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CONCEPT: SKELETAL MUSCLE CELLULAR ANATOMY—MUSCLES TO SARCOMERES

● **Skeletal Muscles** connect different ________________ to each other, allowing for *voluntary* body movement.

Hierarchy of Organization within a Single Muscle:

● Skeletal muscle (e.g. the bicep, quadriceps) is a bundle of **muscle fascicles**.

□ Muscle fascicles are bundles of **muscle fibers.**

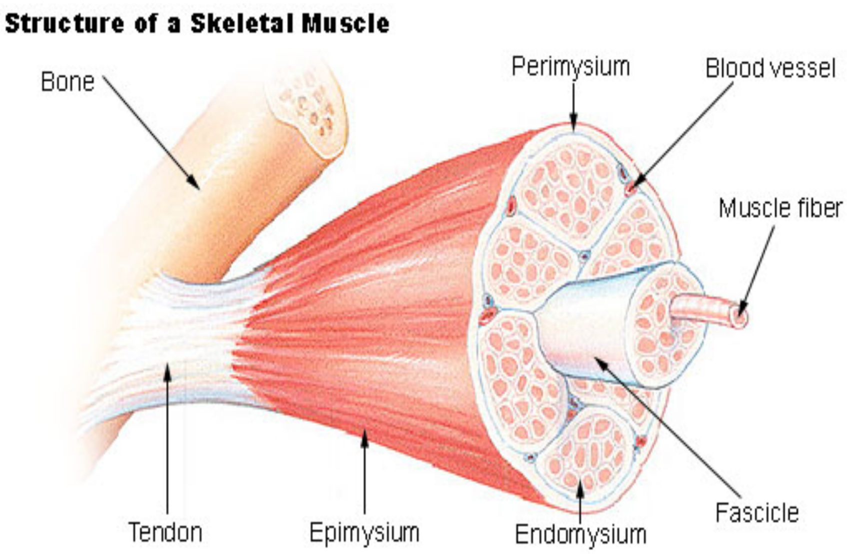
-Muscle fiber=muscle "cell."

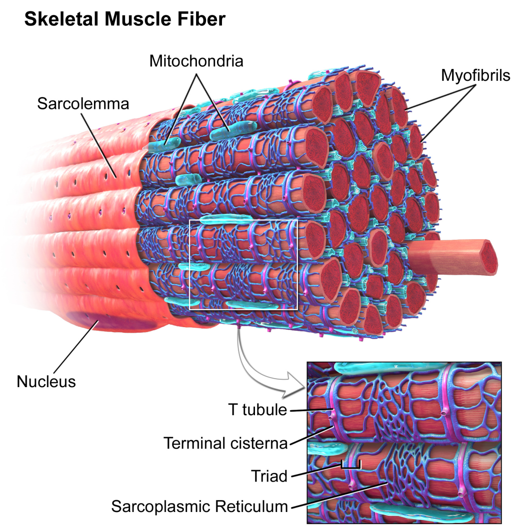
● Muscle fibers/cells are unique: really long (whole length of muscle) with many nuclei.

□ Have all usual cell organelles.

□ **Myofibrils**—which fill the rest of the muscle fiber—are the parts that allow for ___________________________.

EXAMPLE: The organization of a skeletal muscle.





Sarcomeres:

● **Sarcomeres** are repeating, contractile units that, when chained together, make a ________________________________.

□ Made of overlapping patterns of two **myofilaments:**

- **Actin** (the **thin filament**) - **Myosin** (the **thick filament**)

● Sarcomeres have a very, *very* specific, repeatable pattern. Some names for different sarcomere regions:

□ **Z Disk**=Ends of a sarcomere.

- Actin filaments are anchored here.

□ **M Line**=Middle of a sarcomere.

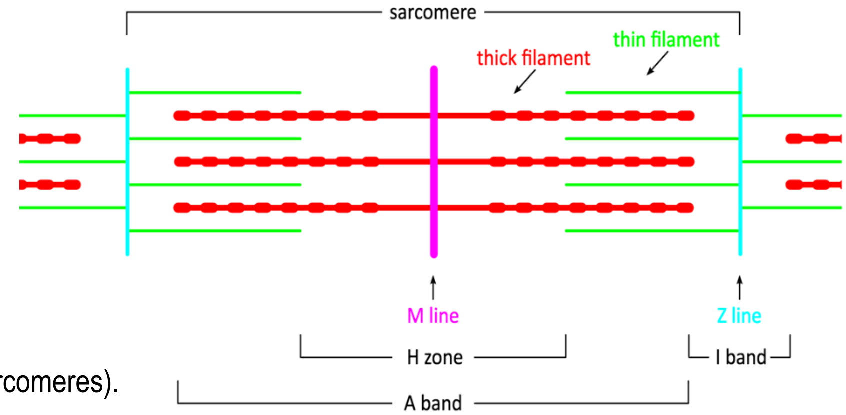
-Myosin filaments are anchored here.

□ **I Band**=Thin filaments *only*.

-Z disks run down the middle (span 2 sarcomeres).

□ **A Band**= Entire length of thick filaments.

□ **H Zone**= Middle of A band, with thick filaments *only*.

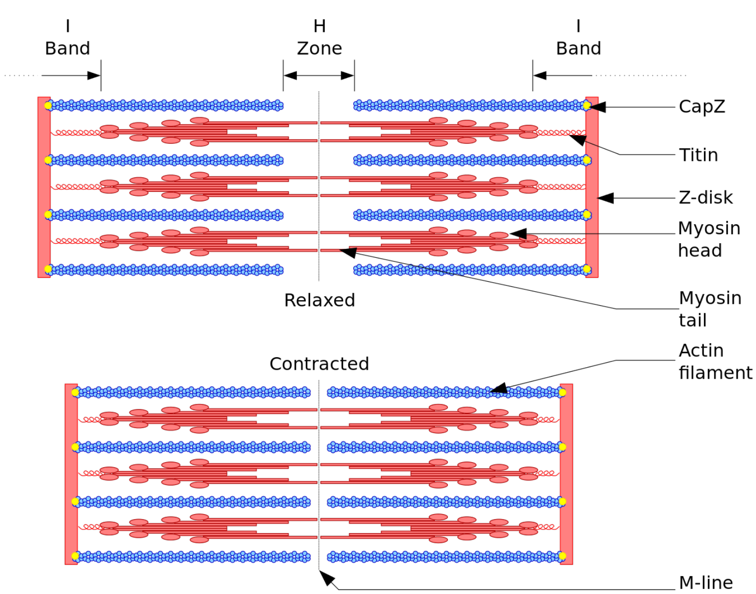


● **Sliding Filament Theory** describes how sarcomeres allow muscles to contract.

□ Thin and thick filaments slide *past* each other.

-Z disks get closer to M line, H zone shrinks.

EXAMPLE: A shortening sarcomere causes muscle contraction.



Muscles and Joints:

● Muscles are arranged around **joints** to allow for movement.

  □ **Flexors**=Muscles that *close* joints.

  □ **Extensors**=Muscles that *open* joints.

● Muscles are arranged in opposing patterns, to allow for all directions of movement.

  □ **Antagonists**=Muscles that have opposite effects on the same joint.

  □ **Synergists**=Muscles that have cooperative effects on the same joint.

EXAMPLE: Biceps and triceps muscles are arranged around the elbow joint. Biceps are an elbow *flexor*; triceps are an elbow *extensor*. Biceps and triceps are antagonists to each other. The brachioradialis—also an elbow flexor—is a synergist with the biceps.

PRACTICE 1: Fill in the blanks:

A __________________________ is a collection of muscle fibers.

A __________________________ is a collection of myofibrils.

a) Skeletal Muscle; muscle fascicle.
b) Muscle fascicle; muscle fiber.
c) Muscle fiber; skeletal muscle.

PRACTICE 2: Which of the following bands in a myofibril include myosin (the thick filament)? (Choose all that apply.)

a) A Band.
b) H Band.
c) I Band.
d) Z Disk.

PRACTICE 3: Which of the following bands in a myofibril include actin (the thin filament)? (Choose all that apply.)

a) A Band.
b) H Band.
c) I Band.
d) Z Disk.

PRACTICE 4: The quadriceps are knee extensors; the hamstrings are knee flexors. Which of the following describes the relationship between the quadriceps and hamstring muscle groups?

a) Synergists.
b) Antagonists.
c) Agonists.
d) Inverse Agonists.

CONCEPT: SKELETAL MUSCLE CONTRACTION I: THE CELLULAR LEVEL

Motor Neurons and Skeletal Muscle Contraction:

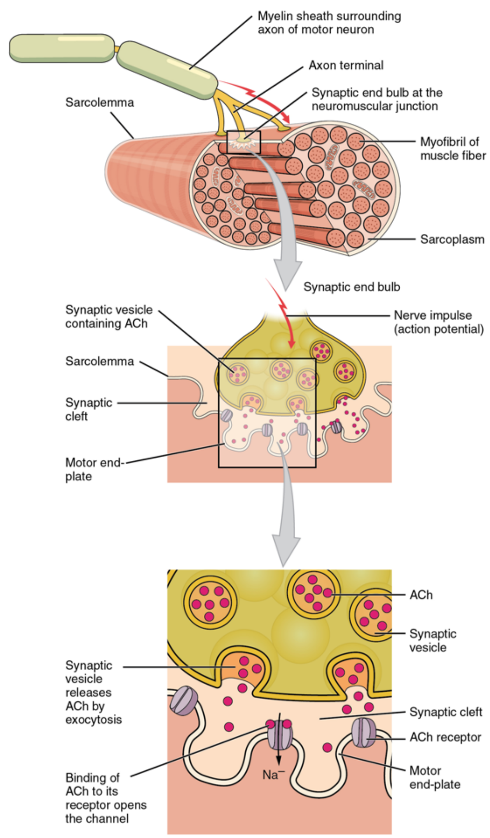
● Skeletal muscle contraction is **neurogenic**—a muscle fiber must be “activated” by a motor neuron via an NMJ.

