Sensory and Motor

Lecture 4

Nervous System

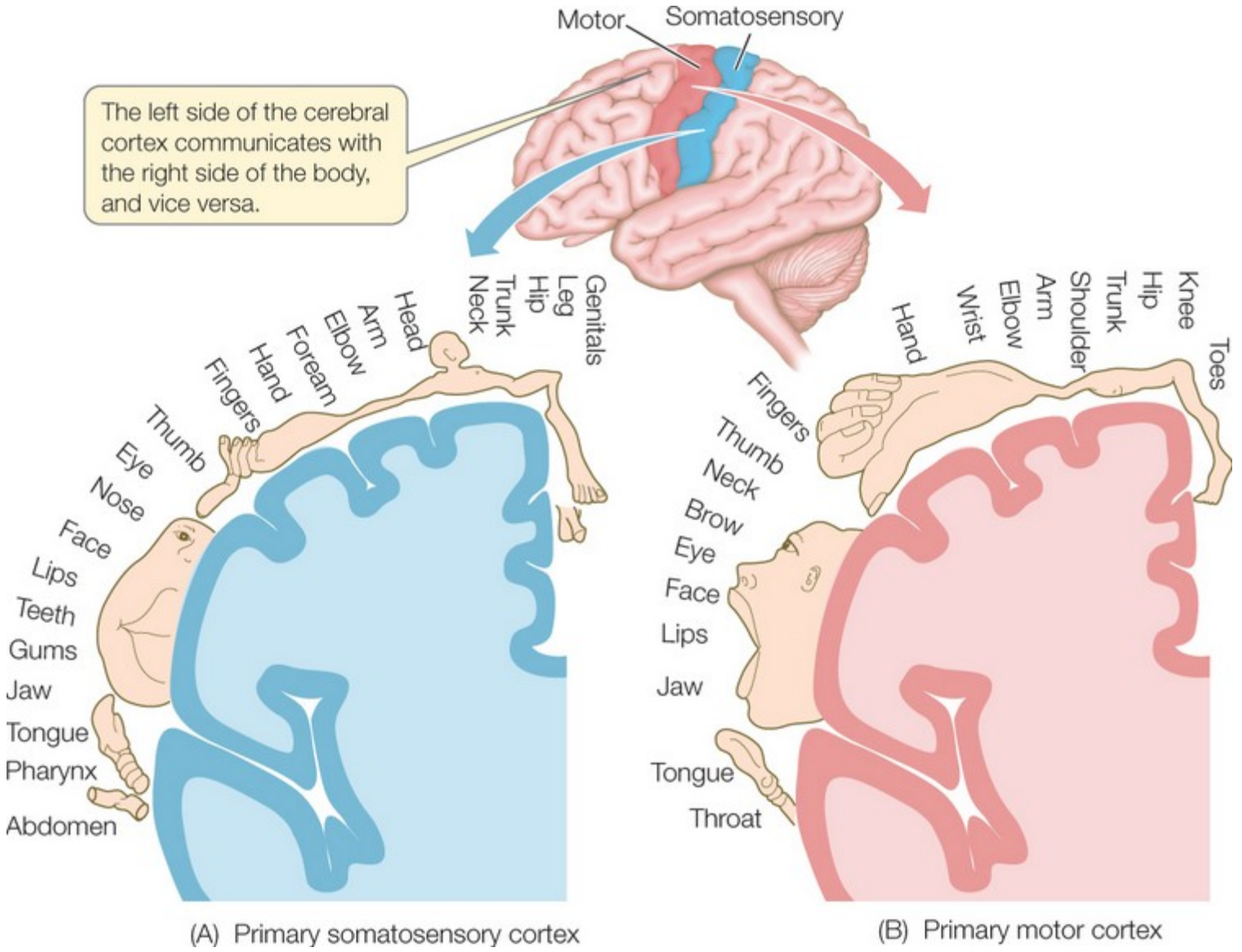
- Sensory- Afferent
  -Primary Sensory Cortex (Postcentral Gyrus)
  - Dorsal Root
  - Dorsal Root Ganglia
  - Dorsal Horn
  - Lissauers tract
  - Spinothalamic Tract, Dorsal Columns of the Medial Lemniscus, Spinocerebellar Tract
- **Motor- Efferent**
  -Primary Motor Cortex (Precentral Gyrus)
  - Ventral Root
  - Ventral Horn
  - Corticospinal Tract
  - Neuromuscular Junction

The Efferent Nervous System

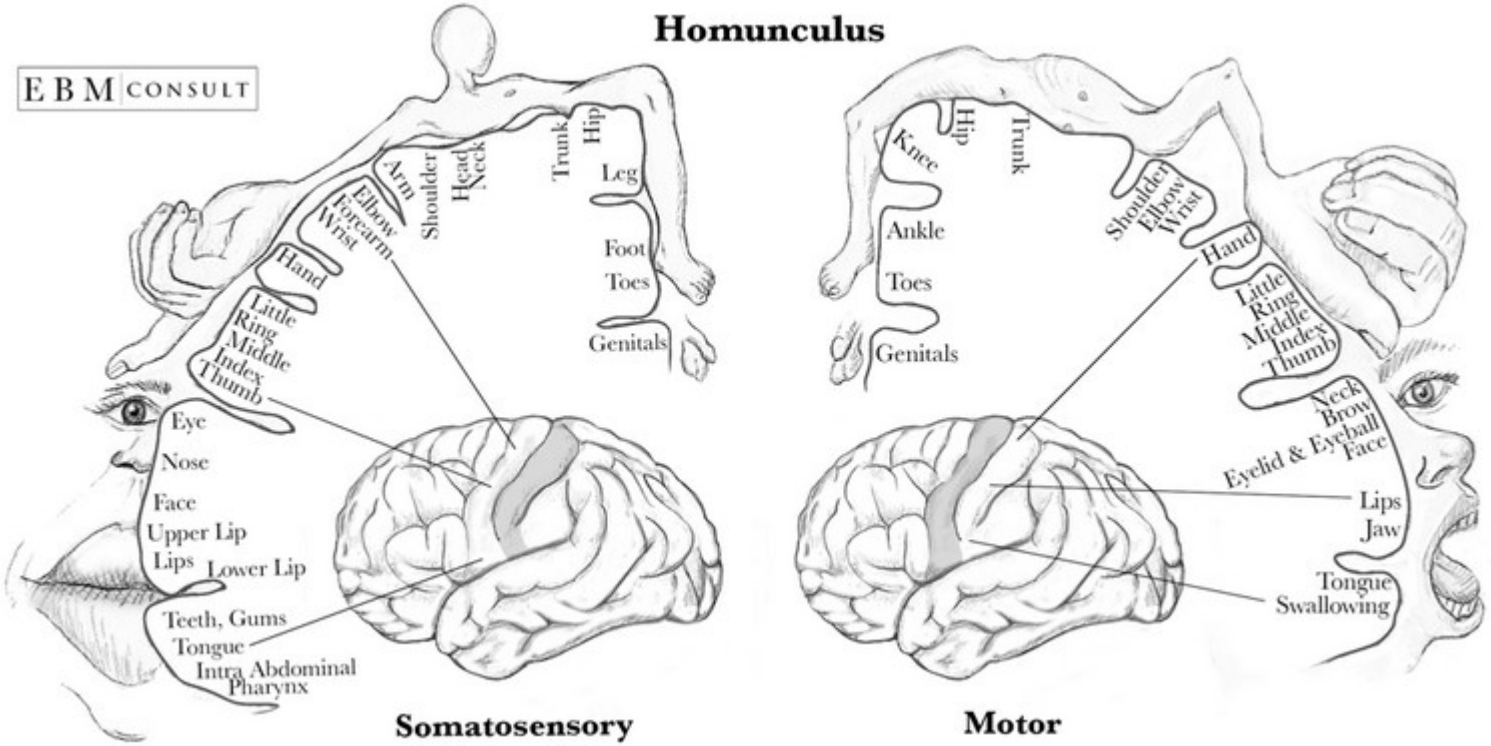
- **Somatic Nervous System-** Skeletal Muscle
  - Posture
  - Balance
  - Planned body movement

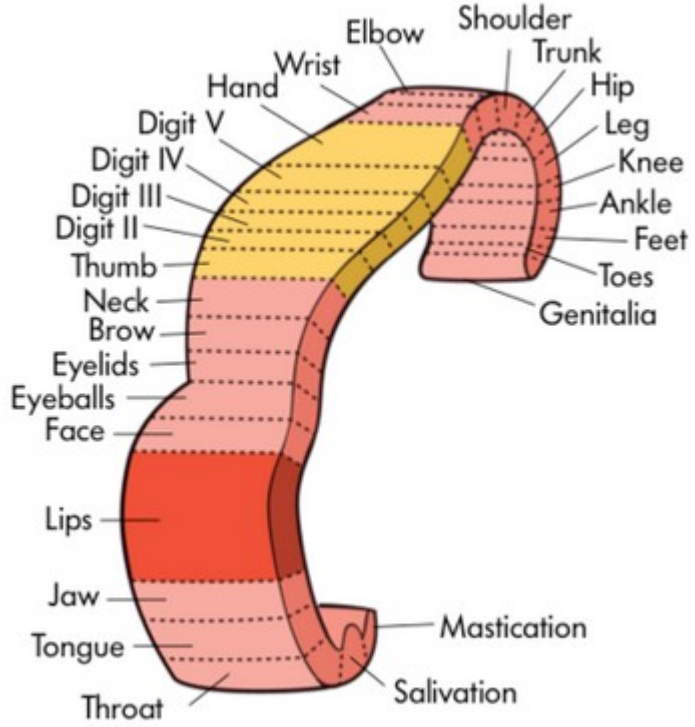
- Autonomic Nervous System

The Somatic Nervous System Homunculus

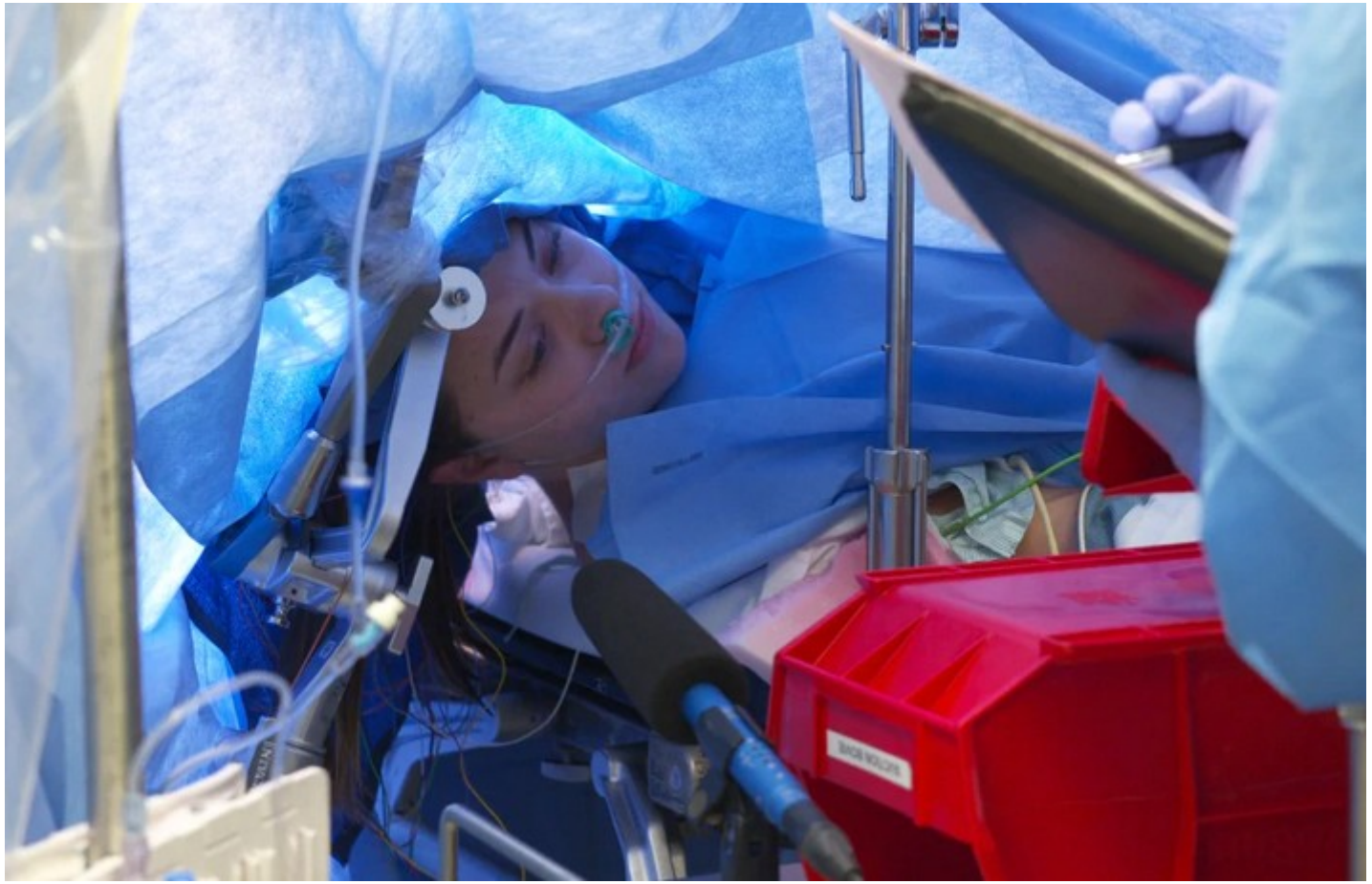


The Somatic Nervous System Homunculus



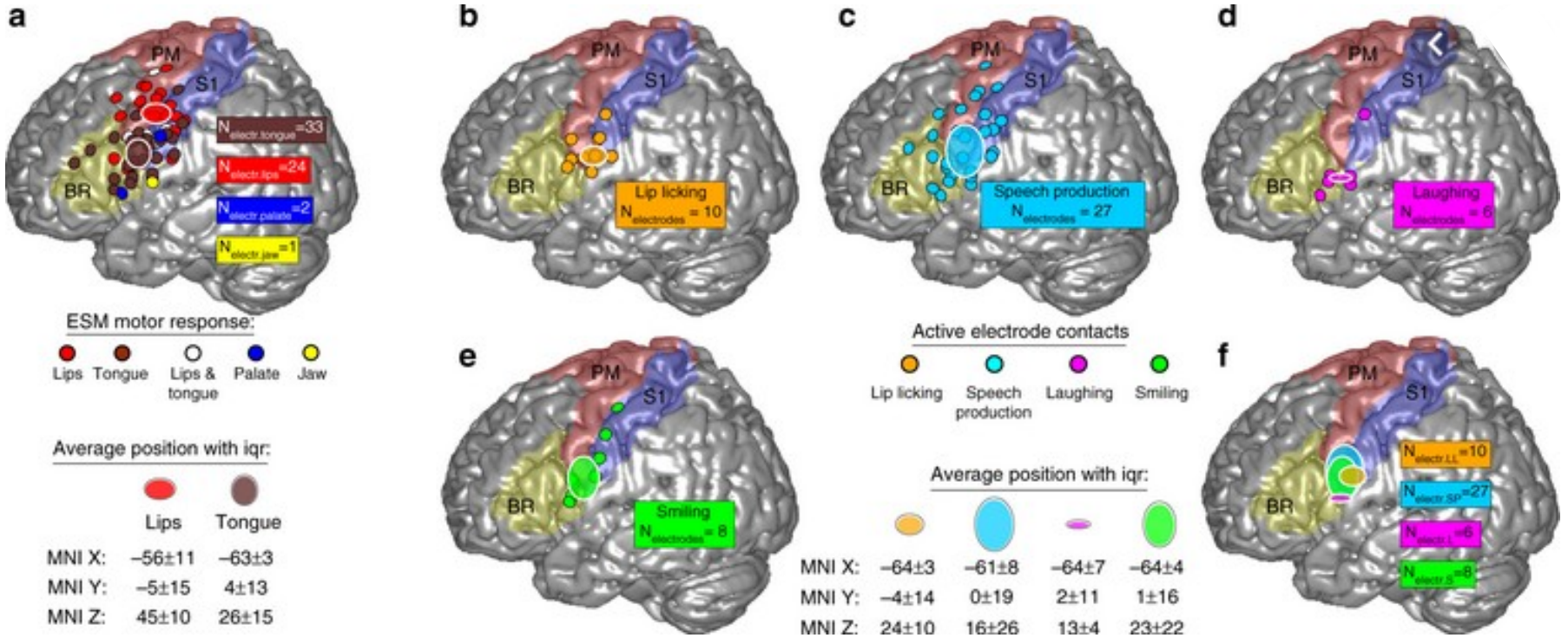


How are these areas discovered?



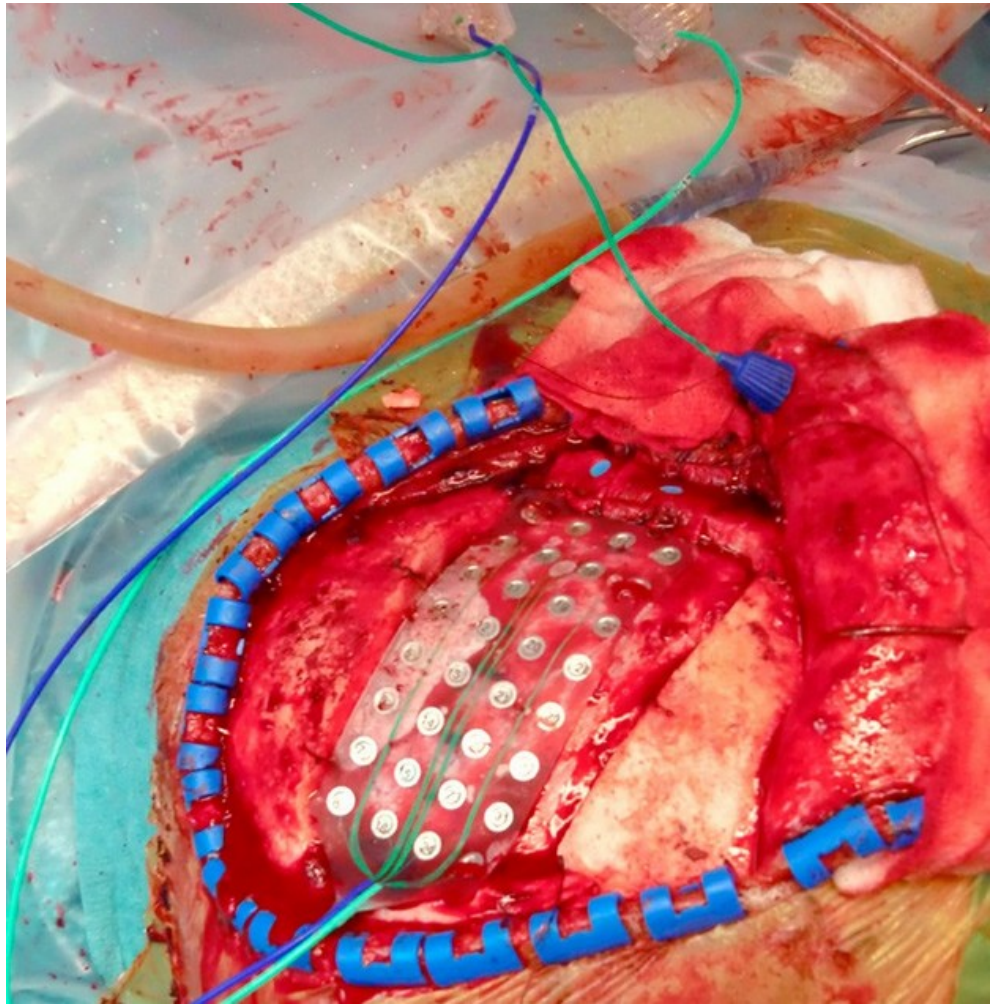
- Patients are required to stay awake during brain surgery
- Researchers can stimulate distinct areas on the surface of the cortices to determine their physiological correlate
- This is a painstaking process done with consent of patient in addition to surgical procedure.

fMRI can also help determine neural correlates of motor control



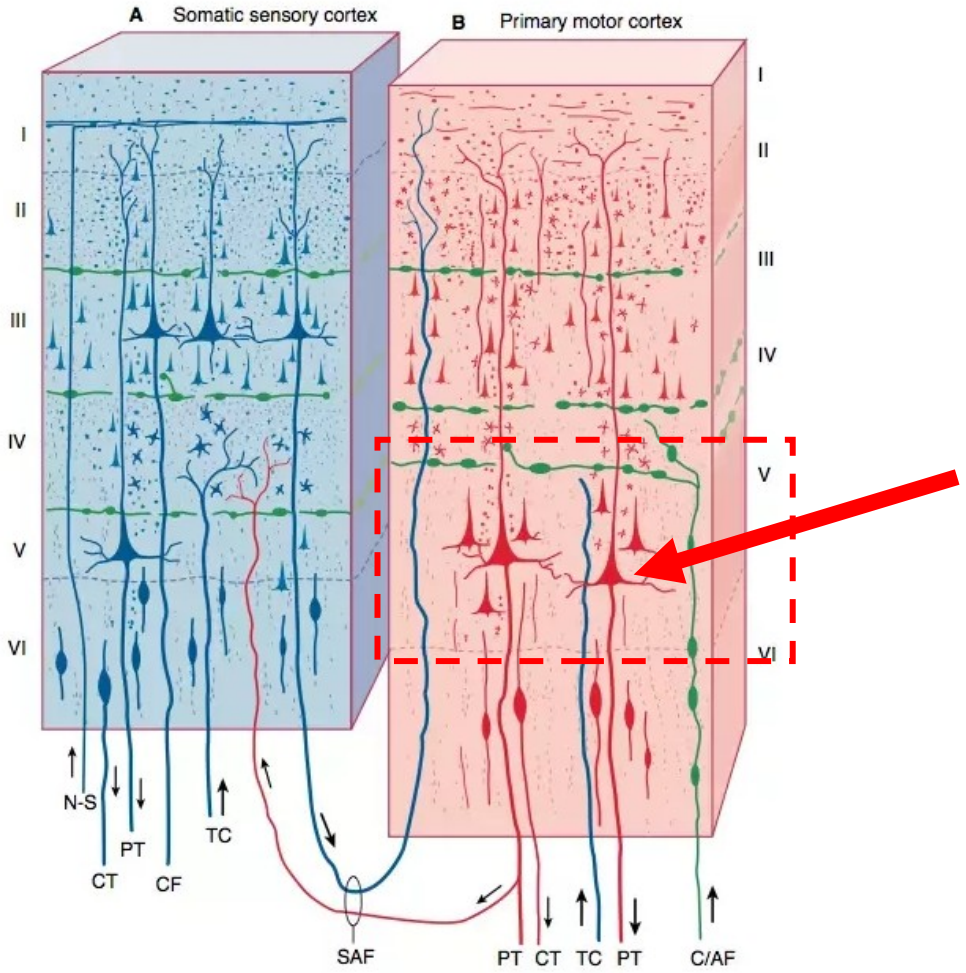
- fMRI detects changes in oxygen consumption within a given tissue
- Neural activity typically results in local increases blood supply and O_2 consumption
- Therefore we can infer activation of certain brain regions based on local O_2 consumption

