Muscle Physiology

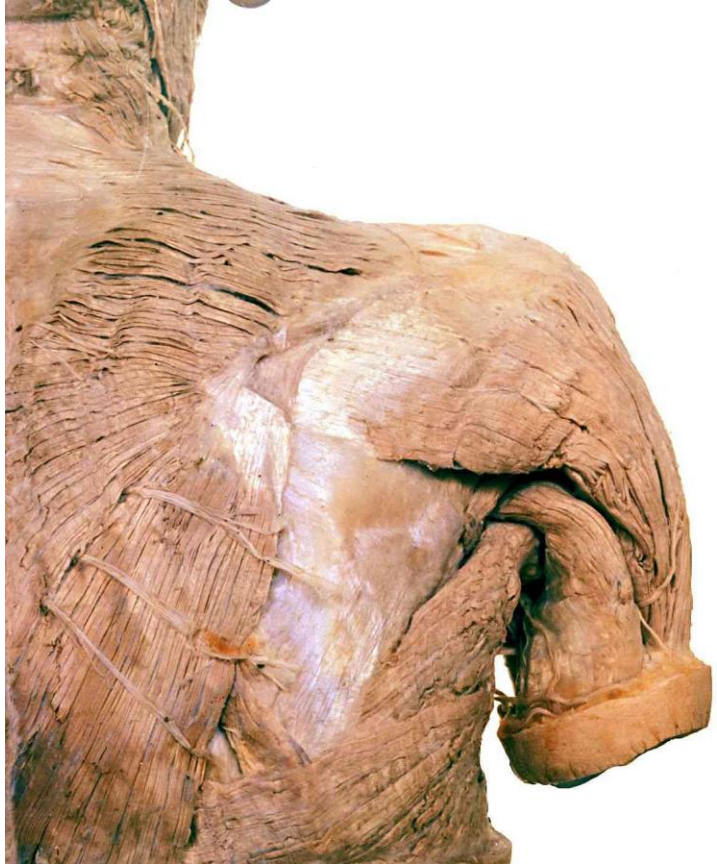
- Muscle is one of our 4 tissue types
- Found being combined with nerves, blood vessels, and various connective tissues.
- Muscles are quite complex and are marvel of both biology and physics.

Muscle Functions

1. **Produces Movement**
   - Movement of body parts
   - Movement of blood throughout the body
   - Movement of lymph through the lymphatic vessels
   - Movement of food through the GI tract
   - Movement of bile out of the gallbladder into the digestive tract
   - Movement of urine through the urinary tract
   - Movement of semen through the male and female reproductive tracts
   - Movement of a newborn through the birth canal

Muscle Functions

2. **Maintenance of posture**
   - Muscle contraction is constantly allowing us to remain upright.
   - The muscles of your neck keep your head up right now.
   - As you stand, your leg muscles keep you on two feet.
3. **Thermogenesis**
   - Generation of heat. Occurs via shivering – an involuntary contraction of skeletal muscle.



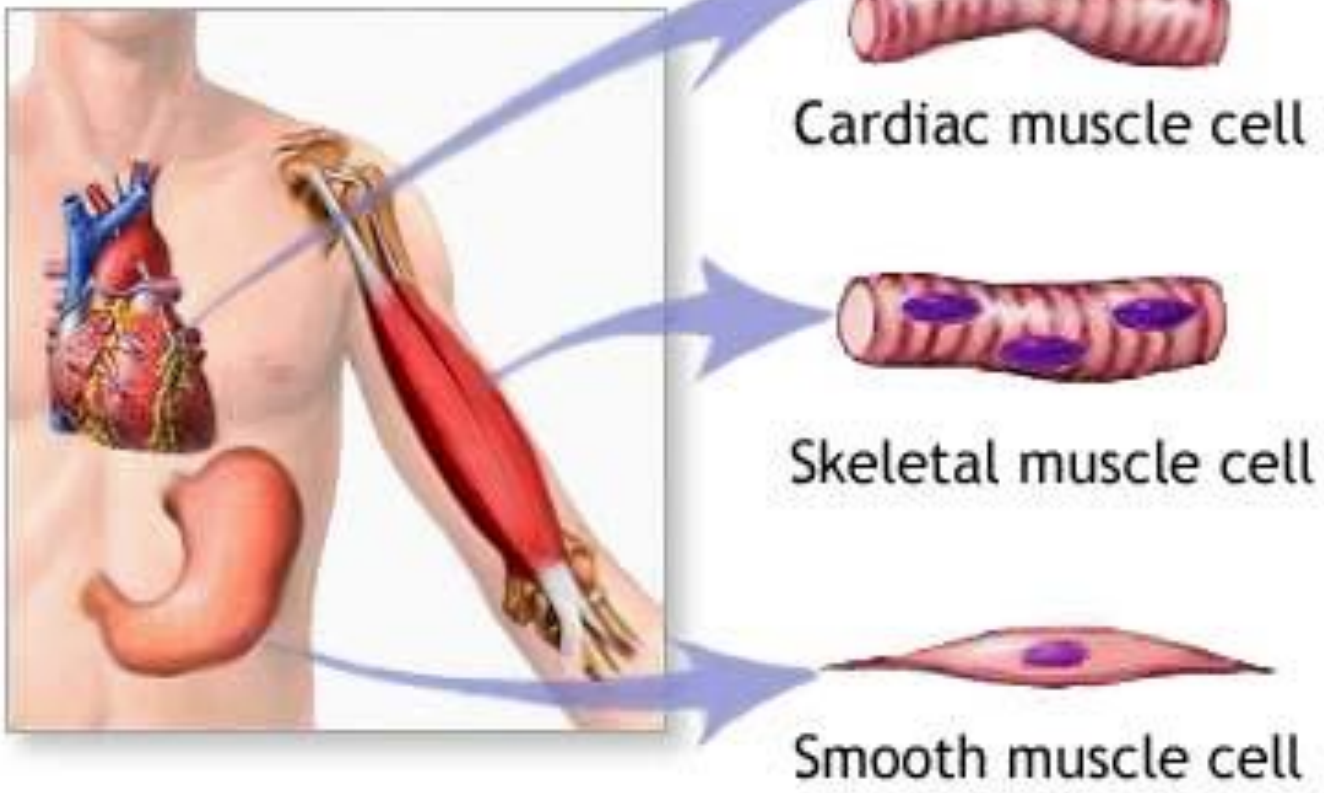
Muscle Functions

4. Stabilization of joints

- Muscles keep the tendons that cross the joint nice and firm
- This does a wonderful job of maintaining the integrity of the joint.

All the things muscles do fall under one of these 4 categories.

3 Types of Muscle Tissue



Three Types of Muscle Tissue

❑ Skeletal Muscles

- Striated
- Multi-nucleatd
- Controlled by somatic nervous system (voluntary)

❑ Cardiac Muscle

- Striated
- Mono-nucleated
- Controlled by ANS (involuntary)

❑ Smooth Muscle

- Non-striated
- Mono-nucleated
- Controlled by ANS (involuntary)

Characteristics of Muscle Tissue

1. Excitability

- The ability to receive and respond to a stimulus
  - In smooth muscle, the stimulus could be a neurotransmitter, a hormone, stretch, ΔpH, ΔPco_2, or ΔPo_2.
  - In cardiac muscle, the stimulus could be a neurotransmitter, a hormone, or stretch. Also autorhythmic
  - In skeletal muscle, the stimulus is a neurotransmitter released by a neuron only.
- The response is the generation of an AP that travels along the plasma membrane of the muscle cell.

Characteristics of Muscle Tissue

2. Contractility

The ability to shorten and become thicken forcibly when adequately stimulated.

This is the hallmark of muscle tissue.

3. Extensibility

- The ability to be stretched

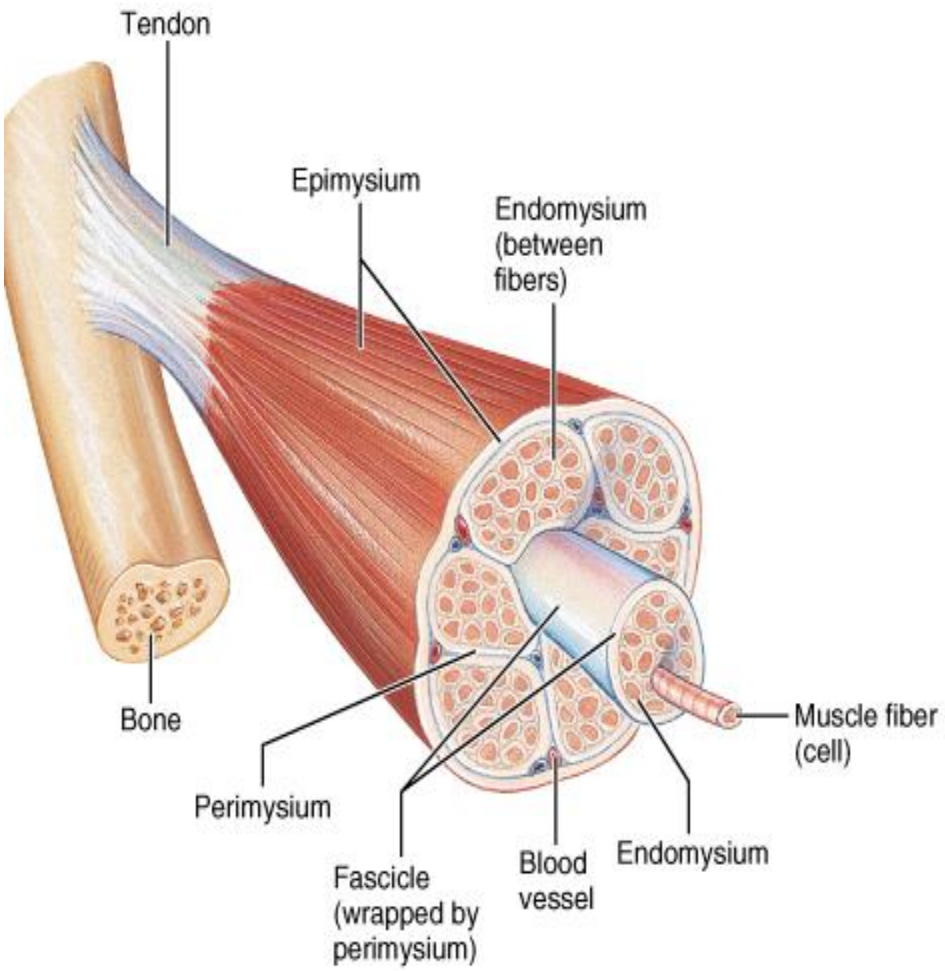
4. Elasticity

- The ability to recoil and resume original length and size after being stretched or contracted.

Skeletal Muscle –As the organ

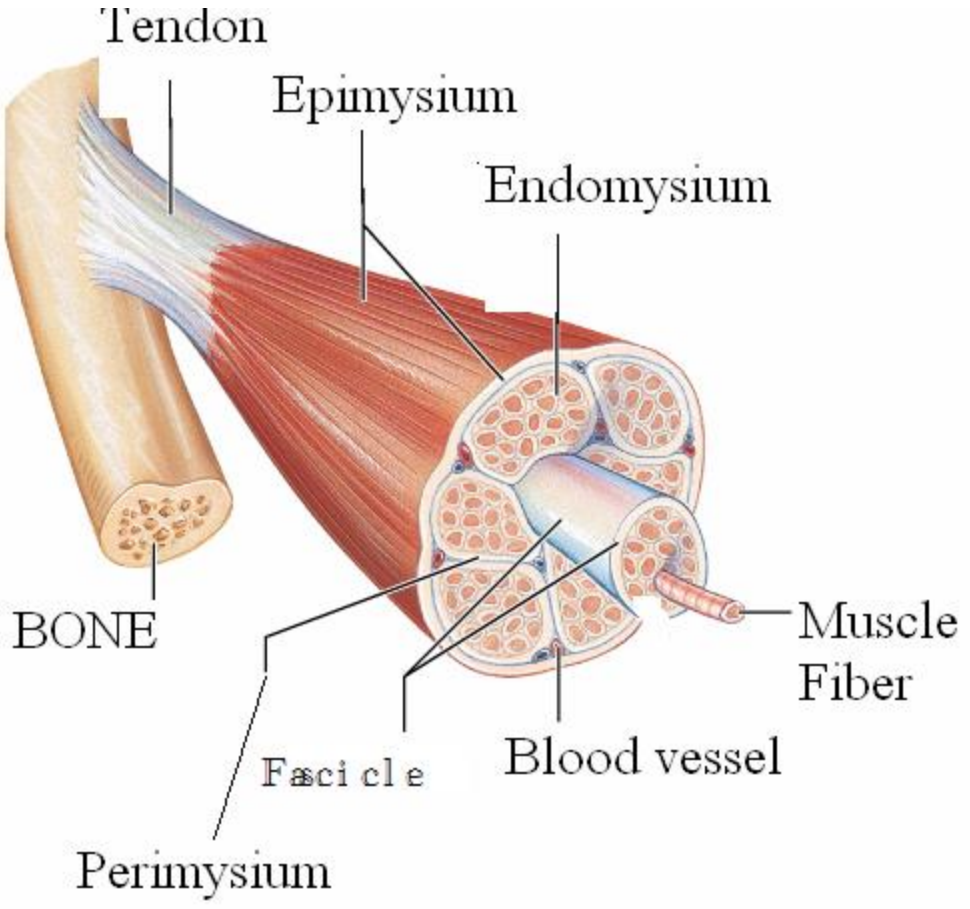
- Skeletal muscles are dominated by
- ➢ muscle tissue
- ➢ Also contain
- ✓ Nerve
- ✓ Blood vessels and
- ✓ Connective tissues.

They are surrounded by dense irregular connective tissue known as the epimysium



Skeletal Muscle – the organ

- Epimysium surrounds several bundles known as fascicles.
- Each fascicle is a bundle of super-long skeletal muscle cells (muscle fibers), surrounded by a layer of dense irregular CT called the perimysium (*peri*=around).
- Each muscle cell extends the length of the whole muscle organ and is surrounded by a fine layer of loose connective tissue, the endomysium.



Skeletal Muscle – Blood & Nerve Supply

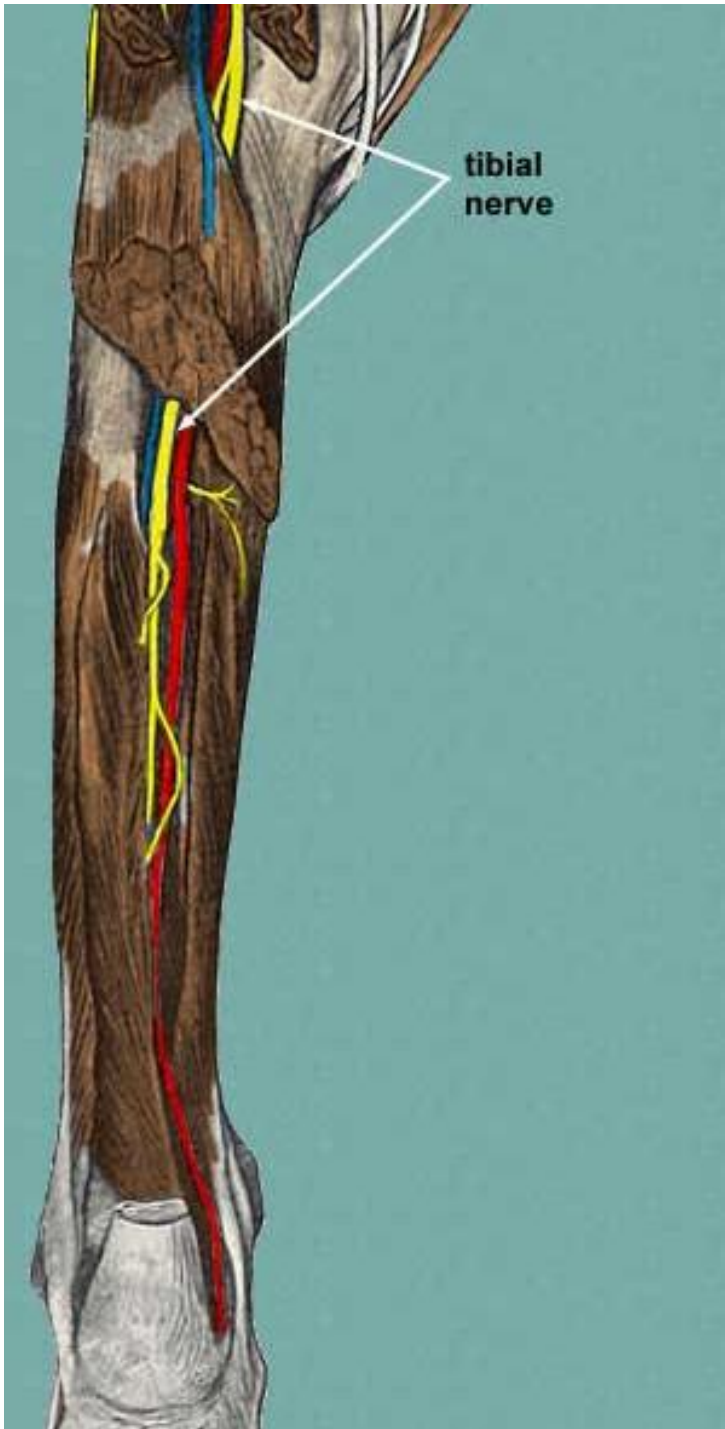
- Each skeletal muscle is supplied by:

I. One nerve, forming motor unit (the neuron innervating and the muscle itself)

II. An artery and

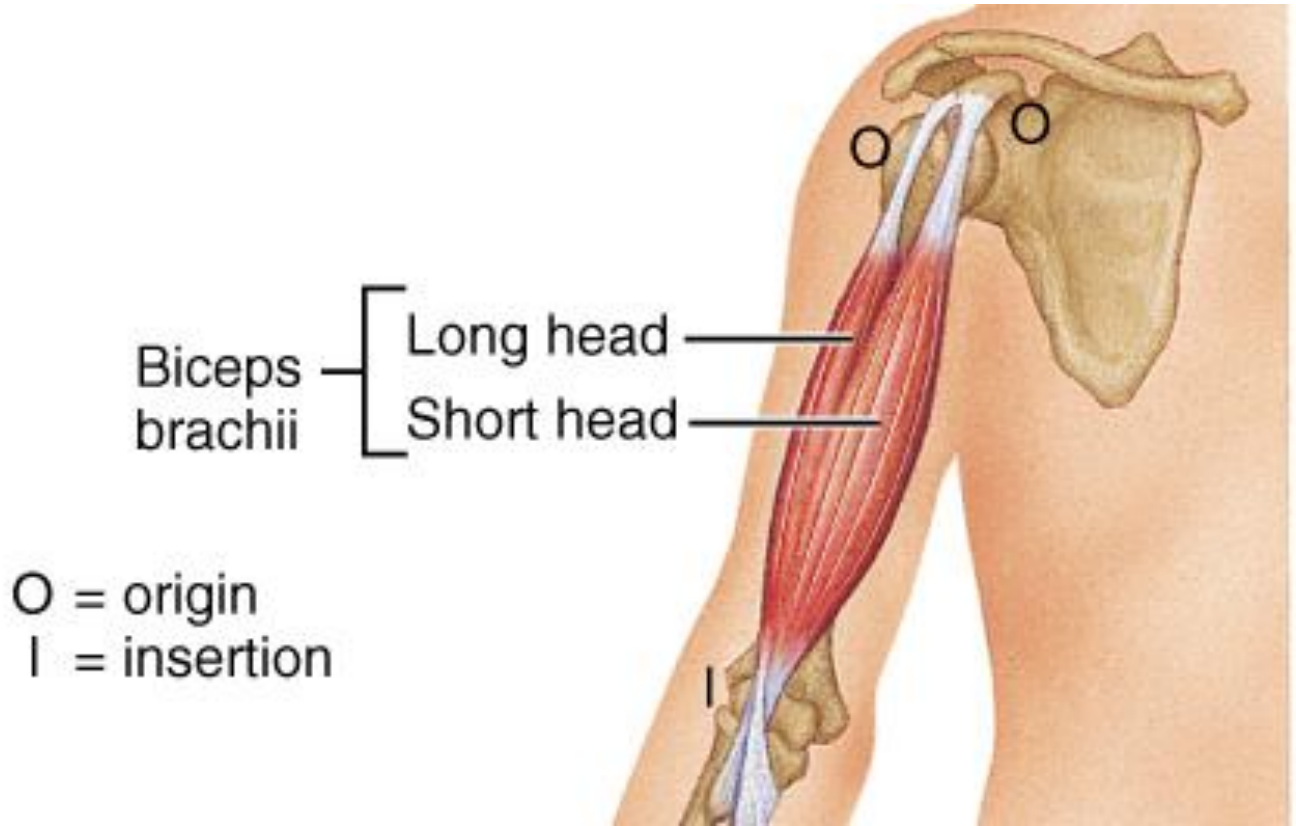
III. One or more veins.

- They all enter/exit via the connective tissue coverings and branch extensively.



Skeletal Muscle Attachments

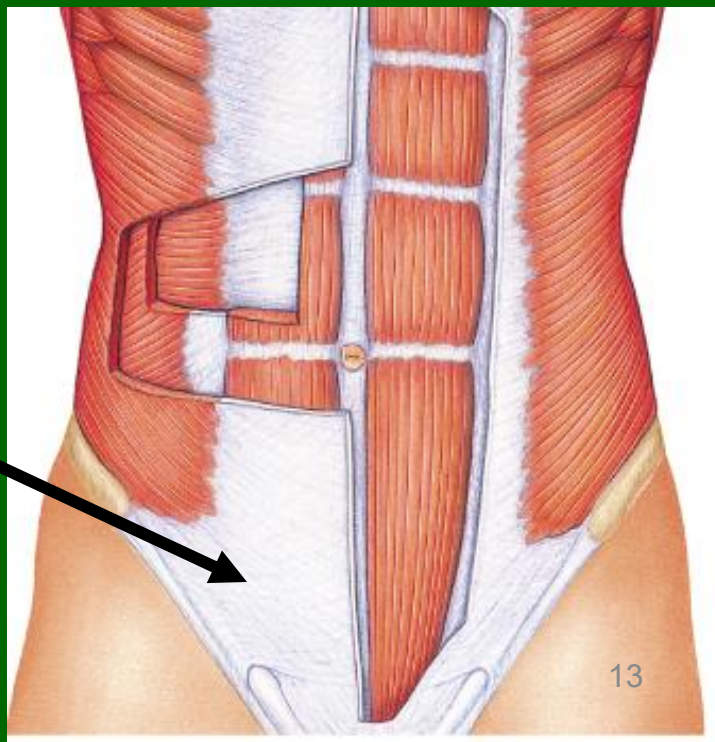
- Muscles often are attached to bones at joints.
  - They have two ends: origin (immovable end)
  - Insertion end (movable end).