● The process of contraction is initiated by a ___________ signal in the skeletal muscle fiber. Two questions:

1) How does AP in a motor neuron become a Ca^{2+} signal in the muscle fiber?→**Excitation-Contraction Coupling.**

2) How does a Ca^{2+} signal cause sarcomeres to start shortening?→**Sliding Filament Theory** and **Power Strokes.**

EXAMPLE: Skeletal muscle fibers are controlled by motor neurons.



Skeletal Muscle Excitation-Contraction Coupling:

● To get from a motor neuron AP to a Ca^{2+} signal in a skeletal muscle fiber:

1. Motor neuron AP reaches axon terminal→Ach in synaptic cleft.

2. Ach binds to nicotinic AchRs. These mixed-cation channels open→Na^{+} enters cell→depolarization.

   -Graded potential called an **endplate potential (EPP).**

3. EPP depolarizes V_m to V_{thresh}, activates VGNaCs and VGKCs→skeletal muscle AP.

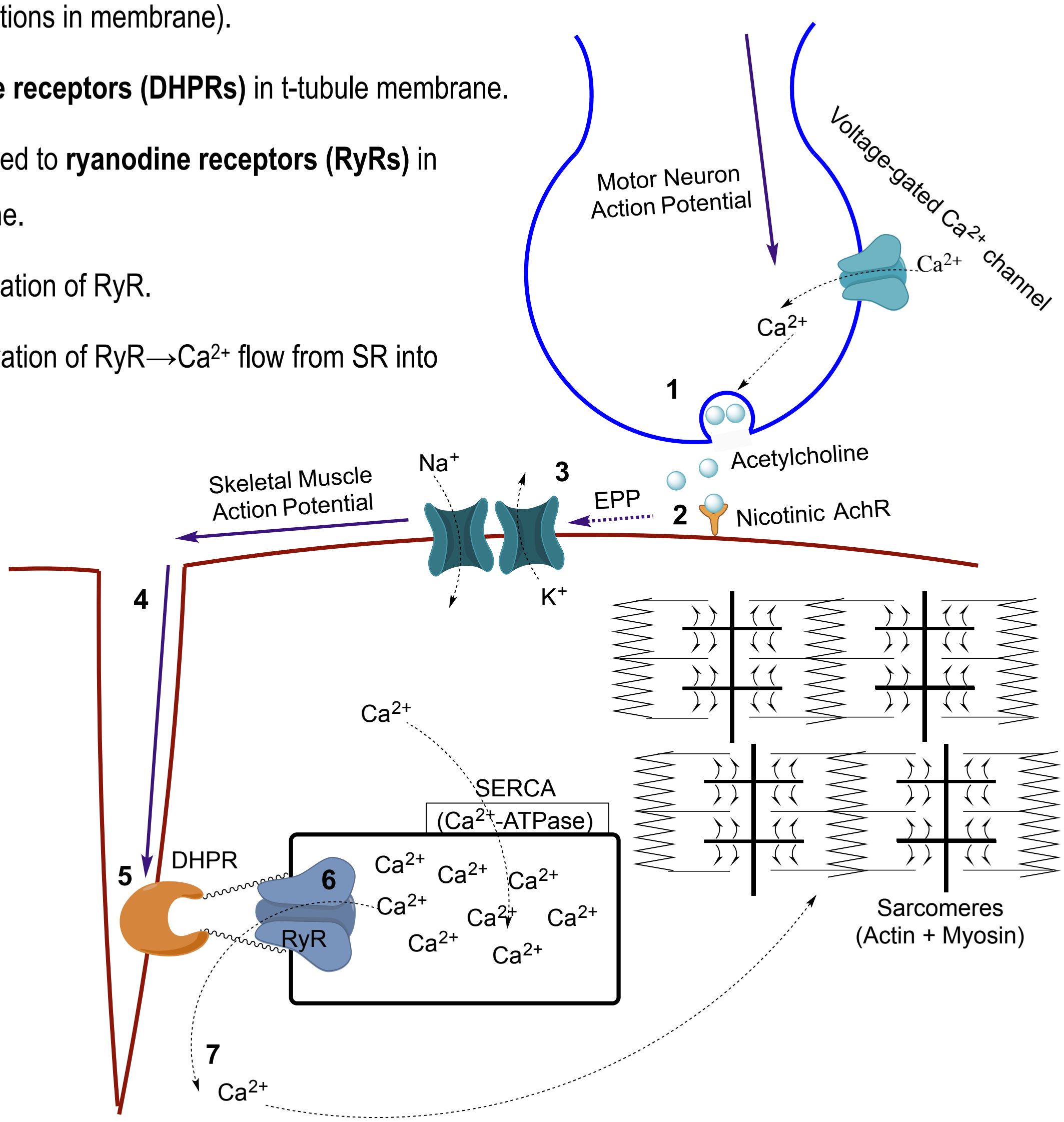
4. AP invades **t-tubules** (indentations in membrane).

5. AP activates **dihydropyradine receptors (DHPRs)** in t-tubule membrane.

6. DHPRs are physically connected to **ryanodine receptors (RyRs)** in sarcoplasmic reticulum membrane.

   -Activation of DHPR→Activation of RyR.

7. RyRs are Ca^{2+} channels. Activation of RyR→Ca^{2+} flow from SR into cytosol. Ca^{2+} signal!



The Myofilaments in Detail:

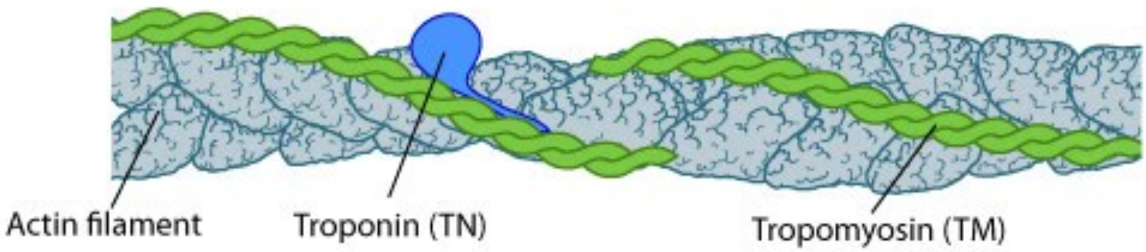
● "Actin" in skeletal muscle is actually 3 proteins: *actin*, *tropomyosin*, and *troponin.*

□ **Actin** is a long filamentous protein with **myosin binding sites** spaced along it.

□ **Tropomyosin** is a helical protein wrapped around actin, covering the myosin binding sites (at rest).

□ **Troponin** is a Ca^{2+} binding/sensing protein that also interacts with tropomyosin (more soon).

EXAMPLE: An actin filament.



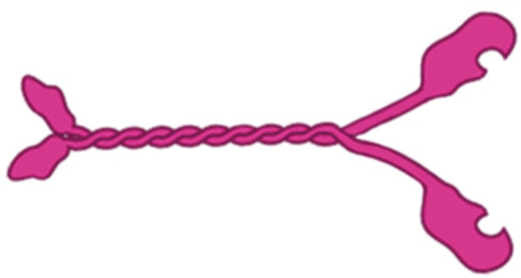
● Myosin has "heads" projecting off the filamentous part.

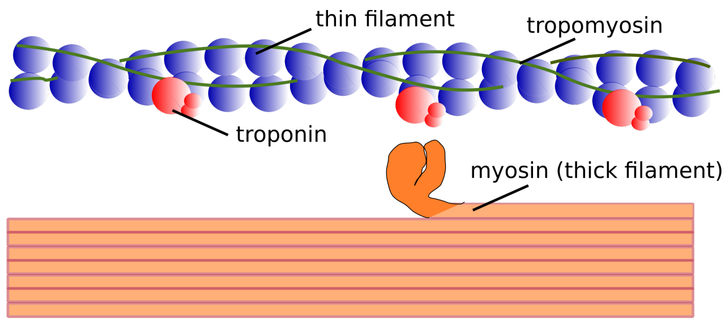
□ **Myosin ATPase**=Part of head with ability to bind to and hydrolyze/use ATP.

-ATP hydrolysis allows head to "swivel" from low-energy to high-energy conformation.