Intracranial electrodes also help



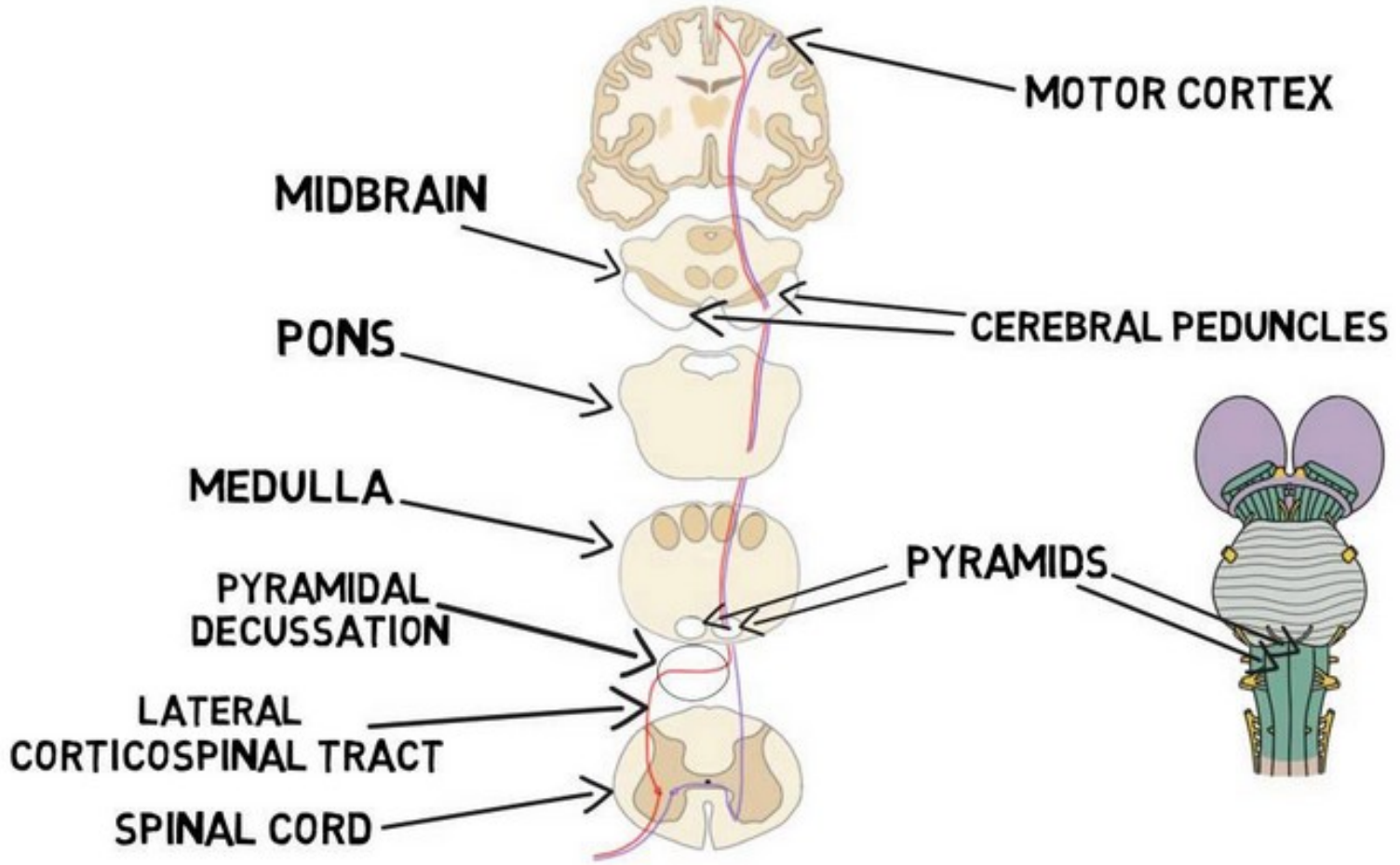
- Patients with epilepsy will occasionally need to get intracranial electrodes placed to monitor seizure activity.
- Computer algorithms have been developed to resolved complex activity to single neuron firing.
- Researchers can ask question about specific neural activity when the patient is living their lives in the world.

Where are the **upper-motor** neurons of the **primary motor cortex** located?



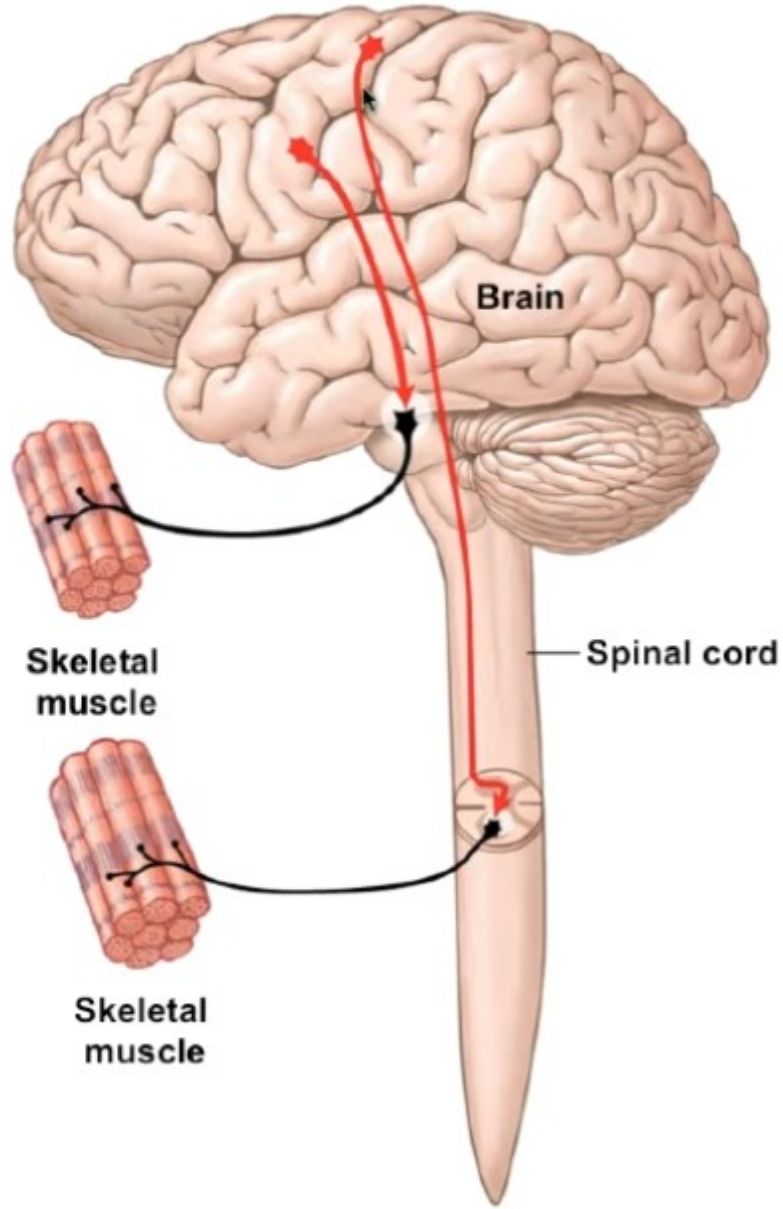
- Upper motor neurons that exit the brain for the spinal cord reside within Layer V (5) of the primary motor cortex.
- These specialized pyramidal neurons are known as Betz Cells.

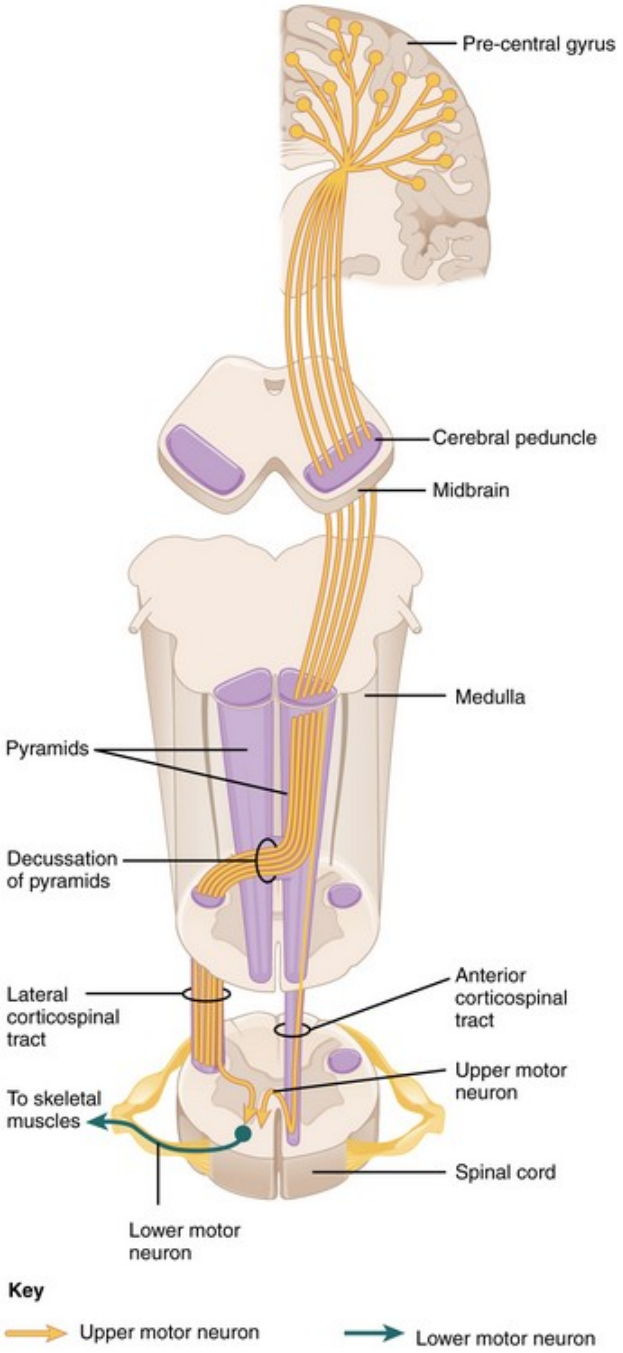
Where do neurons from the brain go?



Corticospinal Pathway

- **<u>Corticospinal Pathway:</u>** the major somatic efferent pathway
- Primary Motor Cortex
  - upper motor neuron; cell body in the cerebrum, axon descends
- Spinal Cord
  - lower motor neuron; cell body in the ventral horn, axon exits ventral root of the spinal cord
- Skeletal Muscle
  - Neuromuscular junction
  - Acetylcholine release → muscle contraction





A More Detailed Look

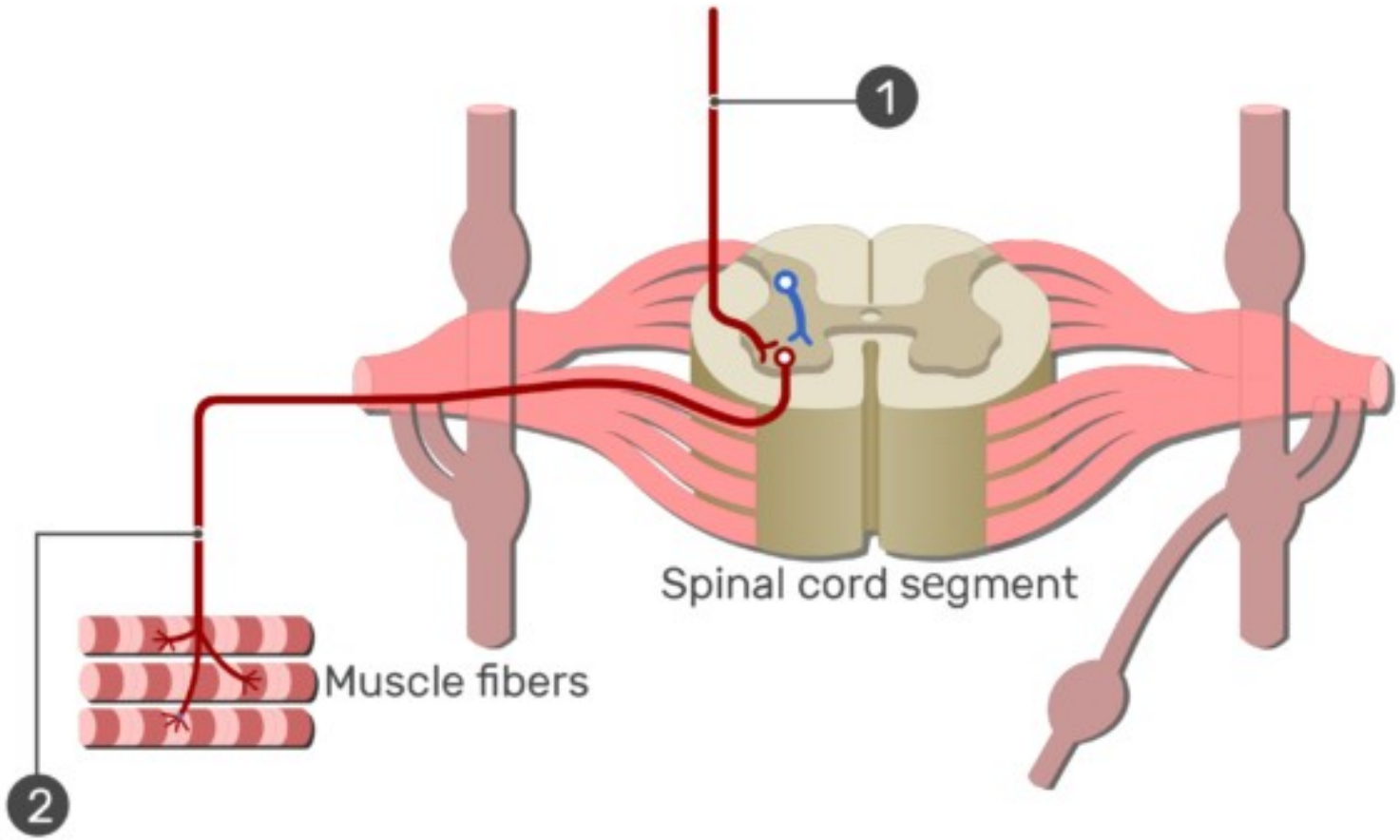
- Betz cells leaving layer V of cortex making up the precentral gyrus must pass through the brainstem prior to the spinal cord.
- 85% of these neurons will decussate to the contralateral side to the lateral corticospinal tract within the brainstem.
- The remainder will travel down the anterior corticospinal tract before decussating at the anterior commissure.
- All corticospinal neurons eventually synapse with primary motor neurons in the ventral horn of the spinal cord.

Take some time and lets draw it out!!!!!

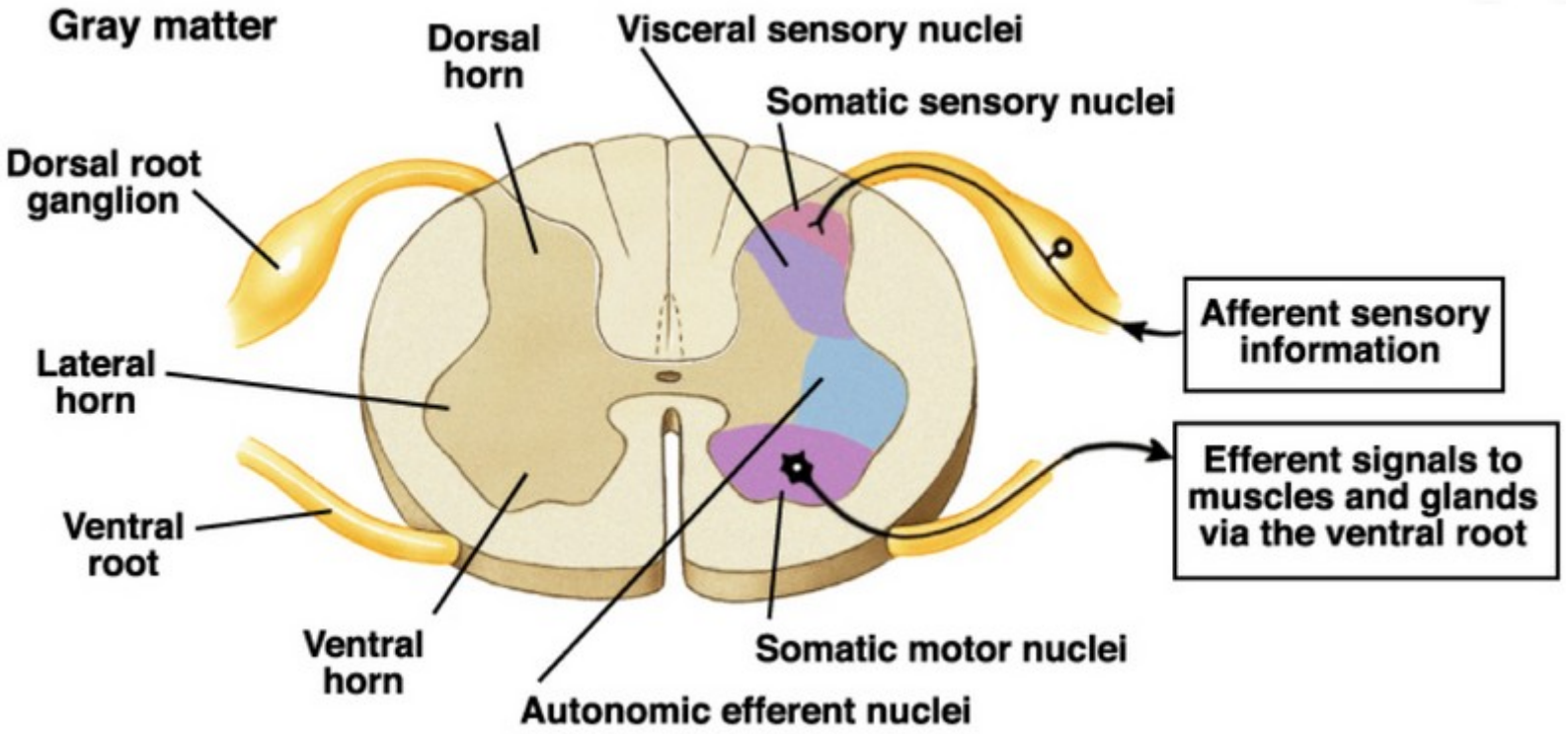
Motor Unit

- **CNS control**: motor cortex, basal ganglia, cerebellum, brainstem, spinal cord
- **The motor unit**:
  - motor neuron originating in the spinal cord
  - long axon exits ventral horn of the spinal cord
  - excitatory synapses to skeletal muscle fibers
    - **Neuromuscular Junction**
- **Neurotransmitter**: Acetylcholine
- **Neurotransmitter receptor:** Nicotinic Acetylcholine Receptor

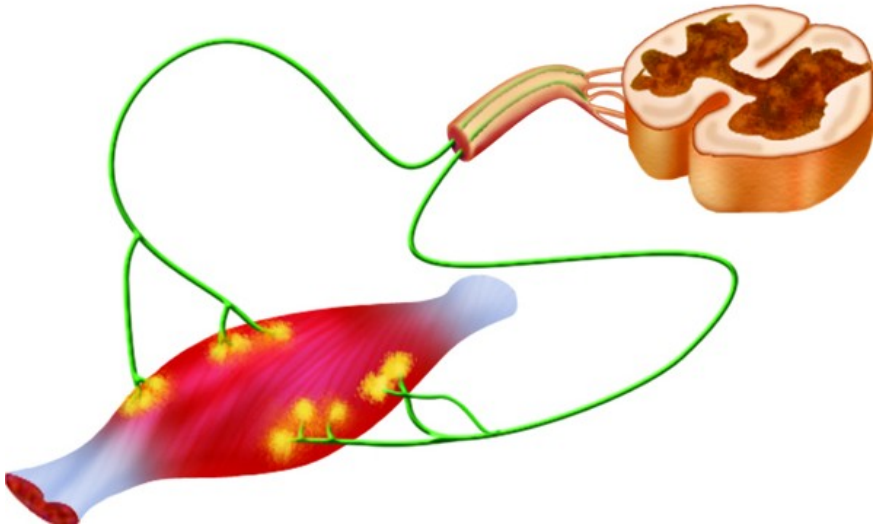
What happens within the spinal cord???