Muscle attachments may be direct or indirect.

Direct attachments are less common. The epimysium is fused to a periosteum or a perichondrium.

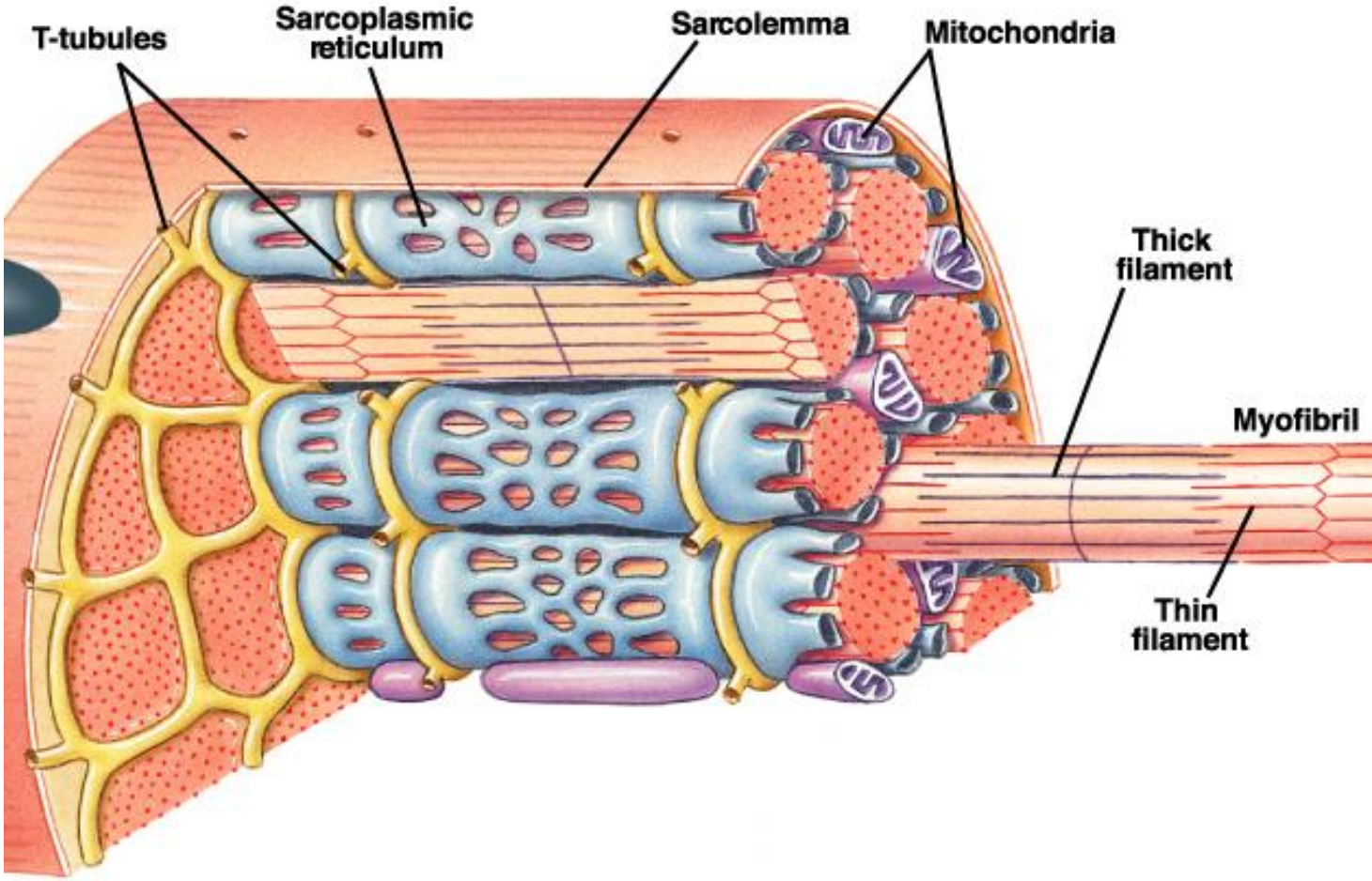
Indirect attachments are typical. The muscle CT extends and forms either a cordlike structure (a tendon) or a sheetlike structure (aponeurosis) which attaches to the periosteum or perichondrium.



Skeletal Muscle Microanatomy

- Each skeletal muscle cell is known as a skeletal muscle fiber because
- They are so long.
  - Their diameter can be up to 100µm
  - Their length can be as long as 30cm.
  - They are so large because a single skeletal muscle cell results from the fusion of hundreds of embryonic precursor cells called myoblasts.
    - A cell made from the fusion of many others is known as a syncytium.

Muscle fiber PM is known As sarcolemm muscle fiber cytoplasm is known as sarcoplasm



Sarcolemma has invaginations that penetrate through the cell called transverse tubules or T tubules.

Sarcoplasm has lots of mitochondria (*why*?), lots of glycogen granules (to provide glucose for energy needs) as well as myofibrils and sarcoplasmic reticuli.

Microanatomy

Sarcolemma.

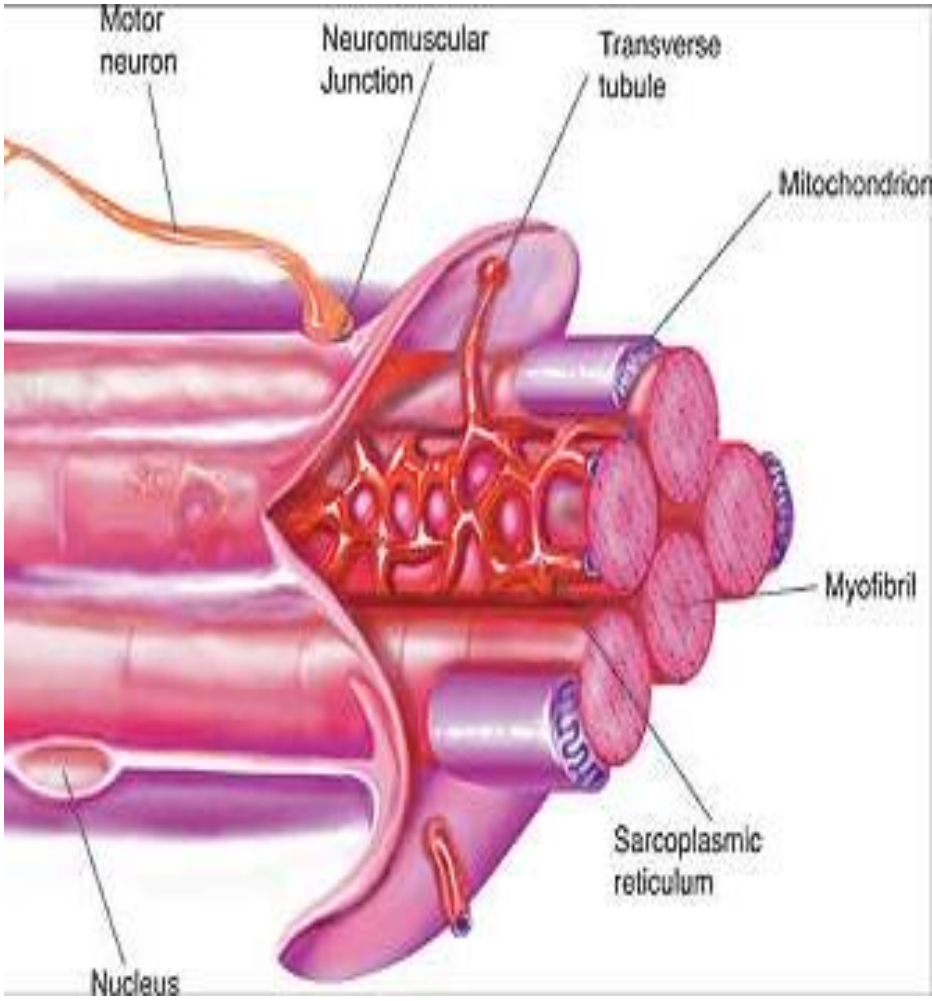
- The sarcolemma is the cell membrane of the muscle fiber.

- The sarcolemma consists of a true cell membrane, called the *plasma membrane,* and an outer coat made up of a thin layer of polysaccharide material that contains numerous thin collagen fibrils.

- At each end of the muscle fiber, this surface layer of the sarcolemma fuses with a tendon fiber, and the tendon fibers in turn collect into bundles to form the muscle tendons that then insert into the bones.

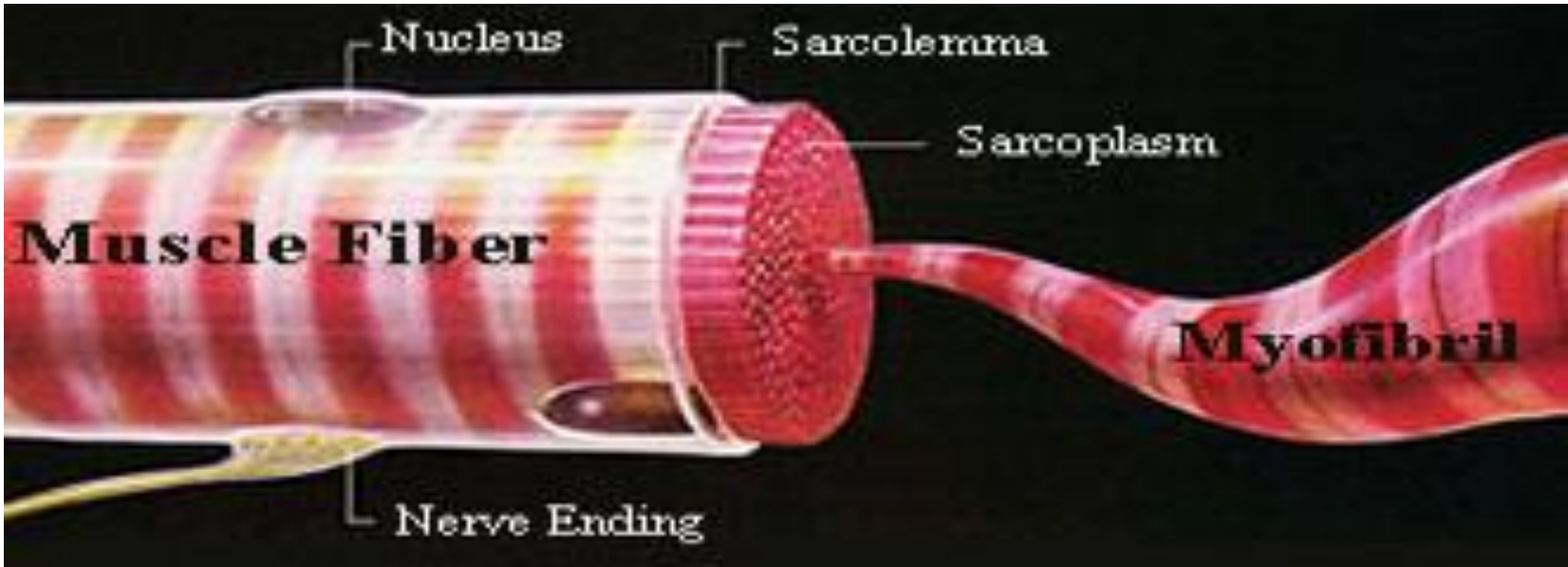
Sarcoplasmic Reticulum-SR

- SR is muscle cell version of the smooth endoplasmic reticulum.
- Functions as a calcium storage depot in muscle cells.
- Well developed in the skeletal muscle
- Loose network of this membrane bound organelle surrounds all the myofibrils in a muscle fiber.
- We will see why this is so important soon.



Myofibrils → ACTIN and MYOSIN

- ✓ Each muscle fiber contains rod-like structures called myofibrils extend the length of the muscle cell.
- ✓ They are basically long bundles of protein structures called myofilaments and their actions give muscle the ability to contract.
- ✓ The myofilaments are classified as thick filaments and thin filaments.

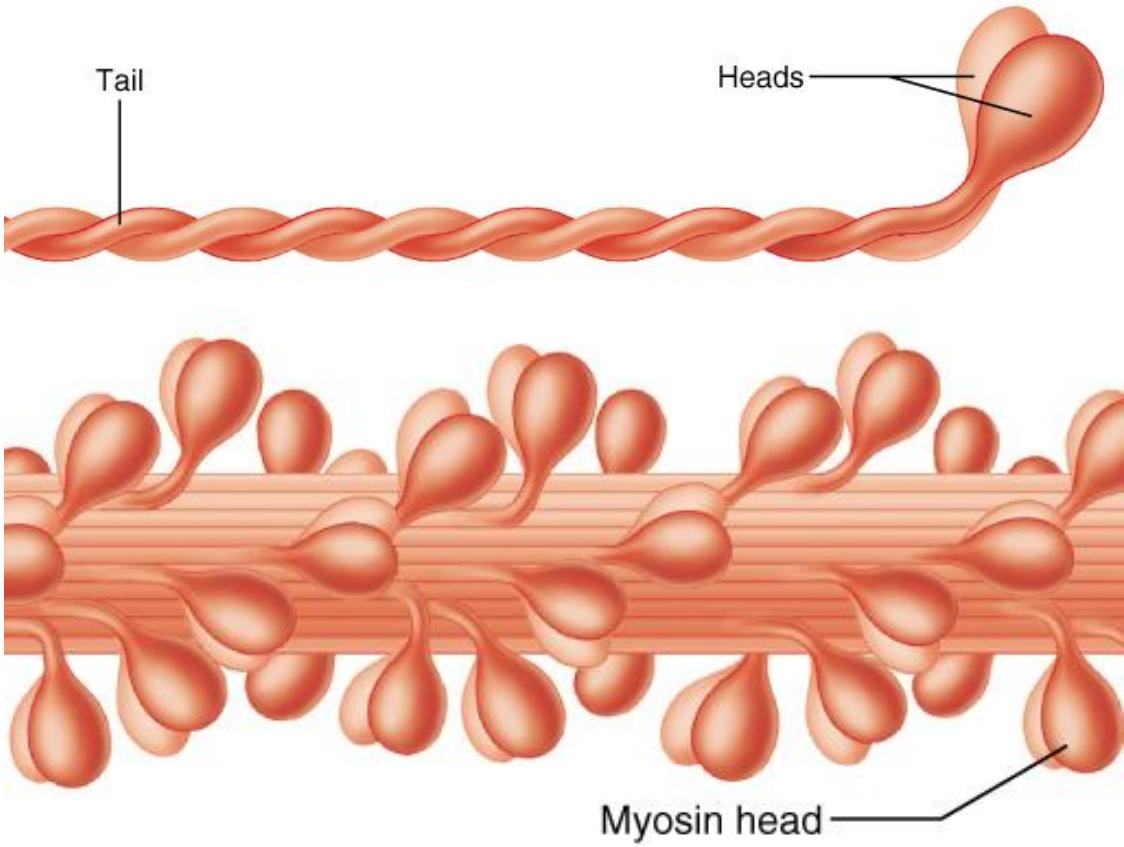


Myofilaments

- ✓ 2 types of myofilaments (thick & thin) make up myofibrils.
- ✓ Thick myofilaments are made up of the protein myosin

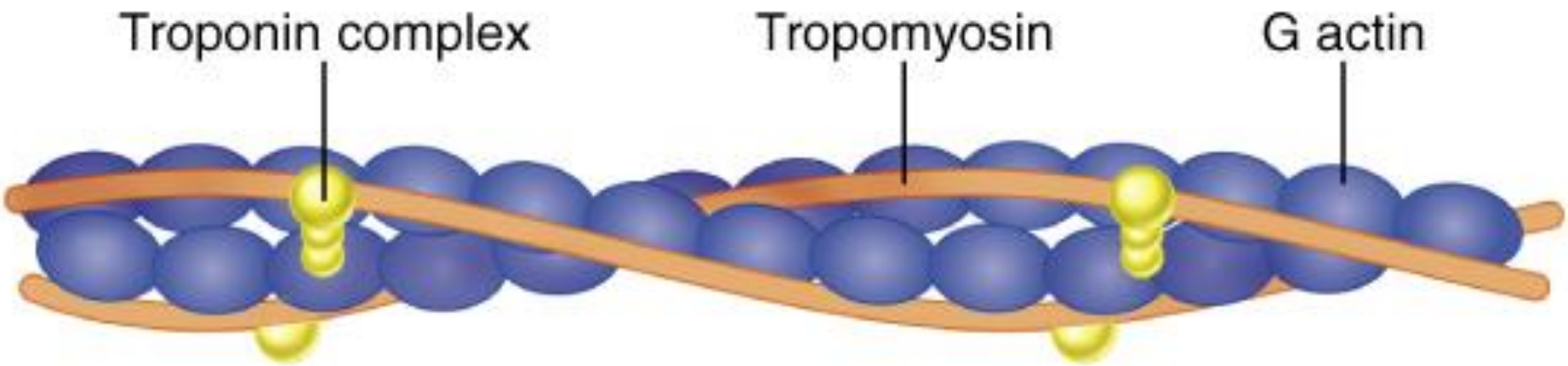
A single myosin protein resembles 2 golf clubs whose shafts have been twisted about one another

About 300 of these myosin molecules are joined together to form a single thick filament

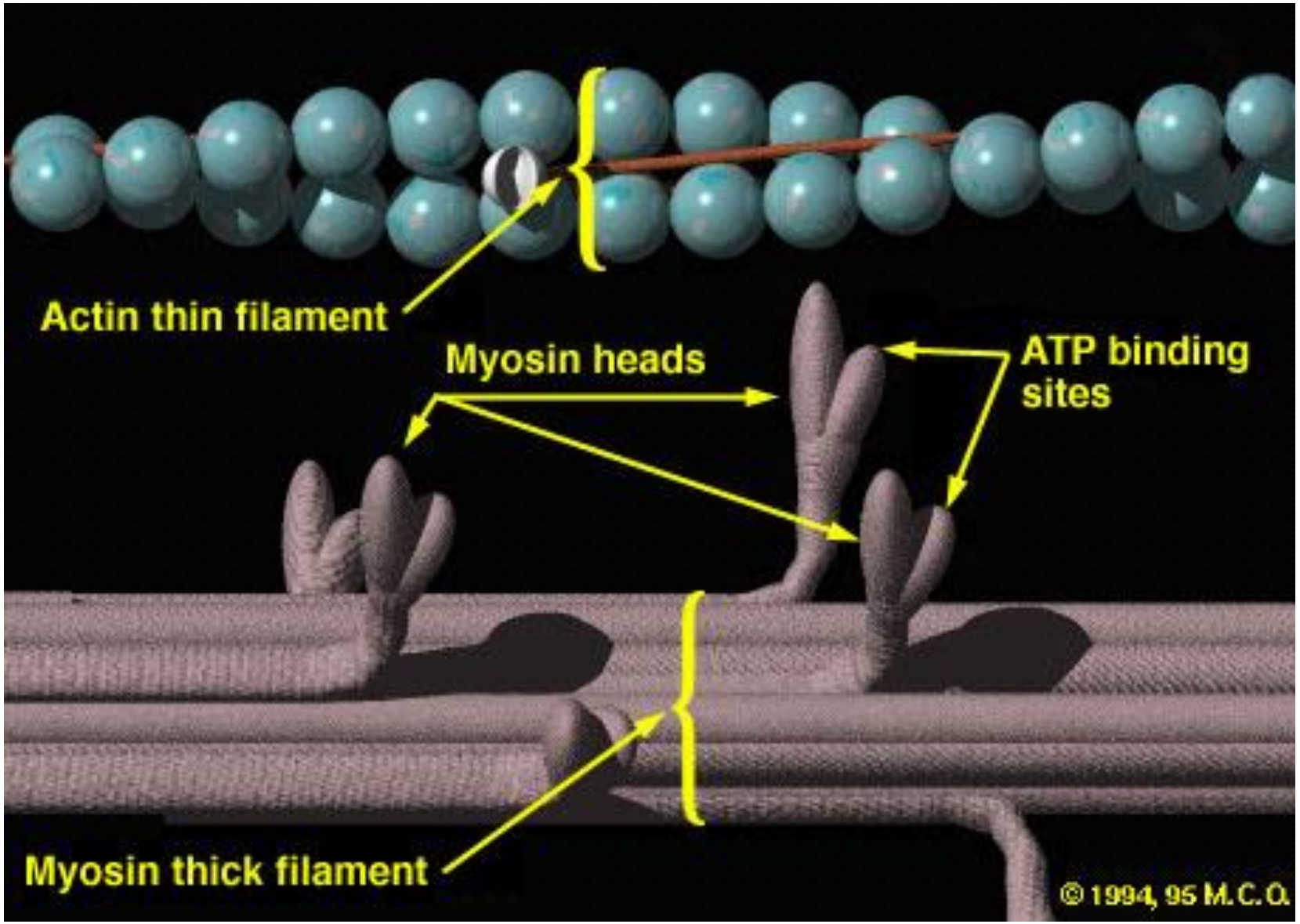


Portion of a thick filament

- Each **thin filament** is made up of 3 different types of protein: **actin, tropomyosin**, and **troponin.**
  - Each thin filament consists of a long helical double strand.
  - This strand is a polymer that resembles a string of beads.
  - Each "bead" is the globular protein **actin**.
  - On each actin subunit, there is a **myosin binding site**.
  - Loosely wrapped around the actin helix and covering the myosin binding site is the filamentous protein, **tropomyosin.**
  - Bound to both the actin and the tropomyosin are proteins collectively known as **troponin (A, I, C).**