□ Heads can bind to the myosin binding sites on actin, forming a **cross-bridge** (if binding site is uncovered)**.**

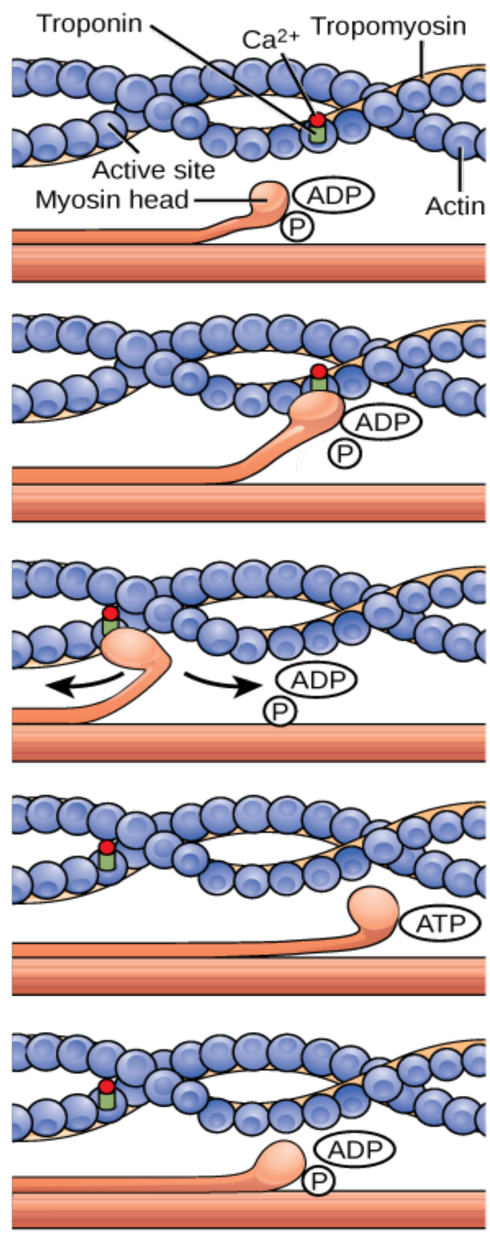
EXAMPLE: Myosin and its heads.





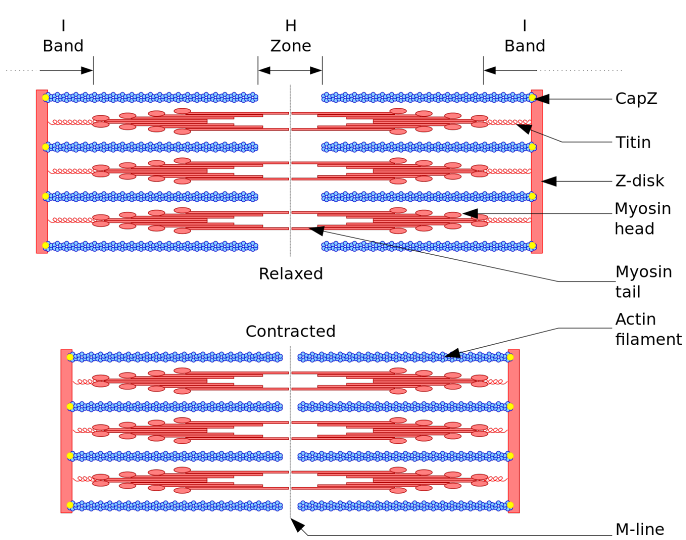
Sliding Filament Theory and Power Strokes:

- At "rest," myosin heads have hydrolyzed ATP (holding ADP+P_i) and are swiveled back into high-energy conformation.
  - □ But, can't bind to actin because myosin binding site on actin covered by tropomyosin.
- When ↑[Ca^{2+}], Ca^{2+} binds to troponin.
  - □ Causes troponin to make tropomyosin move away from the myosin binding site, so cross bridges possible.



- Now, **Power Stroke** cycle to actually shorten sarcomere:
  1. Myosin head binds to actin.
  2. Myosin head releases P_i, causes swivel from high-energy to low-energy conformation.
     - -Drags actin—therefore Z-disk—toward M line.
  3. Myosin head releases ADP, binds new ATP.
  4. ATP binding breaks cross-bridge.
  5. Myosin hydrolyzes new ATP, swivels back to high-energy conformation.
  6. If Ca^{2+} still around→go again.

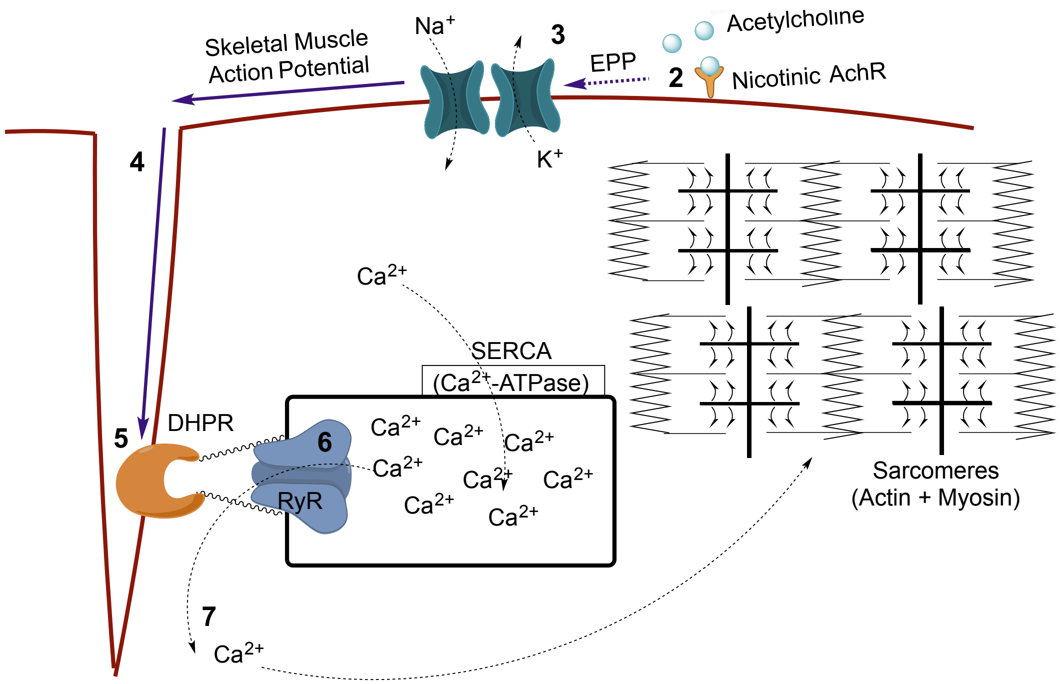
EXAMPLE: Power strokes cause the sarcomere to shorten because myosin heads pull on actin, dragging the Z disks toward the M line.



Relaxation—The SR/ER Ca^{2+} ATPase:

- To allow relaxation, Ca^{2+} must get away from troponin so tropomyosin can cover the myosin binding site again.
- Ca^{2+} is cleared from the cytosol back into the SR by the SR/ER Ca^{2+} ATPase (SERCA).
  - □ Hydrolyzes ATP, uses the energy to pump Ca^{2+} back into SR against its concentration gradient.

EXAMPLE: SERCA pumps Ca^{2+} back into the SR, clearing it from the cytosol.

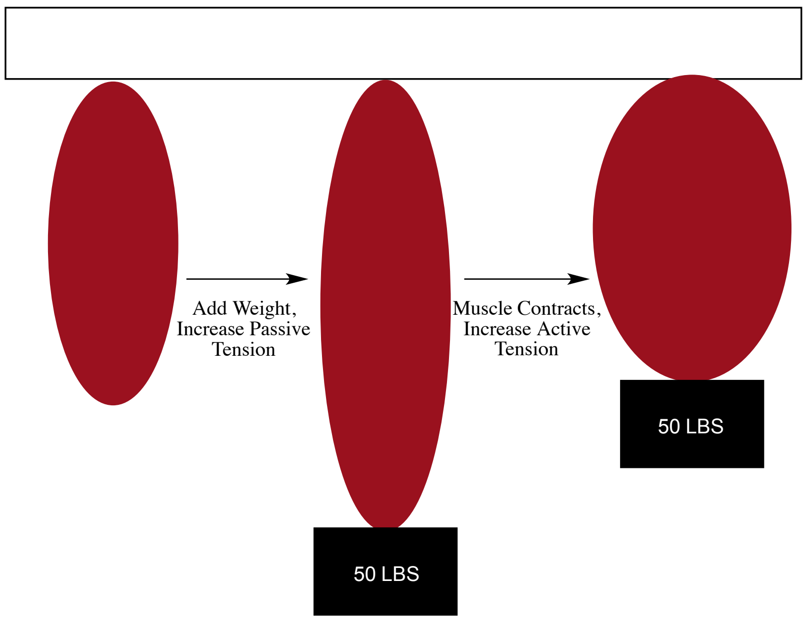


CONCEPT: SKELETAL MUSCLE CONTRACTION II: TENSION AND LENGTH-TENSION CURVES

Types of Tension:

- **Tension** is used to measure the contraction of a muscle. Two kinds:
  - □ **Passive Tension** is just the result of _____________ in the muscle—like a rubber band pulling back.
  - □ **Active Tension** is from actin/myosin cross-bridges.

EXAMPLE: Passive vs active tension.