Spinal cord motor processing

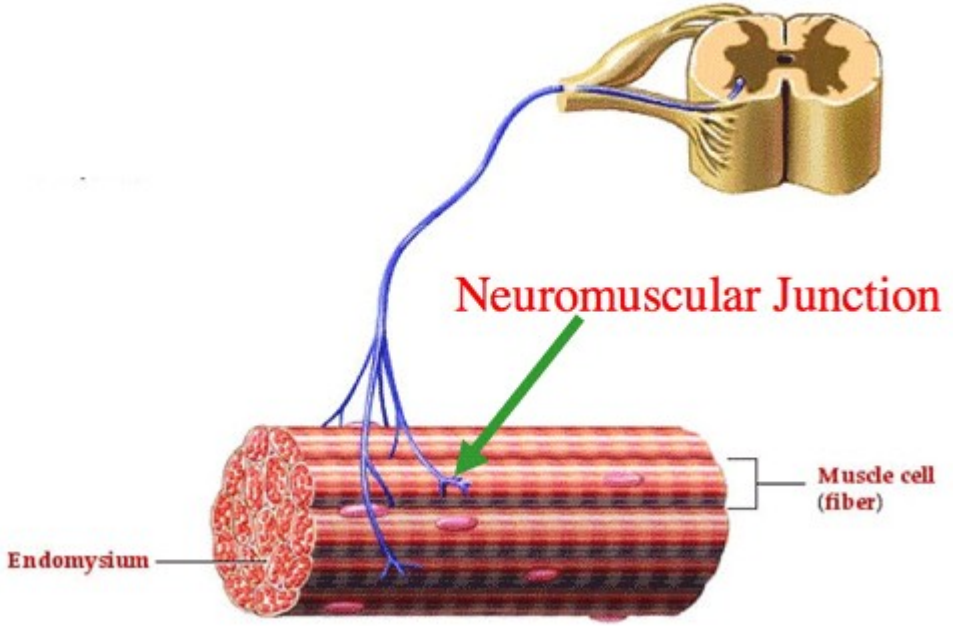


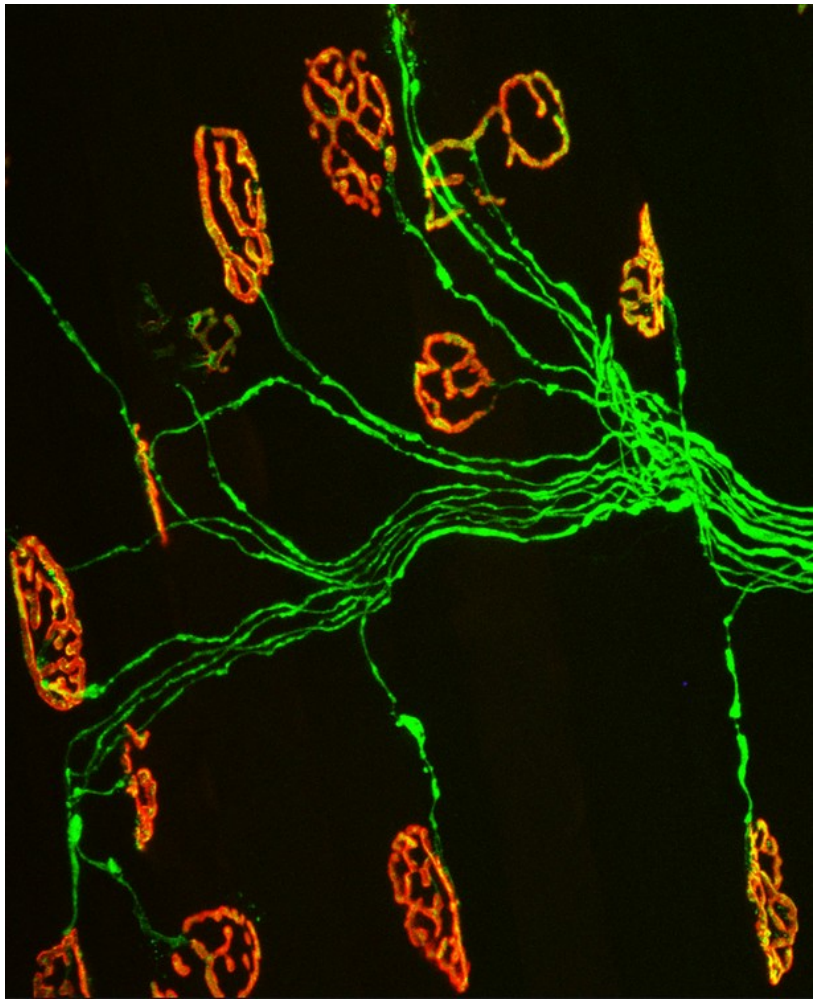
- The spinal cord has distinct regions that serve to process either sensory or motor information.
- The cell bodies of primary motor neurons of the efferent somatic nervous system reside within the ventral horn of the spinal cord.
- They exit the CNS via the ventral root.

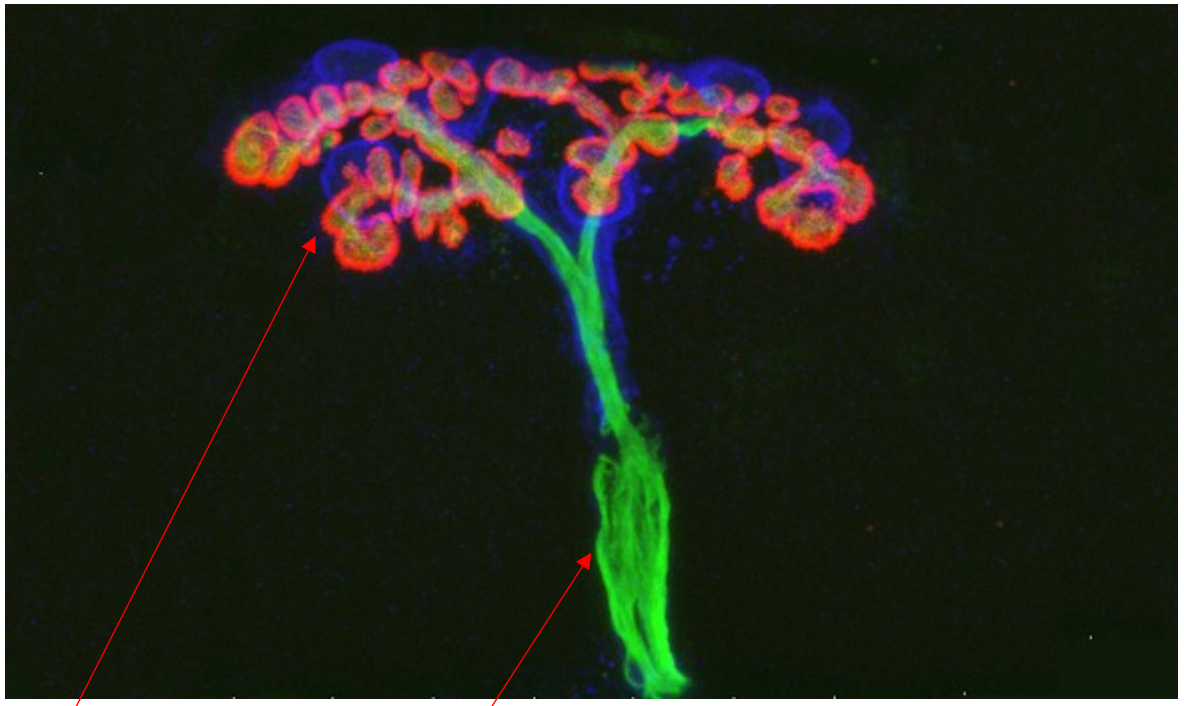


Motor Neuron Synapses

- Each neuron that exits the ventral horn will form multiple synapses with multiple muscle cells (or fibers).
- These neurons follow the blue print laid out by the motor homunculus within the primary motor cortex.

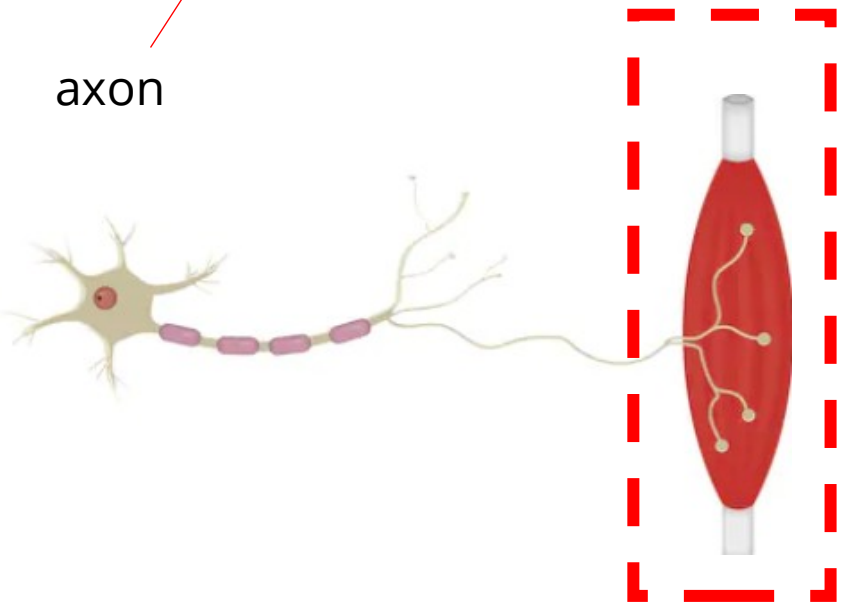






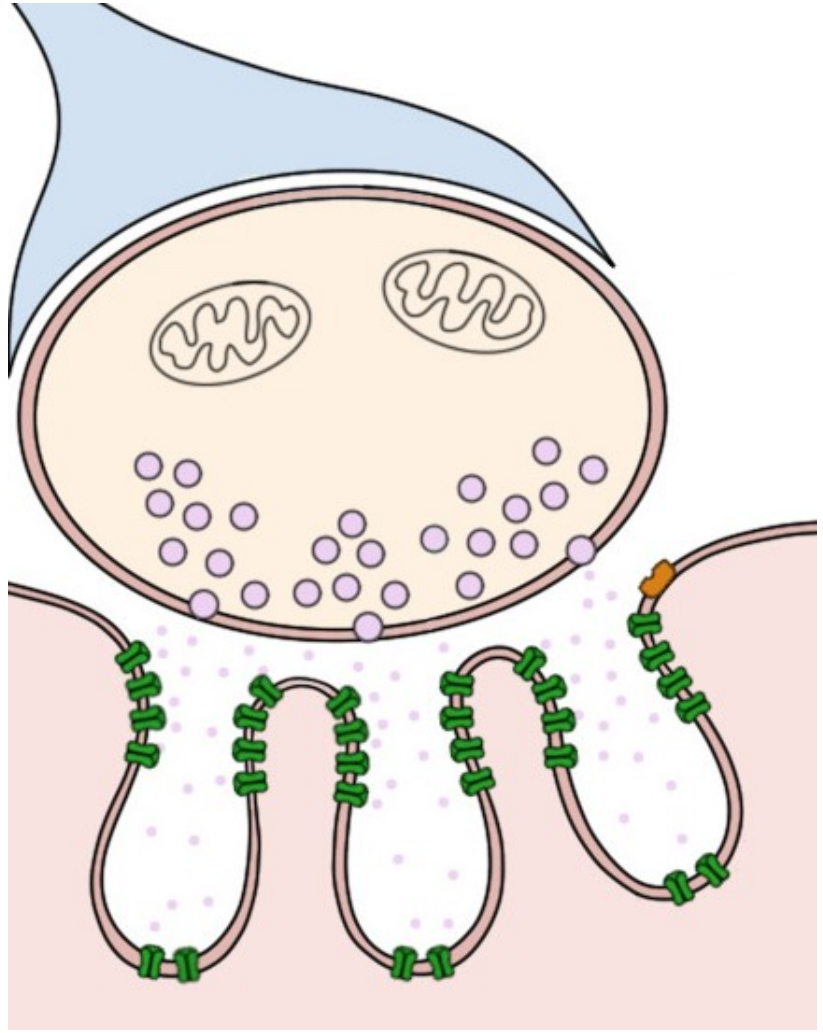
Nerve Terminal

axon



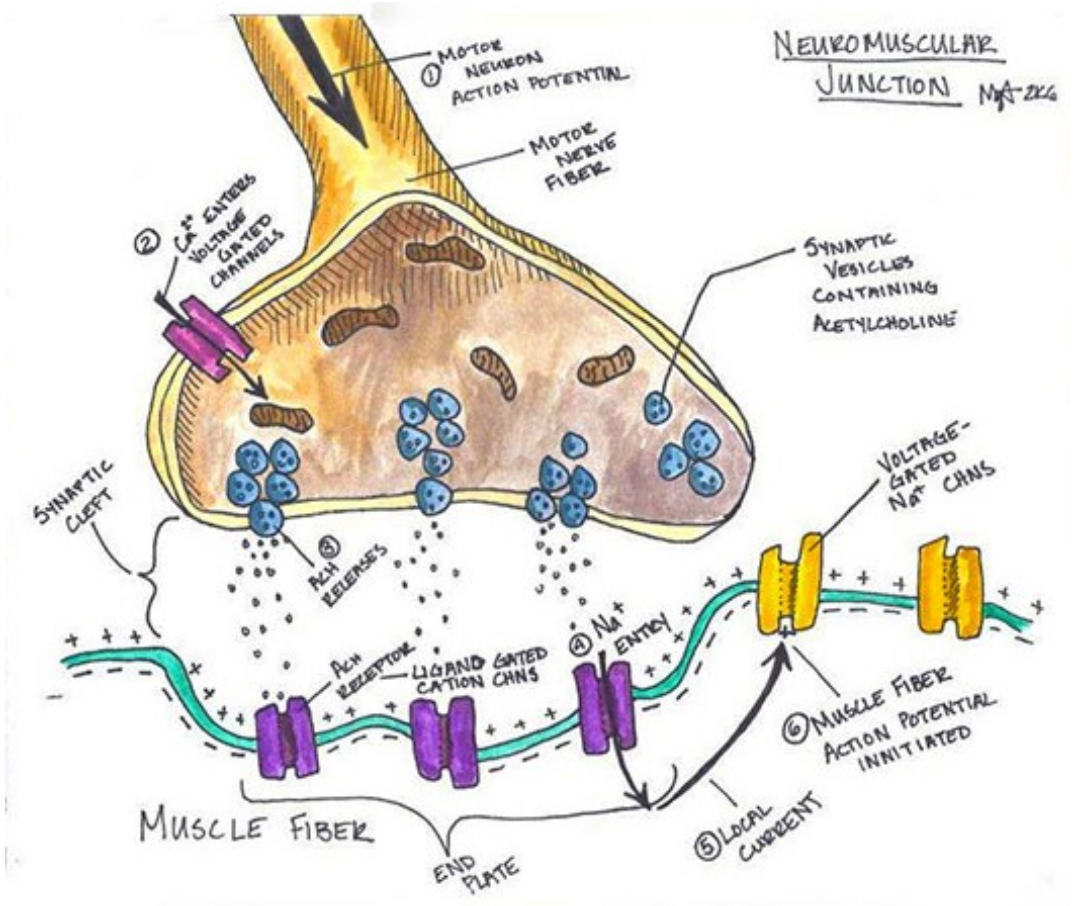
Specialization of the Neuromuscular Junction

- Neurons leaving the ventral horn of the spinal cord project sometimes long distances to their muscle targets.
- The synapses between muscle and the incoming neuron is called the neuromuscular junction.
- These synapses are extremely specialized in terms of their nts used, their special organization, and their electrical properties.



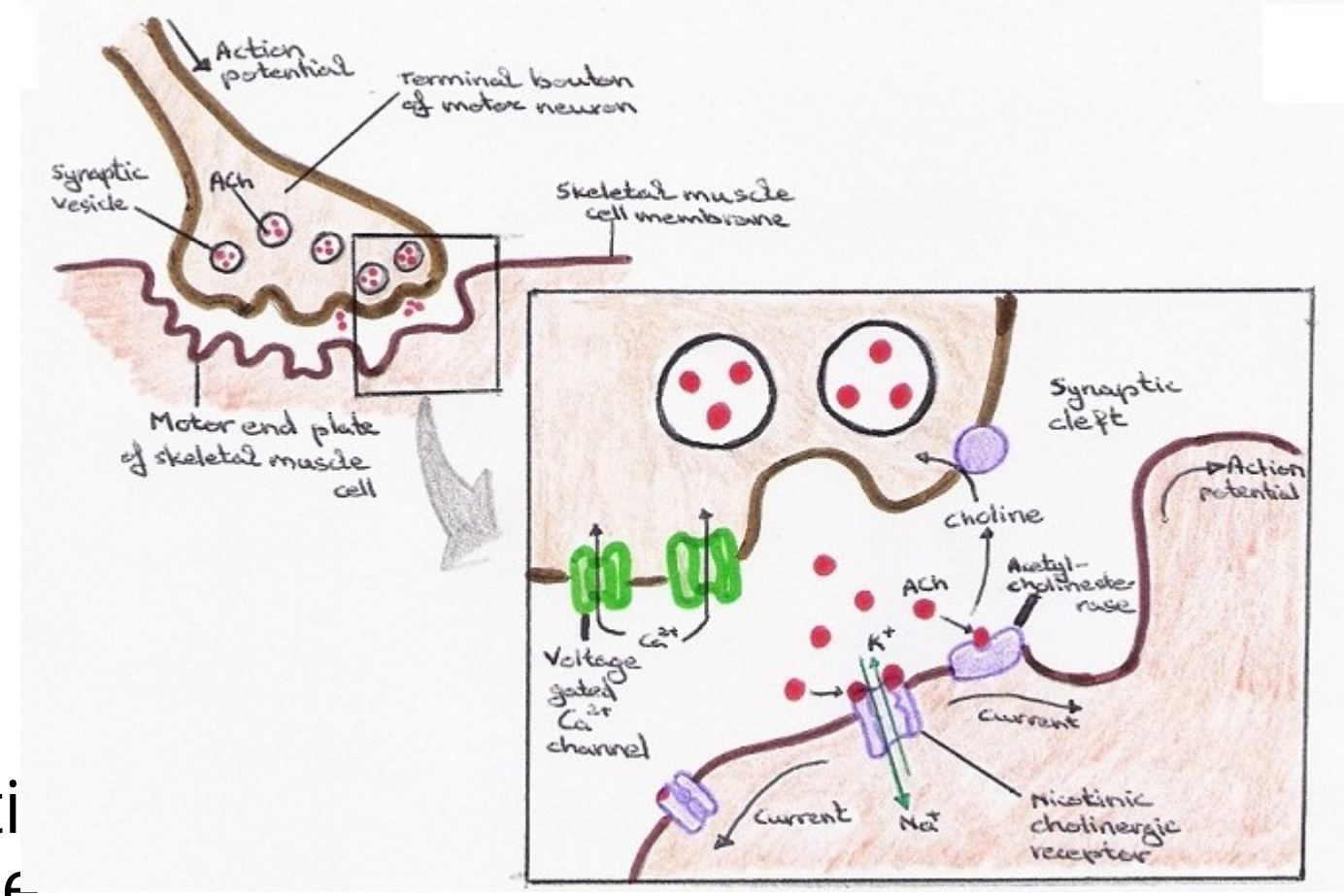
The Neuromuscular Junction

- Upon presynaptic AP firing, Calcium enters the presynaptic terminal causing fusion of vesicles containing Acetylcholine to fuse with the plasma membrane.
- Acetylcholine will bind to and open (gate) nicotinic acetylcholine receptors- ligand gated ion channels.