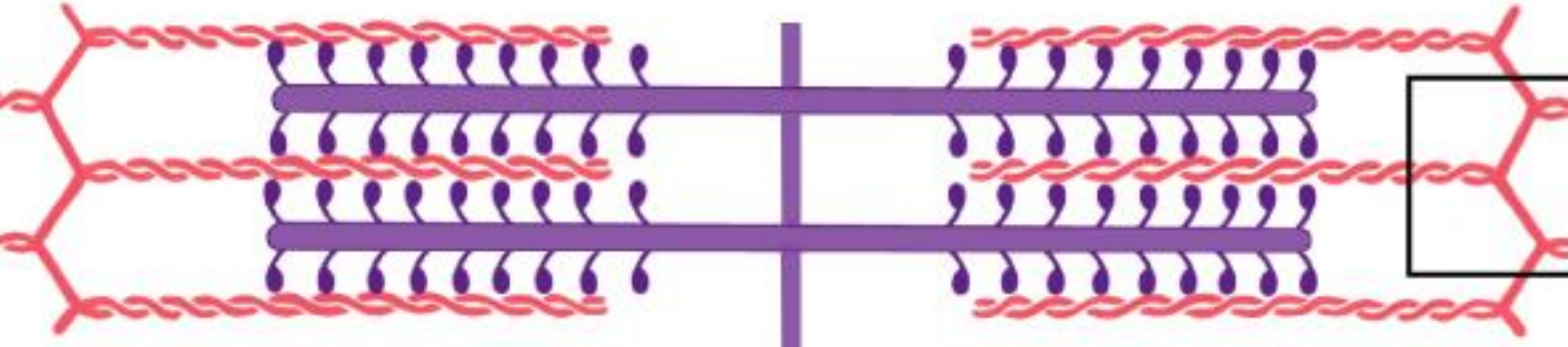


Note the relationship between the thin and thick filaments



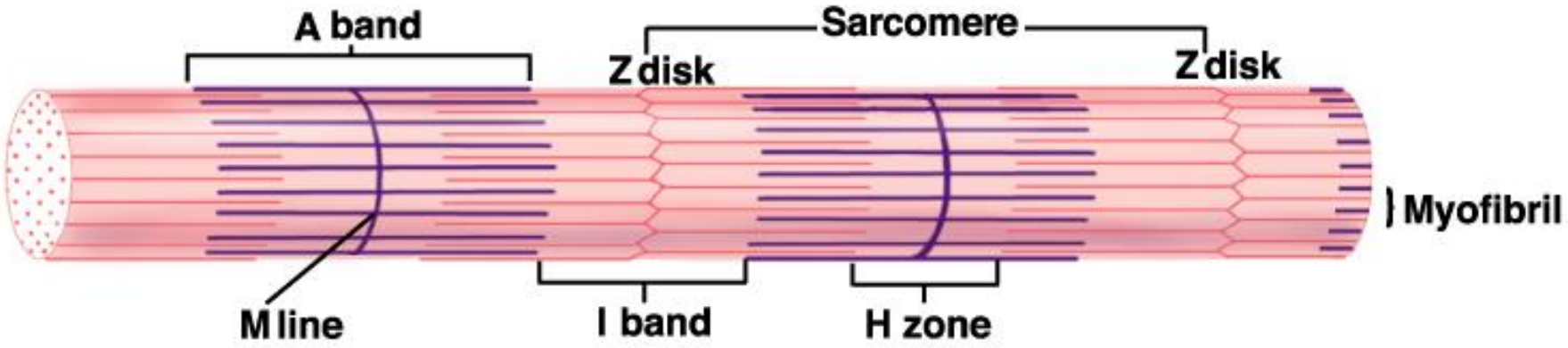
Myofibrils

- Each myofibril is made up 1000 of repeating individual units known as sarcomeres.
- Each sarcomere is an ordered arrangement of thick and thin filaments.
- Notice that it has:
  - Regions of thin filaments by themselves (pinkish fibers)
  - Region of thick filaments by themselves (purple fibers)
  - Regions of thick filaments and thin filaments overlapping.



Sarcomere

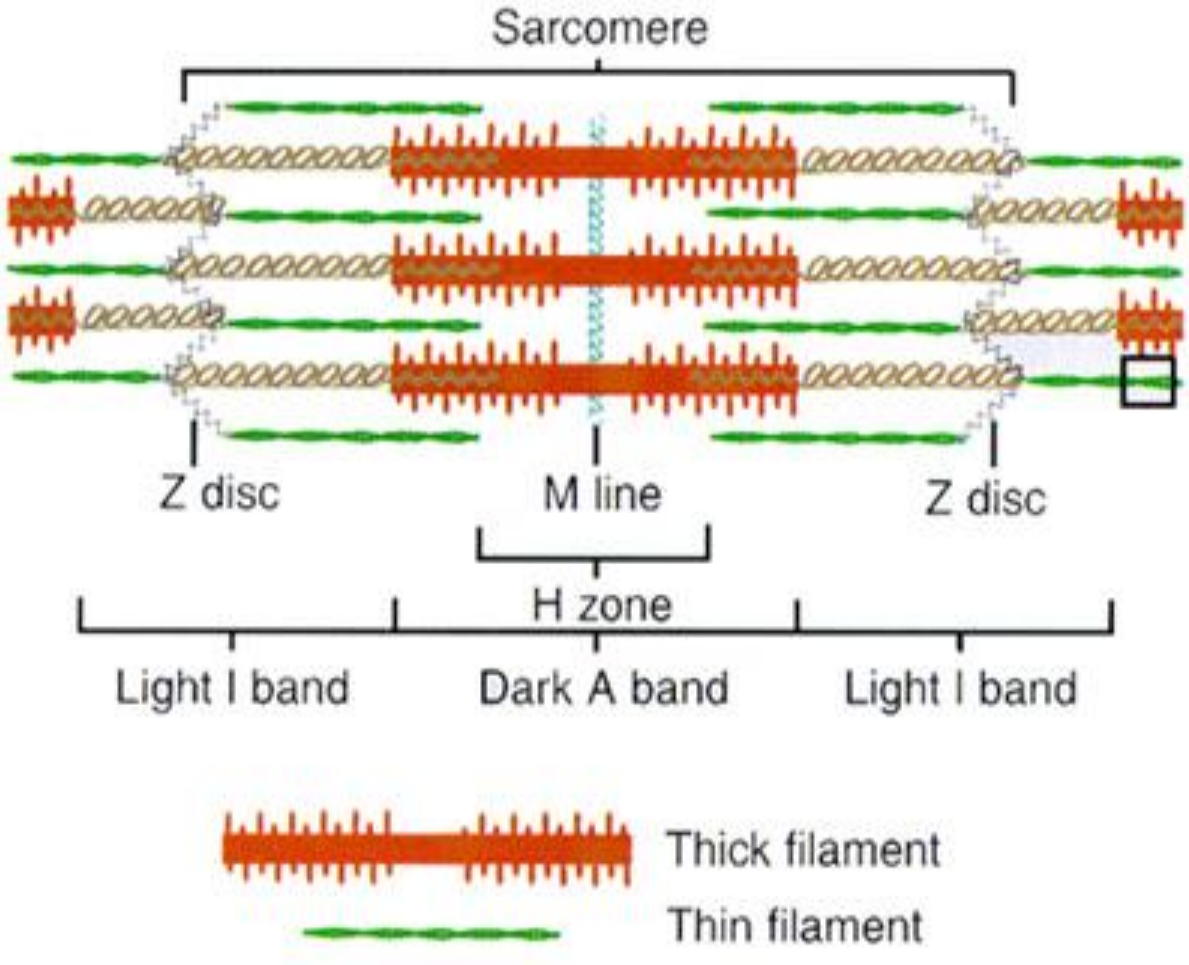
- The sarcomere is borderd by 2 protein structures known as Z discs.
- The portion of the sarcomere which contains the thick filament is known as the A band.
- *A* stands for *anisotropic* which is a fancy way of saying that it appears dark under the microscope.
  - The A band contains a zone of overlap (btwn thick & thin filaments) and an H zone which contains only thick filaments



The portion of the sarcomere which does not contain any thick filament is known as the I band.

The I band contains only thin filament and is light under the microscope (*it is isotropic*).

One I band is actually part of 2 sarcomeres at once.



In the middle of the H zone is a structure called the M line which functions to hold the thick filaments to one another

What Keeps the Myosin and Actin Filaments in Place?

- **T**he side-by-side relationship between the myosin and actin filaments is difficult to maintain.

- This is achieved by a large number of filamentous molecules of a protein called *titin*.

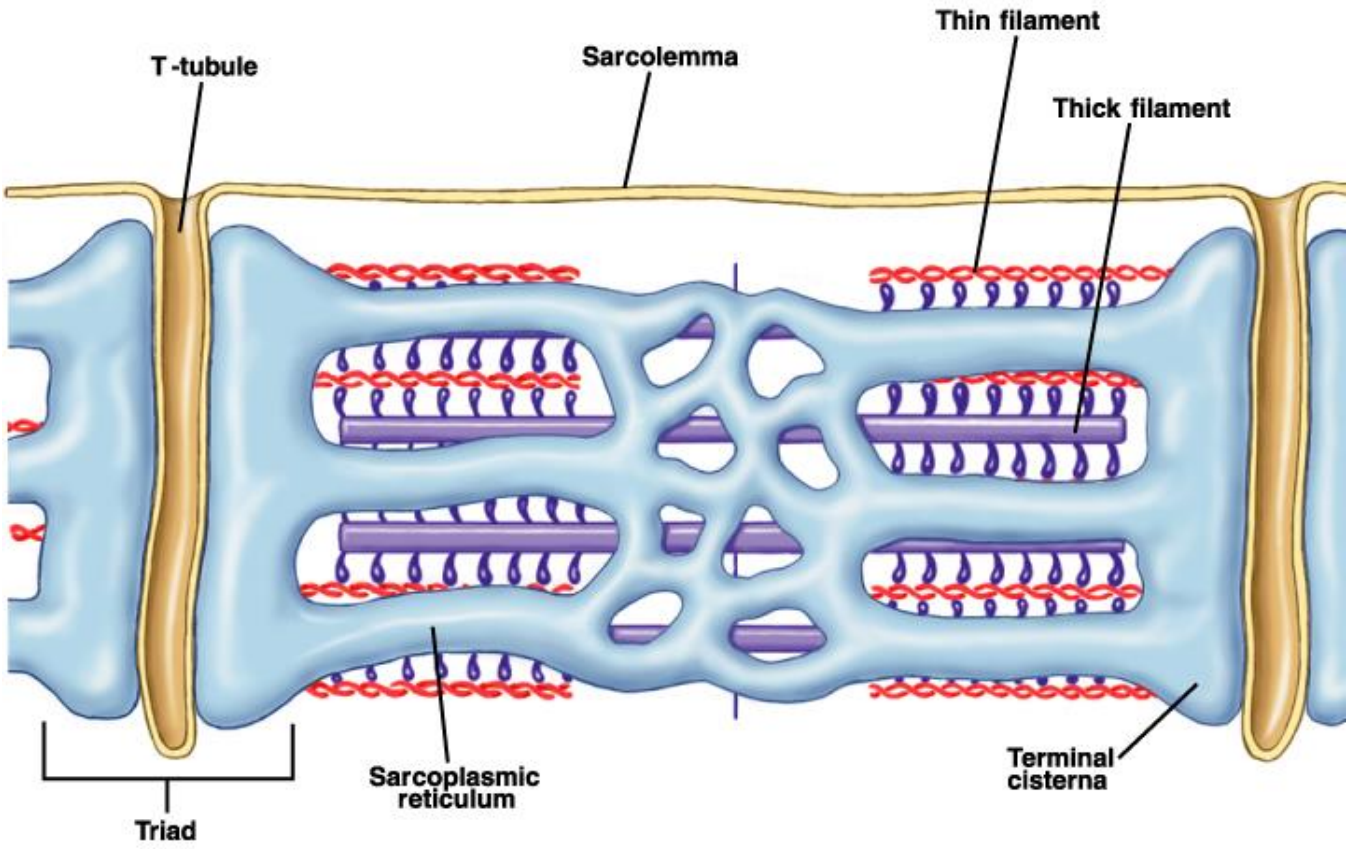
- Each titin molecule has a molecular weight of about 3 million, which makes it one of the largest protein molecules in the body.

- Also, because it is filamentous, it is *very springy (Elastic).*

- These 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.

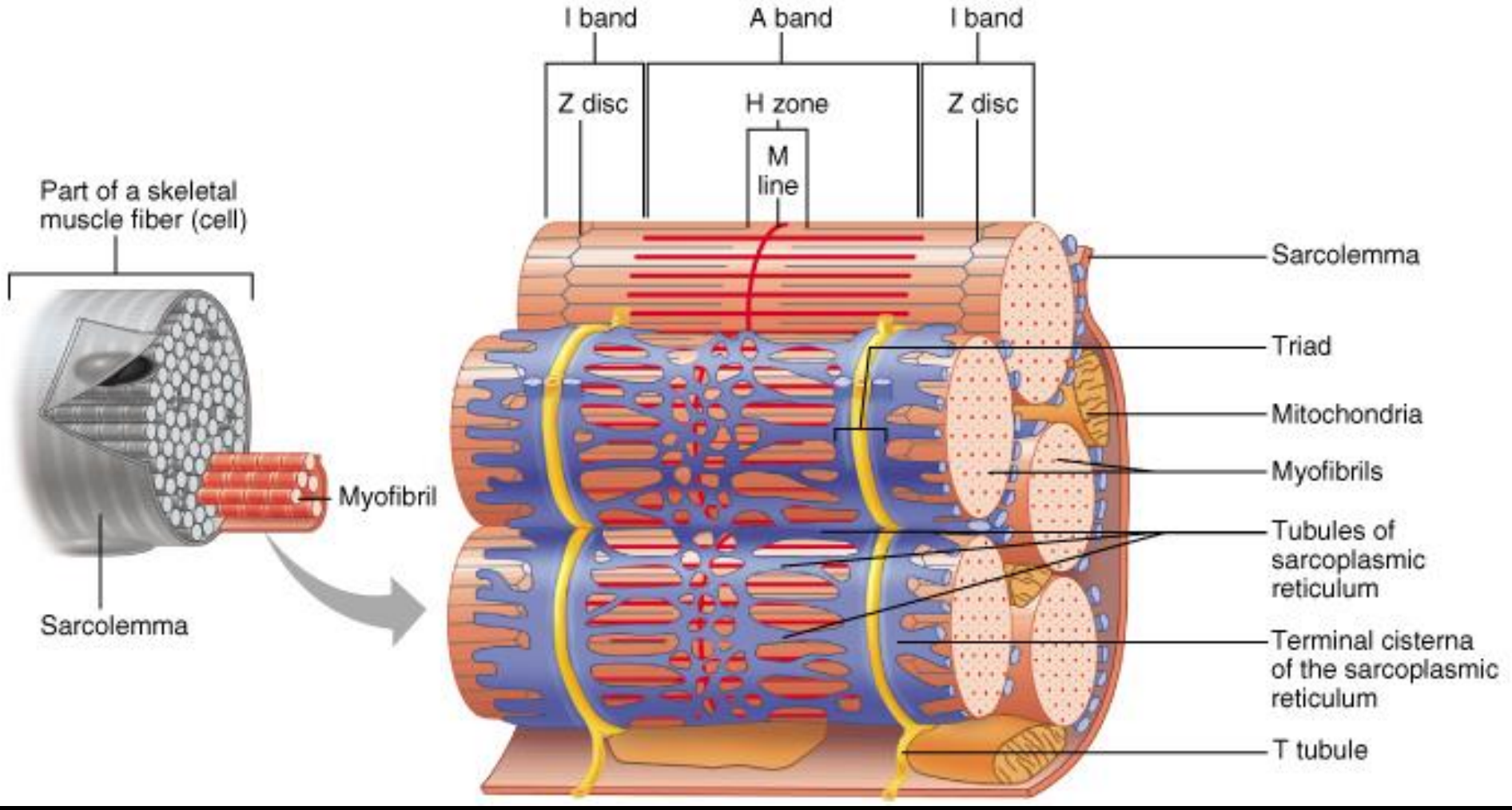
T-Tubules and the SR

- Each muscle fiber has many T-tubules
- Typically each myofibril has a branch of a T-tubule encircling it at each A-I junction
- At each A-I junction, the SR will expand and form a dilated sac (terminal cisterna).



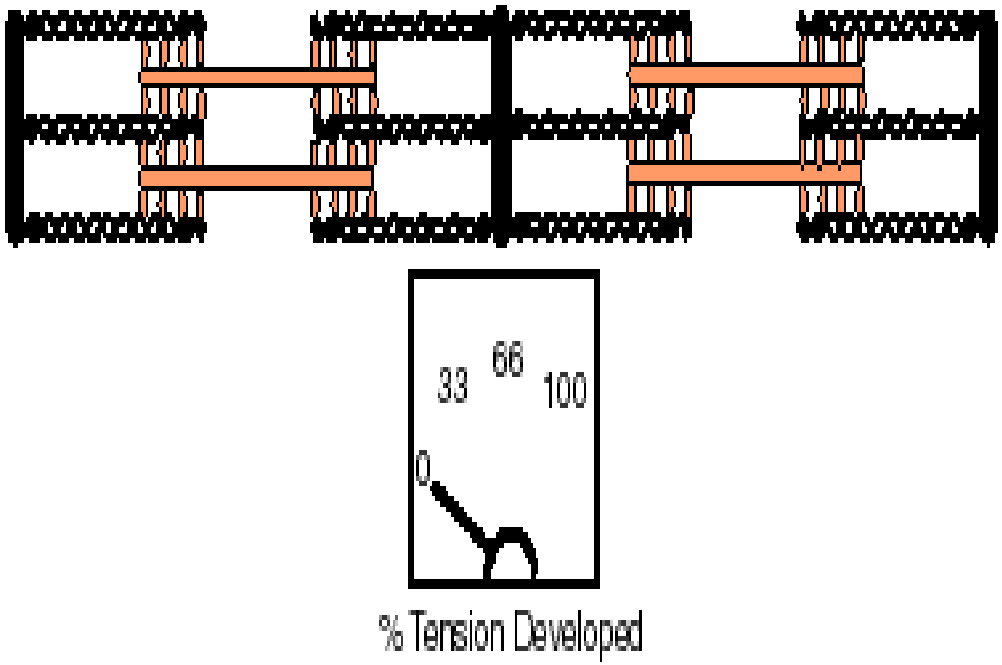
Each T-tubule will be flanked by a terminal cisterna.

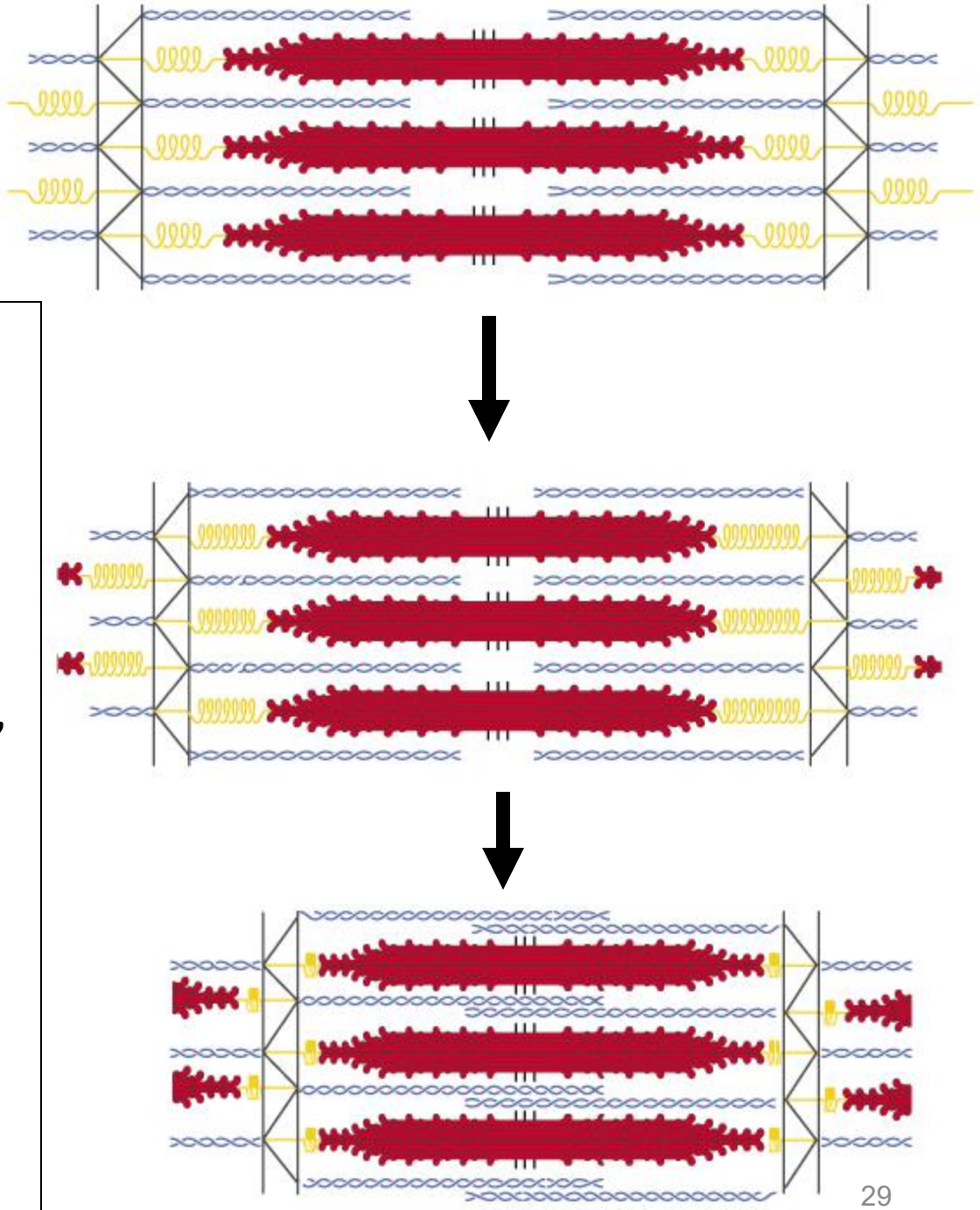
This forms a so-called triad consisting of 2 terminal cisternae and one T-tubule branch.