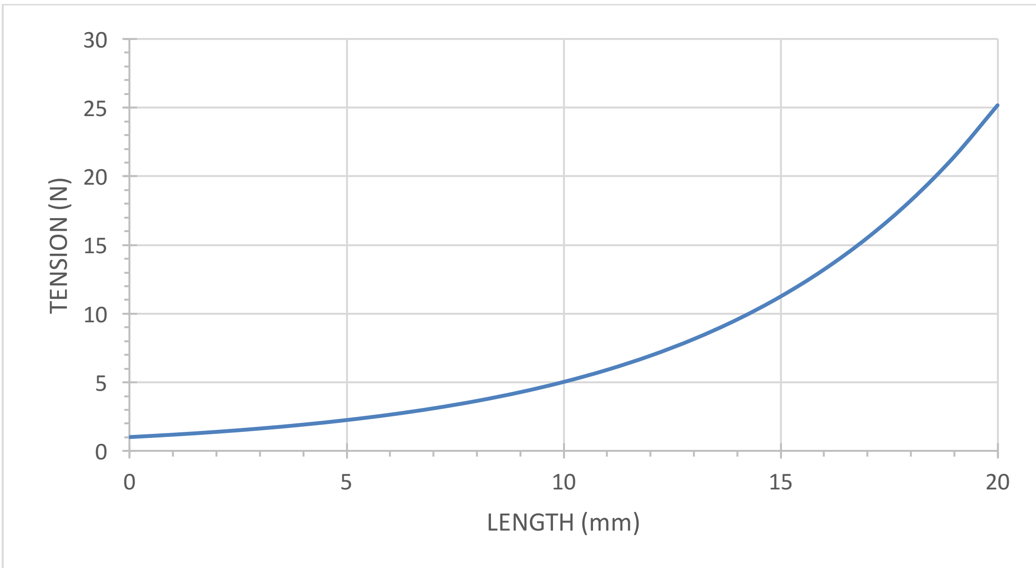
Length-Tension Curves—Passive Tension:

● **Length-Tension Curves** show the tension a muscle can generate *at a given, set length*.

● The length-tension curve for passive tension increases as length increases.

□ ↑Stretch in Muscle→↑Length→Elastic parts of muscle pull back→↑Passive Tension

EXAMPLE: Length-tension curve for passive tension in a skeletal muscle.



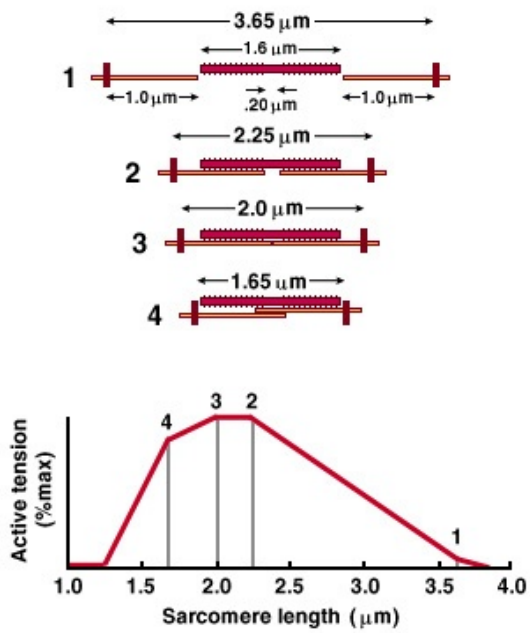
Length-Tension Curves—Active Tension:

● The active tension a muscle can generate relies *entirely* on *the number of myosin heads that can bind to actin*.

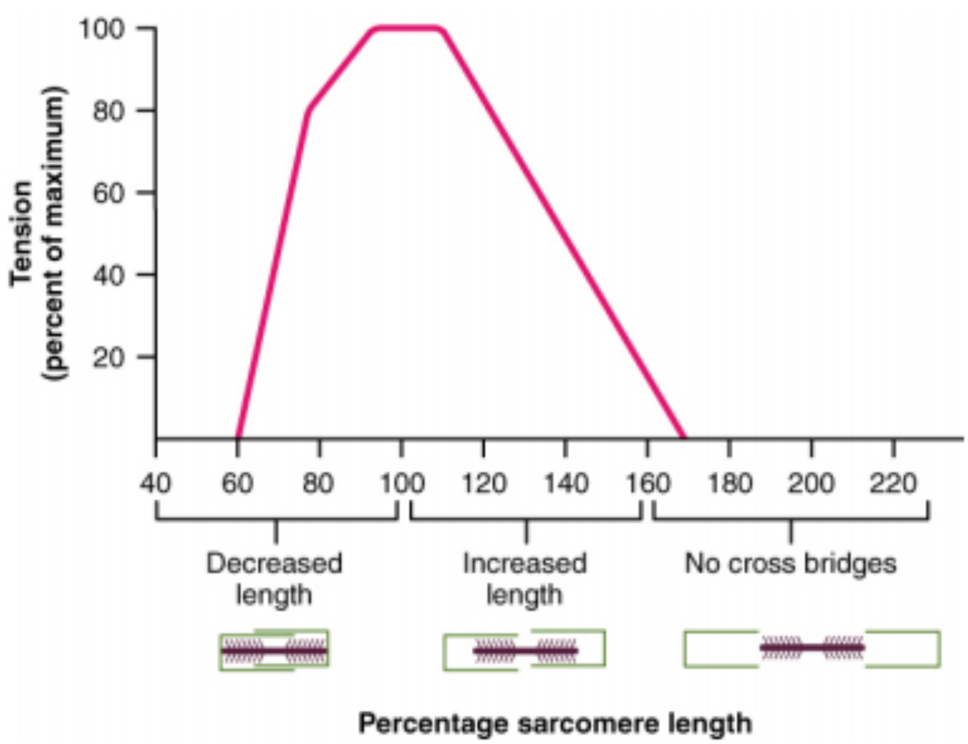
● Amount of myosin/actin overlap within individual sarcomeres changes as length of muscle changes.

- □ Really long lengths→actin and myosin pulled too far apart→no overlap→~no active tension.
- □ Medium lengths→optimal myosin/actin overlap→maximum possible active tension.
- □ Really short lengths→Z disks crammed together (nowhere to shorten)→~no active tension.

● As length increases, active tension increases, then plateaus at optimal lengths, then decreases.



EXAMPLE: Length-tension curve for active tension in a skeletal muscle.



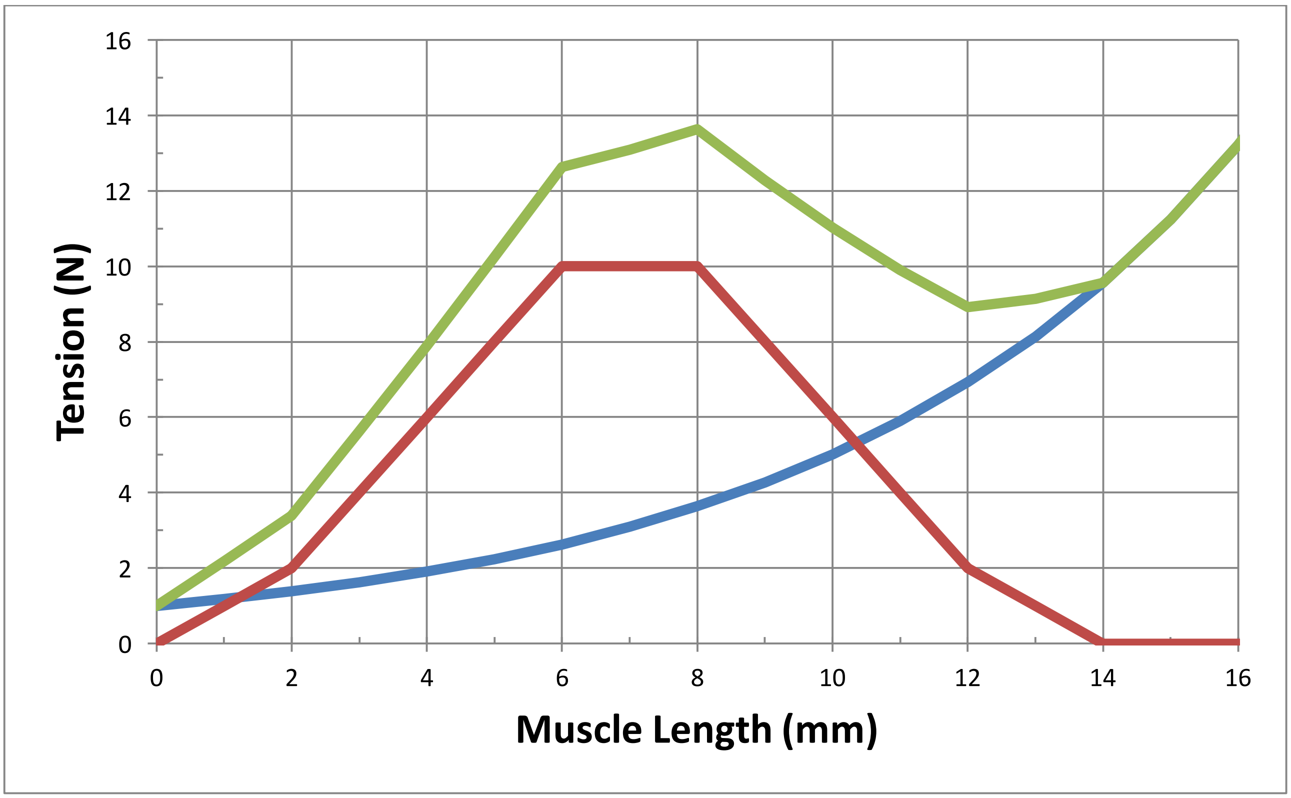
Length-Tension Curves—Total Tension:

● **Total Tension** is the tension you'd actually *measure* in a muscle while it's contracting.

