours after death // tension in tissue peaks after twelve hours /// muscle tension then diminishes over the next 48 to 60 hours

At time of death all myosin molecules are “loaded with ATP”. No new ATP maybe created. Since the myosin heads are “cocked” the fiber could initiating a “power stroke”

The active calcium channels used to keep calcium in the SR is no longer working. /// Calcium starts to leak out of the SR. Now rigor mortis starts to develop slowly over time.

Released Ca^{+2} exposes myosin binding site on actin // all myosin heads were pre-loaded with ATP and cocked before death // now contraction cycle occurs and myosin-actin cross-bridges are formed – Since the dead cell can not make new ATP there is no available ATP to break the cross bridges // Muscle tension stays in the muscle and increases. /// See next slide

Rigor Mortis

- Furthermore, SR membranes start to break down which allows more calcium to bind to troponin
- Over time, as more calcium leaves SR, muscle generates greater tension as more myosin-actin cross bridges are formed
- During this phase of rigor mortis, the muscle can not relax. If enough tension is developed, then the deceased person may move.
- ATP is required to break the actin-myosin cross bridge // after death - new ATP can not be formed. /// Any ATP formed prior to death only last a few millisecond (ATP is not stored)
- After 48 to 60 hours muscle tension starts to decrease. This occurs because now the myofilaments (i.e. the proteins) are hydrolyzed by lysosomes' enzymes

Neuromuscular Toxins

Some toxins interfere with synaptic function and can result in either skeletal muscle spastic paralysis or flaccid paralysis

Spastic paralysis = over stimulated and muscle can not relax

Some pesticides contain cholinesterase inhibitors // bind to acetylcholinesterase and prevent Ach hydrolysis

Spastic paralysis - a state of continual contraction of the muscles

This may cause paralysis of diaphragm // possible death

Tetanus (lockjaw) is a form of spastic paralysis caused by toxin of *Clostridium tetani*

Tetanus toxin blocks glycine release in the spinal cord /// lack of glycine causes over stimulation and spastic paralysis of the muscles /// glycine in the spinal cord normally stops motor neurons from producing unwanted muscle contractions

Neuromuscular Toxins

Some toxins interfere with synaptic function and can result in either spastic paralysis or flaccid paralysis of the muscles

Flaccid paralysis – a state in which the muscles are limp and cannot contract

Curare – compete with ACh for receptor sites, without causing an action potential (prevents muscle contraction)

Plant poison used by South American natives to poison blowgun darts

Botulism – type of food poisoning caused by a neuromuscular toxin secreted by the bacterium *Clostridium botulinum*

Blocks release of ACh causing flaccid paralysis

Use botox cosmetic injections to remove wrinkles in skin