I band
A band
I band
Z disc
H zone
Z disc
M line
Part of a skeletal muscle fiber (cell)
Myofibril
Sarcolemma
Sarcolemma
Triad
Mitochondria
Myofibrils
Tubules of sarcoplasmic reticulum
Terminal cisterna of the sarcoplasmic reticulum
T tubule

Muscle Contraction: The Sliding Filament Hypothesis

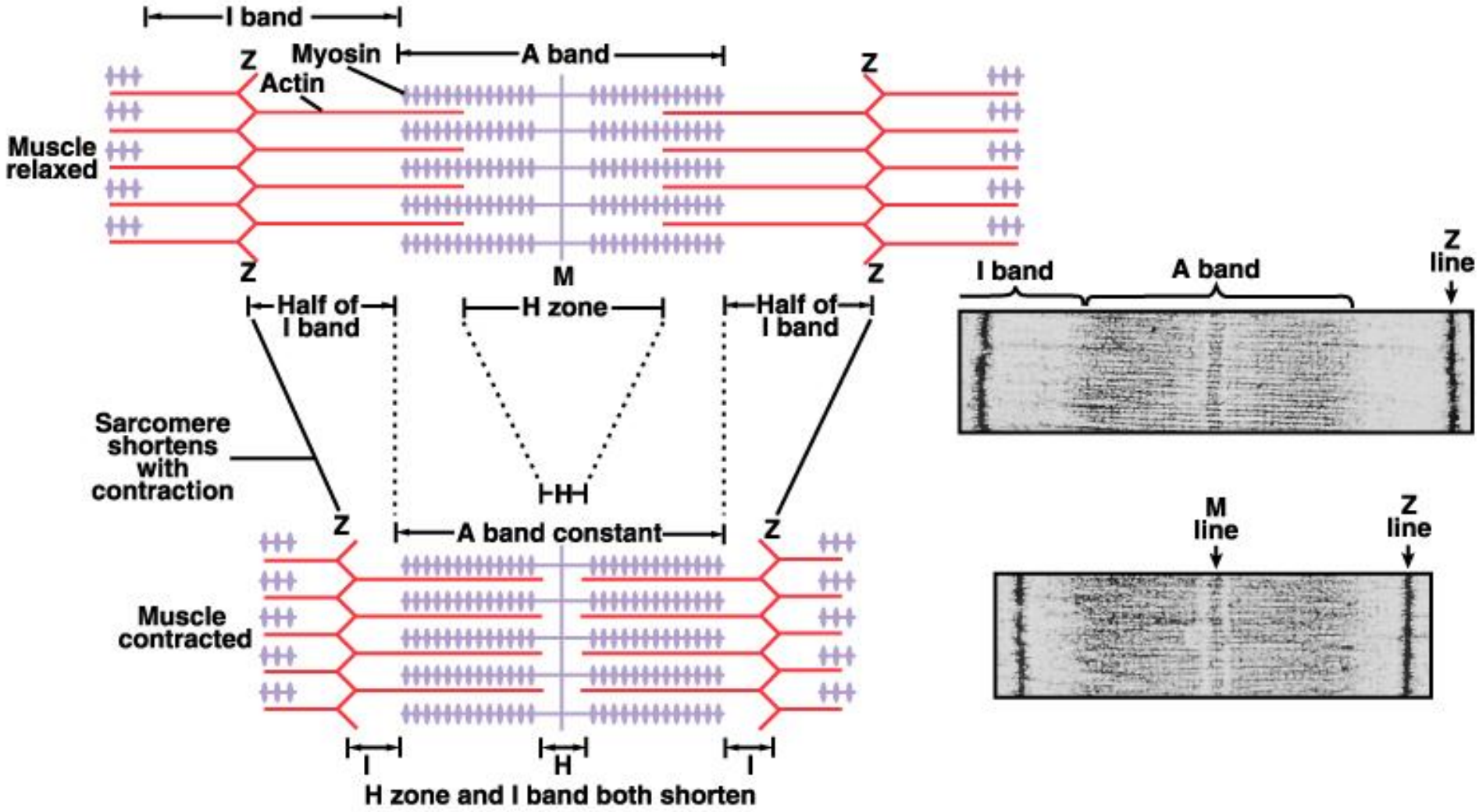
- Place your right palm on the back of your left hand.
- Now slide your right palm toward your left elbow.
  - What happened to the distance between your elbows?
    - It got shorter!
  - This is how muscle contraction occurs.
  - The thin filaments slide over the thick filaments. This pulls the Z discs closer together. When all the sarcomeres in a fiber do this, the entire fiber gets shorter which pulls on the endomysium, perimysium, epimysium and attached tendon and then pulls on the bone.





Here is what happens as the filaments slide and the sarcomere and the muscle fiber shortens. In the process of contraction, what happens to the:

1. **Distance btwn Z discs**
2. **Length of the A band**
3. **Length of the H zone**
4. **Length of the I band**

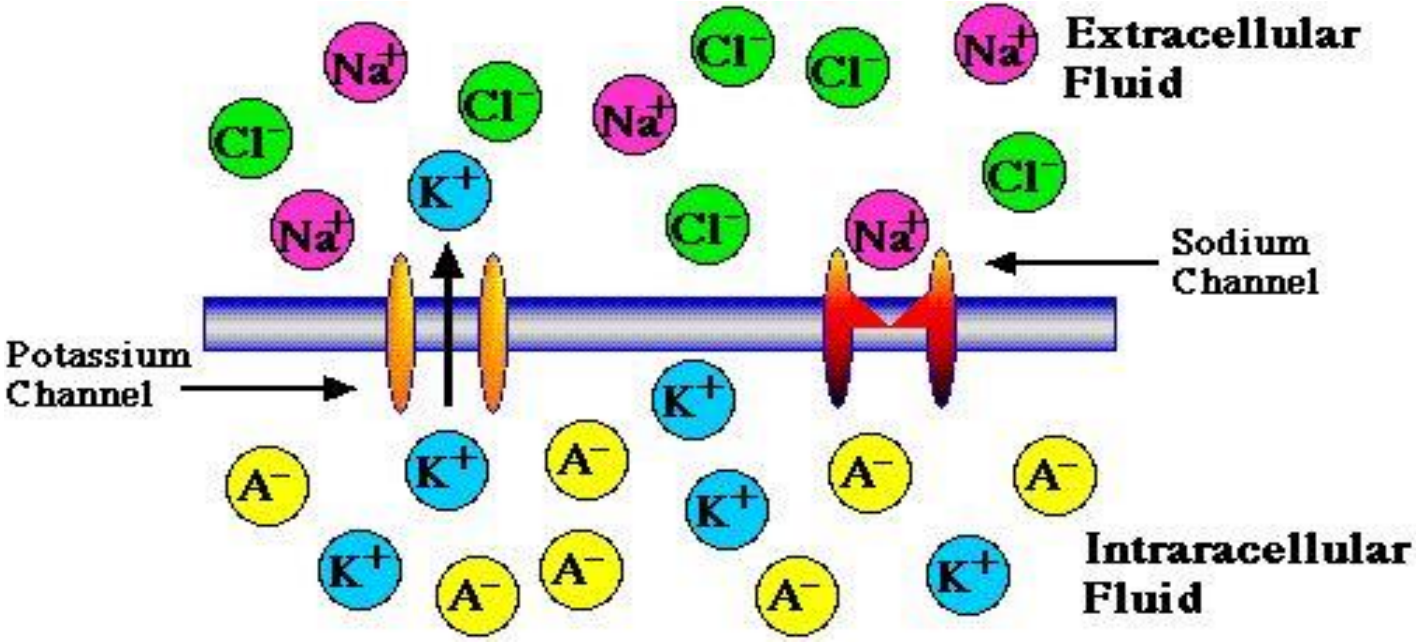

I band
Myosin
A band
Actin
Z
Muscle relaxed
M
Half of I band
H zone
Sarcomere shortens with contraction
A band constant
Muscle contracted
H zone and I band both shorten
I band
A band
Z line
M line

Sliding Filaments

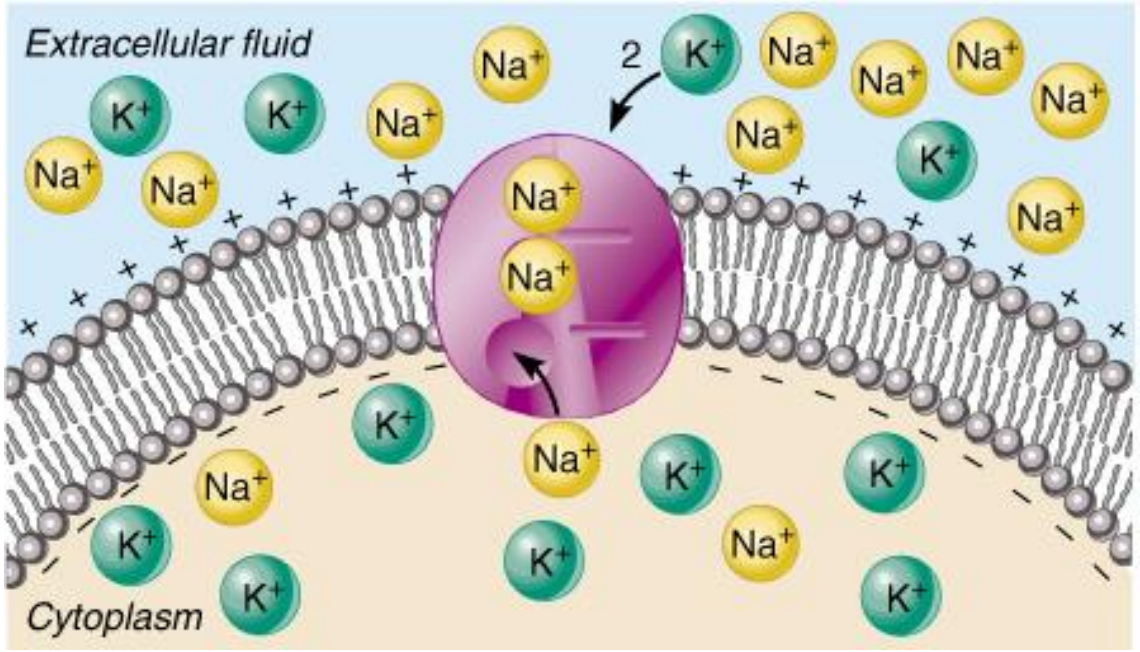
- All the sarcomeres in a fiber will contract together. This contracts the fiber itself.
- The number of fibers contracting will determine the force of the contraction of the whole muscle.
- The whole process of muscle contraction can be divided into 4 steps:
  - Excitation
  - Excitation-contraction coupling
  - Contraction
  - Relaxation

Excitation

- All cells have a voltage difference across their plasma membrane. This is the result of several things:
  1. The ECF is very high in Na^+ while the ICF is very high in K^+. The PM is impermeable to Na^+ but slightly permeable to K^+. As a result, K^+ is constantly leaking out of the cell. In other words, positive charge is constantly leaking out of the cell.



Excitation



2. The Na^+/K^+ pump is constantly pumping 3 Na^+ ions out and 2 K^+ ions in for every ATP used. Thus more positive charge is leaving than entering.
3. There are protein anions (i.e., negatively charged proteins) within the ICF that cannot travel through the PM.

- What this adds up to is the fact that the inside of the cell is negative with respect to the outside. *The interior has less positive charge than the exterior*.

Excitation

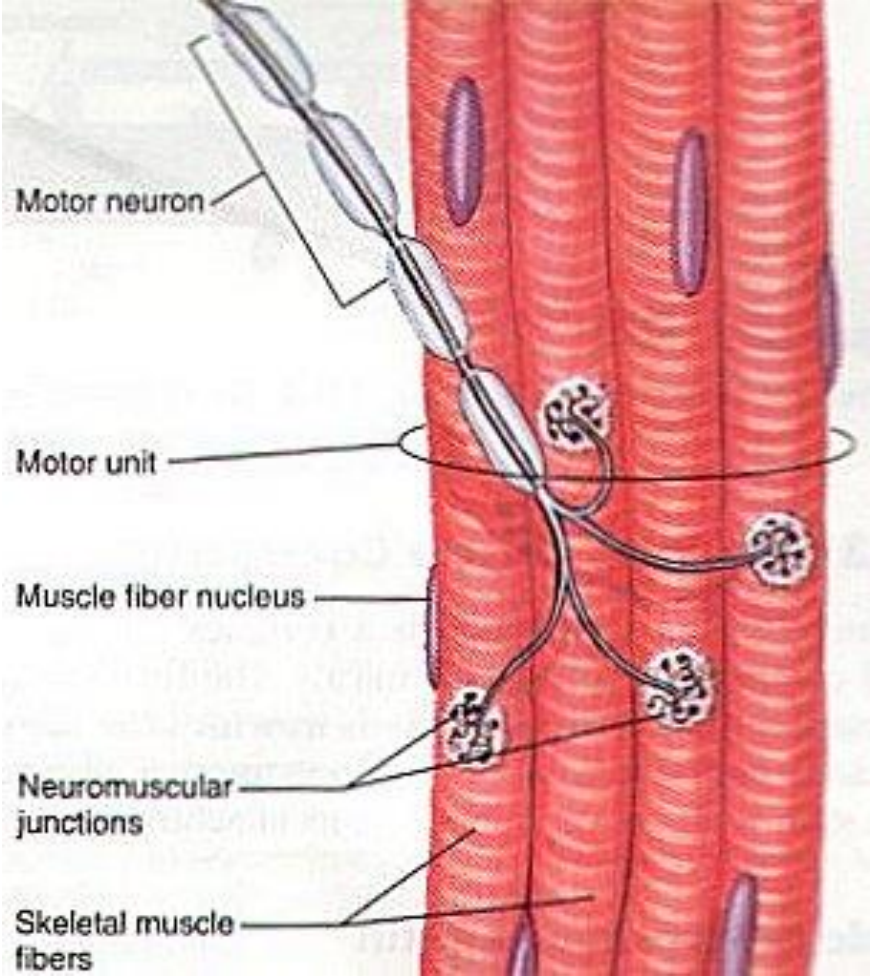
- This charge separation is known as a membrane potential (MP).
- The value for MP in inactive muscle cells is typically btwn –80 and –90 millivolts.
- Cells that exhibit a MP are said to be *polarized*.
- MP can be changed by influx or efflux of charge.

Excitation

- The PM has integral proteins that act as gated ion channels. These are channels that are normally closed, but in response to a certain signal, they will open and allow specific ions to pass through them.
- Ion channels may be:
  - Ligand-gated → the binding of an extracellular molecule (e.g., hormone, neurotransmitter) causes these channels to open.
  - Voltage-gated → Δ MP causes these channels to open.
  - Mechanically-gated → stretch or mechanical pressure opens these channels.
- When a channel is open, its specific ion(s) will enter or exit depending on their electrochemical gradient.

Excitation

- In general each muscle is served by one nerve – a bundle of axons carrying signals from the spinal cord to the muscle.
- W/i the muscle, each axon will go its own way and eventually branch into multiple small extensions called telodendria. Each telodendrium ends in a bulbous swelling known as the synaptic end bulb.



The site of interaction btwn a neuron and any other cell is known as a synapse. The synapse btwn a neuron and a muscle is known as the neuromuscular junction.

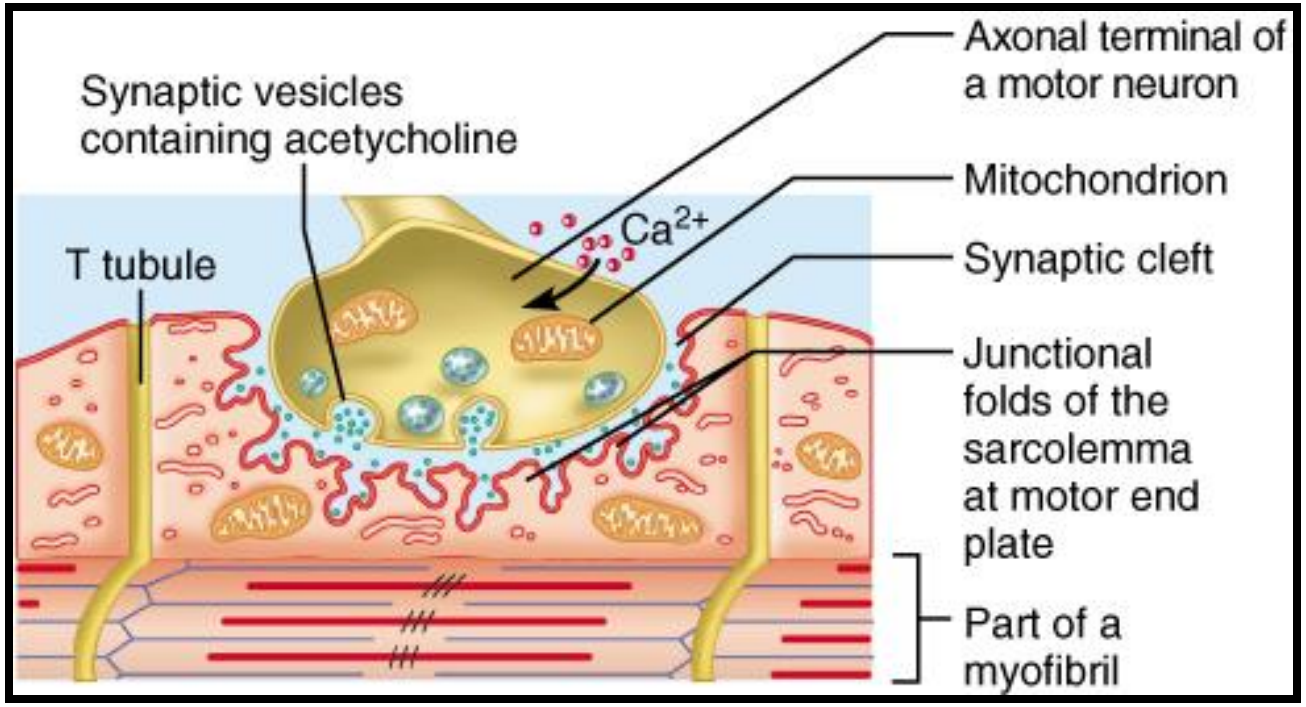
Excitation

The minute space between the synaptic end bulb and the sarcolemma is known as the synaptic cleft.

There is a depression in the sarcolemma at the synaptic cleft known as the motor end plate.

The synaptic end bulb is filled with vesicles that contain the neurotransmitter, acetylcholine.

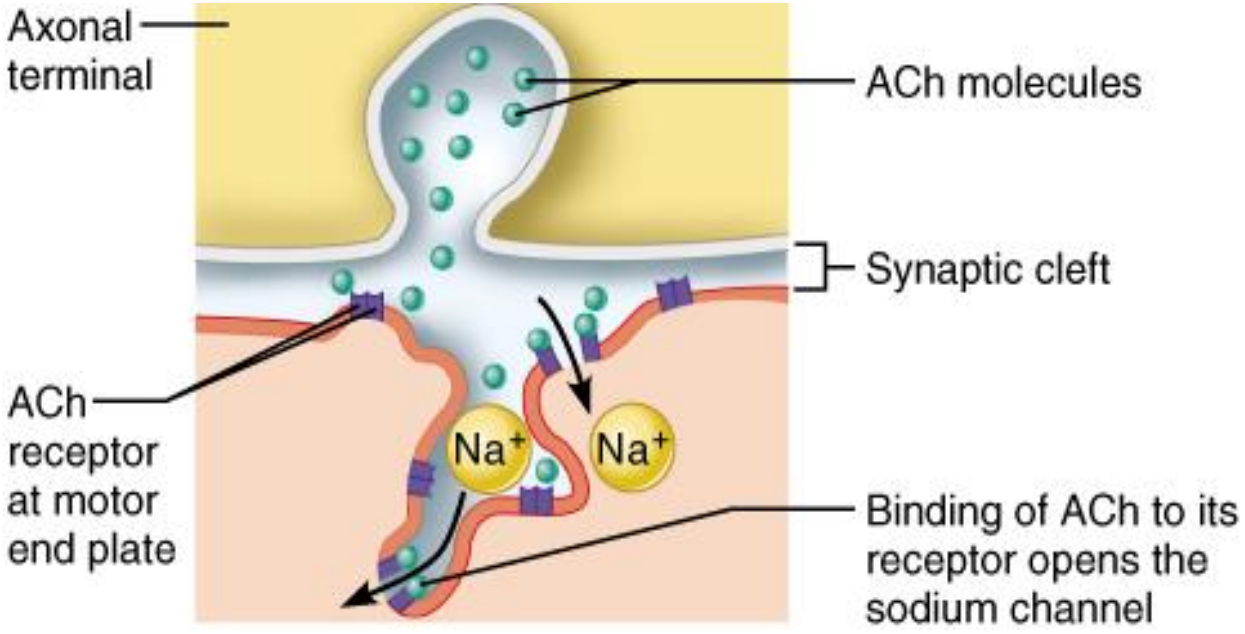
The motor end plate is chock full of acetylcholine receptors.



Excitation

1. A nerve signal will arrive at the synaptic end bulb and this will cause the ACh-containing vesicles to undergo exocytosis.
2. ACh will diffuse across the synaptic cleft and bind to the ACh receptors. These receptors are actually ligand-gated Na^+ channels. The binding of ACh causes them to open.

3. Na^+ will rush into the cell, making the local cell interior more positive. This is known as depolarizatio n. It is a local event!



Excitation

- Adjacent to the motor end plate, the sarcolemma contains voltage-gated ion channels.
- In order for these channels to open, the MP must depolarize from its resting value of –90mV to approximately –50mV.
- This is the threshold. MP must become this much positive for the voltage-gated channels to open.
- The degree of depolarization depends on how much Na^+ influx occurred which in turn depends on how many Na^+ channels were opened by binding Ach leading to the generation of end plate potential (EPP)

Excitation

- If the MP fails to depolarize to threshold, nothing will happen.

- The MP will soon return to normal and no muscle contraction will occur.
- If the MP does reach threshold, 2 types of voltage-gated ion channels will open:
  - Fast Na^+ channels
  - Slow K^+ channels

- If MP reaches threshold, fast Na^+ channels open and Na^+ rushes in causing the MP to depolarize to +30mV.
- The depolarization stops when the Na^+ channels become inactivated.
- At this point, slow K^+ channels shall open & K^+ efflux occurs.
- This returns MP back to its resting level. This is repolarization.
- If we were to graph this change in MP over time, it would look somewhat like the animation below.
- This is known as an action potential.