□ Total Tension=Active Tension+Passive Tension.

-When measuring, can't separate active and passive.

EXAMPLE: The three different length-tension curves for a skeletal muscle.



PRACTICE 1: A muscle is sitting at rest. It has a tension of 3 N. Which of the following describes that tension?

a) Active tension.
b) Passive tension.

PRACTICE 2: A muscle at rest has a tension of 3 N. It is then activated with an electrode; after activation and contraction, the muscle has a tension of 10 N. Which of the following is the active tension in the muscle after activation?

a) 3 N.
b) 7 N.
c) 10 N.
d) 13 N.

PRACTICE 3: At a length of 5 cm, a muscle generates a maximal active tension of 10 N. At a length of 10 cm, the same muscle generates an active tension of 3 N. Which of the following describes the reason for this change?

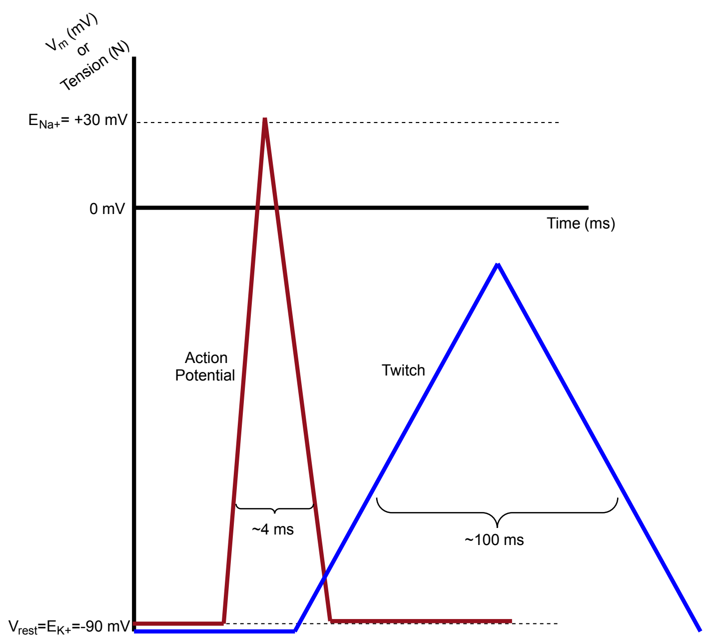
a) Suboptimal contraction from crowding of myosin heads into the Z disk.
b) Reduction in myosin/actin overlap.
c) Fatigue from multiple stimulations.

CONCEPT: SKELETAL MUSCLE CONTRACTION III: SUMMATION AND TETANUS

Skeletal Muscle Action Potentials and Twitches:

- A skeletal muscle fiber contracts when it carries an AP. (APs caused by a motor neuron activating its NMJ.)
  - □ One AP→One muscle **"twitch"**—a brief contraction, then relaxation.
- Skeletal muscle action potentials are very ___________________—like 4 ms.
  - □ Twitches, however, last much ________________—like 100 ms.

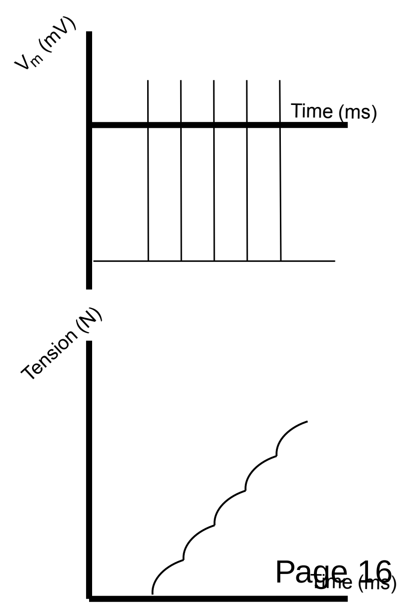
EXAMPLE: A temporal comparison of a skeletal muscle action potential and twitch.



Summation:

- Twitches being longer than APs means that multiple APs can happen before the resulting twitches die away.
- **Summation**—multiple APs→multiple twitches that happen "on top" of each other→a stronger contraction.

EXAMPLE: Multiple APs leading to summation in a skeletal muscle.

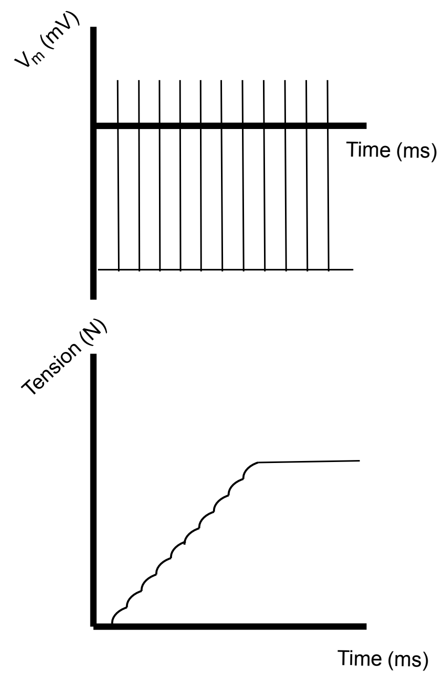


Tetanus:

● **Tetanus**- A steady, sustained, maximal contraction in a skeletal muscle resulting from many high-frequency APs.

□ (The disease "tetanus" is something different.)

EXAMPLE: A tetanic contraction.



CONCEPT: SKELETAL MUSCLE CONTRACTION IV: ISOTONIC VS. ISOMETRIC CONTRACTIONS

● The "point" of a muscle contraction is to move a **load**.

- □ Two types of contraction (depending on the load): *isotonic* or *isometric* contractions.

Isotonic Contractions:

● **Isotonic Contractions** are those where the muscle's tension is ______________________, but its length changes.

- □ Means that active tension generated > the load.

EXAMPLE: Isotonic contractions occur when muscle can generate enough active tension to move load→muscle shortens.

Isometric Contractions:

● **Isometric Contractions** are those when the muscle builds up tension, but its length _______________ changes.

- □ Means that active tension generated < the load.

EXAMPLE: Isometric contractions occur when muscle can *not* generate enough active tension to move load→muscle "activates," but length remains constant.

PRACTICE 1: Your Clutch physio tutor goes to the gym and tries to do a 200-lb deadlift. Unsurprisingly, he cannot. Which of the following types of contractions is occurring in his muscles when he's trying—but failing—to do this lift?

a) Isometric contractions.
b) Isotonic contractions.

PRACTICE 2: Your Clutch physics tutor goes to the gym and tries to do a 200-lb deadlift. He does it with perfect form. Which of the following types of contractions is occurring in his muscles when he's completing this lift?

a) Isometric contractions.
b) Isotonic contractions.

CONCEPT: ENERGY REQUIREMENTS OF SKELETAL MUSCLES—FIBER TYPES AND FATIGUE

Skeletal Muscle Fiber Types:

● Not all skeletal muscle fibers are equal. Three different types of skeletal muscle fiber in humans: *types I, IIA, and IIX*.

□ (Type IIX often also called IIB.)

□ Differ mostly in *the speed of the myosin ATPase*. This can have many effects on muscle function:

-↑Myosin ATPase→↑Rate of ATP use→↑Force generated per time ("Power")→↑Fatigue

	Type I **(Slow-Twitch; Oxidative; Red)**	**Type IIA** **(Fast-Twitch; Oxidative-Glycolytic; Red)**	**Type IIX** **(Fast-Twitch; Glycolytic; White)**
Myosin ATPase Activity	Slowest	Middle	Fastest
Time to Max Tension (Power)	Slowest	Middle	Fastest
Time to Fatigue	Slowest	Middle	Fastest
Get ATP by…	Aerobic Metabolism	Glycolysis/Lactic Acid Fermentation & Aerobic Metabolism	Glycolysis/Lactic Acid Fermentation
Color	Red (because of myoglobin, an O_2-binding protein)	Red	White
Good for…	Posture, Endurance Events	Supporting the other two.	High power events e.g. sprints, lifts.

● Every muscle has all three fiber types—only the ____________________ changes.

● Myosin ATPase activity and rate of ATP use explain rate of fatigue.

□ ↑ATPase activity→↑ATP use→↓Time to ATP depletion→↑Fatigability.

EXAMPLE: Genetically gifted marathon runners tend to have a high ratio of Type I fibers, and so are slow to fatigue.

PRACTICE 1: A muscle is stimulated so that it is continuously, constantly contracting. Immediately after activation it generates a tension of 20 N. One hour after continuous activation it is generating a tension of 5 N. Which of the following fiber types is generating the 5 N of tension?

a) Type I.
b) Type IIA.
c) Type IIX.

CONCEPT: NEURAL CONTROL OF SKELETAL MUSCLE

Motor Neurons and Skeletal Muscle Fibers:

● Skeletal muscle contraction is **neurogenic**—to contract, a muscle must be activated by a motor neuron (MN).