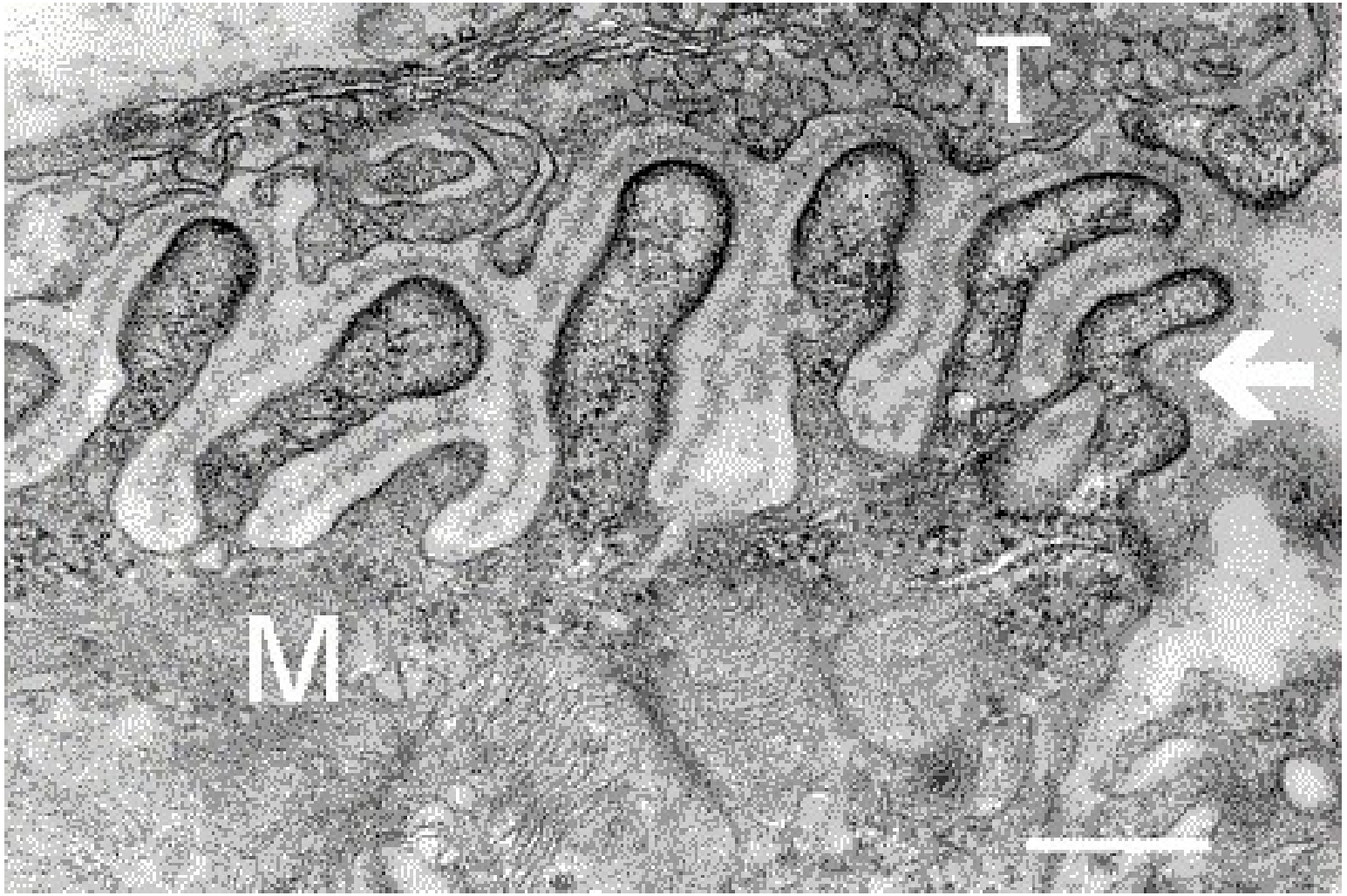


The Neuromuscular Junction

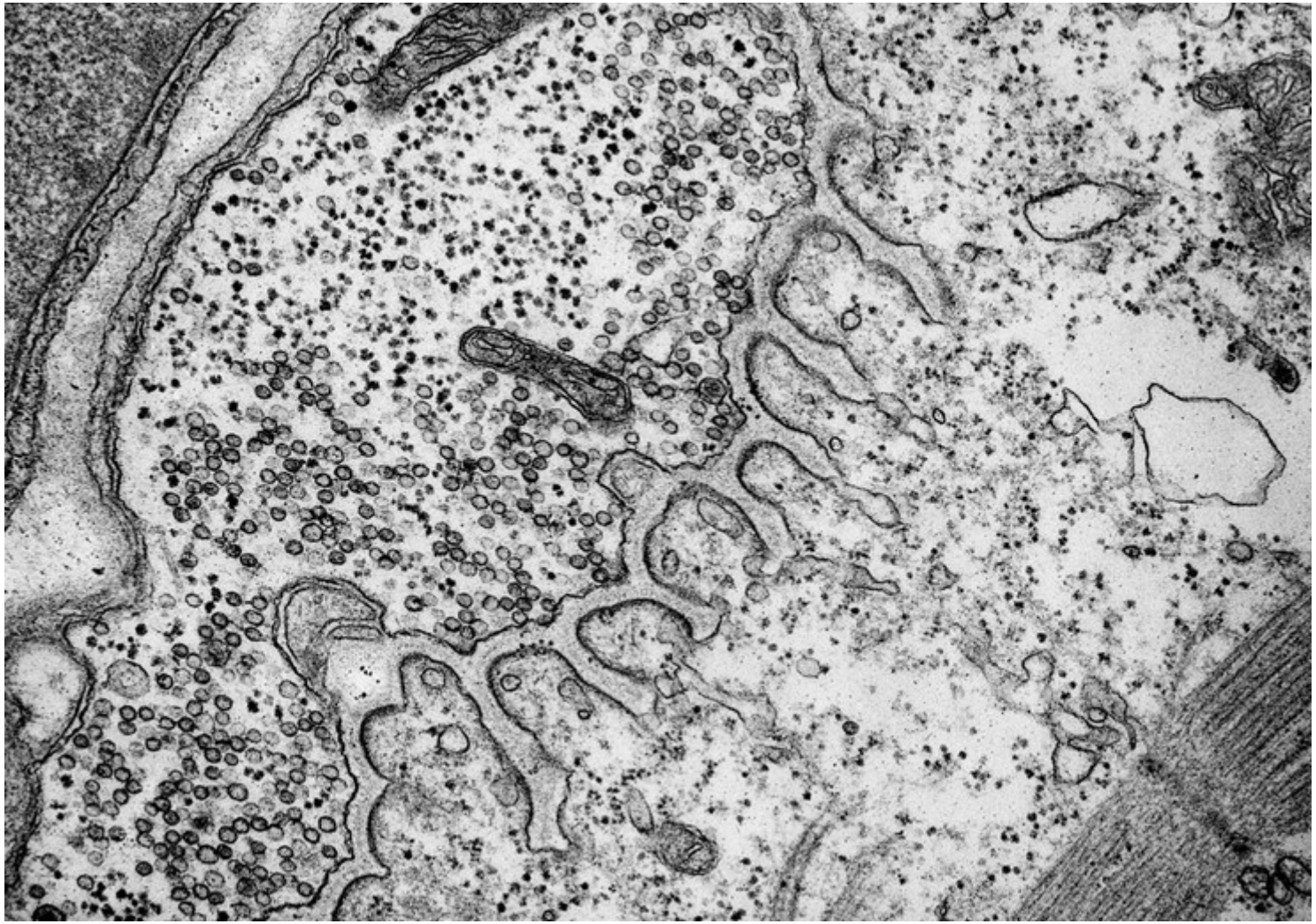
- The opening of nicotinic acetylcholine receptors causes the muscle membrane to depolarize.
- Membrane depolarization activates extrasynaptic voltage gated sodium channels=>AP.
- Acetylcholine is degraded extracellulary in the synapti cleft by acetylcholinesterase.



EM Image of the Neuromuscular Junction

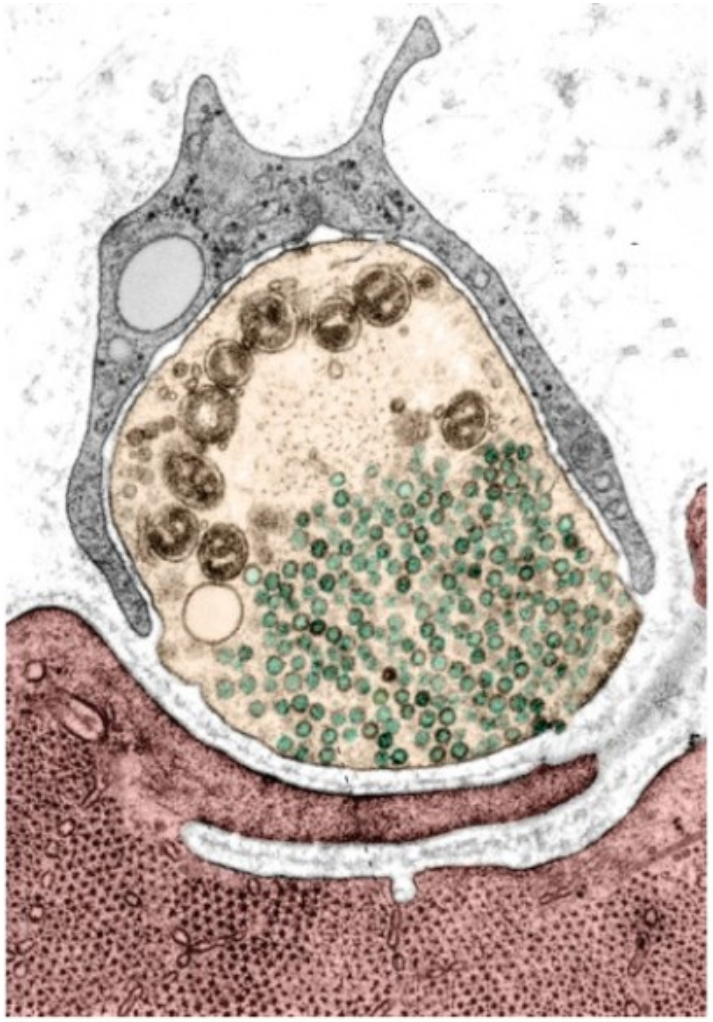


EM Image of the Neuromuscular Junction



EM Image of the Neuromuscular Junction

- Colorized:
- Yellow-Presynaptic Neur
- Green-Vesicles
- Red- Postsynaptic muscl



Major neurotransmitter receptors and their channel permeability

TABLE 2. COMMON LIGAND-GATED CHANNELS OF VERTEBRATE NEURONS

Transmitter	Receptor	Antagonists	Potentiators	Permeability
GABA	$GABA_A$	Bicuculline[a] Picrotoxin	Barbiturates Benzodiazepines Alcohol Glutamate	Anions
Glycine	Glycine	Strychnine[a]	—	Anions
Glutamate	Kainate	CNQX[a]	—	Cations
Glutamate	AMPA	CNQX[a]	—	Cations
Glutamate	NMDA	APV[a] Mg^{2+} (outside[b])	Glycine	Ca^{2+} + cation
ACh	Neuronal nACh	Neuronal bungarotoxin (at some)	—	Cations

Abbreviations: CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; AMPA, α-amino-3-hydroxy-5-meth 4-isoxazole propionic acid; NMDA, *N*-methyl-D-aspartate; APV, D-2-amino-5-phosphonovaler (also frequently called AP5).
[a]Competitive antagonist.
[b]Pore blocker.

inhibitory

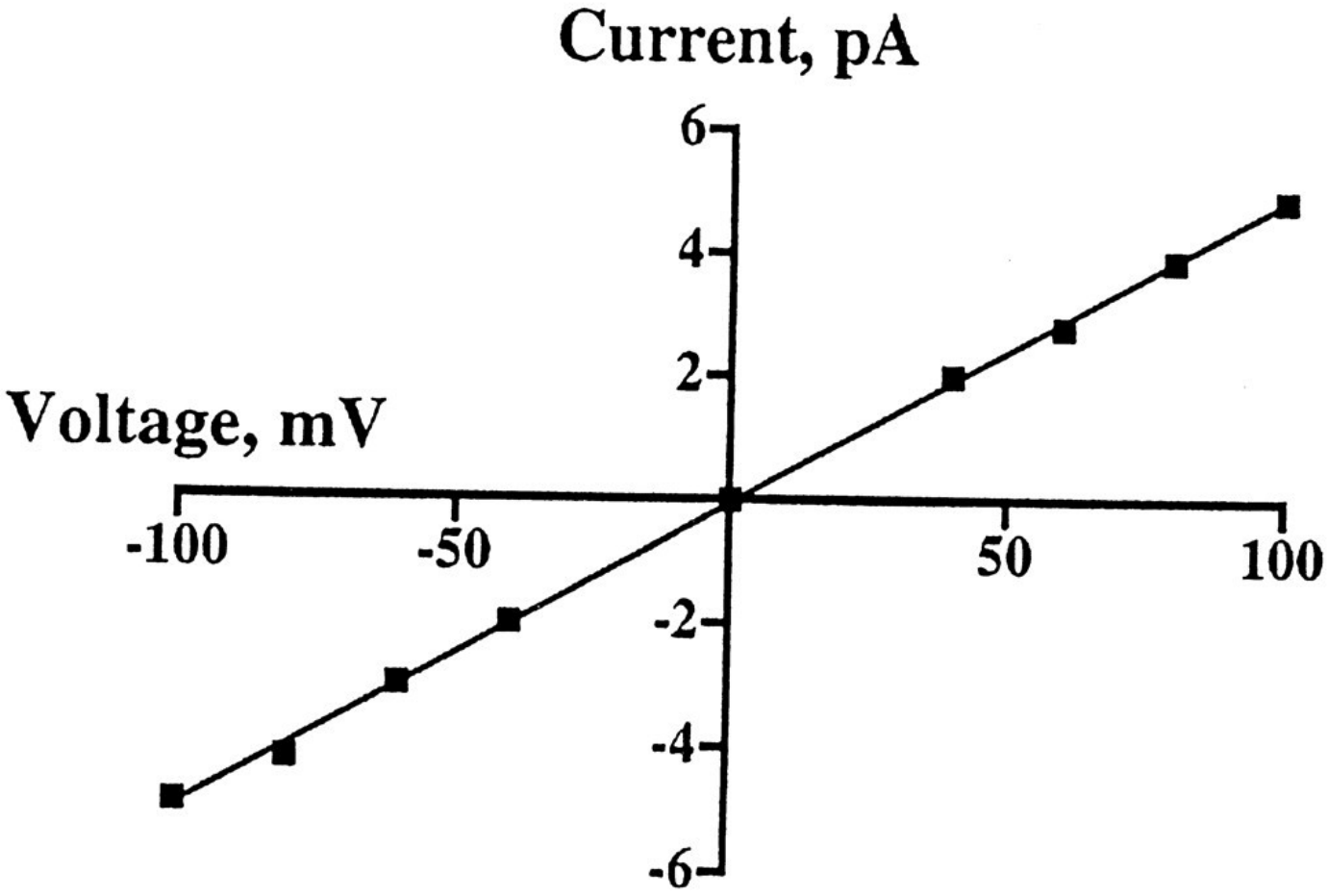
excitatory

Cl^-

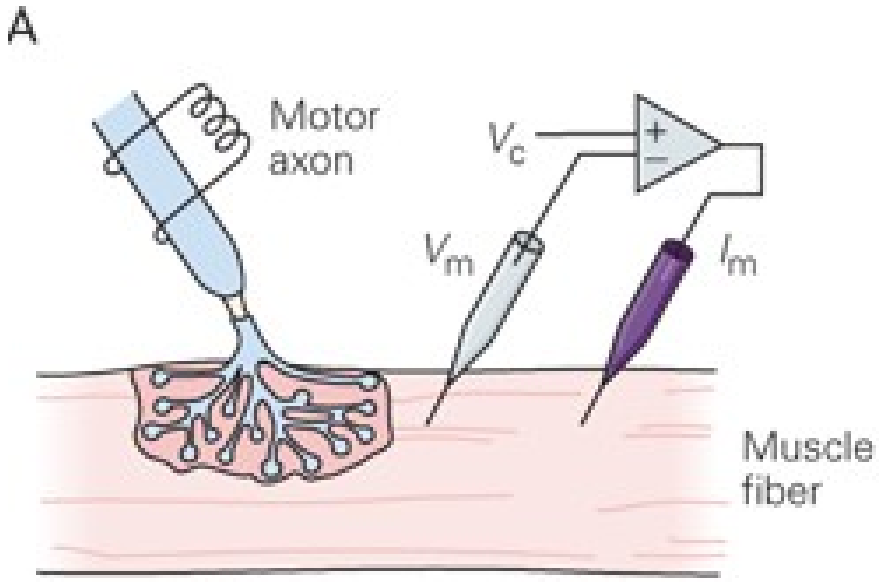
Na+ & K+

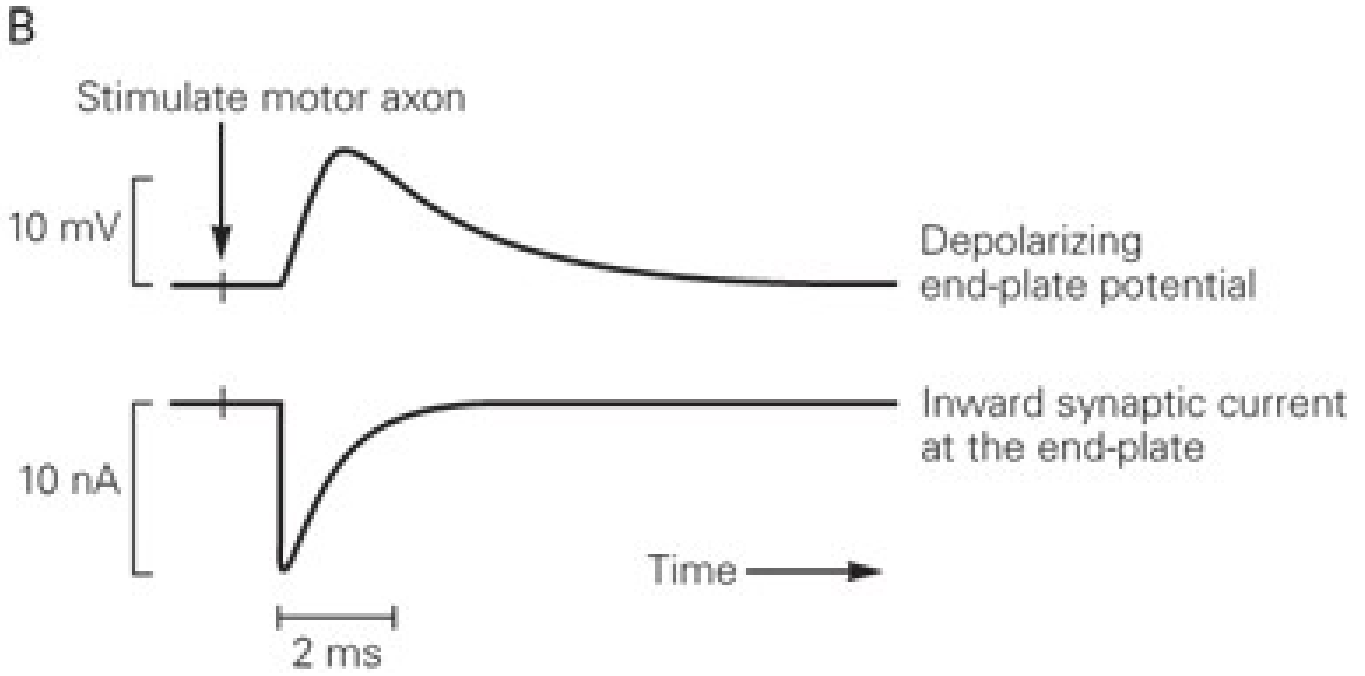
Hille

I-V curve for acetylcholine (ACh) receptor

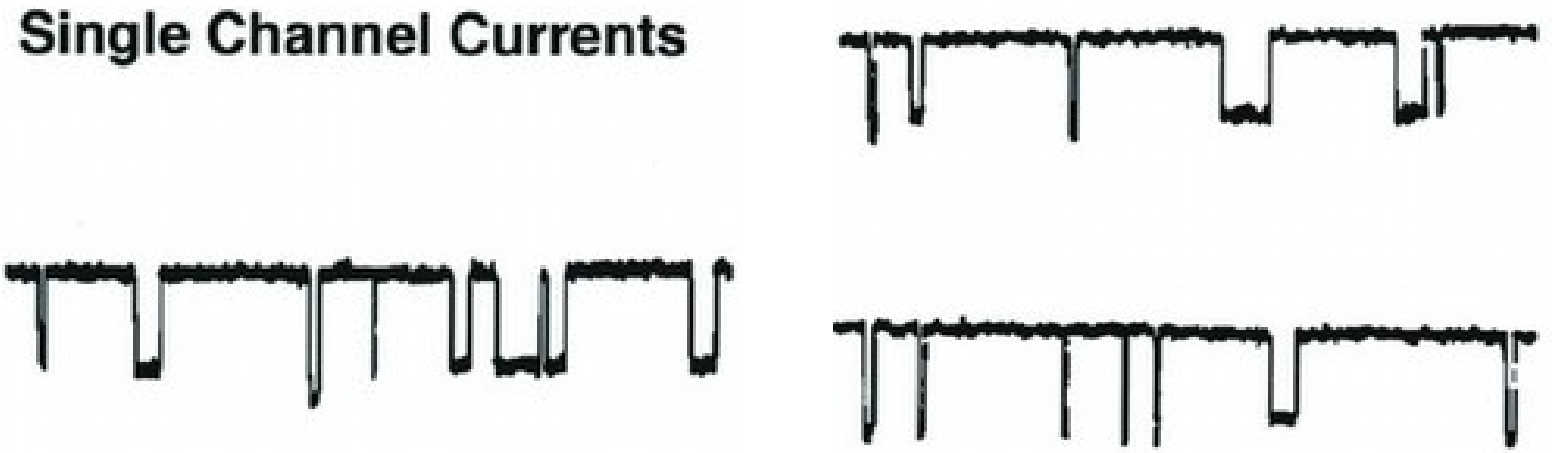


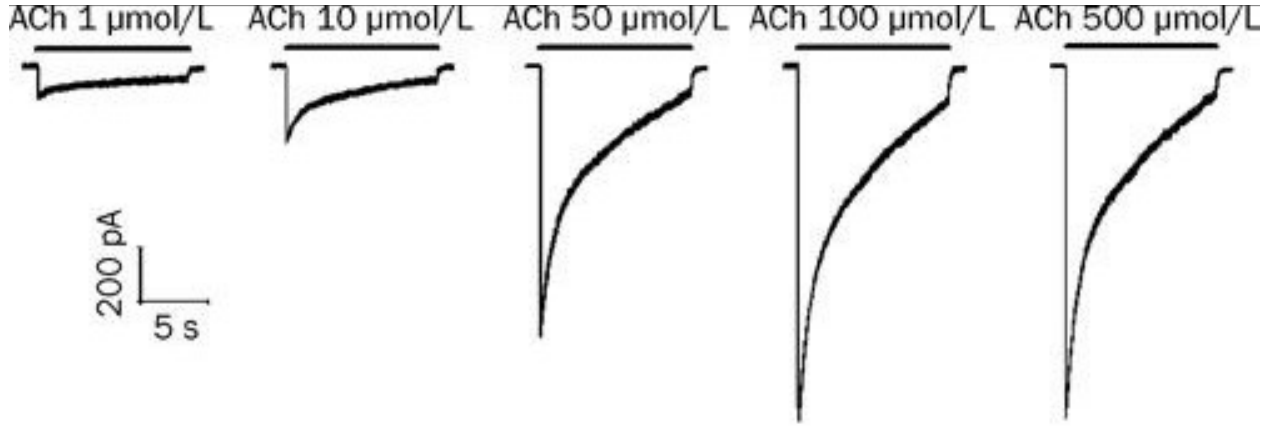
Functional α6-Containing Nicotinic Receptors Are Present in Chick Retina
Vailati et al, Molecular Pharmacology, 1999

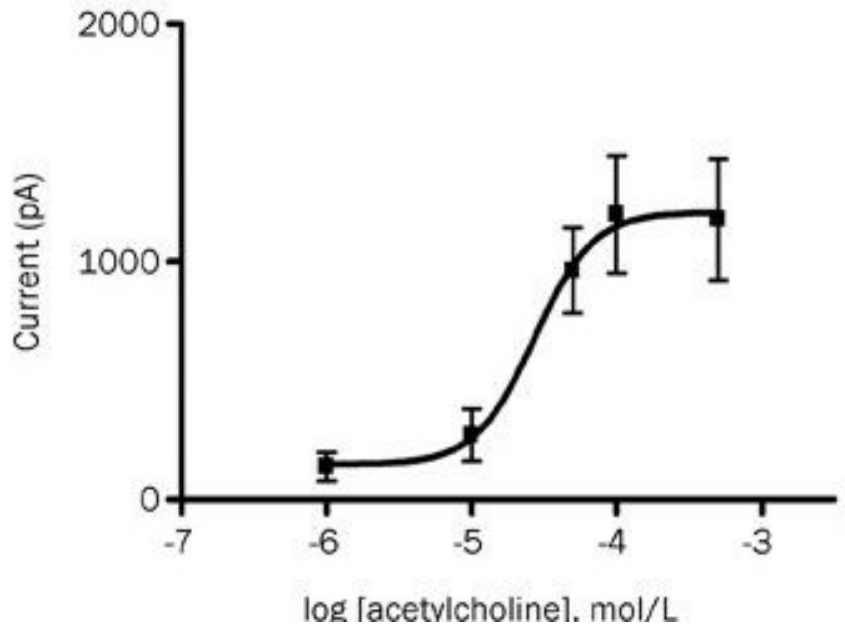

A
Motor
axon
V_c
V_m
I_m
Muscle
fiber


B
Stimulate motor axon
10 mV
Depolarizing
end-plate potential
10 nA
Inward synaptic current
at the end-plate
Time
2 ms