Excitation-Contraction Coupling

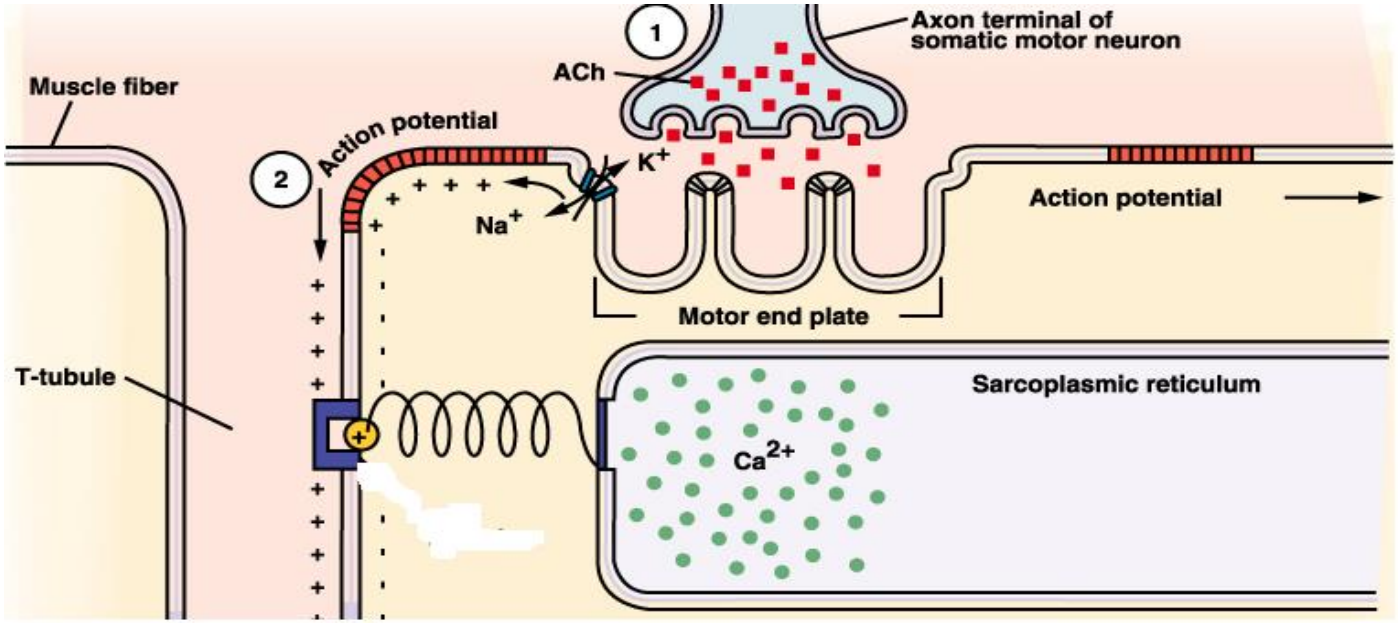
It is a mechanism by which an action potential spreads in to the skeletal muscle.

The AP travels along the sarcolemma going in both directions away from the motor end plate.

Since T-tubules are simply invaginations of the sarcolemma, the AP will spread down and through them as well. This is really important!

Excitation-Contraction Coupling

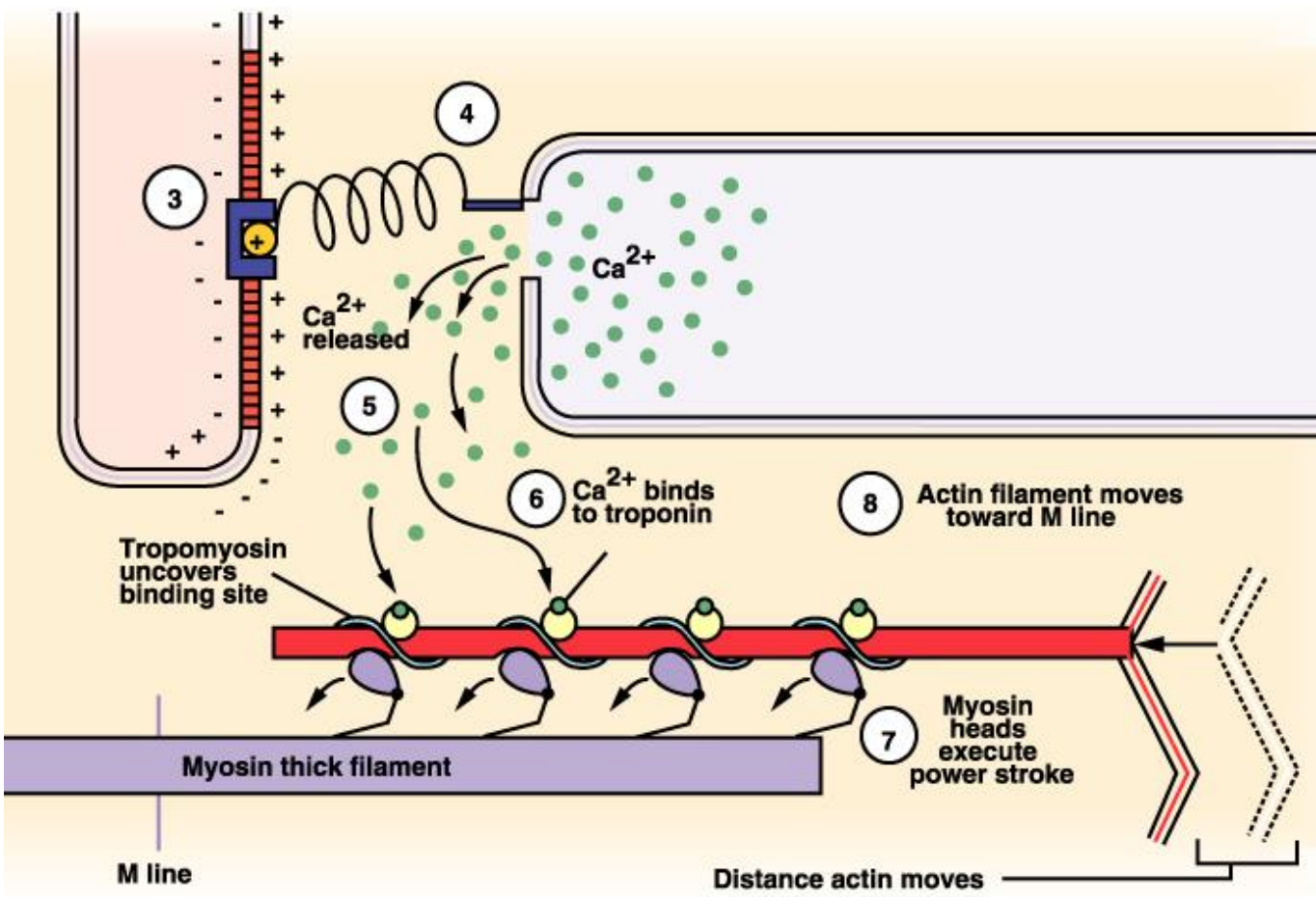
- The T-tubular sarcolemma contains voltage sensitive proteins that change their conformation in response to a significant ΔV_m.
  - These are physically linked to calcium channels in the SR membrane
  - Upon ΔV_m, the voltage sensors change their conformation. This mechanically opens the Ca^{2+} channels in the SR membrane.



Excitation-Contraction Coupling

The SR Ca^{2+} channels are only open briefly, but a large Ca^{2+} gradient exists so a large amount of calcium enters the sarcoplasm.

The Ca^{2+} interacts with the 2 regulatory proteins of the sarcomere so that the 2 contractile proteins can slide & the sarcomere can shorten.

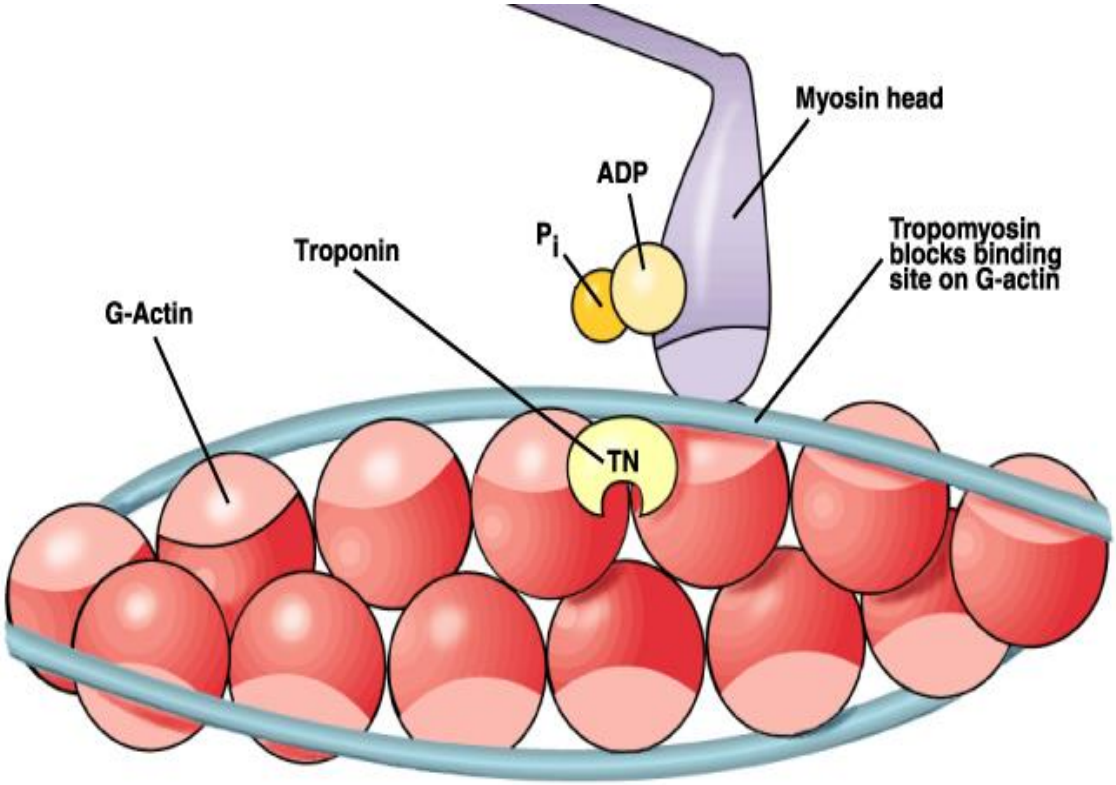


Let's backtrack for just a moment…

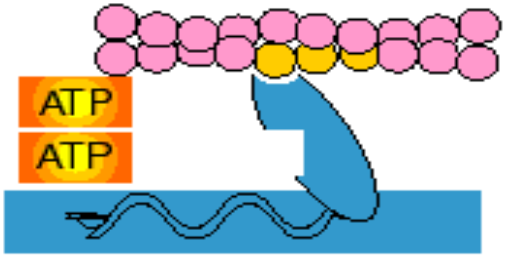
- Now that we know what an action potential is, it should be noted that the exocytosis of the ACh vesicles is caused by the arrival of an AP at the synaptic end bulb.
- The AP causes the opening of voltage-gated Ca^{2+} channels in the synaptic end bulb plasma membrane. The resulting calcium influx causes the exocytosis of the vesicles.

Contraction

- Normally, tropomyosin obstructs the myosin binding site on the G-actin subunits.
- Calcium binds to the troponin-C polypeptide of the troponin triad.
- This changes the conformation of troponin which changes the conformation of tropomyosin which exposes the myosin binding site on actin.



Contraction



- Once actin's myosin binding site is exposed, myosin will attach to it.
  - At this point myosin has just hydrolyzed ATP into ADP and P_i – however both molecules are still bound to the myosin.
  - The ATP hydrolysis provides the energy for the "cocking" of the myosin head
- Once myosin is bound to actin, the myosin head will release the ADP and P_i which will cause it change conformation.
- This results in the thin filament sliding along the thick filament.
- Myosin then remains bound to actin until it binds to another ATP.
- Myosin then hydrolyzes the new ATP and the cycle can begin again.

Contraction Strength

- Strength of is a function of:
  1. The number of crossbridges that can be made per myofibril
  2. The number of myofibrils per muscle fiber
  3. The number of contracting muscle fibers

Mechanism of muscle contraction (Excitation-contraction coupling)

Summary

When a muscle fibre membrane is depolarized, contraction of the fibre follows.

The process by which depolarization initiates contraction is called excitation contraction coupling.

It has several steps as follows:

1. Action potential initiated & propagated along the motor nerve fibre and arrives at the end feet.
2. Opening of VG-Ca-channels and influx of Ca^{2+} to trigger the release of Ach.
3. Ach released by Ca-dependent exocytosis and diffuse through the synaptic cleft and binds to nicotinic receptors on post-junctional membrane.
4. Opening of ligand gated Na-channels and influx of Na^{+} to produce EPP.
5. Spread of depolarization through the sarcolemma
6. Spread of depolarization through the T-tubules

Mechanism of muscle contraction (Excitation-contraction coupling

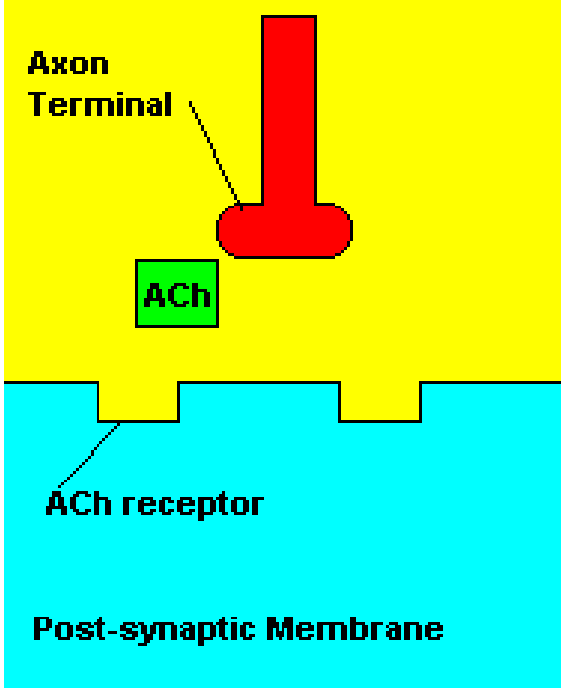
7. Depolarization of T-tubules stimulate SR to release Ca^{2+} into sarcoplasm
8. Ca^{2+} binds to troponin-C
9. Ca^{2+} and troponin-C combination detaches troponin-I from the active sites of actin
10. The detachment of troponin-I from actin displaces tropomyocin, uncovering the active sites of actin filaments.
11. When the active site of actin is exposed, the heads of myosin connect to them, making cross-bridges b/n myosin and actin.
12. The ATPase enzyme on the myosin heads hydrolyze ATP into ADP + -P plus energy.
13. The released energy causes the movement of the head (power stroke) towards the centre.
14. The head of myosin is charged with a new molecule of ATP and then detached from actin leading to relaxation.

Relaxation

- Calcium pumps in the SR membrane work constantly to get the calcium out of the sarcoplasm and back into the SR. Ca^{2+} - pump

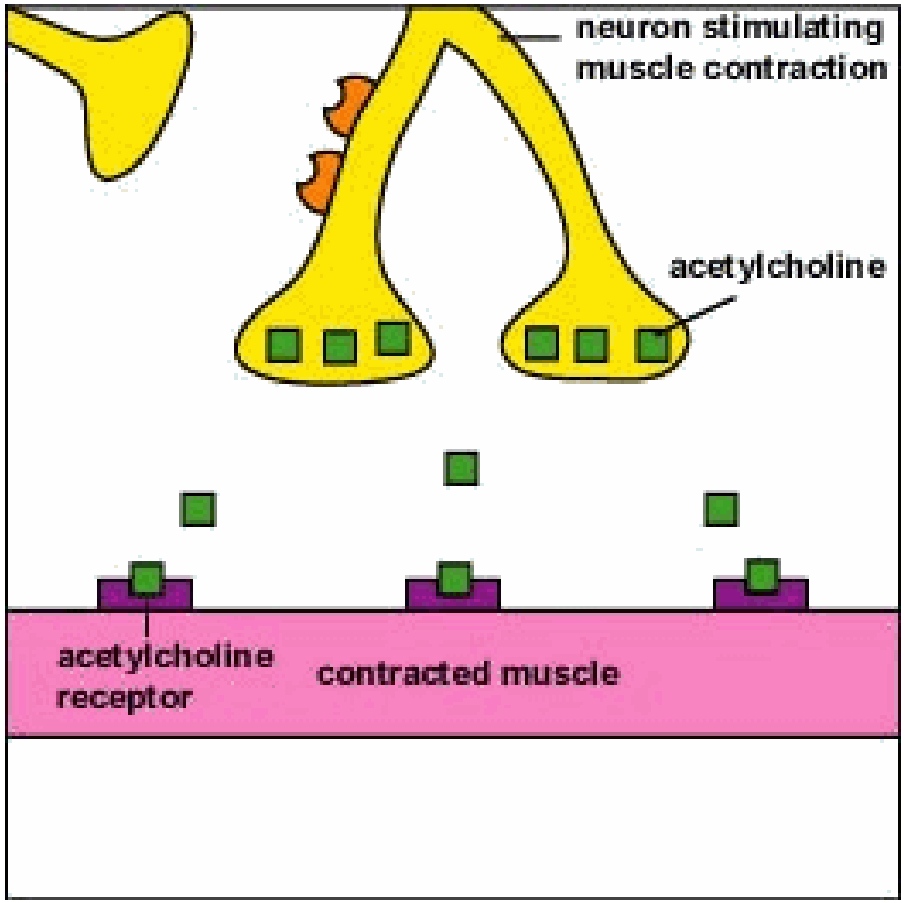
- They are unable to do this as long as the muscle is still binding ACh.

- ACh is released by the motor neuron as long as it keeps being stimulated.
- Note that ACh does not remain bound to the AChR for very long.
- It quickly releases and either binds again or more likely is hydrolyzed by the enzyme acetylcholinesterase which exists as part of the sarcolemma and free within the synaptic cleft



Relaxation

- When the muscle ceases being stimulated, the calcium pumps "win" and sarcoplasmic [Ca^{2+}] drops.
  - Calcium stops being available for troponin and tropomyosin shifts back into its inhibitory position.
- The muscle then returns back to its original length via the elasticity of the connective tissue elements, plus the contraction of antagonistic muscles, and gravity.



This animation shows another way to induce muscle relaxation.

Mechanism of muscle relaxation

It has the following steps

1. Following muscle contraction, Ca^{2+} is re-up-taken back into SR by Ca-pump, this requires ATP.
2. Decreased Ca^{2+} in the sarcoplasm→ Ca^{2+} detaches from troponin-C →Tropomyosin covers the active sites of actin.
3. Head of myosin charged with ATP, and detached from actin

   Therefore, muscle relaxation is an active process requiring energy.

- Large amount of energy (ATP) is consumed during muscular performance for the following activities:

1. To move the head of myosin (power stroke)
2. Active Ca^{2+} pump from sarcoplasm to SR
3. For Na-K-pump in the membrane
4. To remove the head of myosin from actin

Drugs Acting in the Neuromuscular Junction

Some drugs facilitate synaptic trans mission in NMJ.

These include:

- Pilocarpin
- carbachol

Some drugs potentiate the effect of acetylcholine in NMJ.

These include:

- Neostigmine
- Physiostigmine

Some drugs block NMJ.

These include

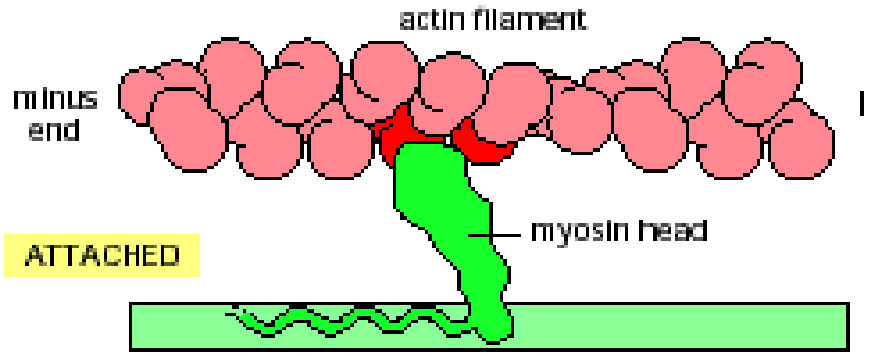
- Detubo curarie

Rigor Mortis

- Upon death, muscle cells are unable to prevent calcium entry.

- This allows myosin to bind to actin.

- Since there is no ATP made postmortem, the myosin cannot unbind and the body remains in a state of muscular rigidity for almost the next couple of days.

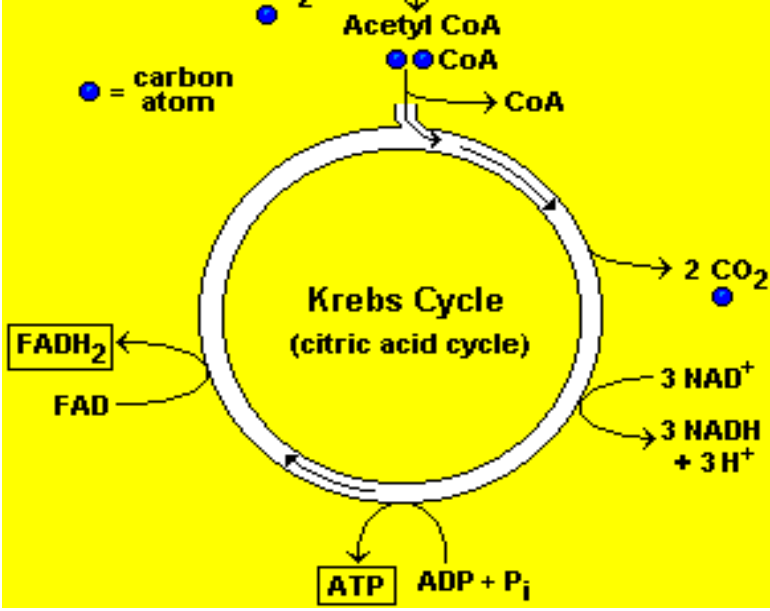


Muscle Metabolism

- The chemical energy released by the hydrolysis of ATP is necessary for both muscle contraction and muscle relaxation.

- Muscles typically store limited amounts of ATP – enough to power 4-6s of activity.
  - So resting muscles must have energy stored in other ways.