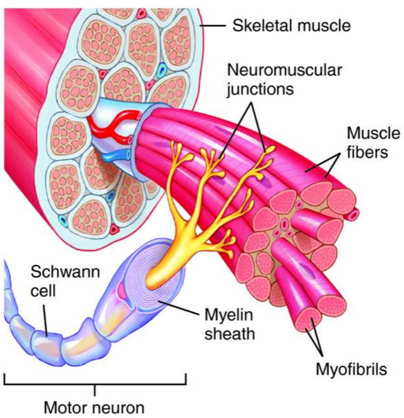
● **Motor Unit**= *one* motor neuron + all the muscle fibers it innervates.

□ May be very large—one motor neuron for 1000s of muscle fibers.

□ Or very small—one motor neuron for a few muscle fibers.

□ Motor units activate as a whole—if a motor neuron has an AP, so will __________ the muscle fibers it innervates.

EXAMPLE: A motor unit.



● The size of a muscle's/body part's motor units determines resolution of motion.

□ Small motor units let you activate only a few muscle fibers at a time→very fine control over movement.

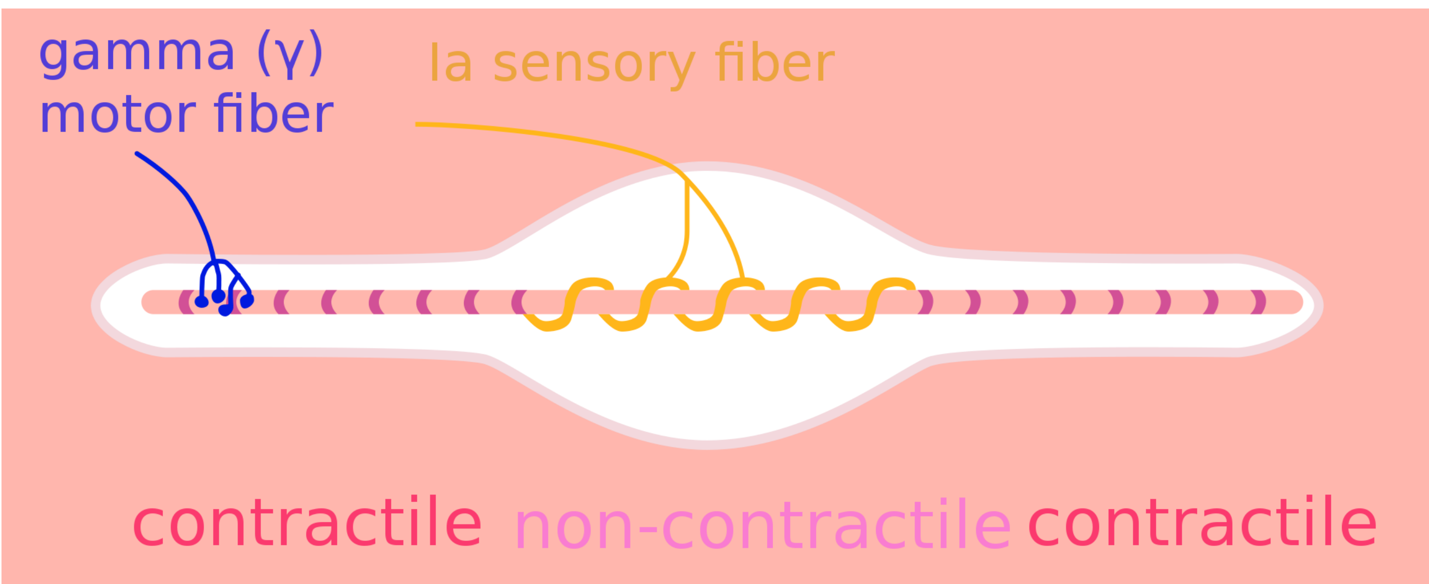
□ Large motor units mean many fibers are activated at once→poor resolution of movement.

EXAMPLE: Muscles in the fingers have small motor units; muscles in back have larger motor units.

Reflexes and Muscle Spindles:

- *Voluntary* movement of skeletal muscle happens via motor neurons from commands originating in motor cortex.
  - □ But, skeletal muscles are also controlled via involuntary *reflexes.*
- Reflexes require a sensory receptor, some CNS processing, and resulting change in motor neuron activity.
  - □ Sensory receptor for skeletal muscle reflexes is the *muscle spindle.*
- **Muscle Spindles**- Stretch receptors embedded in muscles to monitor muscle length/stretch.
  - □ Scattered throughout muscle pretty randomly.
  - □ Enclosed in capsule of non-contractile connective tissue with special contractile **intrafusal** muscle fibers on ends.
    - -Intrafusal fibers maintain tension in muscle spindles.
    - -Innervated by special γ motor neurons (more soon).

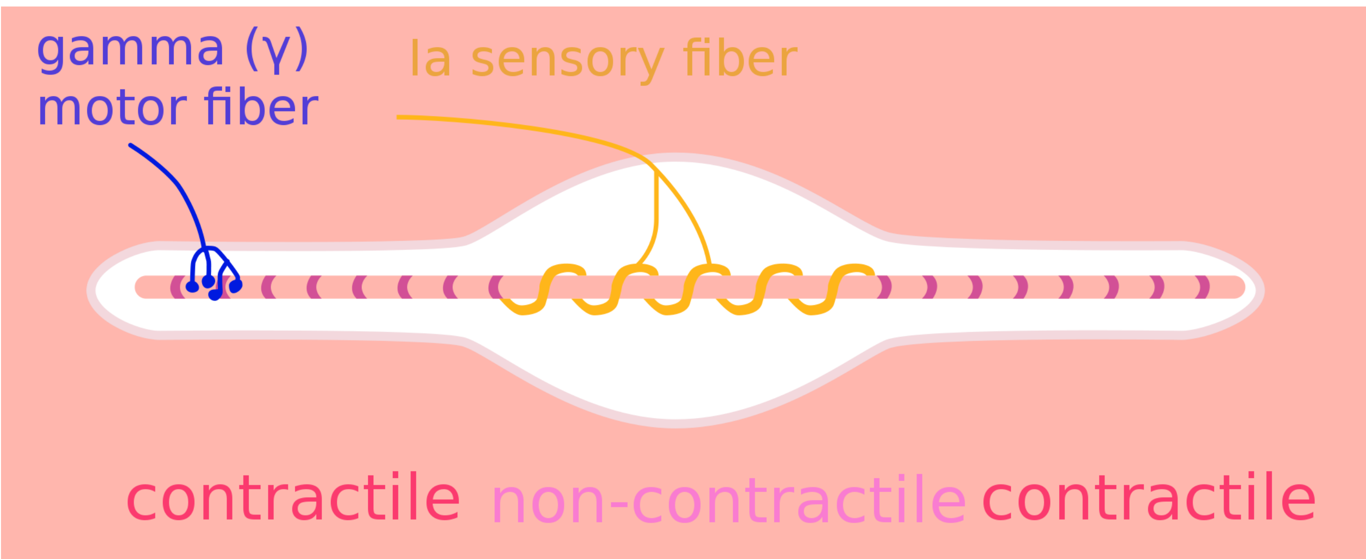
EXAMPLE: A muscle spindle.



Alpha-Gamma Coactivation:

- Muscle spindles monitor muscle stretch: ↑stretch in the muscle→↑ activity in muscle spindle sensory neurons.
    - □ But, muscle contraction could generate slack in the muscle spindle, rendering them useless.
- **Alpha-Gamma Coactivation**- When α motor neurons cause contraction of muscle fibers, γ motor neurons cause contraction of intrafusal fibers (at the ends of the muscle spindle).
    - □ Maintains some tension in the muscle spindle, so they can keep firing APs.

EXAMPLE: A muscle spindle and its intrafusal fibers are innervated by γ motor neurons.



<u>The Knee-Jerk/Patellar Tendon/Muscle Stretch Reflex:</u>

● **Knee-Jerk Reflex** is the classic skeletal muscle reflex arc.

□ It's **monosynaptic**—only one synapse (the one between the sensory and motor neuron) involved.

● Function: Sense ↑Stretch in the quadriceps muscle and increase quadriceps contraction to counter that stretch.