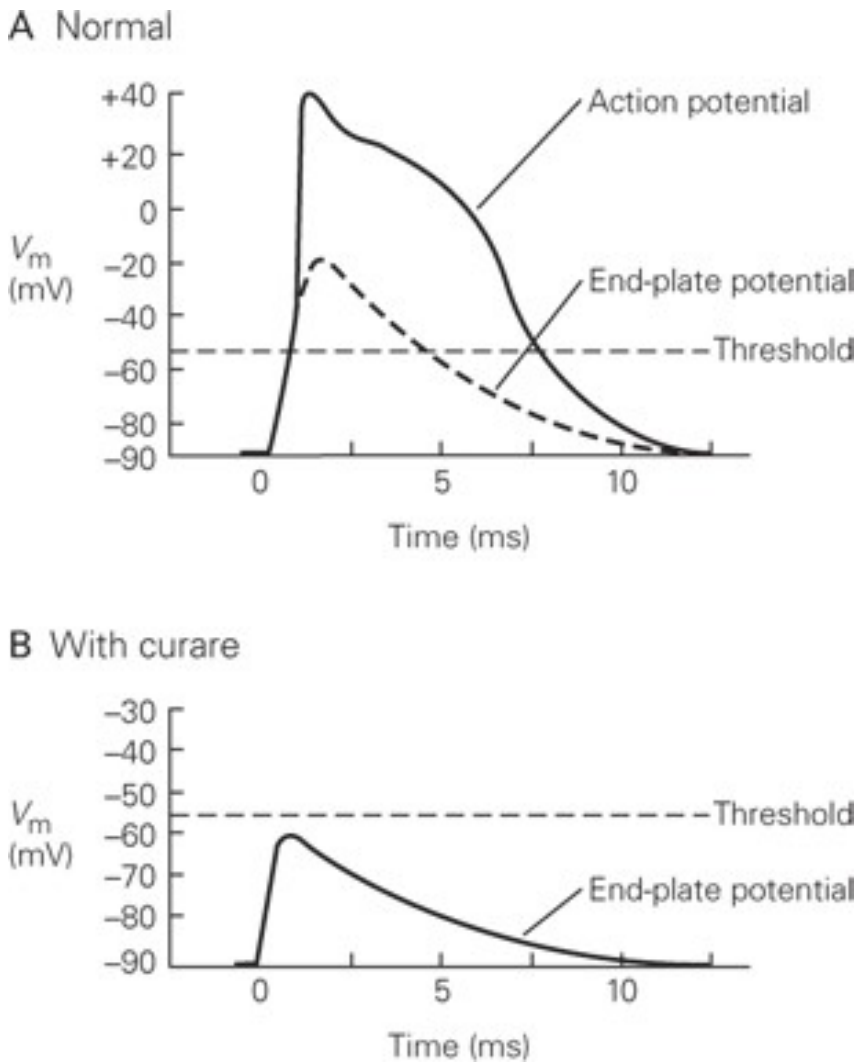

MONITORED
CHANNEL

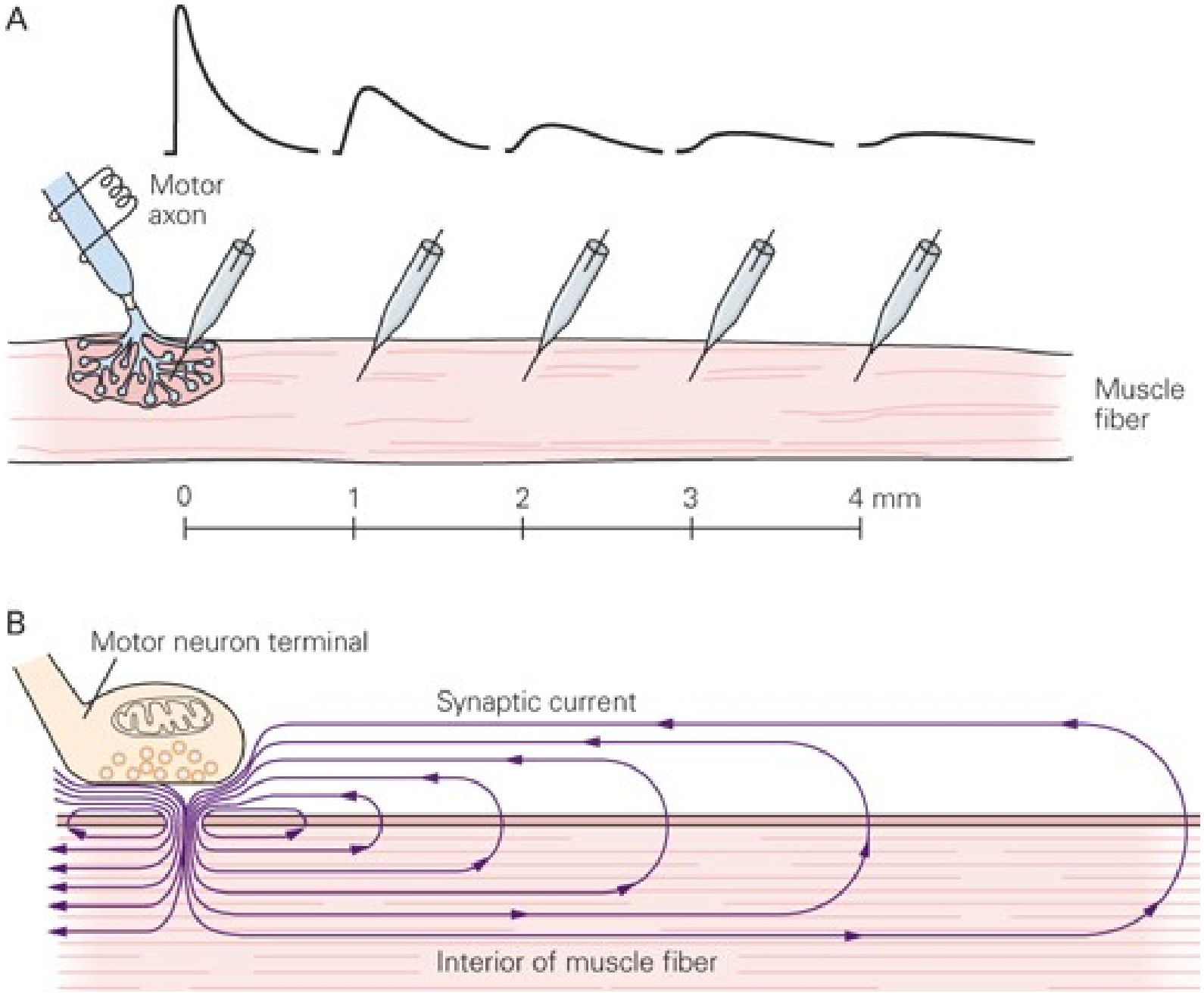

Single Channel Currents


ACh 1 μmol/L
ACh 10 μmol/L
ACh 50 μmol/L
ACh 100 μmol/L
ACh 500 μmol/L
200 pA
5 s


2000
1000
0
Current (pA)
-7
-6
-5
-4
-3
log [acetylcholine], mol/L

How EPPs translate to APs




A
Motor
axon
Muscle
fiber
0
1
2
3
4 mm
B
Motor neuron terminal
Synaptic current
Interior of muscle fiber

Muscle Functions

Skeletal Muscle Functions:

Voluntary Movement of the Body

Heat Generation

- **examples**: limb movement, chewing and swallowing movements, breathing

Smooth Muscle Functions:

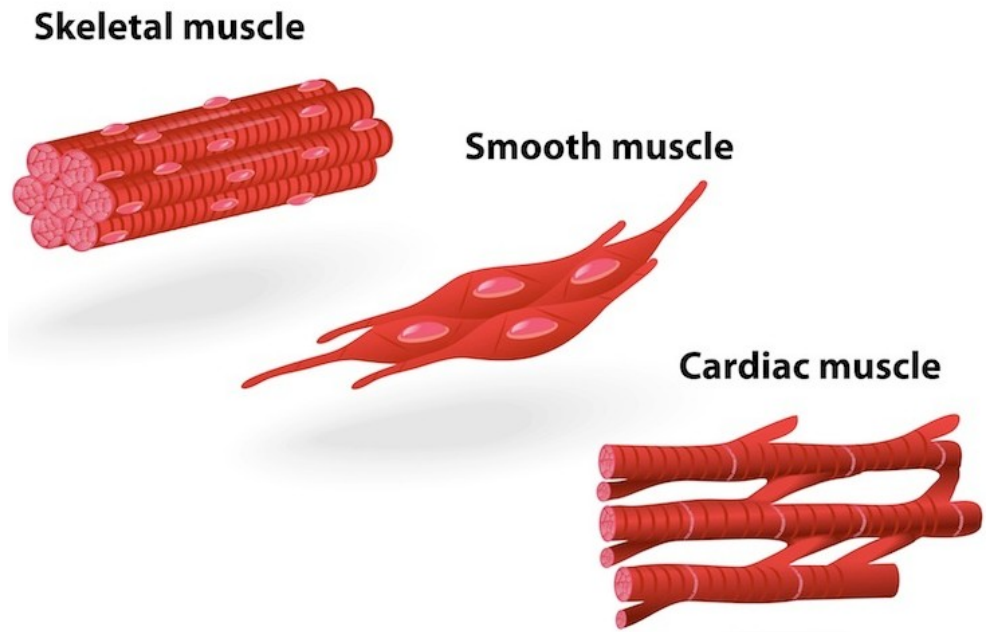
Involuntary movement of organs, blood vessels

- **examples**: control of blood vessels, airways, digestive tract, urinary tract

Cardiac Muscle Functions:

Involuntary movement of heart

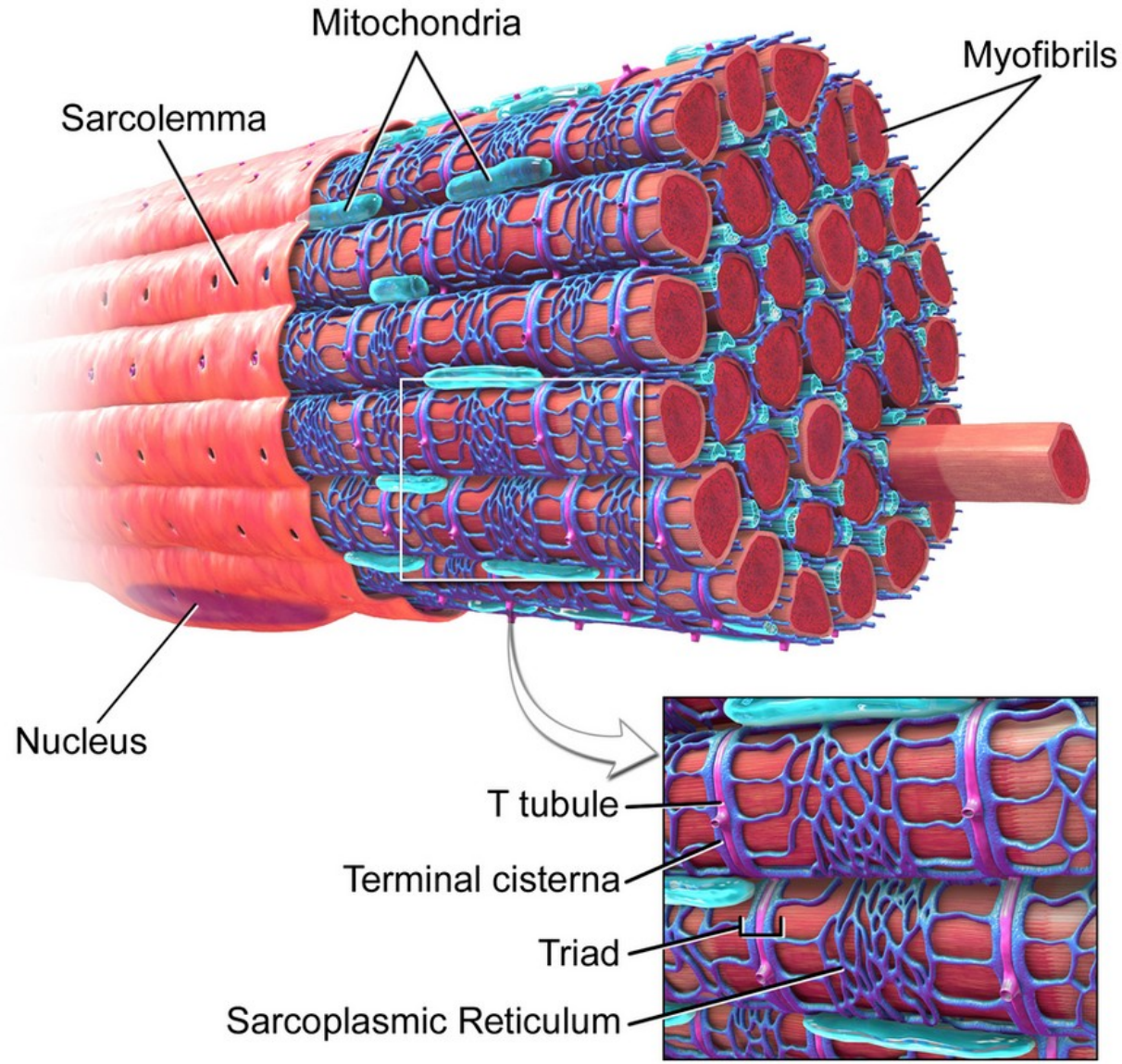
- **examples**: pumping of blood through atria and ventricles



Skeletal muscle is highly organized from the macroscopice level to the microscopic level, containing many specialized organelles and proteins to support muscle contraction

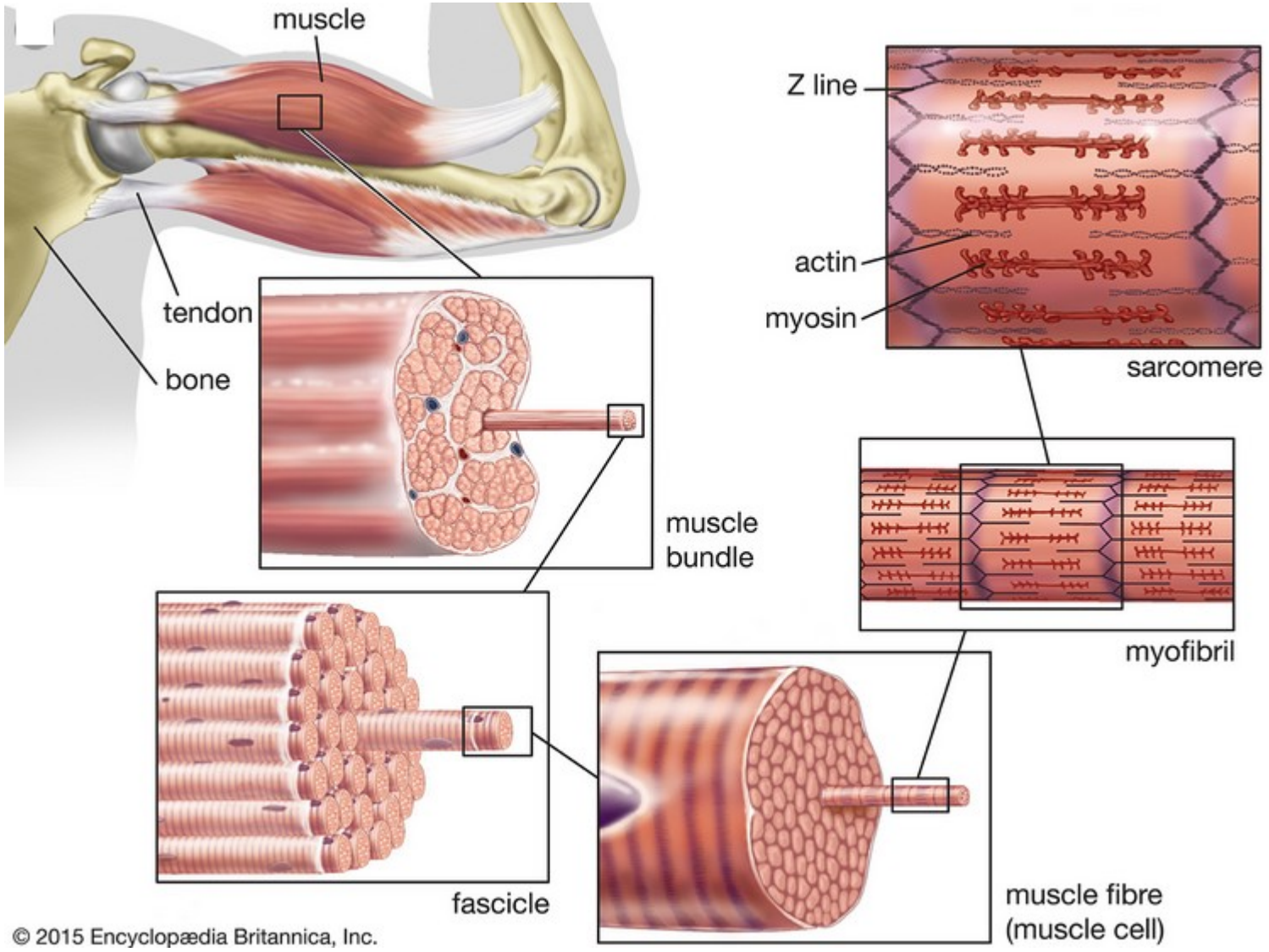
Skeletal Muscle Anatomy:

- whole muscle (organ)
- muscle cell (fiber)
- myofibrils (contractile organelles)
- thick (myosin) and thin (actin) filaments (contractile proteins)
  - Sarcomere arrangement
- Other organelles:
  - transverse-tubules
  - sarcoplasmic reticulum

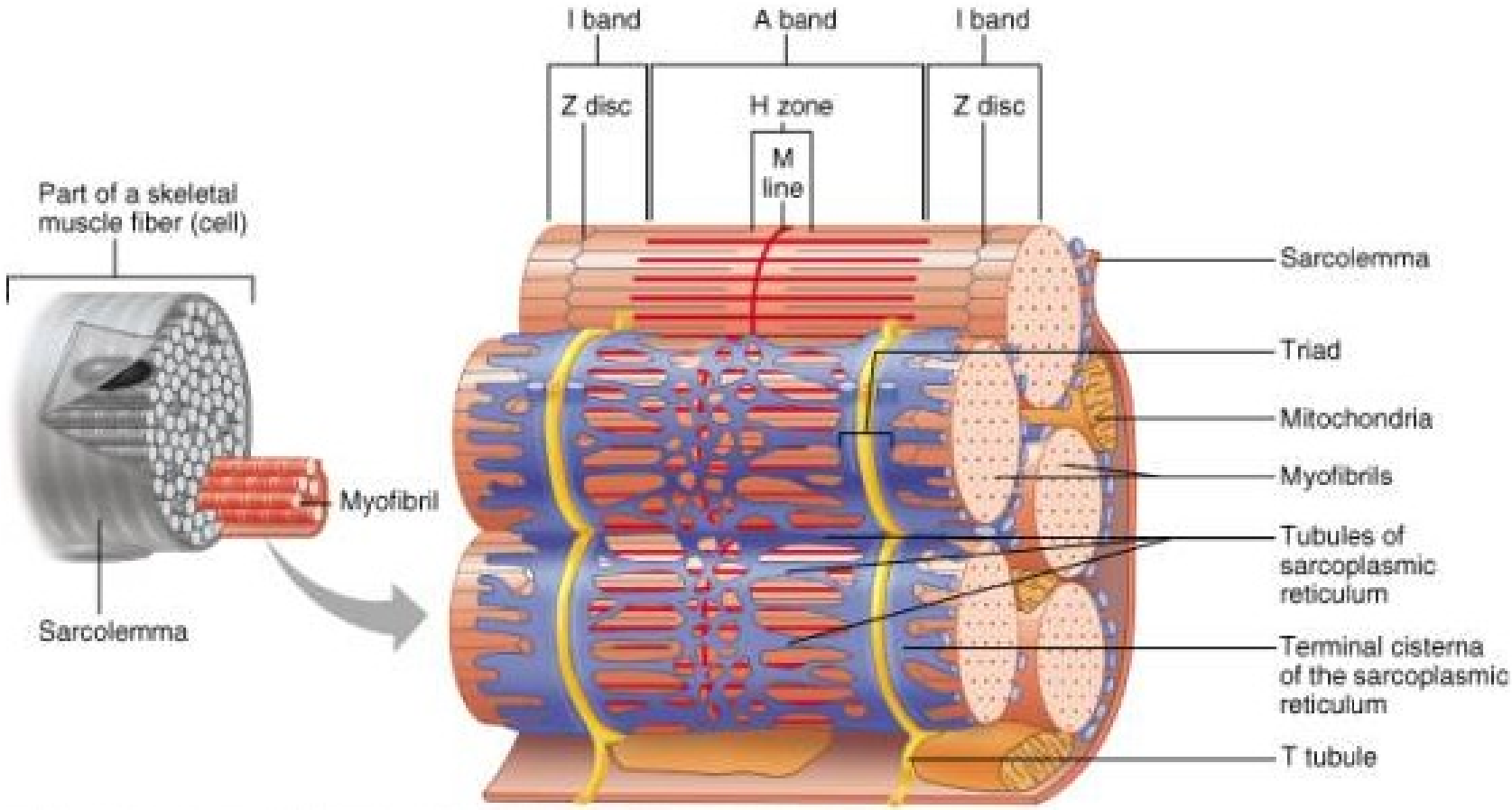


Anatomy of a Muscle

- If we slice a muscle in half we find individual fascicles.
- Within a fascicle we have several muscle cells.
- Muscle cell and muscle fiber can be used interchangeably.
- Muscle fiber is densely packed with contractile organelles known as myofibril.
- Within a myofibril there are protein arrangements known as sarcomeres.



Sarcomeres are the contractile unit of muscle



Organization of the sarcomere

Actin and myosin are the contractile proteins within a myofibril. They are tightly packed and organized within each myofibril.