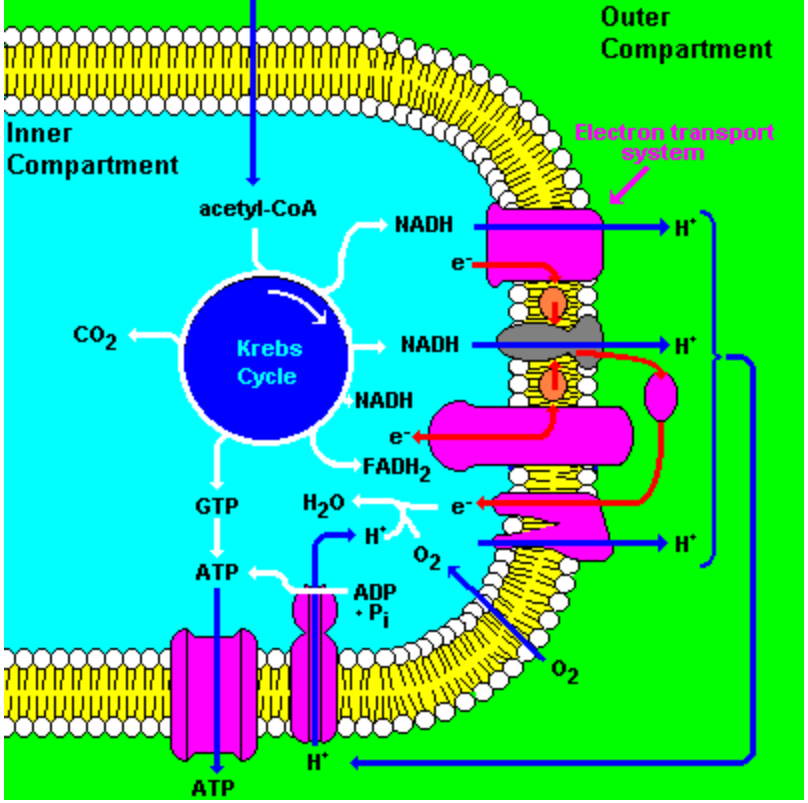
Resting Muscle and the Krebs Cycle



- Resting muscle fibers typically takes up fatty acids from the blood stream.
  - How might they enter the cell?
  - Inside the muscle fiber, the FA's are oxidized to several molecules of a compound called Acetyl-CoA. This oxidation will also produce several molecules of NADH and $FADH_2$.
  - Acetyl-CoA will then enter a cyclical series of reactions known as the Krebs cycle or Tricarboxylic Acid cycle.
  - In the Krebs cycle, acetyl-CoA combines with the compound oxaloacetate and then enters a series of reactions.
  - The end products of these reactions are: CO_2, ATP, NADH, $FADH_2$, and oxaloacetate (thus we call it a cycle)

Krebs Cycle Products

Oxaloacetate will simply combine with another molecule of acetyl-CoA and reenter the cycle.



NADH and FADH will enter another series of reactions known as the Electron Transport Chain.

These reactions occur along the inner membrane of the mitochondrion and they basically consist of the passing of electrons from compound to another compound with energy being released each time and used to drive the synthesis of ATP.

The final electron acceptor is oxygen when it combines with 2 hydrogen atoms to yield water.

Krebs Cycle Products

- CO_2 will diffuse out of the mitochondria, out of the muscle fiber, and into to the blood stream which will take it to the lungs for expiration.

- The ATP made in the Krebs cycle plus the ATP made during the ETC will be used in many ways.

ATP Use in the Resting Muscle Cell

- ATP is necessary for cellular housekeeping duties.
- ATP powers the combination of glucose monomers (which have been taken up from the blood stream) into the storage polymer glycogen.
- ATP is used to create another energy storage compound called creatine phosphate or phosphocreatine:

Working Muscle

- As we begin exercising, we almost immediately use our stored ATP.
- For the next 15 seconds or so, we turn to the phosphagen system, the energy stored in creatine-phosphate.

  - The ATP is then available to power contraction and relaxation: myosin ATPase, Ca^{2+} ATPase in the SR membrane, and Na^{+}/K^{+} ATPase in the sarcolemma.
  - The phosphagen system dominates in events such as the 100m dash or lifting weights.

Muscle at rest

ATP from metabolism + creatine → ADP + phosphocreatine

Working muscle

Phosphocreatine + ADP —(creatine kinase)→ Creatine + ATP

Creatine + ATP → needed for →

- Myosin ATPase (contraction)
- Ca^{2+}-ATPase (relaxation)
- Na^{+}-K^{+}-ATPase (restores ions that cross cell membrane during action potential to their original compartments)

Working Muscle

- After the phosphagen system is depleted, the muscles must find another ATP source.

- The process of anaerobic metabolism can maintain ATP supply for about 45-60s.

- Anaerobic means "without air," and it is the breakdown of glucose without the presence of oxygen.
  - It usually takes a little time for the respiratory and cardiovascular systems to catch up with the muscles and supply O_2 for aerobic metabolism.

Anaerobic Metabolism

- Glucose is supplied by the breakdown of glycogen or via uptake from the bloodstream.

- Glucose is broken down into 2 molecules of pyruvic acid, with the concomitant of 2 ATP generation and the conversion of 2 molecules of NAD^+ into NADH.

- This process is known as glycolysis and it occurs in the sarcoplasm.
  - Unfortunately, without O_2, we cannot use the NADH in the ETC.
  - In order for more glycolysis to proceed, the muscle cell must regenerate the NAD^+.
  - It does this by coupling the conversion of pyruvic acid into lactic acid with the conversion of NADH into NAD^+

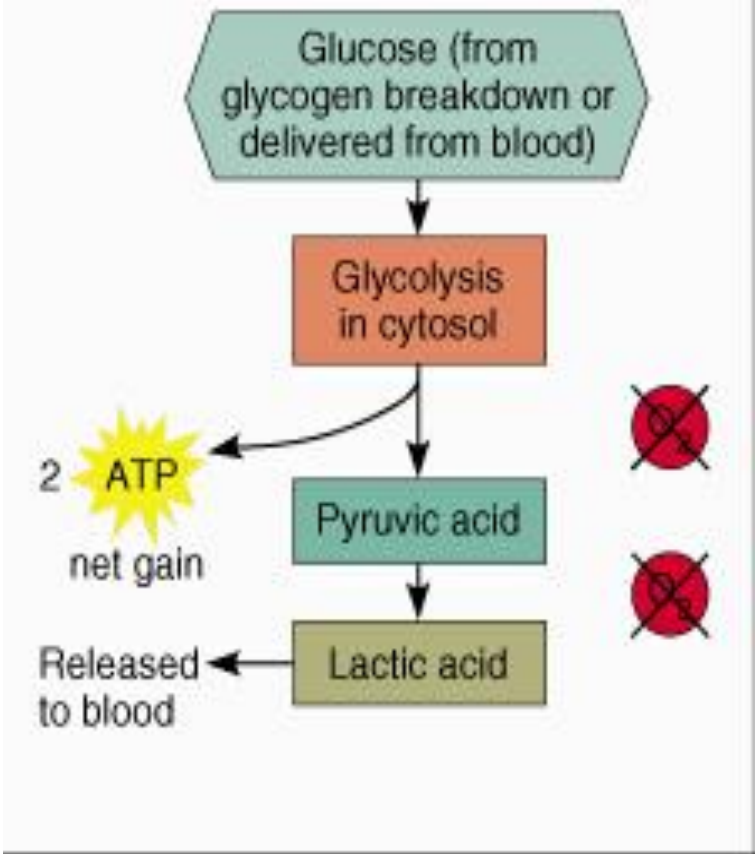
Anaerobic Metabolism

- Lactic acid typically diffuses out of muscles into the blood stream and is taken to the liver, kidneys, or heart which can use it as an energy source.

- Anaerobic metabolism is inefficient.
- Large amounts of glucose are used for very small ATP returns.

- Plus, lactic acid is a toxic end product whose presence contributes to muscle fatigue.

- Anaerobic metabolism dominates in sports that requires bursts of speed and activity, e.g., basketball.



(b) Anaerobic mechanism (glycolysis and lactic acid formation)

Energy source: glucose

Oxygen use: None
Products: 2 ATP per glucose, lactic acid
Duration of energy provision: 30–60 sec.

Aerobic Metabolism

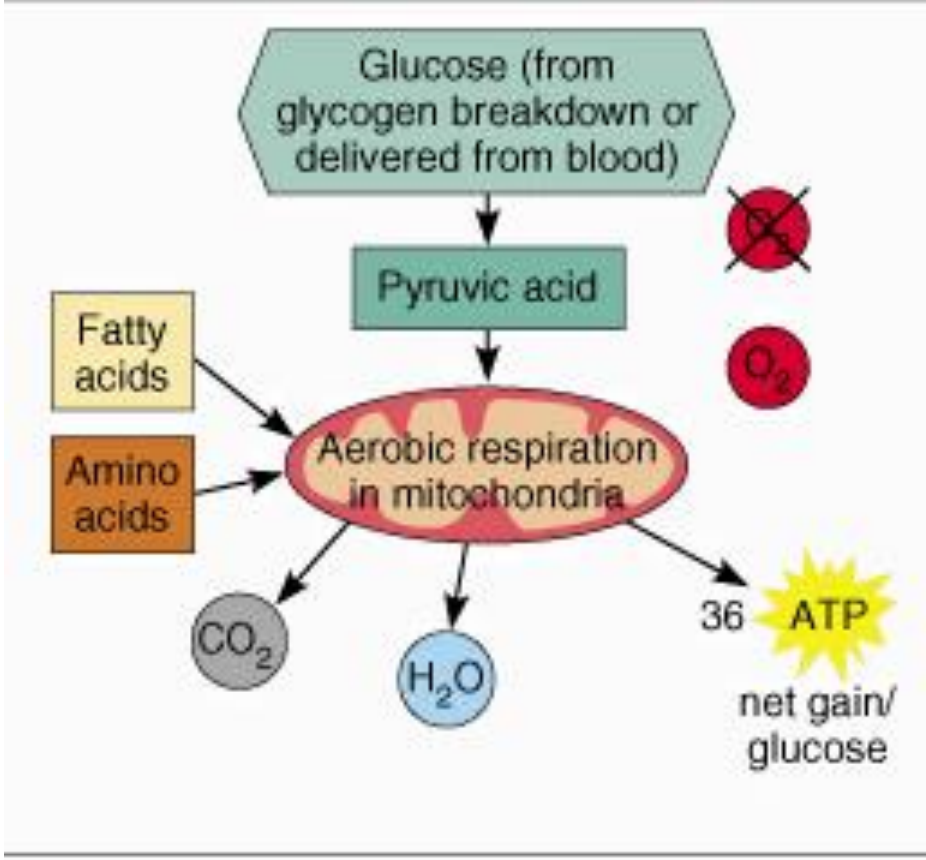
- Occurs when the respiratory and cardiovascular systems have "caught up with" the working muscles.
  - Prior to this, some aerobic respiration will occur thanks to the muscle protein, myoglobin, which binds and stores oxygen.

- During rest and light to moderate exercise, aerobic metabolism contributes 95% of the necessary ATP.

- Substrates which can be aerobically metabolized include:
  - Pyruvic acid (made via glycolysis), fatty acids, and amino acids.

Aerobic Metabolism

- It occurs in the mitochondria.
- Pyruvic acid from glycolysis is the primary substrate. The cell also utilizes fatty acids and amino acids.
- Aerobic respiration typically yields 36 ATP per molecule of glucose. Compare this to anaerobic metabolism.



(c) **Aerobic mechanism (oxidative phosphorylation)**

Energy source: glucose; pyruvic acid; free fatty acids from adipose tissue; amino acids from protein catabolism

Oxygen use: Required
Products: 36 ATP per glucose, CO_2, H_2O
Duration of energy provision: Hours

Muscle Fatigue

- Physiological inability to contract
- Results primarily from a relative deficit of ATP.
- Other contributing factors include the decrease in sarcoplasmic pH, increased sarcoplasmic [ADP], and ionic imbalances.

Oxygen debts

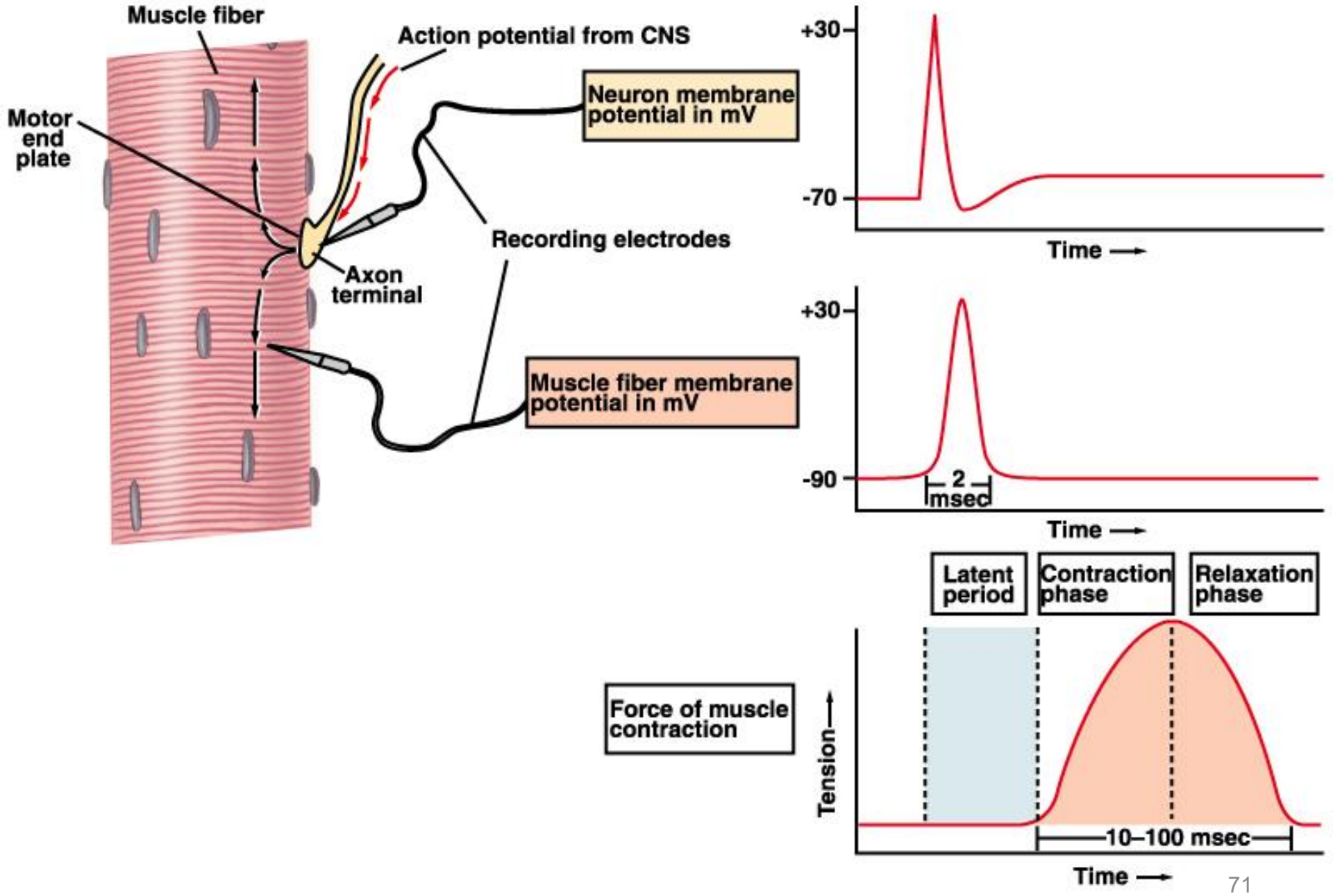
- Refers to the fact that **post-exercise breathing rate is much much greater than resting breathing rate**

- This excess oxygen intake serves many tasks:

  - Replenish the oxygen stored by myoglobin and hemoglobin
  - Convert remaining lactic acid back into glucose
  - Used for aerobic metabolism to make ATP which is used to:
    - Replenish the phosphagen system
    - Replenish the glycogen stores
    - Power the Na+/K+ pump so as to maintain RMP

Whole Muscle Contraction

- A sub-threshold stimulus would not cause contraction because no AP would be produced!
- The response of a muscle to a single supra-threshold stimulus would be a twitch – the muscle quickly contracts and then relaxes.
- Let's take a look at a measurement of a neuron's AP, a muscle fiber's AP, and the tension developed by that muscle fiber.

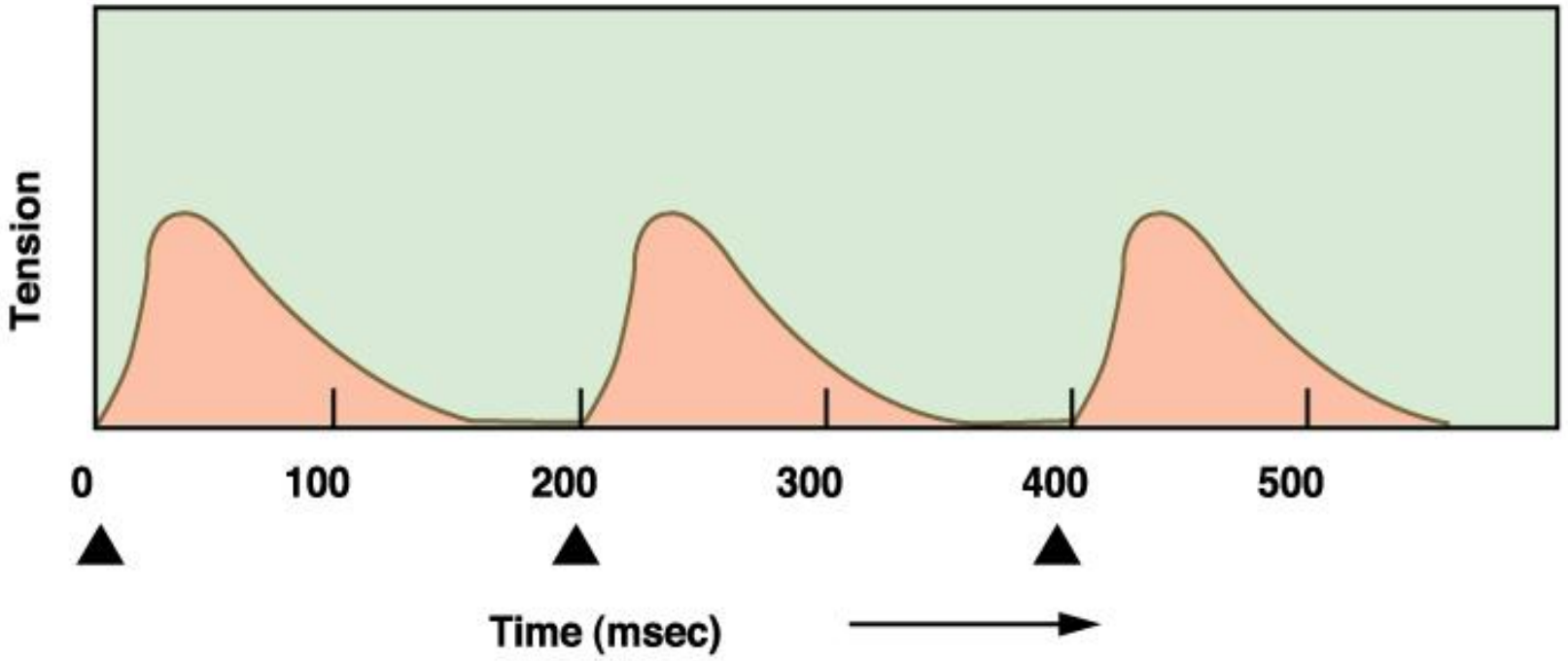

Muscle fiber
Action potential from CNS
Motor end plate
Neuron membrane potential in mV
Recording electrodes
Axon terminal
Muscle fiber membrane potential in mV
+30
-70
Time
+30
-90
2 msec
Time
Latent period
Contraction phase
Relaxation phase
Force of muscle contraction
Tension
10–100 msec
Time

Phases of the Muscle Twitch

1. Latent Period
   - Time between stimulus and generation of tension
   - Includes all time required for excitation, excitation-contraction coupling, and stretching of the series of elastic components.
2. Contraction
3. Relaxation

Now, let's look at various types of muscle twitches

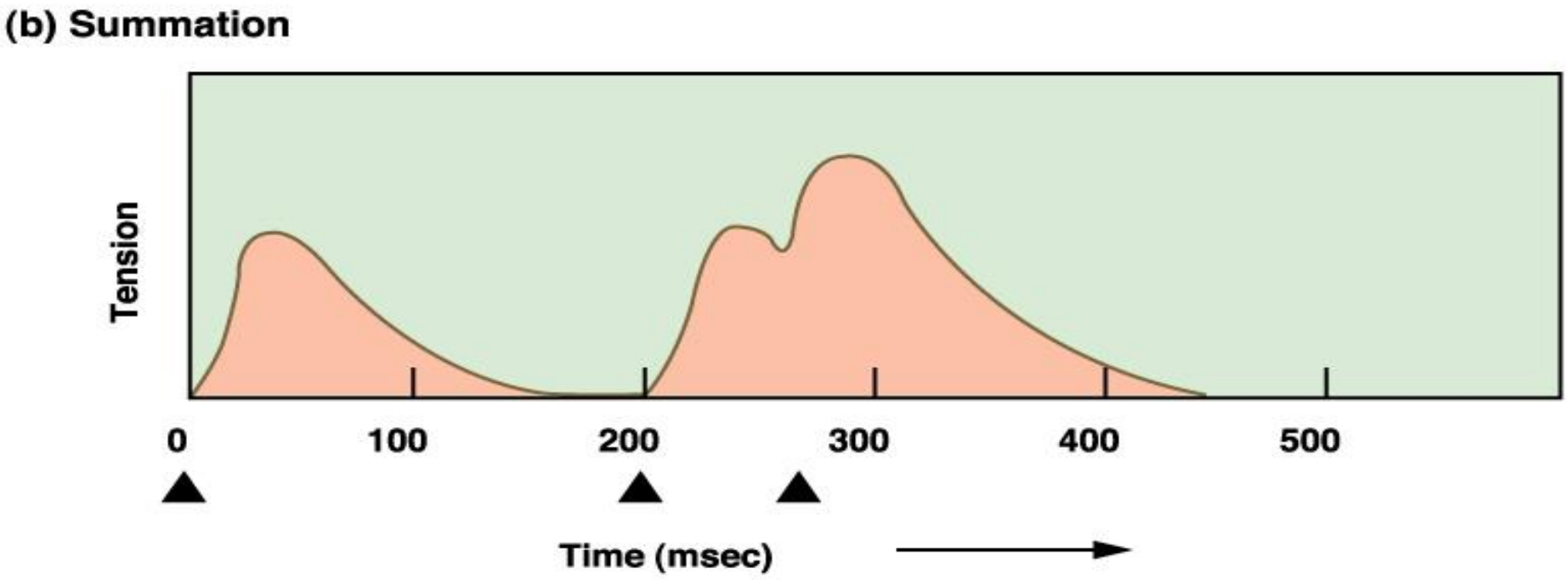
Here we have multiple twitches separated by ample time. Notice that the previous twitch has no effect on a new twitch and that these twitches are similar in size. This is why we can say that muscle contraction – at least on the level of a single fiber – is an all-or-none event.