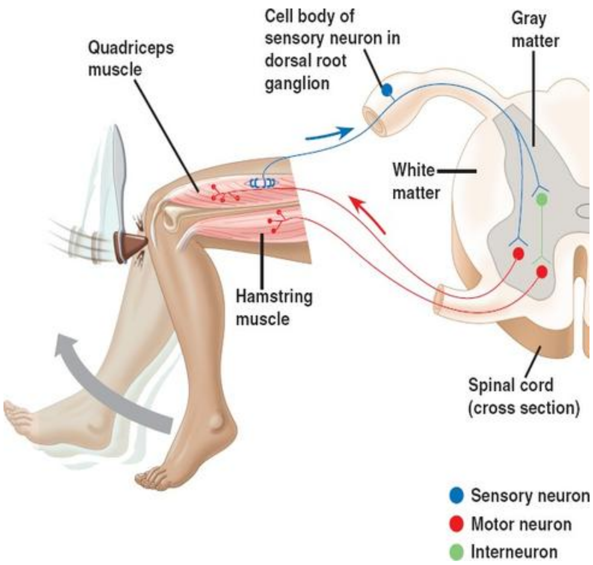
□ ↑Stretch→↑Sensory Neuron Activity→↑Motor Neuron Activity→↑Quadriceps Contraction→↓Stretch

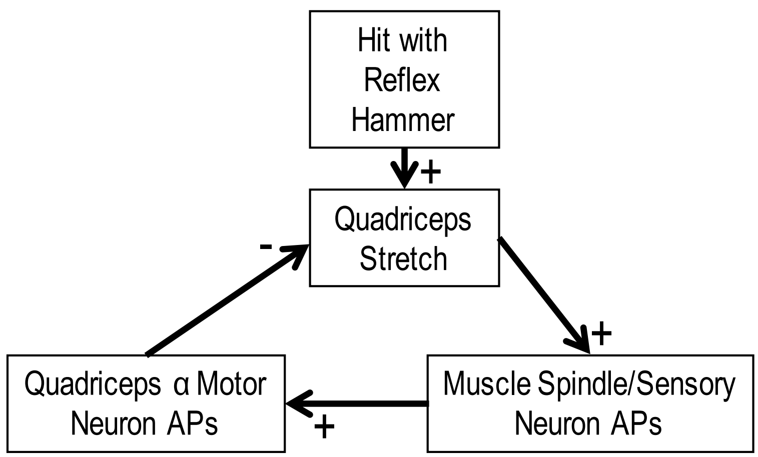
□ **Reciprocal Inhibition**- Sensory neuron also activates *inhibitory interneuron* that synapses on *hamstring* MNs.

-Inhibition of hamstring motor neurons→more dramatic quadriceps contraction.

● Clinically, this reflex is tested by hitting patellar tendon, which causes quick stretch in quadriceps→quick quadriceps kick.

EXAMPLE: An anatomical and feedback loop diagram of the knee jerk reflex.



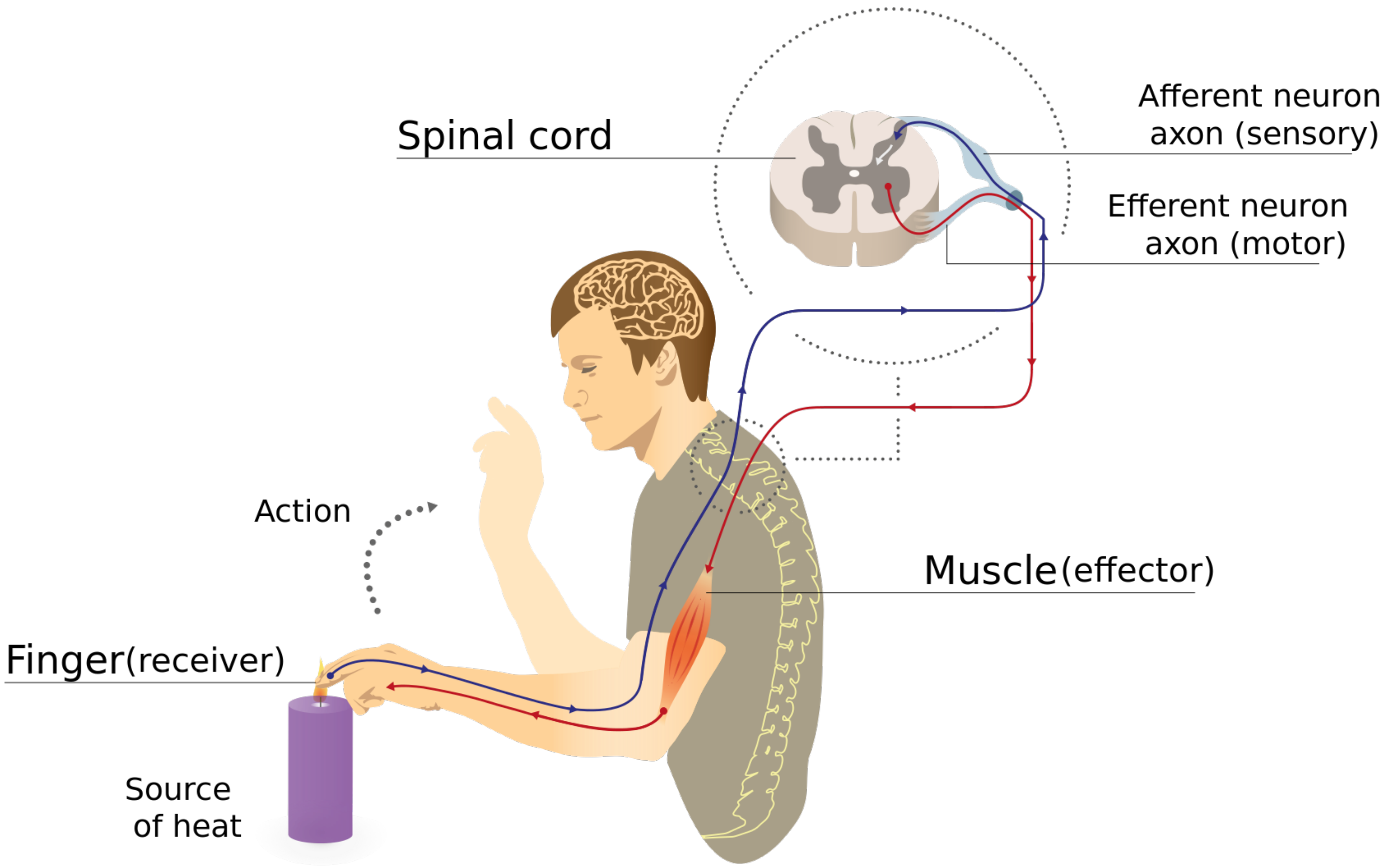


The Nociceptive/Withdrawal Reflex:

● **Nociceptive Reflex** causes reflexive withdrawal of a limb from ____________________ stimuli.

- □ Pain sensory neuron activates two interneurons: one excitatory and one inhibitory.
  - -Excitatory interneuron excites MNs of flexors; inhibitory interneuron inhibits MNs of extensors.
  - -Net result: Flexion of limb away from painful, damaging stimulus.

EXAMPLE: The nociceptive/withdrawal reflex.



PRACTICE 1: Flexor pollicis longus is a muscle in the hand that pulls the thumb toward the palm. Deltoid is a muscle in the shoulder that helps pull the arm away from the body (i.e. from hanging by the side up to horizontal). Which of the following describes the relative size of *motor units in flexor pollicis longus compared to motor units in deltoid?*

a) They are larger.
b) They are smaller.
c) They are the same size-- motor units are all the same size.
d) It's impossible to know.

PRACTICE 2: Which of the following describes the function of intrafusal muscle fibers?

a) Generate tension and cause shortening of the muscle during activation.
b) Maintain tension on the muscle spindle after shortening of the muscle.
c) Carry sensory information about the tension on muscle spindles to the CNS.
d) Cause contraction of muscle fibers that are part of the muscle spindle

PRACTICE 3: A 65-year-old man presents to his physician's office because he keeps falling down. The man has no patellar reflexes bilaterally. Damage to which of the following structures could be the direct cause of this man's absent patellar tendon reflexes? (Choose all that apply.)

a) Sensory neurons in the patellar tendon.
b) α motor neurons innervating the quadriceps muscle.
c) α motor neurons innervating the hamstrings muscle.
d) Interneurons synapsing onto α motor neurons that innervate the quadriceps muscle.

CONCEPT: SMOOTH MUSCLE

Introduction to Smooth Muscle:

● **Smooth Muscle** is a highly-varied class of muscle that generally functions in involuntary/autonomic control of body parts.

□ Lining of blood vessels, intestinal tract, pupil constriction/dilation in the eye, etc.

● “Smooth” because no real myofibrils or organized sarcomeres—just actin and myosin scattered around.

● Some differences between smooth and skeletal muscle—smooth muscle:

□ Contraction is entirely involuntary—controlled by ______________________ nervous system.

-May be neurogenic or myogenic.

□ Doesn’t really fatigue (myosin ATPase is really slow).

□ Has small, single-nucleated cells.

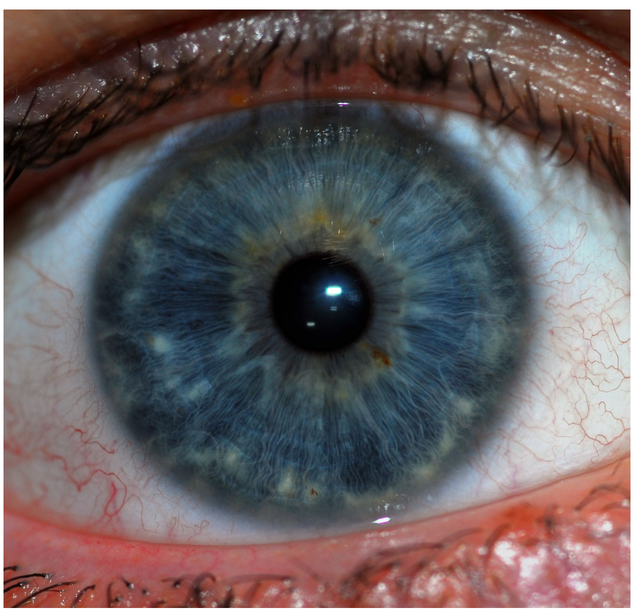
● Smooth muscle may be *multi-unit* or *single-unit*.