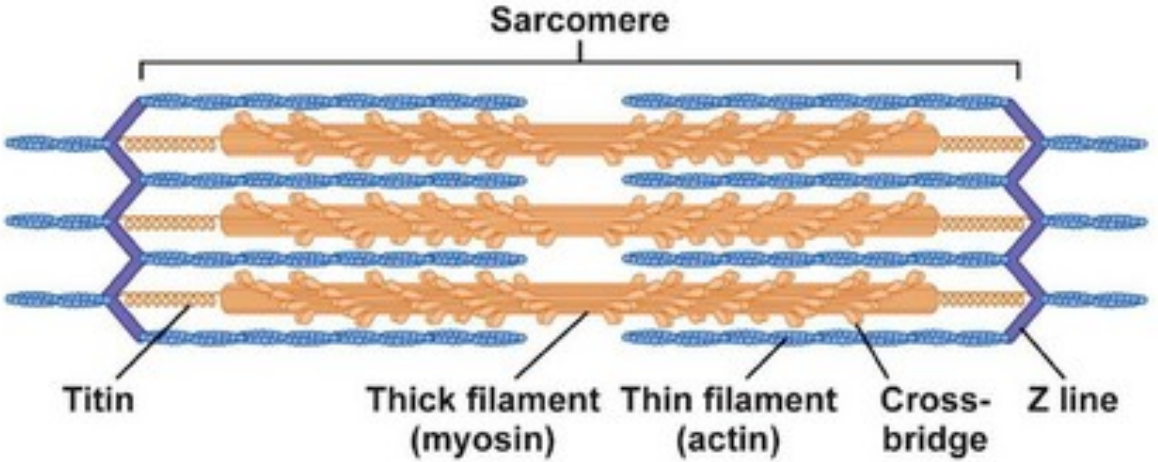
Myosin – THICK filaments within a myofibril

Actin – THIIN filaments within a myofibril

The myosin and actin are arranged in a very specific overlapping pattern, its base unit or organization is a Sarcomere

Sarcomere:

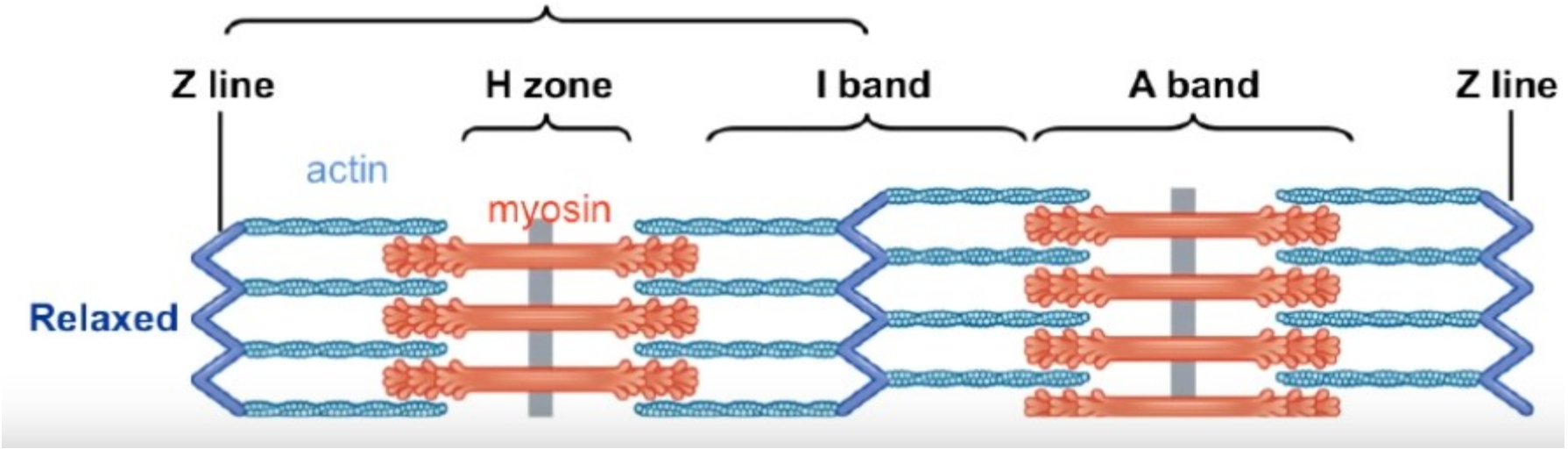
- Z-line
- A band
- H zone
- I band
- M-line



(d) Sarcomere

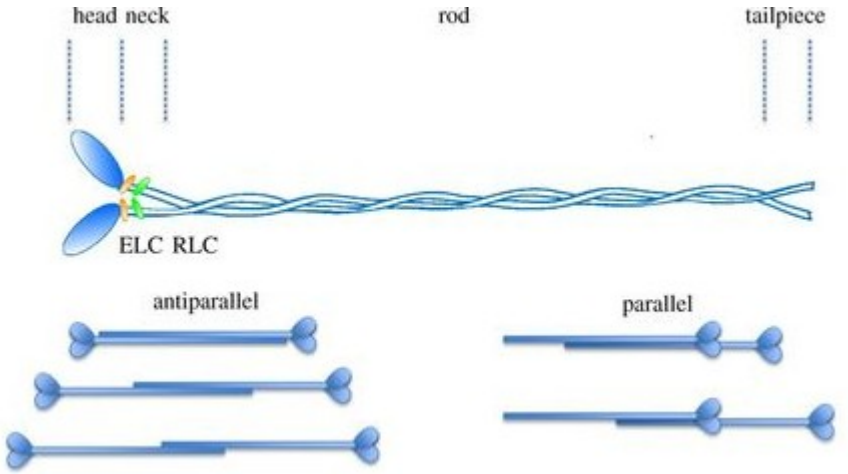
Sarcomeres

- **Sarcomere**: arrangement of overlapping contractile proteins, actin and myosin within a myofibril, forms light and dark striations
  - **Z-line**: boundary of sarcomere where actin attaches to adjoining sarcomeres
  - **A band** (dark band): stretches end to end of myosin, contains both actin and myosin filaments
  - **I band** (light band): space between myosin, contains only actin
  - **H zone**: non-overlapped regions of myosin only, no actin
  - **M-line**: center of sarcomere holding adjacent myosin together with supporting proteins



Lets draw it out!!!!!!!!

Myosin vs. Actin



- Myosin is made up of thick filamentous material that has:

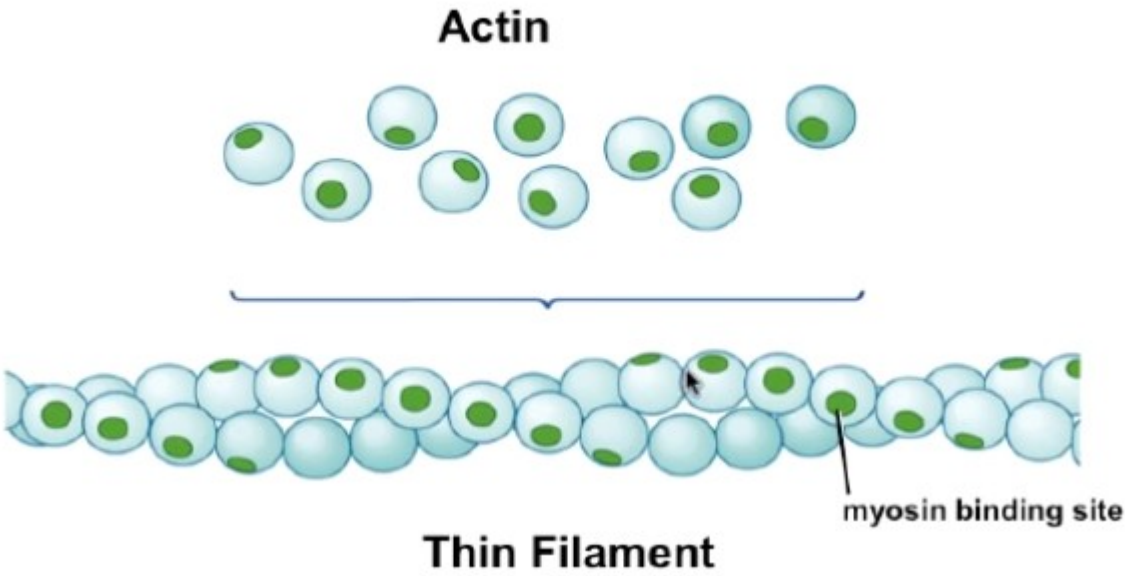
1. A distal binding region for actin- So it can grip during periods of contraction and relaxation.

2. An ATPase domain- ATP must be “burned” so energy can be released in order to move the myosin head along the actin.

Myosin vs. **Actin**

- Actin is made up of individual subunits that arrange themselves into a thin filamentous double helix formation.

- It contains specific binding sites for myosin.

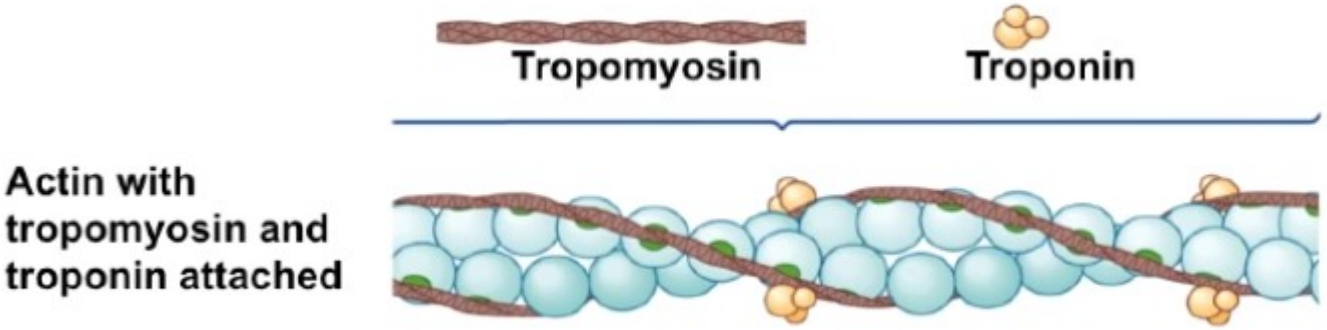


What proteins regulate interactions between

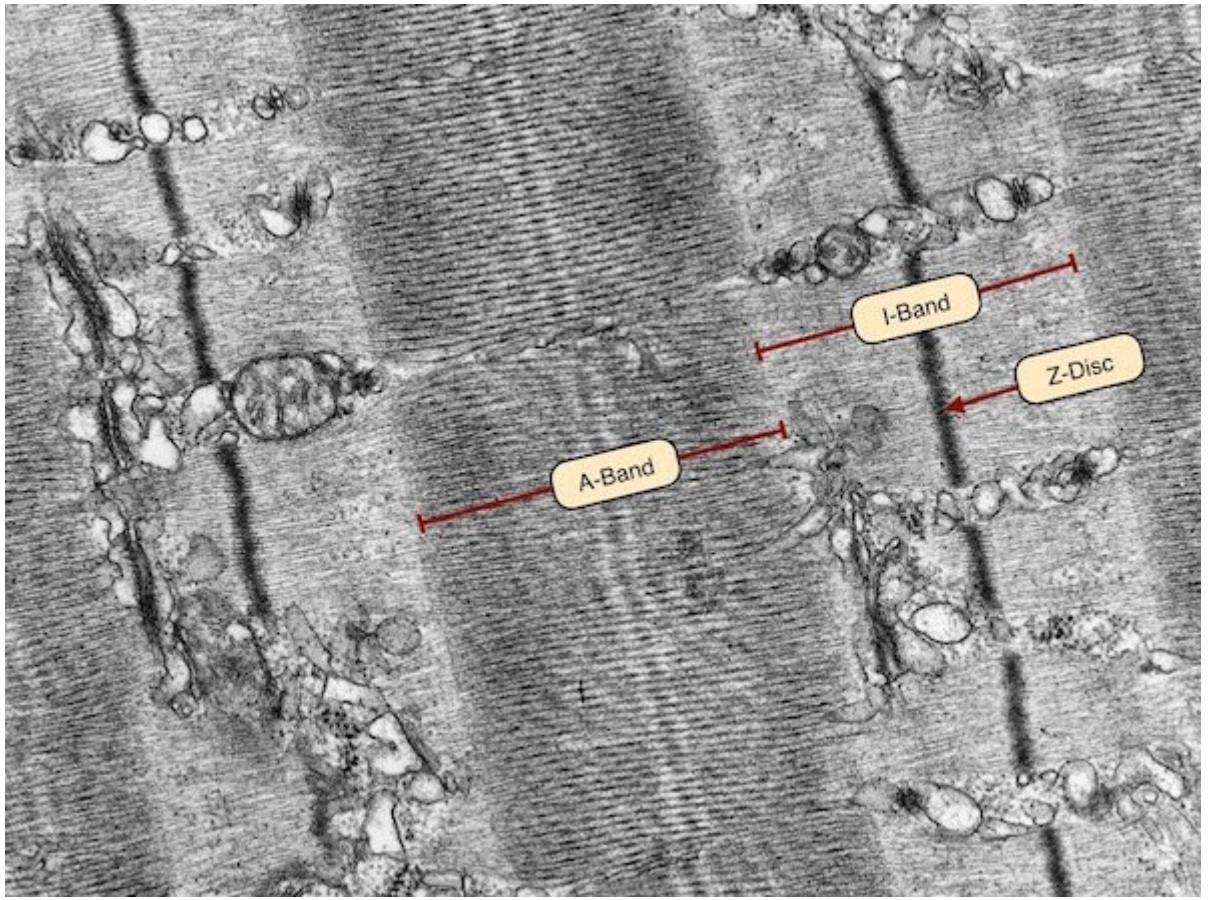
Why aren’t they simply locked into a specific

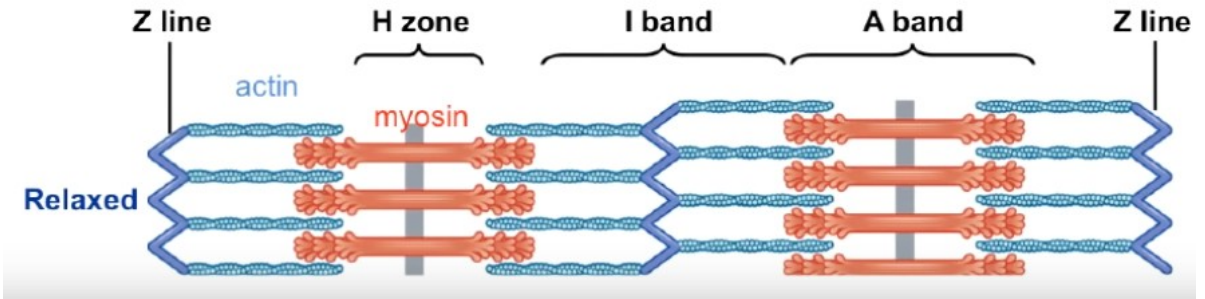
Troponin and Tropomyosin

- These are two proteins that, when bound to actin, INHIBIT interactions between actin and myosin.
- Whereas tropomyosin blocks access to myosin binding sites, troponin locks the tropomyosin in place.



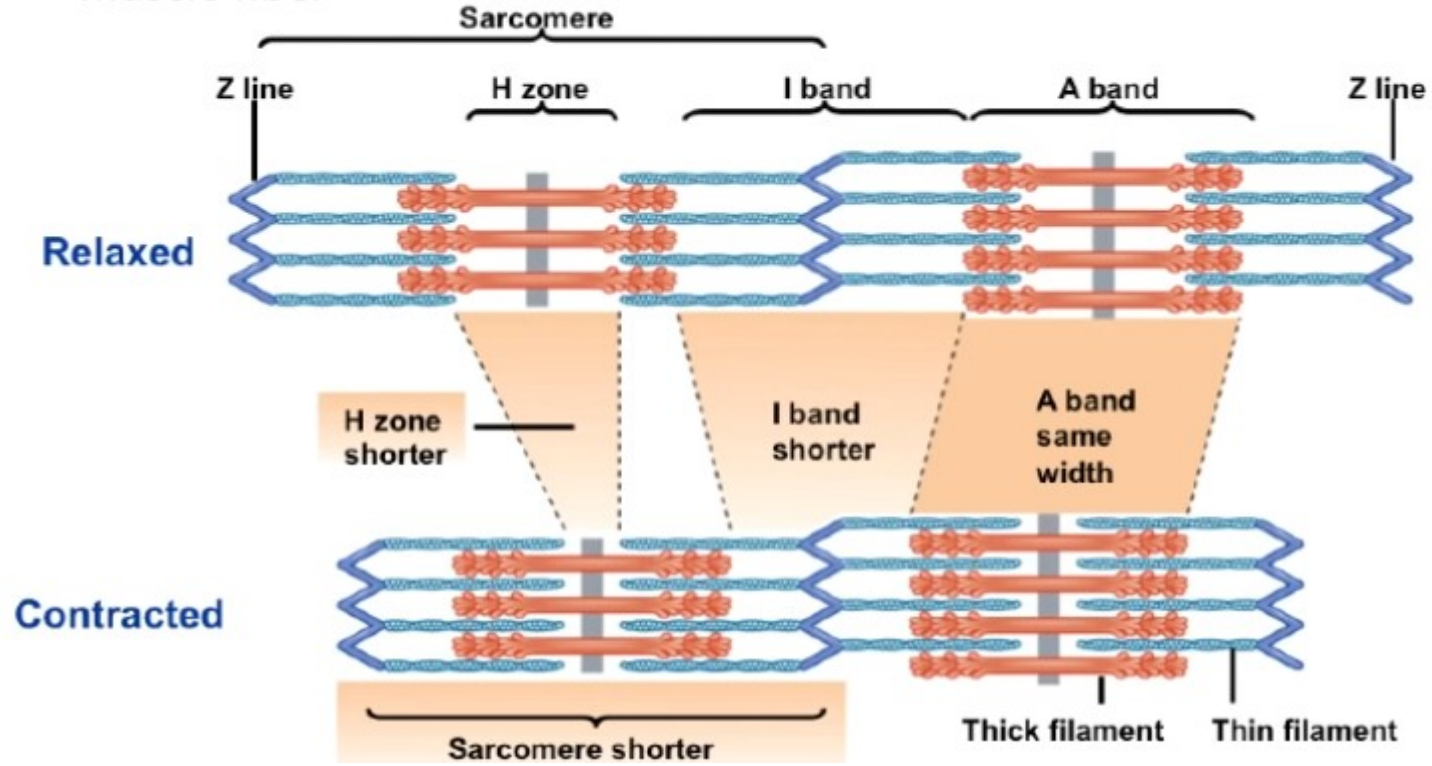
EM image of skeletal muscle





Only Zones Containing Actin Change Size!!!!

- When a muscle contracts, the actin and myosin move, causing the sarcomere to shorten
- A muscle fiber contraction at the microscopic level is "shortening" of the muscle fiber

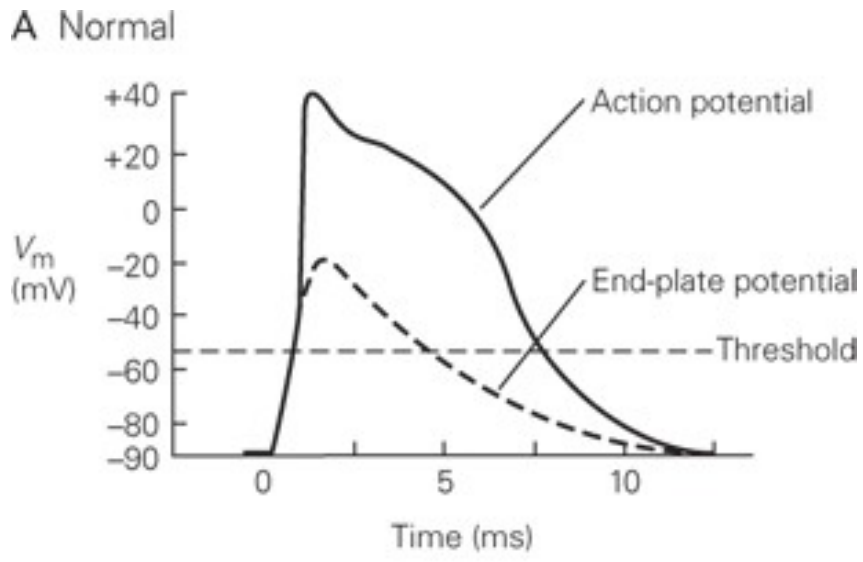


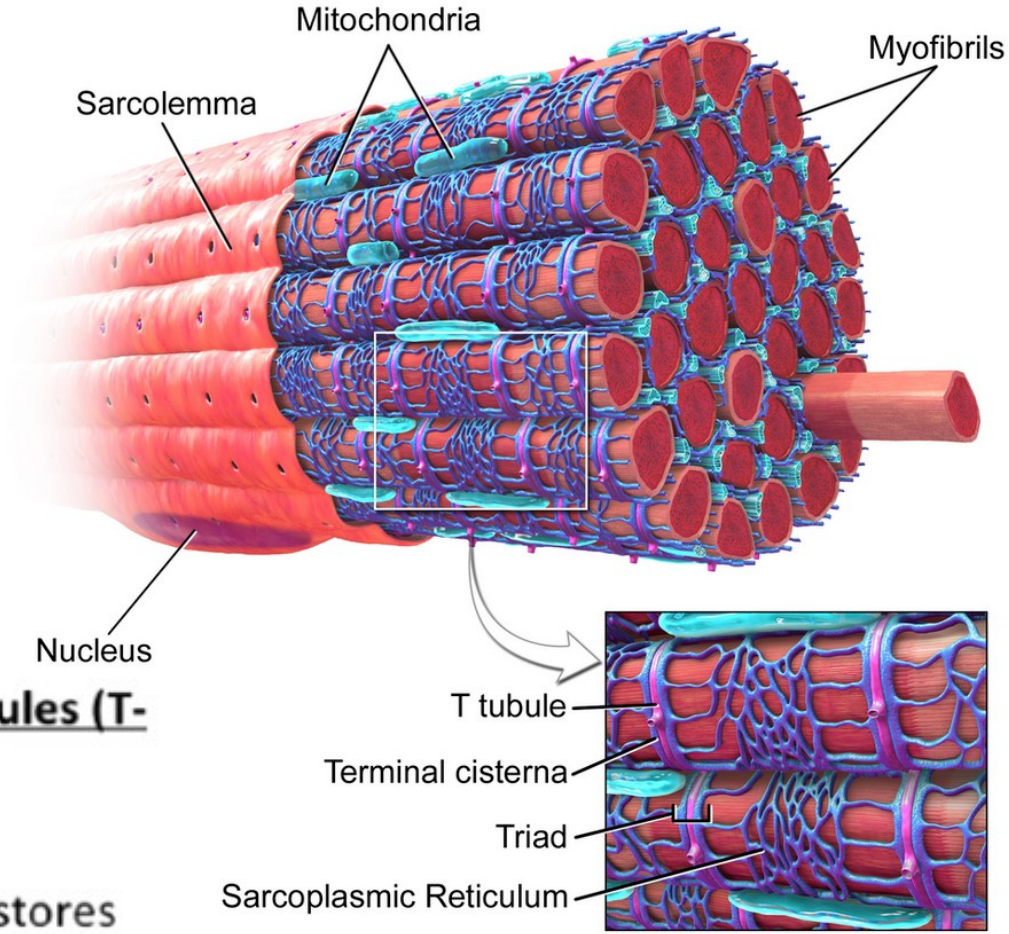
Lets Go Over Where We Are At!