The black arrows signify stimulation

Here, we have an initial stimulation and resulting twitch all by itself. Then we have 2 stimuli in somewhat rapid succession. The 2nd twitch has added on to the first.
This is known as wave or temporal summation.

It occurs because there is still calcium from the 1st twitch in the sarcoplasm at the time of the 2nd twitch.

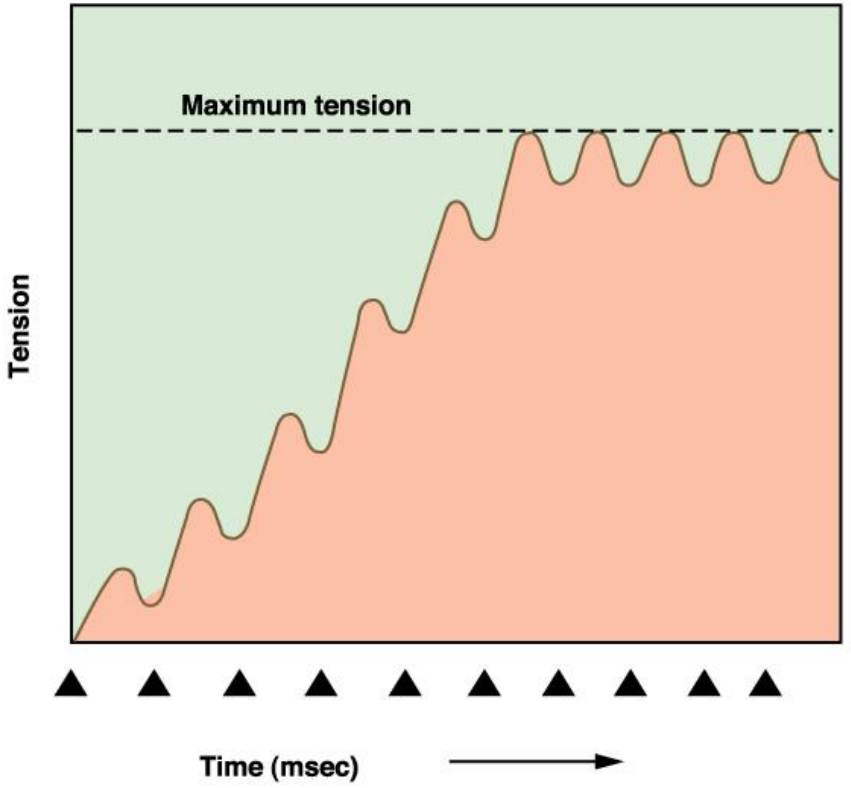


Here, we have wave summation until max tension is achieved. Maximum tension is known as tetanus.

Do not confuse this with the disease caused by the bacterium *Clostridium tetani*.

Its toxins prevent the normal inhibition of muscle contractions as mediated in the spinal cord.

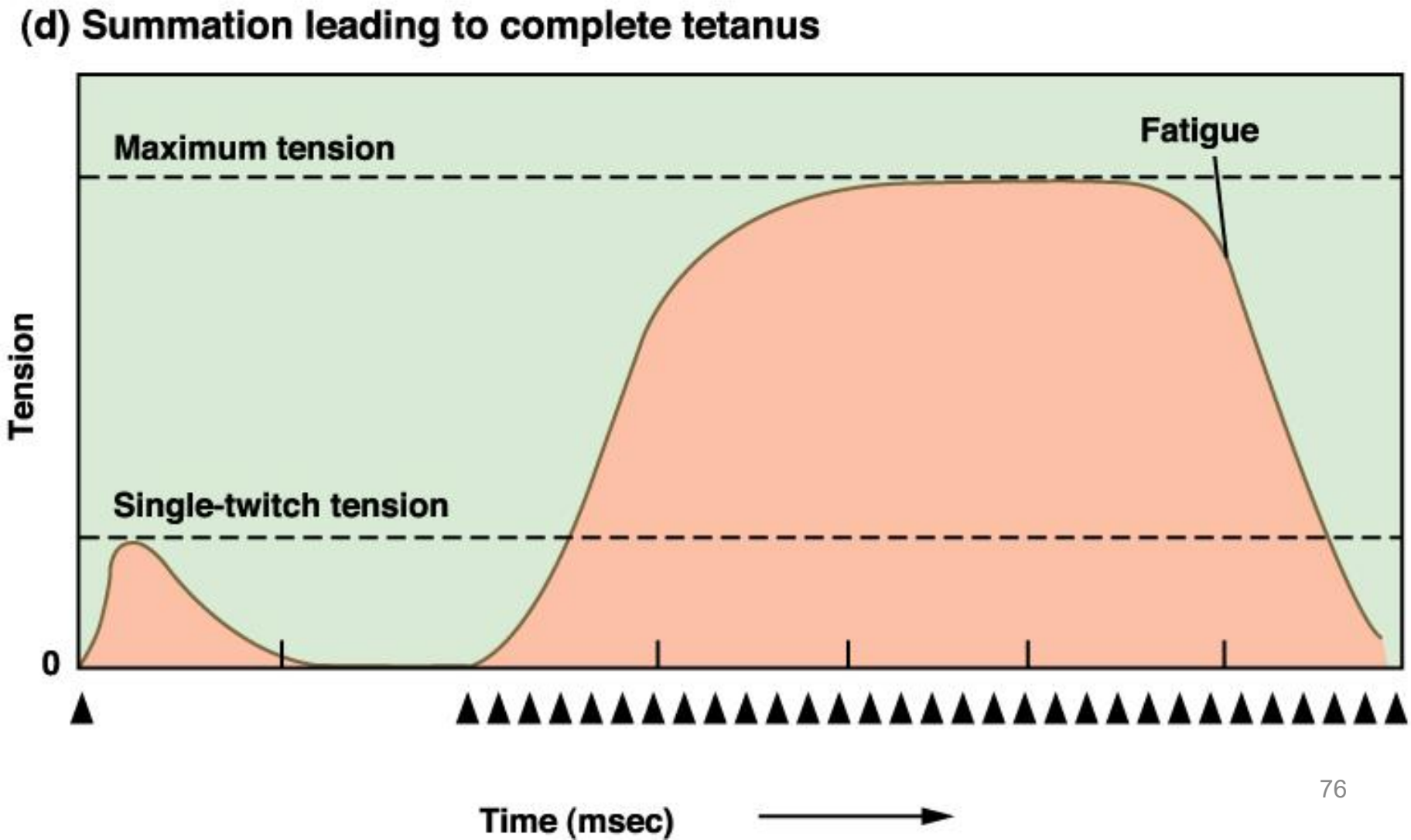
This leads to uncontrolled, unwanted muscle contraction and ultimately respiratory arrest.



Btwn stimulations, only the tiniest bit of relaxation occurs. Since some relaxation does occur, we say the tetanus is unfused or incomplete.

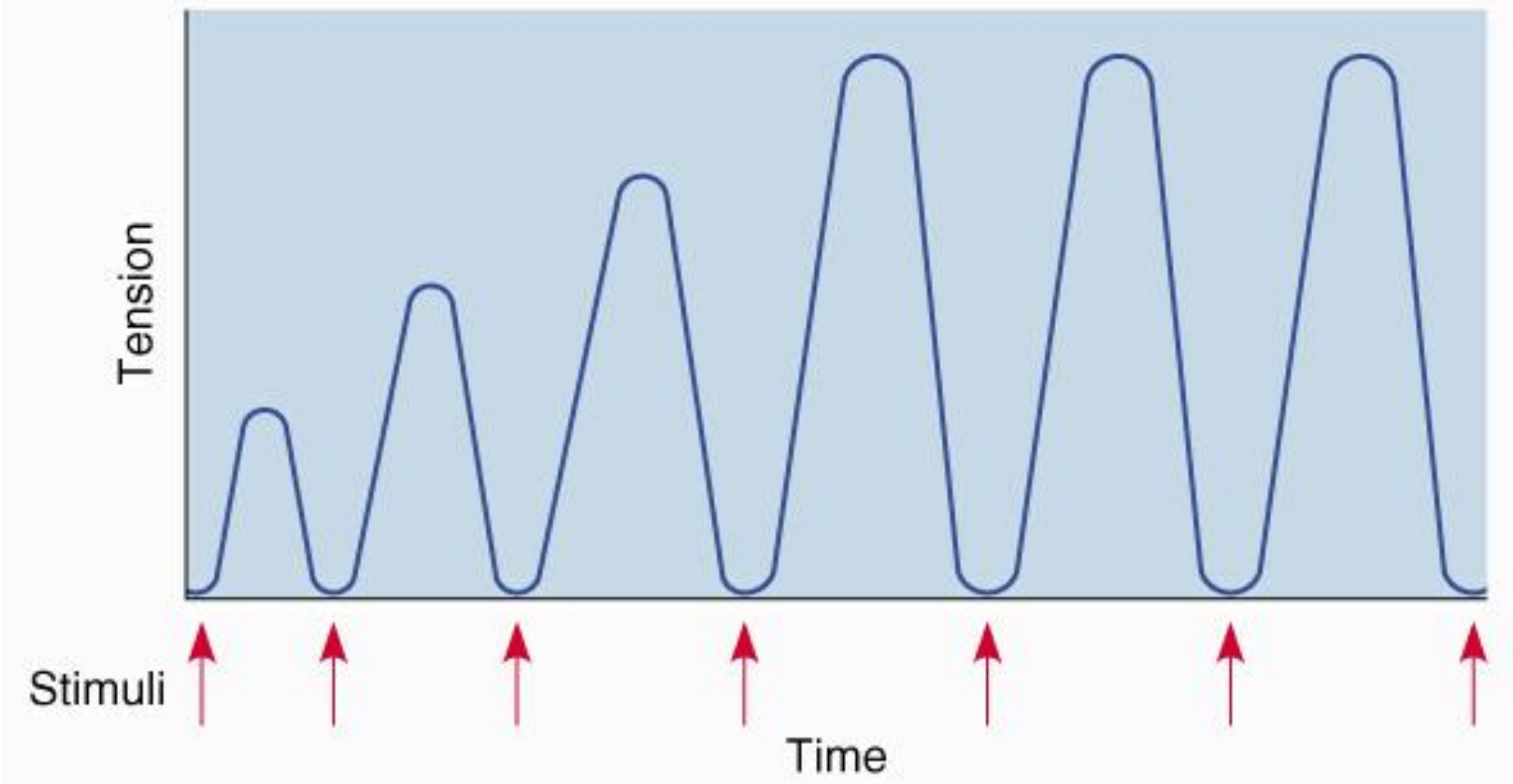
Most muscle actions occur as a result of muscle fibers undergoing asynchronous, unfused tetanus

Here, the stimuli are close enough to one another so that tetanus is complete and no relaxation occurs until fatigue sets in.



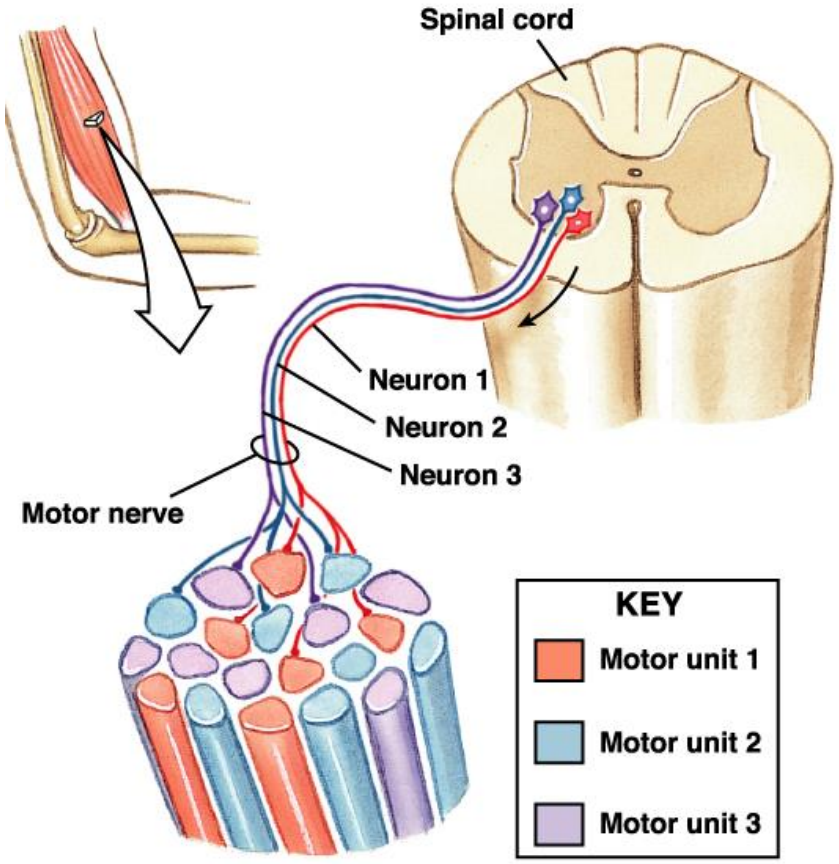
Here we have the phenomenon known as treppe (German for staircase). Notice that the subsequent contractions grow stronger. There 2 reasons for this:

1. **Slight increase in sarcoplasmic [Ca2+]**
2. **Heat liberated by working muscle increases the rate and efficiency of enzyme function within the muscle fiber.**



Motor Units

- A motor unit is defined as a somatic motor neuron and all the skeletal muscle fibers it innervates.
- When this neuron is stimulated, all the muscle fibers it synapses upon will be stimulated and will contract *as a unit*
- The # of muscle fibers per motor unit may be as high as several hundred or as few as four.
  - The smaller the motor unit, the finer and more delicate the movements.
  - Extraocular muscles typically have small motor units while the large postural muscles have large motor units



Notice that the muscle fibers of a single unit are not clustered together but are spread out.

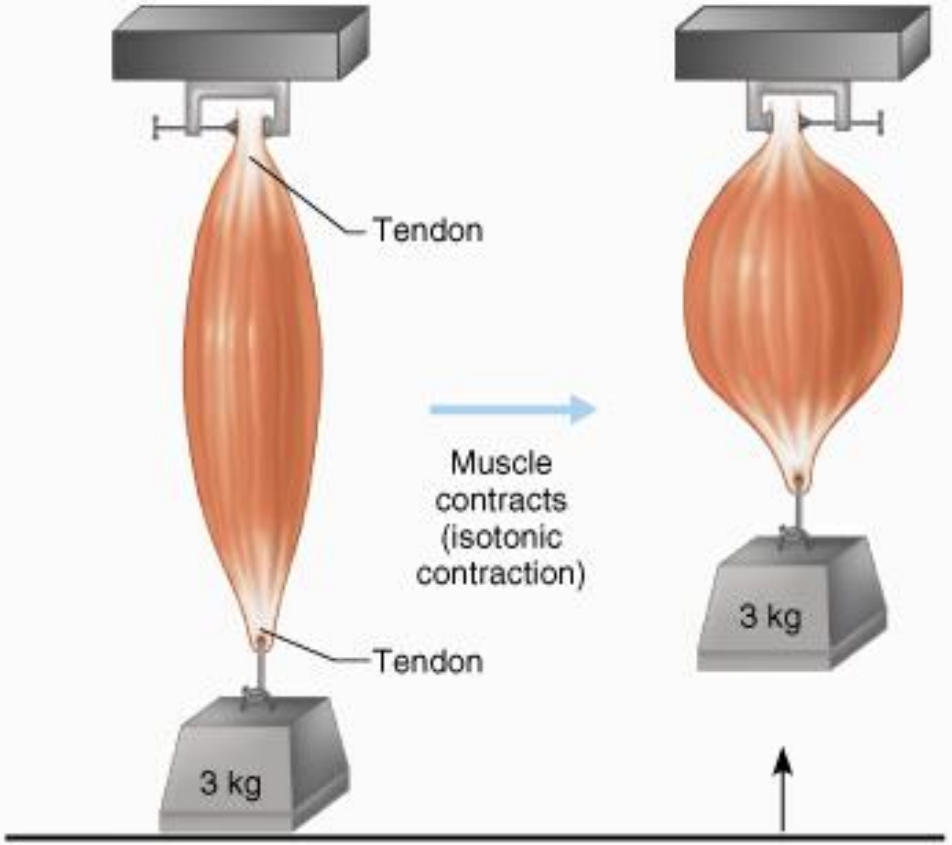
Types of Skeletal Muscle Contractions

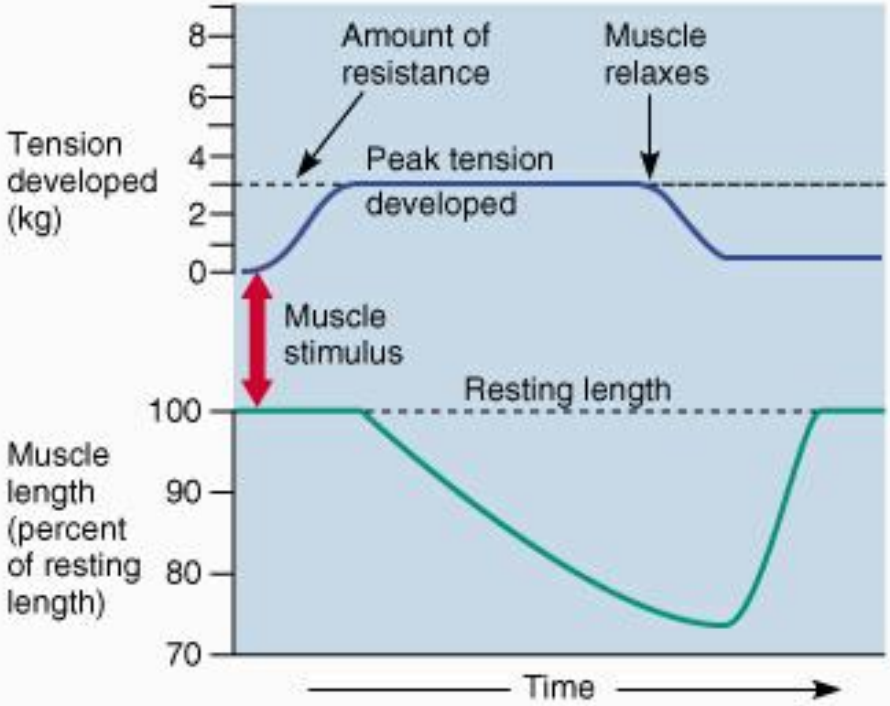
Contractions can be:

1. **Isometric**
   - **Iso= same,**
   - **metr=lelngth**
2. **Isotonic**
   - **Iso=same, ton=tension**

Isotonic Contraction

- Tension reaches a plateau and then the muscle shortens. Consider the following experiment:
  1. A skeletal muscle 1cm^2 in cross-sectional area can develop roughly 4kg of force in complete tetanus.
  2. If we hang a 3kg weight from that muscle and stimulate it, the muscle will shorten.
  3. Before the muscle can shorten, the cross-bridges must produce enough tension to overcome the resistance – in this case the 3kg weight. Over this period, internal tension in the muscle fibers rises until the external tension in the tendon exceeds the amount of resistance.
  4. As the muscle shortens, the internal and external tensions in the muscle remain constant at a value that just exceeds the resistance.