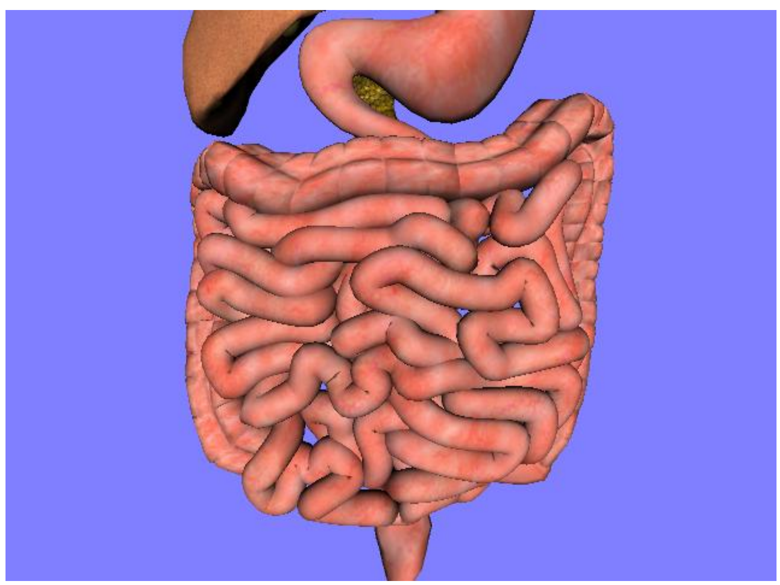
□ **Multi-Unit**- Each smooth muscle cell contracts independently, usually based on neuronal input.

□ **Single-Unit**- Smooth muscle cells connected to each other by gap junctions.

-“Waves” of depolarization—and thus “waves” of contraction—spread through the muscle.

EXAMPLE: Iris is made of multi-unit smooth muscle while the lining of the intestinal tract is single-unit smooth muscle.





Smooth Muscle Excitation-Contraction Coupling:

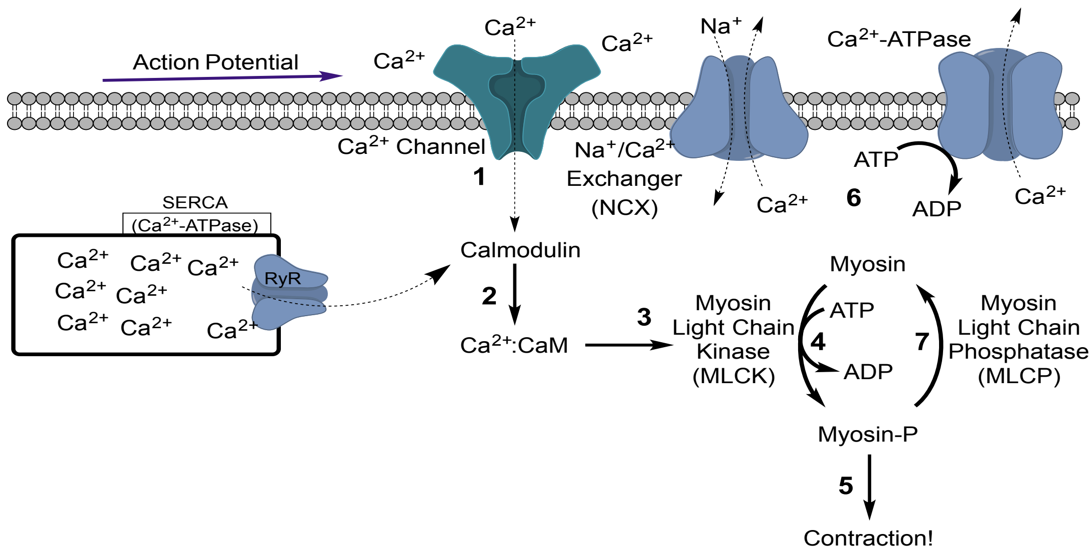
- Smooth muscle contraction, like skeletal muscle, is caused by a Ca^{2+} signal. The effect of ↑$[Ca^{2+}]_{cytosol}$ is different, though.

1. AP activates voltage-gated Ca^{2+} channels (a specific type called *L-type Ca^{2+} channels*). Ca^{2+} enters cell.

    -Some Ca^{2+} maybe also from SR, though SR not really important in smooth muscle.

2. Ca^{2+} binds to the Ca^{2+}-sensing protein **Calmodulin (CaM)**.

3. The Ca^{2+}:CaM complex activates an enzyme called **Myosin Light Chain Kinase (MLCK)**



4. The function of MLCK is to phosphorylate myosin heads (aka the myosin "light chain").

    -This is the control point for smooth muscle—no troponin/tropomyosin present.

5. Phosphorylation of myosin heads→↑Myosin ATPase activity→↑Power Strokes and ↑Contraction

6. To relax, must clear Ca^{2+} from cytosol back into ECF. Done by Na^{+}/Ca^{2+} Exchanger and Ca^{2+} ATPase.

7. **Myosin Light Chain Phosphatase (MLCP)** dephosphorylates myosin heads.

    -Dephosphorylation→↓Myosin ATPase activity→↓Powerstrokes and ↓Contraction

Control of Smooth Muscle Contraction:

● "Signal" for smooth muscle contraction may come in a variety of forms from a variety of sources.

● Smooth muscles contract if depolarized (during an AP) because depolarization→Ca^{2+} channel activation→↑$[Ca^{2+}]_{cytosol}$.

□ Multi-unit smooth muscle (e.g. eye iris) get these APs from autonomic neurons.

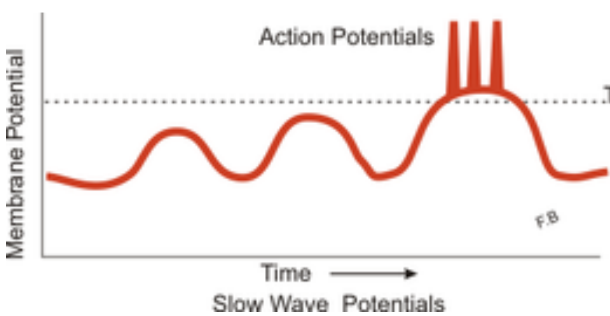
□ Many single-unit smooth muscles generate APs *on their own.*

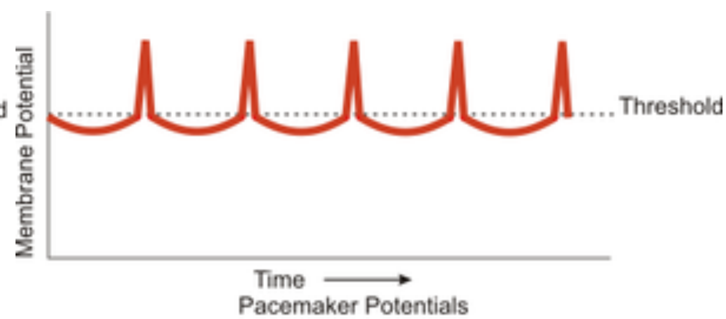
● Smooth muscle may generate their own APs (and have *myogenic* contractions) through *slow-wave depolarization* or *pacemaker potentials.* Both of these are examples of *unstable membrane potentials.*

□ **Slow-Wave Depolarization**- V_m drifts around, sometimes reaching threshold and causing an AP, other times not.

□ **Pacemaker Potentials**- V_m is driven upward consistently, causing APs at consistent intervals.

EXAMPLE: Slow-wave depolarization vs pacemaker potentials.





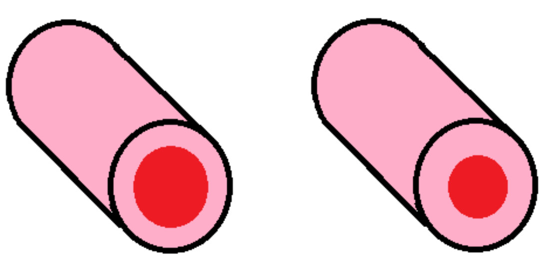
● Smooth muscle contraction is also controlled by many ________________ and drugs.

□ Hormones that activate G_q-coupled receptors—e.g. oxytocin on oxytocin receptors in uterus—cause contraction.

□ Hormones that activate G_s-coupled receptors—e.g. epinephrine on β_2 receptors—cause relaxation.

□ Can happen totally independent of membrane potential changes—just need to activate Ca^{2+} channels.

EXAMPLE: Hormone-mediated vasoconstriction—and subsequent ↑Blood Pressure—are the result of hormones activating receptors on smooth muscle lining blood vessels.



Normal Cross Section Vasoconstriction

PRACTICE 1: Phenylephrine is a drug that activates α_1 adrenergic receptors on smooth muscle. Activation of α_1 adrenergic receptors starts a signaling cascade that increases the activity of Ca^{2+} channels and myosin light chain kinase (MLCK). Which of the following is the likely effect of phenylephrine on smooth muscle?

a) Contraction of smooth muscle.
b) Relaxation of smooth muscle.

PRACTICE 2: Albuterol is a drug that activates β_2 adrenergic receptors on smooth muscle. Activation of β_2 adrenergic receptors starts a signaling cascade that, among other things, increases the activity of K^+ channels in the membranes of smooth muscle cells. Which of the following is the likely effect of albuterol on smooth muscle?

a) Contraction of smooth muscle.
b) Relaxation of smooth muscle.