1. AP travels down corticospinal Betz Cell where it synapses onto a primary motor neuron in the ventral horn. Nt used???
2. The primary motor neuron then initiates its own action potential that travels and terminates at the presynaptic terminal where Acetylcholine is released onto the muscle.
3. The muscle then depolarizes, producing its own action potential.

SOMEHOW THIS ACTION POTENTIAL LEADS TO A CONTRACTION OF THE SARCOMERE===🖧HOW?????

Depolarized Muscle



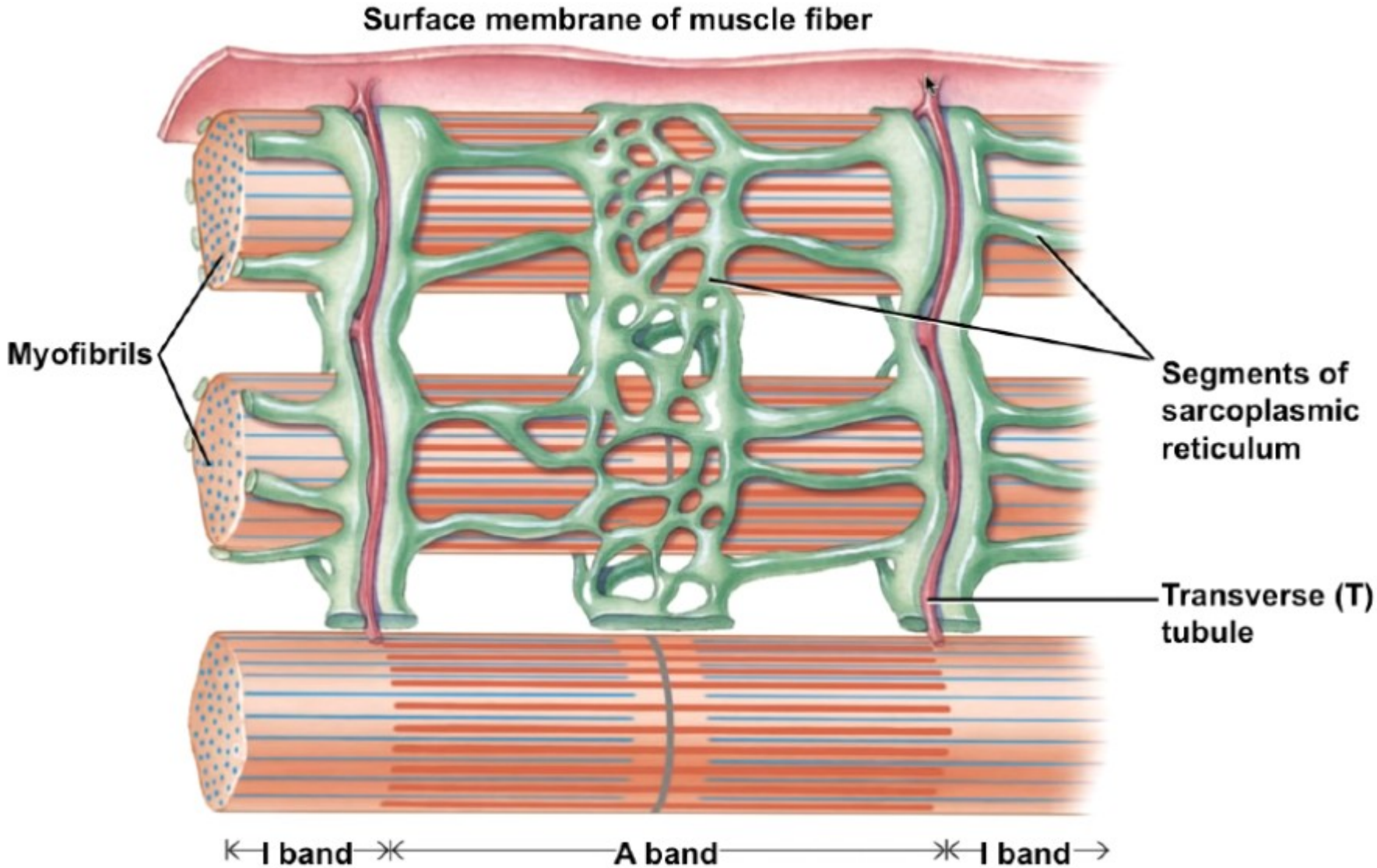


Depolarization spreads into membrane regions called **Transverse Tubules (T-tubules)**

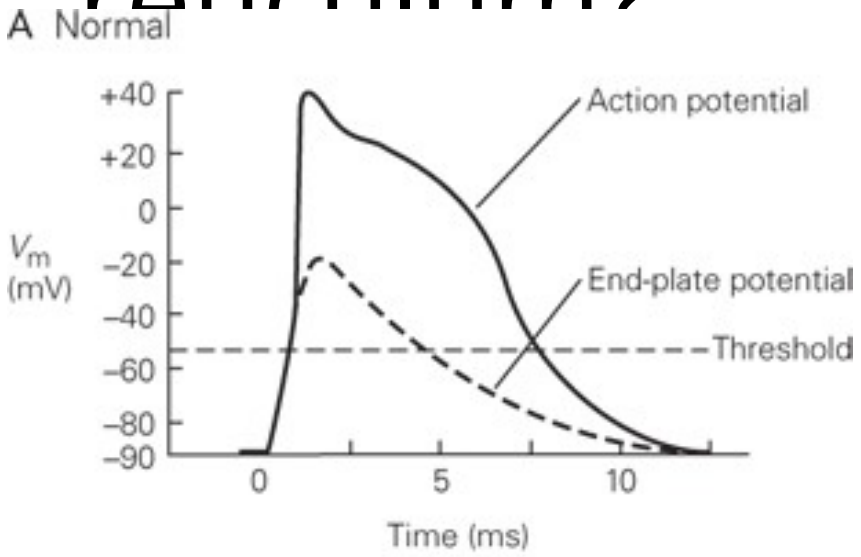
T-tubules contact the **Sarcoplasmic Reticulum**

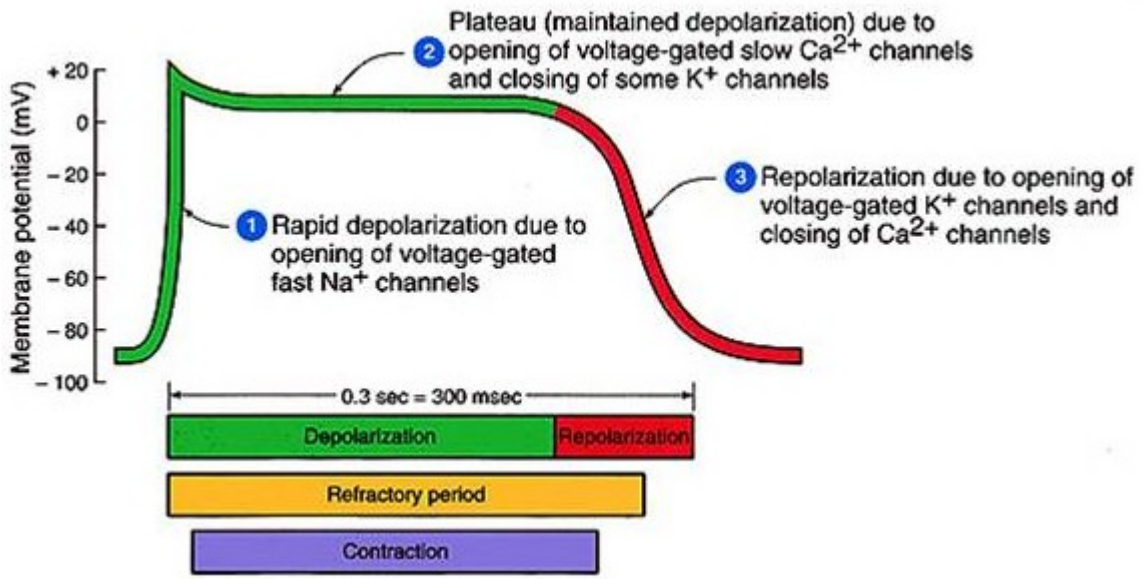
The sarcoplasmic reticulum is a modified endoplasmic reticulum that stores Ca^{2+} and contains Ca^{2+} channels

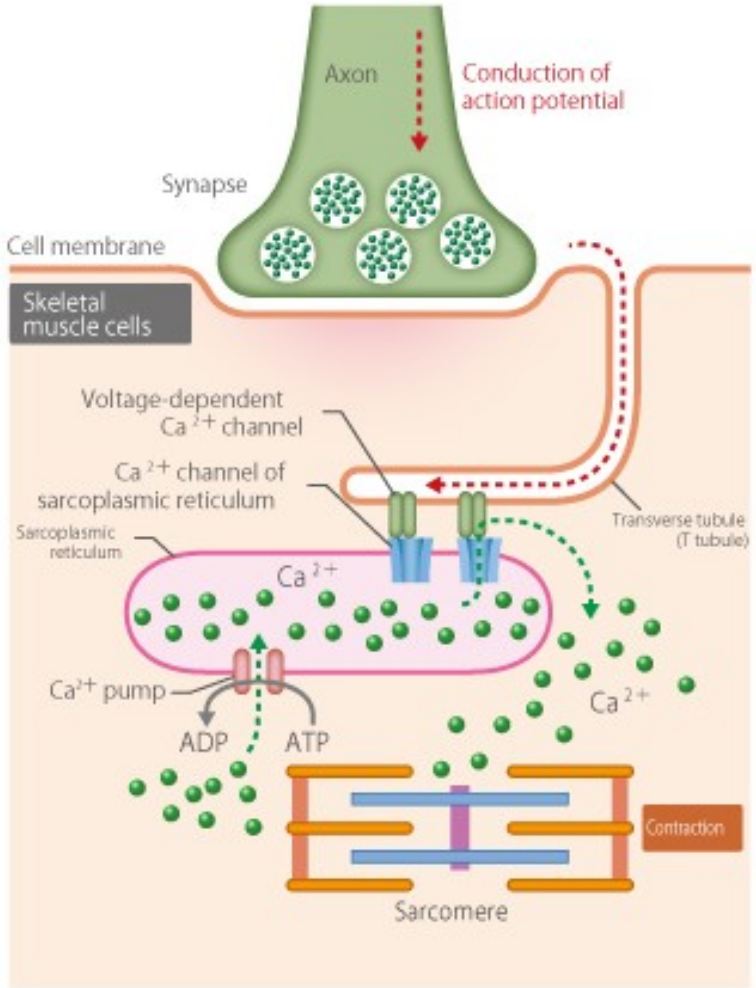
Calcium is released from the sarcoplasmic reticulum into the cytosol of the muscle cell


Surface membrane of muscle fiber
Myofibrils
Segments of sarcoplasmic reticulum
Transverse (T) tubule
I band
A band
I band

How can skeletal muscle APs lead to Calcium release from sarcoplasmic reticulum?







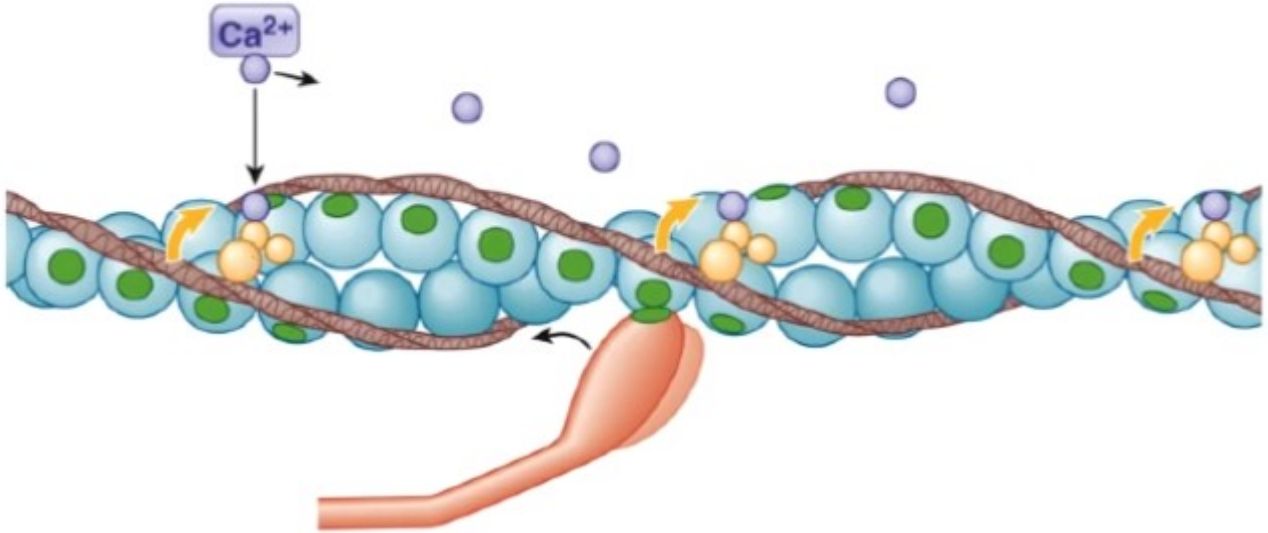
Voltage Gated Ca^{2+} channels and Ryanodine Receptors

- As depolarization spreads via the t-tubules throughout the myofibril the voltage gated calcium channels on the muscle plasma membrane open (Slow to open/Slow to close).
- These channels are physically coupled to Ryanodine receptors that are in the membrane of the sarcoplasmic reticulum.
- The Ryanodine receptors bind to the calcium and open (are gated) releasing significantly more calcium into the myofibril.
- This calcium then interacts with the sarcomere in a manner that promotes a contraction.

Calcium releases tropomyosin from actin

Calcium activates troponin

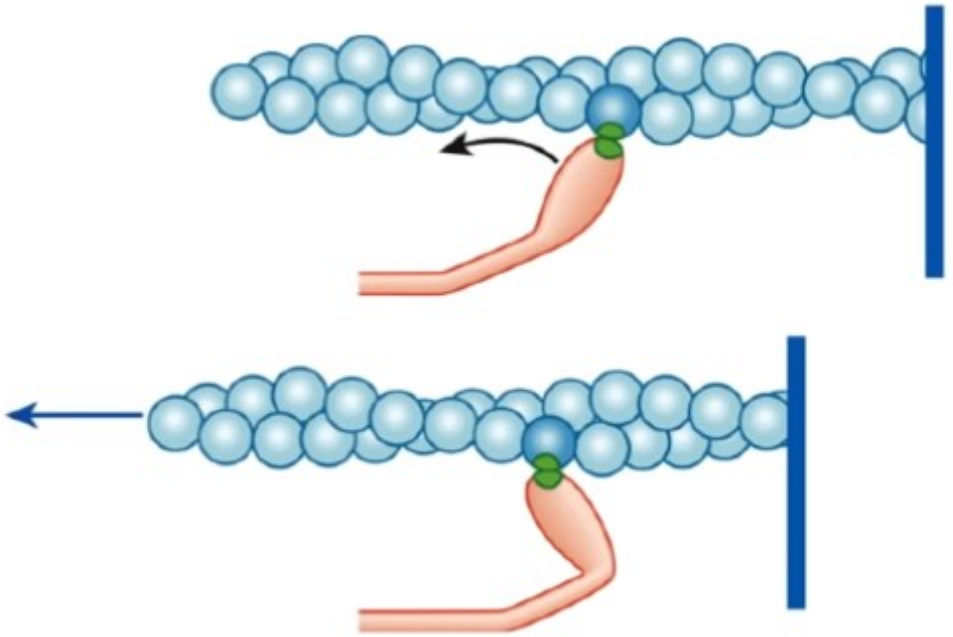
- Troponin normally holds tropomyosin onto actin
- Troponin responds to Ca^{2+} entry and releases from tropomyosin and actin



The result is the binding of the myosin head to actin filament 🖧 known as a **crossbridge**

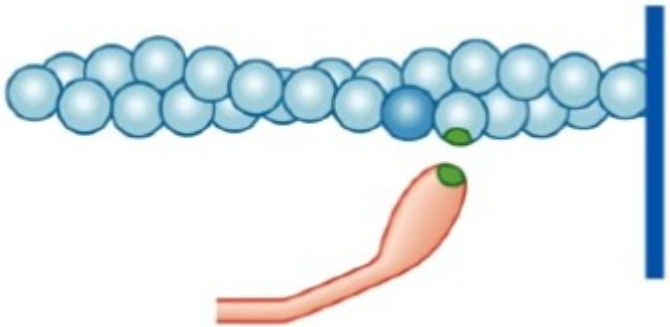
Calcium is not enough for the contraction!!!! NEED ATP!!!!

- Myosin does not move!
- Actin moves inward toward the myosin in a move called the “powerstroke”.
  - This requires ATP!!!!



What about continued contraction/relaxation!!!! STILL NEED ATP!!!!

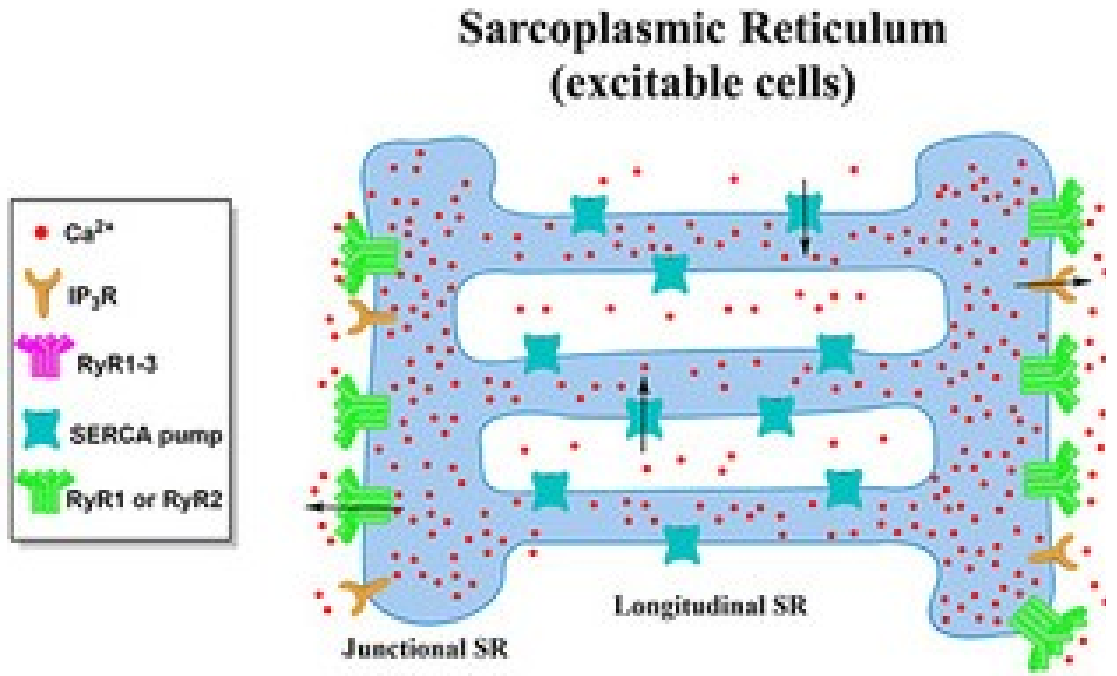
- Myosin does not move!
- Actin continues to move inward toward the myosin in a move called the “powerstroke”.
- Actin also needs a way to relax
  - HOW DO WE GET MYOSIN HEAD UNBOUND FROM ACTIN?
  - These steps also require ATP!!!!



Does Calcium Stay in the SR forever 🖧 NO!

- The SERCA pump (Also relies on ATP) is constantly working to actively transport the calcium back into the sarcoplasmic reticulum within the myofibril.

- Enable the reset after the muscle has relaxed or prior to an additional contraction!!



Birds eye view of the cycle!!!

Action Potential: reaches the muscle fiber

Calcium Release: Ca^{2+} is released

Troponin Activated: Ca^{2+} binds to troponin

Tropomyosin Released: troponin pulls tropomyosin off of myosin binding sites

Cross-Bridge: myosin heads grab onto actin, cross-bridge forms

Power Stroke: myosin heads pull actin inward, using "power stroke"

Reset: myosin detaches from actin, resets

Lets Draw Out the Whole Cycle!!!!

Sliding Filament Theory

Steps 3-6 of excitation-contraction coupling describe the mechanism of myosin heads "sliding" actin toward the center of the sarcomere. This is based on the Sliding Filament Theory

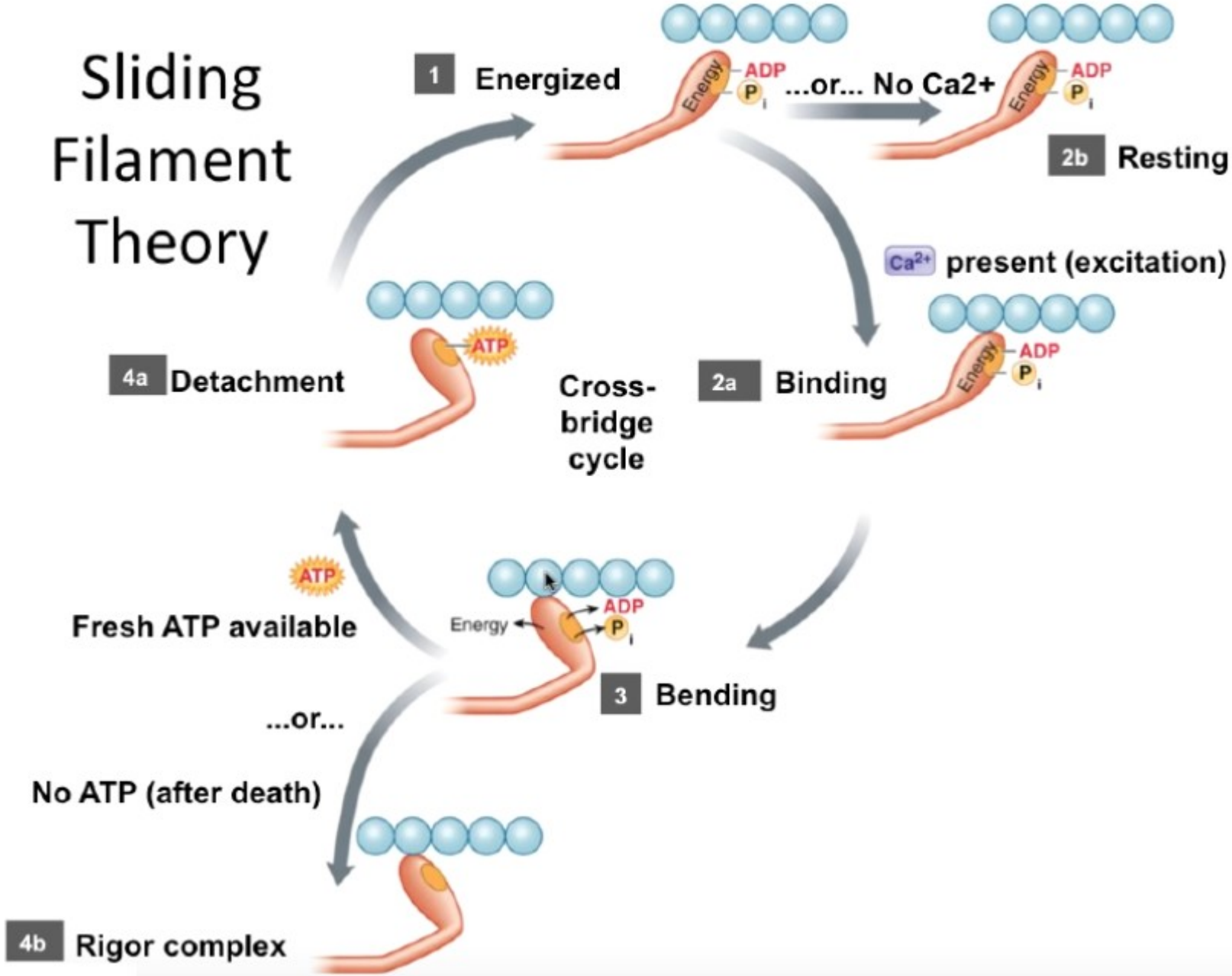
Calcium is the excitation signal, required to free the myosin binding sites

- lack of calcium = no binding, muscle is relaxed

ATP required for Power Stroke

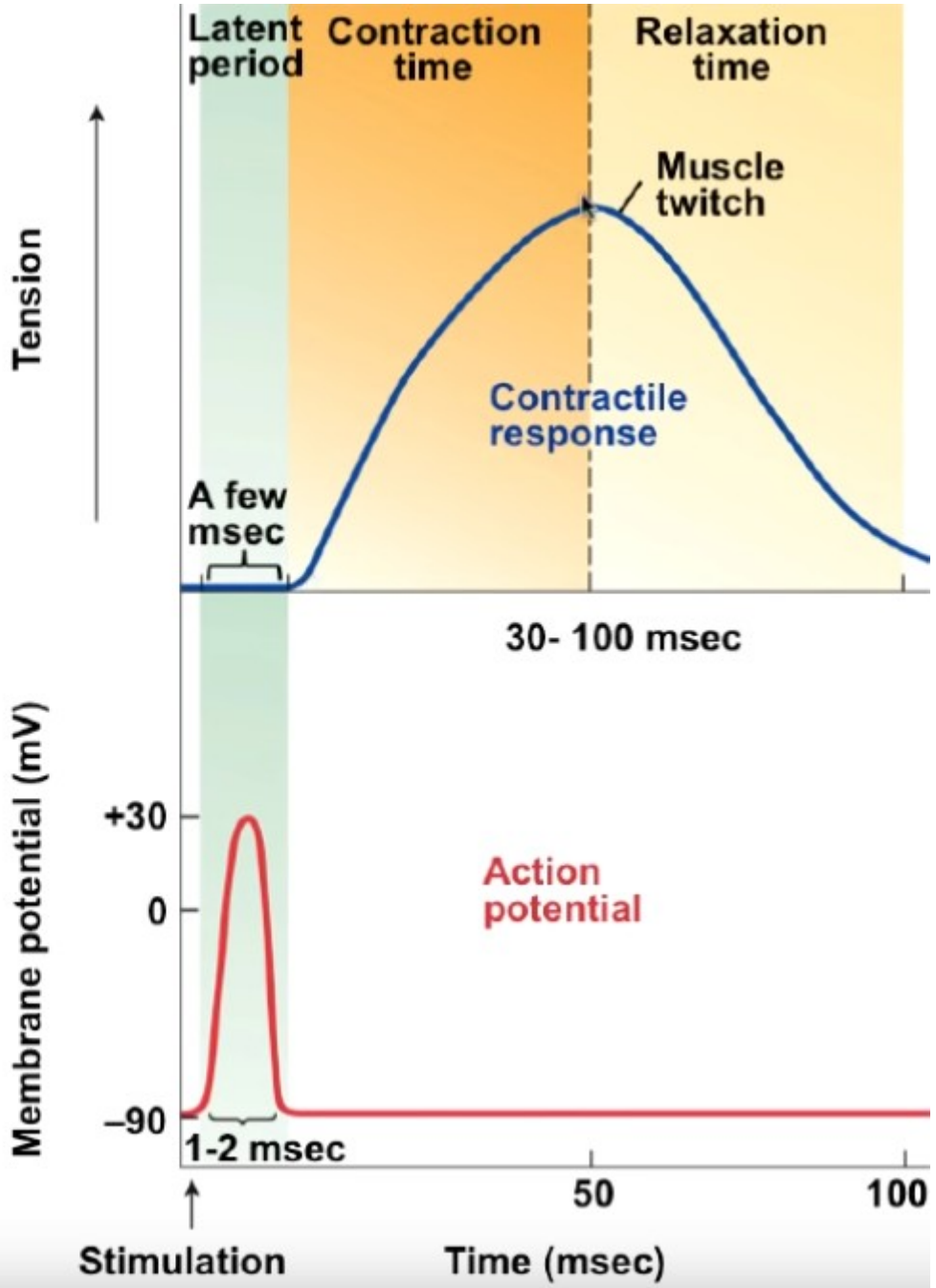
ATP also required for crossbridge release

- lack of ATP = no release
- upon death, no ATP available, rigor mortis (state of constant fixed contraction) sets in


Sliding Filament Theory
1 Energized
ADP
Energy
P i
...or... No Ca2+
2b Resting
Ca2+ present (excitation)
2a Binding
4a Detachment
ATP
Cross-bridge cycle
Fresh ATP available
3 Bending
...or...
No ATP (after death)
4b Rigor complex

Muscle Contraction Timing

- After excitation, the duration of the muscle contraction (15-50 msec) and muscle relaxation (additional 15-50msec) is very long compared to the duration of the action potential (1-2 msec)

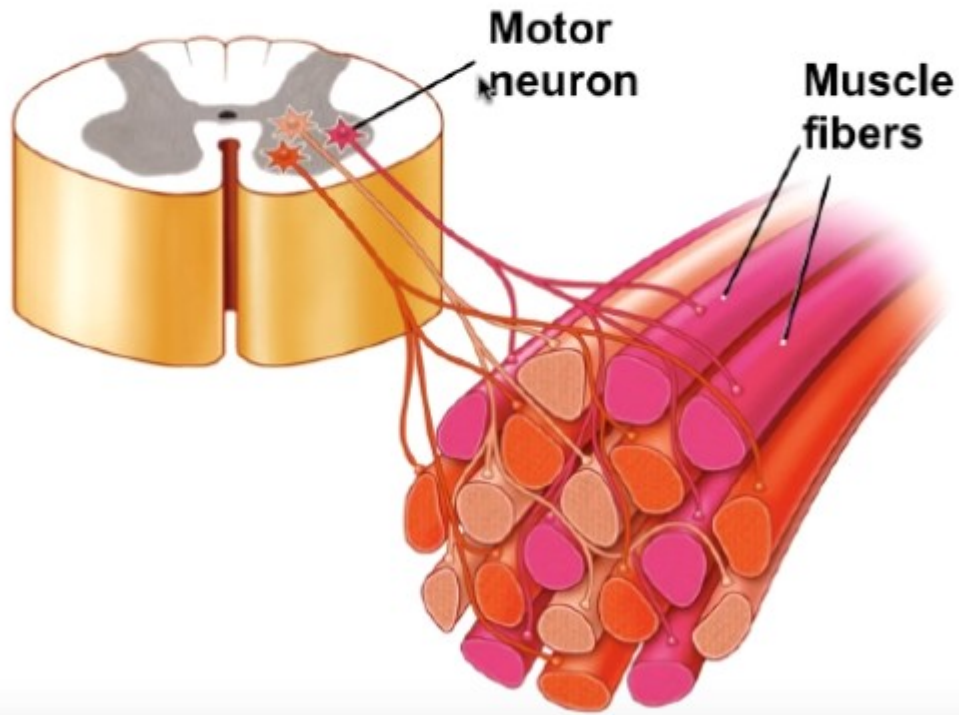


Motor Units

All muscle fibers within a whole muscle are not active during every contraction

A small subset of muscle fibers will be activated based on need

The smallest subset is a **motor unit**: one motor neuron and all the muscle fibers it innervates

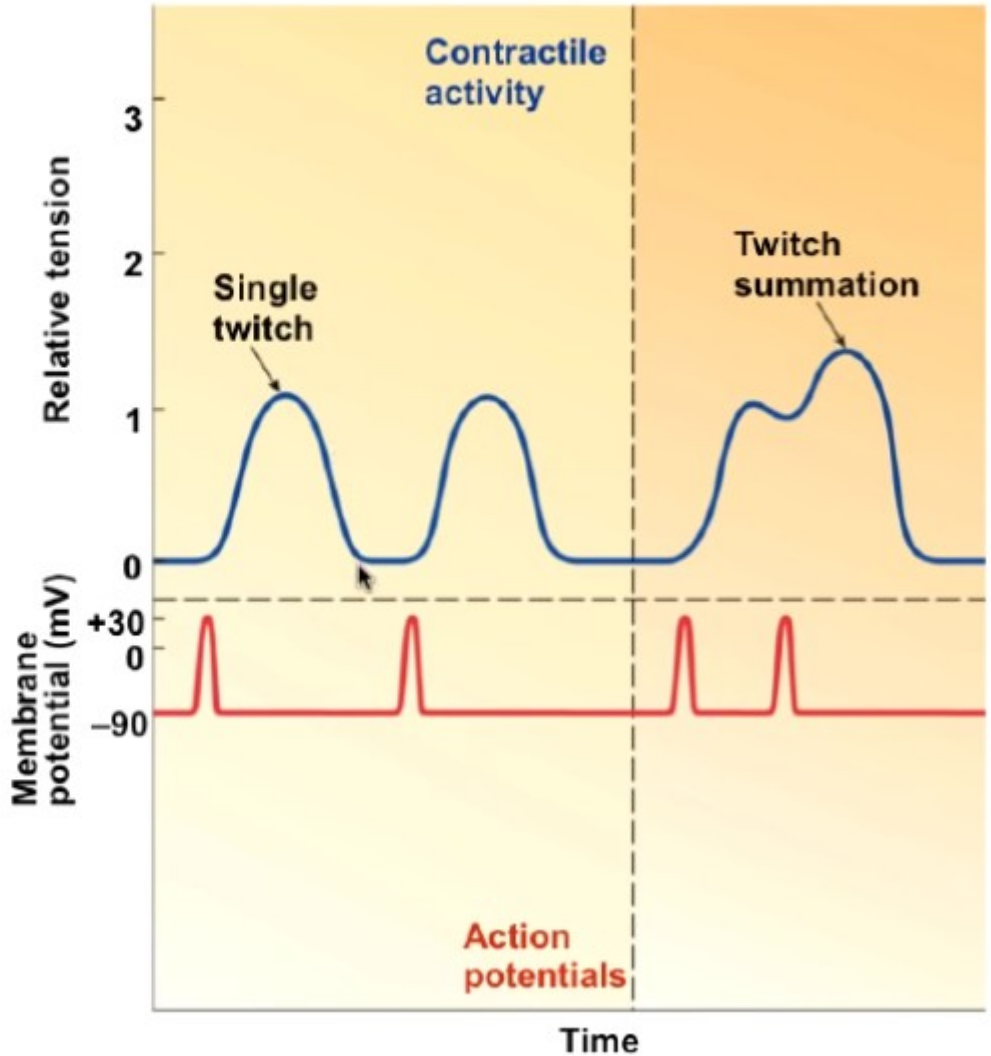


Muscle Twitch Summation

A single action potential in a muscle fiber produces a **muscle twitch**

Repeated stimulation is needed to produce sustained and longer duration contractions of muscles

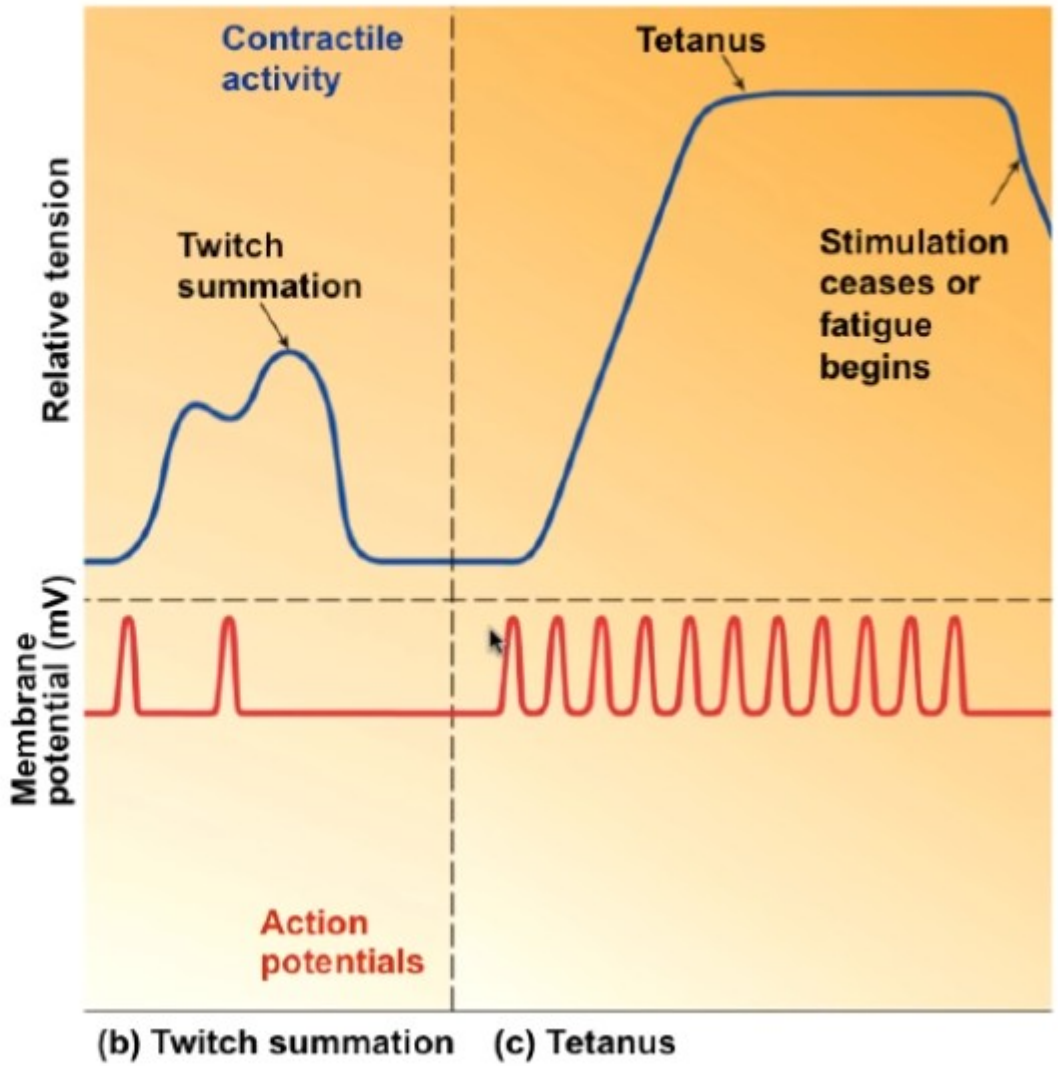
Muscle fibers can respond to repeated stimuli before they are fully relaxed, this is called **twitch summation**

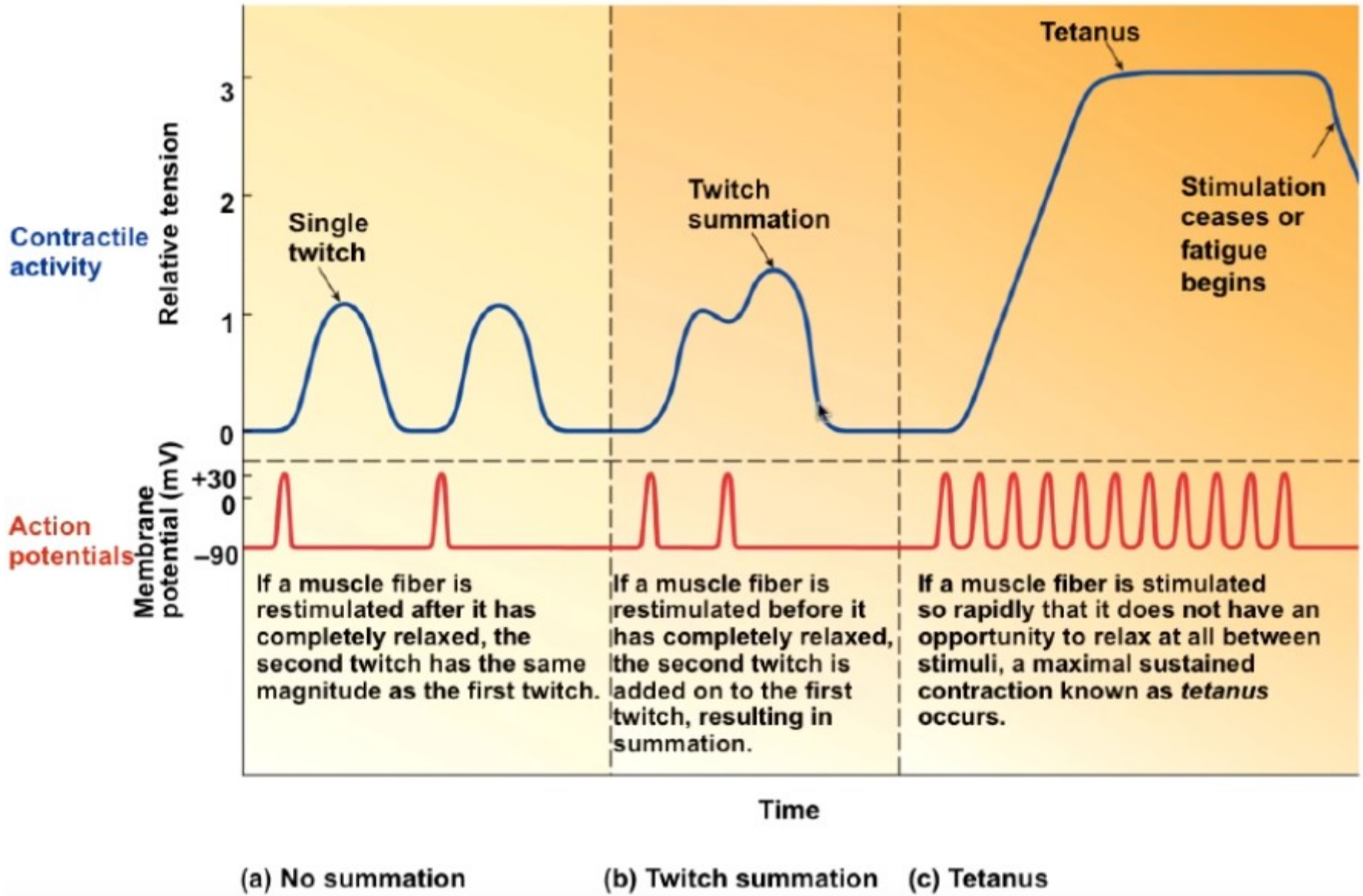


Tetanus

A muscle fiber at maximum stimulation, with no relaxation will reach a sustained maximal contraction called tetanus

Tetanus will last until the muscle becomes fatigued




Contractile activity
Relative tension
3
2
1
0
Single twitch
Twitch summation
Tetanus
Stimulation ceases or fatigue begins
Action potentials
Membrane potential (mV)
+30
0
–90
If a muscle fiber is restimulated after it has completely relaxed, the second twitch has the same magnitude as the first twitch.
If a muscle fiber is restimulated before it has completely relaxed, the second twitch is added on to the first twitch, resulting in summation.
If a muscle fiber is stimulated so rapidly that it does not have an opportunity to relax at all between stimuli, a maximal sustained contraction known as tetanus occurs.
Time
(a) No summation
(b) Twitch summation
(c) Tetanus

Thanks for your time and attention!!!!

Citations:
Neuroscientifically Challenge
Physiopedia
Pierce
From Neuron to Brain
Blausen.com staff (2014)