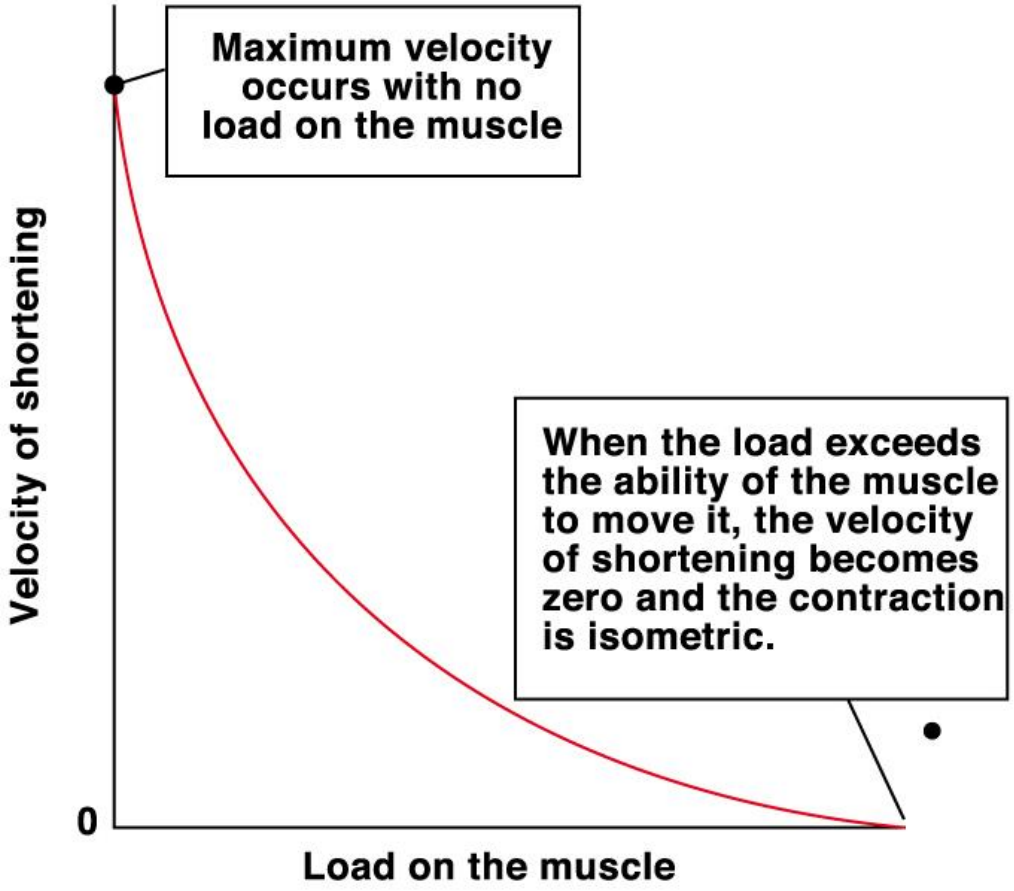




(a) Isotonic (concentric) contraction

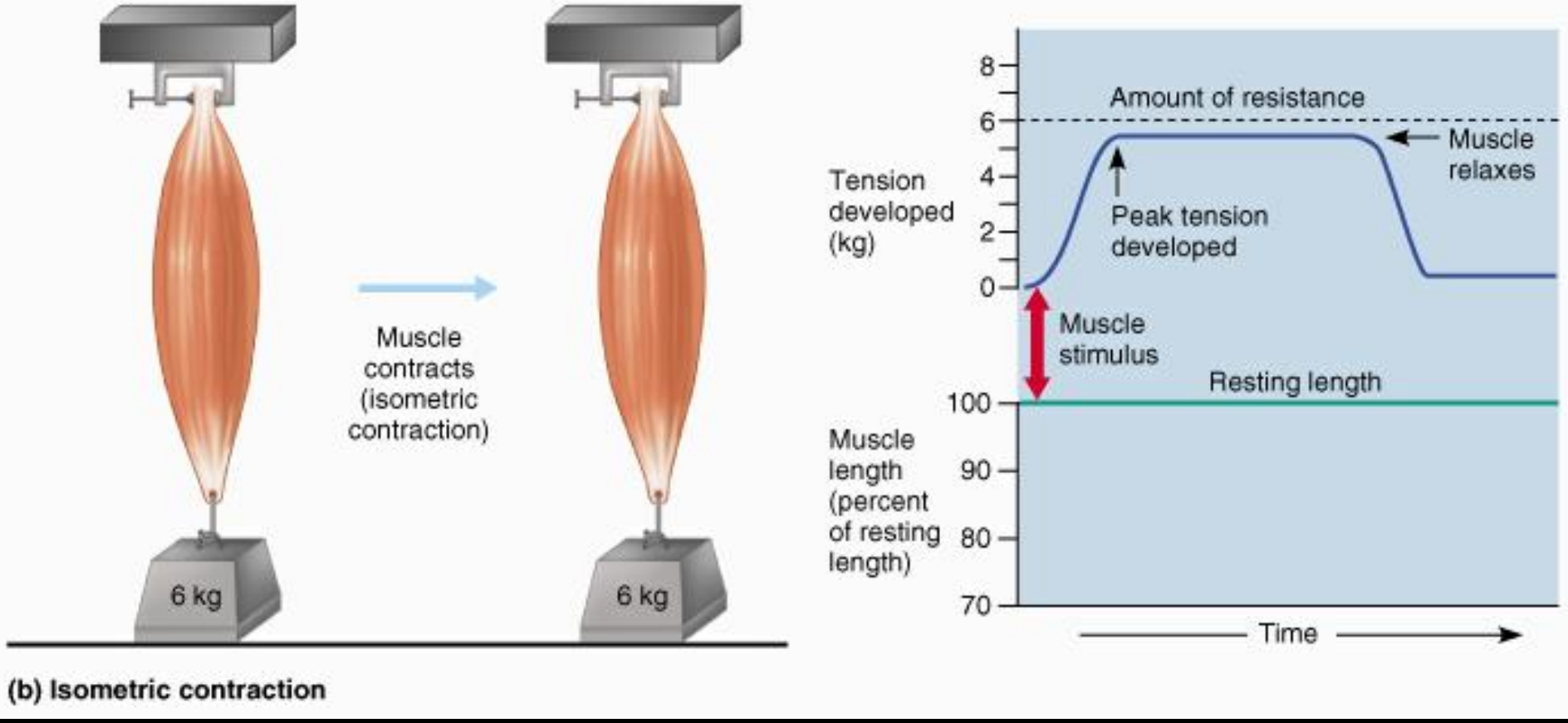
Resistance and Speed of Contraction

- There is an inverse relationship between the amount of resistance and the speed of contraction.
- The heavier the load, the longer it takes for the movement to begin because muscle tension, which increases gradually, must exceed the resistance before shortening can occur
  - More cross-bridges must be formed, more fibers involved. This takes more time.



Isometric Contractions

- The muscle as a whole does not change length and the tension produced never exceeds the resistance.
- Consider the following:
  - To the same muscle as before, we attach a 6kg weight.
  - Although cross-bridges form and tension rises to peak values, the muscle cannot overcome the resistance of the weight and cannot shorten.
  - Although the muscle as a whole does not shorten, the individual fibers shorten until the tendons are taut and the external tension equals the internal tension. The muscle fibers cannot shorten further because the external tension does not exceed the resistance.



(b) Isometric contraction

Muscle Tone

- Some of the motor units with in particular muscle are always active, even when the muscle is not contracting.
  - Their contractions do not produce enough tension to cause movement, but they do tense and firm the muscle.
  - This resting tension in a skeletal muscle is called tone.
  - The identity of the motor units involved changes constantly.
- Resting muscle tone stabilizes the position of bones and joints.

Muscle Fiber Types

2 main types:

1. Slow fibers
2. Fast fibers

Slow Fibers

- Contract slowly because its myosin ATPases work slowly.
- Depends on oxygen delivery and aerobic metabolism.
- Is fatigue resistant and has high endurance.
- Is thin in diameter – large amount of cytoplasm impedes O_2 and nutrient diffusion.

Slow Fibers Cont'd…

- Cannot develop high tension – small diameter means few myofibrils.
- Has rich capillary supply and lots of mitochondria.
- Contains lots of the O_2-storing protein, myoglobin which gives it a red color.
- Uses lipids, CHO, and amino acids as substrates for its aerobic metabolism.
- Best suited for endurance type activities.
- Red fibers, slow oxidative fibers, type I fibers.

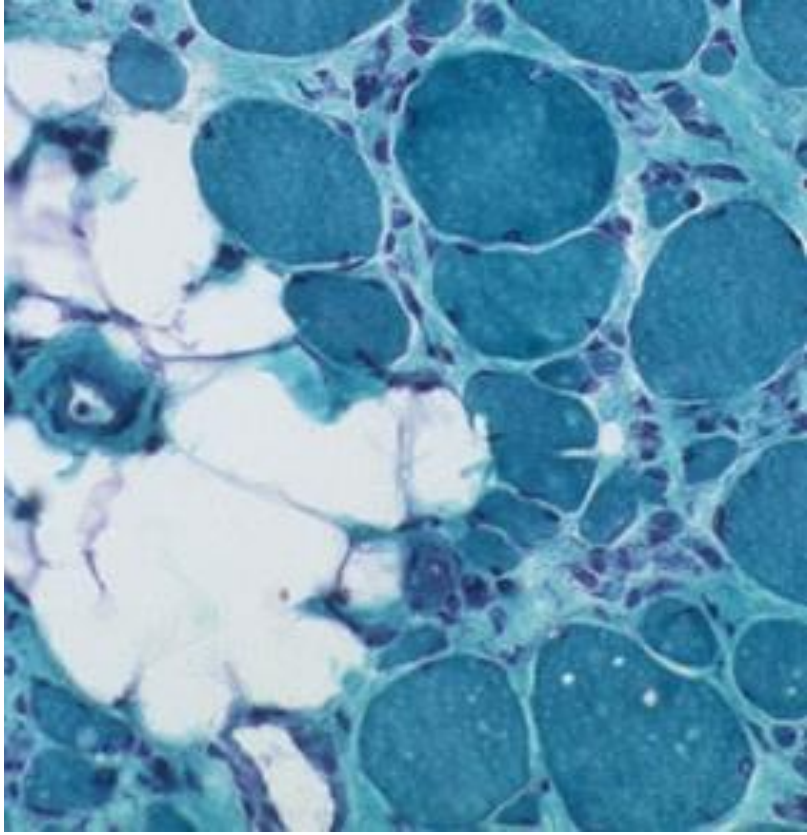
Fast Fibers

- So named because they can contract in 0.01 seconds or less after stimulation.
- Fast fibers are large in diameter; they contain densely packed myofibrils, large glycogen reserves, and relatively few mitochondria.

- Able to develop a great deal of tension b/c they contain a large number of sarcomeres.
- Use ATP in massive amounts. Supported by anaerobic metabolism. Fatigue rapidly.
- fast fatigue (FF) fibers, fast glycolytic (FG) fibers, white fibers.
- Best suited for short term, power activities.

Muscular Dystrophy

- Group of inherited muscle-destroying diseases that generally appear during childhood.
- Dys=faulty; Troph=growth
- Most common is Duchenne muscular dystrophy
  - DMD is caused by an abnormal X-linked recessive gene
  - Diseased muscle fibers lack the protein trophin which normally links the cytoskeleton to the ECM and stabilizes the sarcolemma
  - Age of onset is btwn 2 and 10. Muscle weakness progresses. Afflicted individuals usually die of respiratory failure, usually by age 25.



Here is a slide of skeletal muscle from someone with DMD. Look how much connective tissue there is. Lots of adipose tissue too.

Other Important Terms

- Flaccid paralysis
  - Weakness or loss of muscle tone typically due to injury or disease of motor neurons. E.g., LMNL
- Spastic paralysis
  - Sustained involuntary contraction of muscle(s) with associated loss of function. E.g., UMNL
- Spasm
  - A sudden, involuntary smooth or skeletal muscle twitch. Can be painful. Often caused by chemical imbalances.

Other Important Terms

- Cramp
  - A prolonged spasm that causes the muscle to become taut and painful.
- Hypertrophy
  - Increase in size of a cell, tissue or an organ.
    - In muscles, hypertrophy of the organ is always due to cellular hypertrophy (increase in cell size) rather than cellular hyperplasia (increase in cell number)
    - Muscle hypertrophy occurs due to the synthesis of more myofibrils and synthesis of larger myofibrils.

Other Important Terms

- Atrophy
  - Reduction in size of a cell, tissue, or organ
    - In muscles, its often caused by disuse. Could a nerve injury result in disuse? Why might astronauts suffer muscle atrophy?
- Fibrosis
  - Replacement of normal tissue with heavy fibrous connective tissue (scar tissue). How would fibrosis of skeletal muscles affect muscular strength? How would it affect muscle flexibility?

Smooth Muscle

- Involuntary, non-striated muscle tissue
- Occurs within almost every organ, forming sheets, bundles, or sheaths around other tissues.
- Cardiovascular system:
  - Smooth muscle in blood vessels regulates blood flow through vital organs. Smooth muscle also helps regulate blood pressure.
- Digestive systems:
  - Rings of smooth muscle, called sphincters, regulate movement along internal passageways.
  - Smooth muscle lining the passageways alternates contraction and relaxation to propel matter through the alimentary canal.

Smooth Muscle

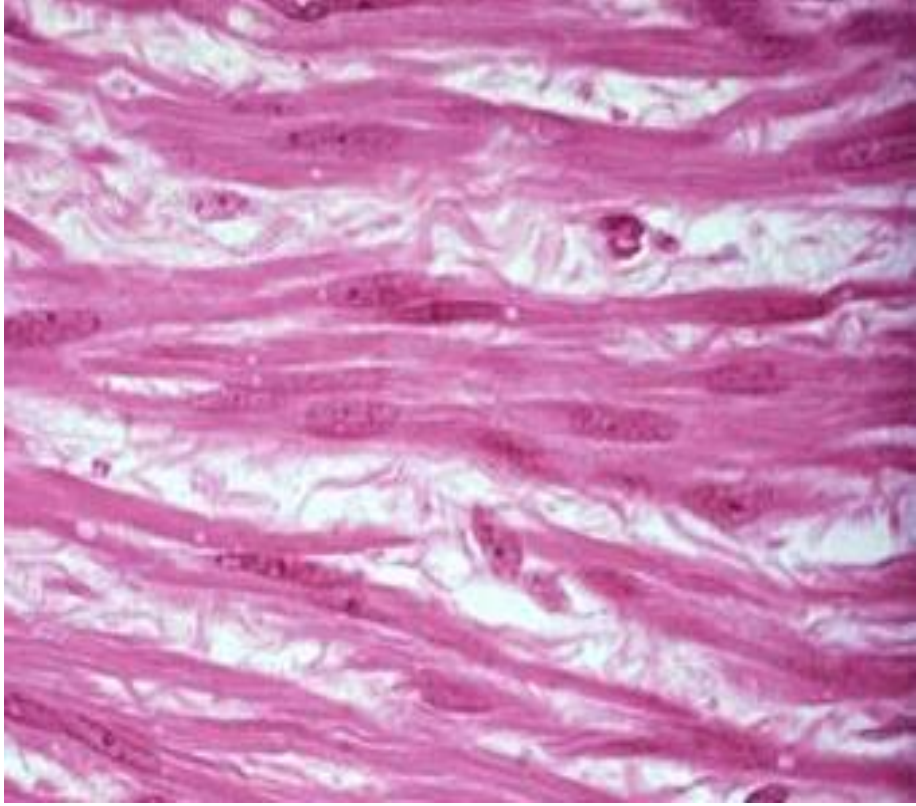
- Integumentary system:
  - Regulates blood flow to the superficial dermis
  - Allows for piloerection
- Respiratory system
  - Alters the diameter of the airways and changes the resistance to airflow
- Urinary system
  - Sphincters regulate the passage of urine
  - Smooth muscle contractions move urine into and out of the urinary bladder

Smooth Muscle

- Reproductive system
  - Females
    - Assists in the movement of the egg (and of sperm) through the female reproductive tract
    - Plays a large role in childbirth
  - Males
    - Allows for movement of sperm along the male reproductive tract.
    - Allows for secretion of the non-cellular components of semen
    - Allows for erection and ejaculation

Smooth Muscle

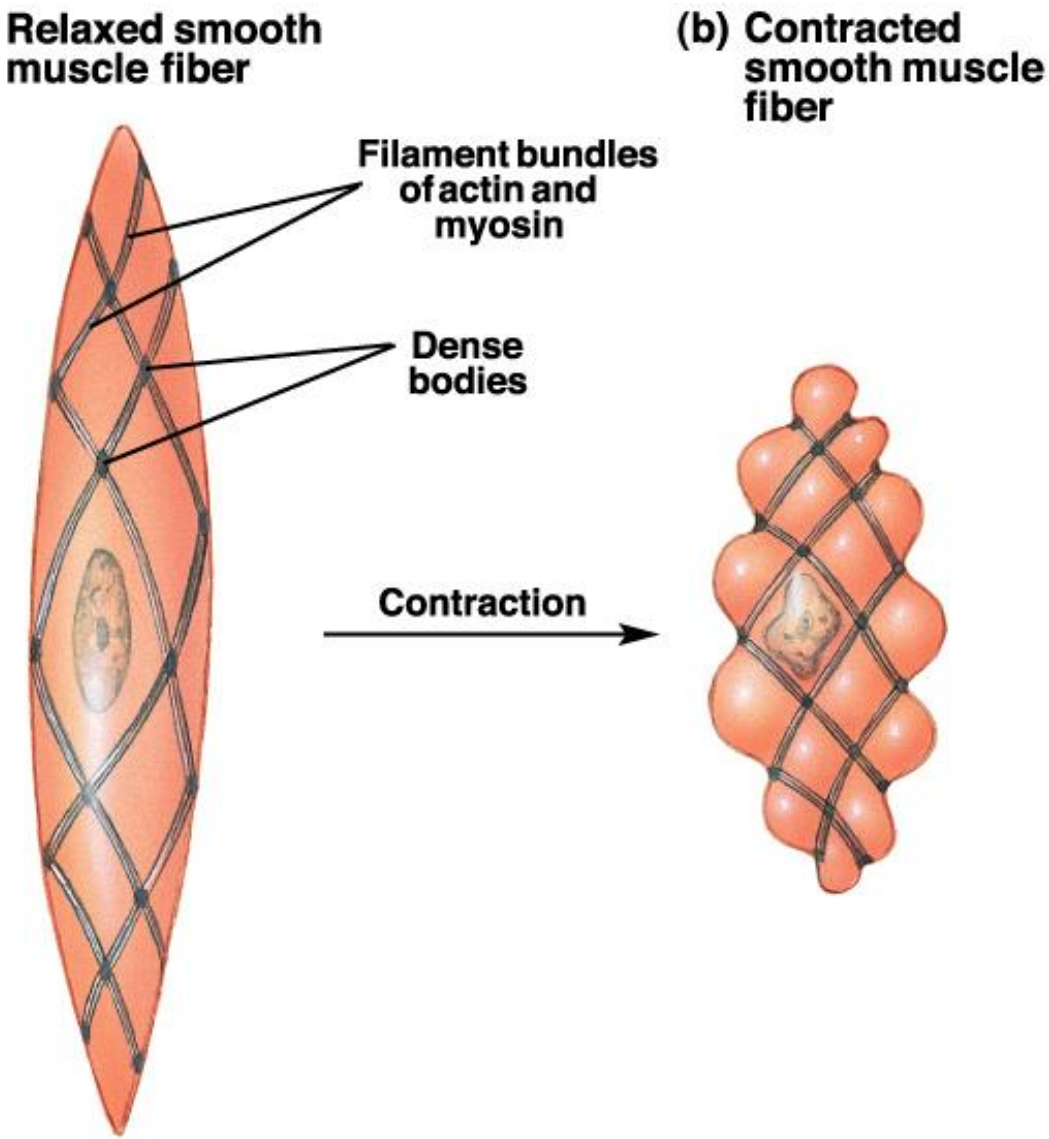
- Smooth muscle cells:
  - Are smaller: 5-10um in diameter and 30-200um in length
  - Are uninucleate: contain one centrally placed nucleus
  - Lack any visible striations
  - Lack T-tubules
  - Have a scanty sarcoplasmic reticulum



- Smooth muscle tissue is innervated by the autonomic nervous system unlike skeletal muscle which is innervated by the somatic nervous system (over which you have control)
- Only the endomysium is present. Nor perimysium or epimysium.

Smooth Muscle Contraction

- Myosin and actin are present and crossbridge formation powers contraction, but the thick and thin filaments do not have the strict repeating arrangement like that found in skeletal muscle.
- There are no Z discs, instead thin filaments are attached to protein structures called dense bodies which attach to the sarcolemma.

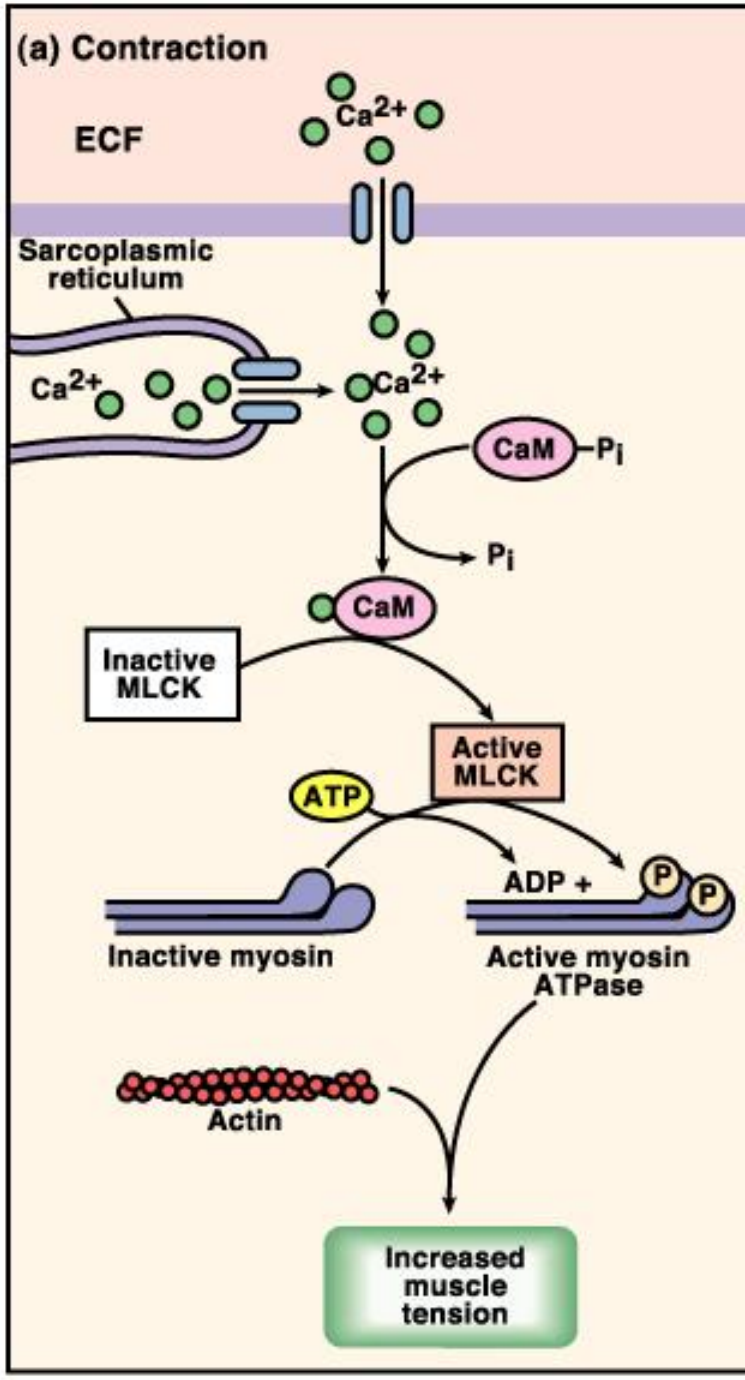


Smooth Muscle

- Smooth muscle is always maintaining a normal level of activity – creating muscle tone.
- Smooth muscle can respond to stimuli by altering this tone in either direction.
  - Smooth muscle can be inhibited and relax
  - Smooth muscle can be excited and contract
- Possible stimuli include neurotransmitters, hormones, ΔpH, ΔPco_2, ΔPo_2, metabolites (such as lactic acid, ADP), or even stretch.

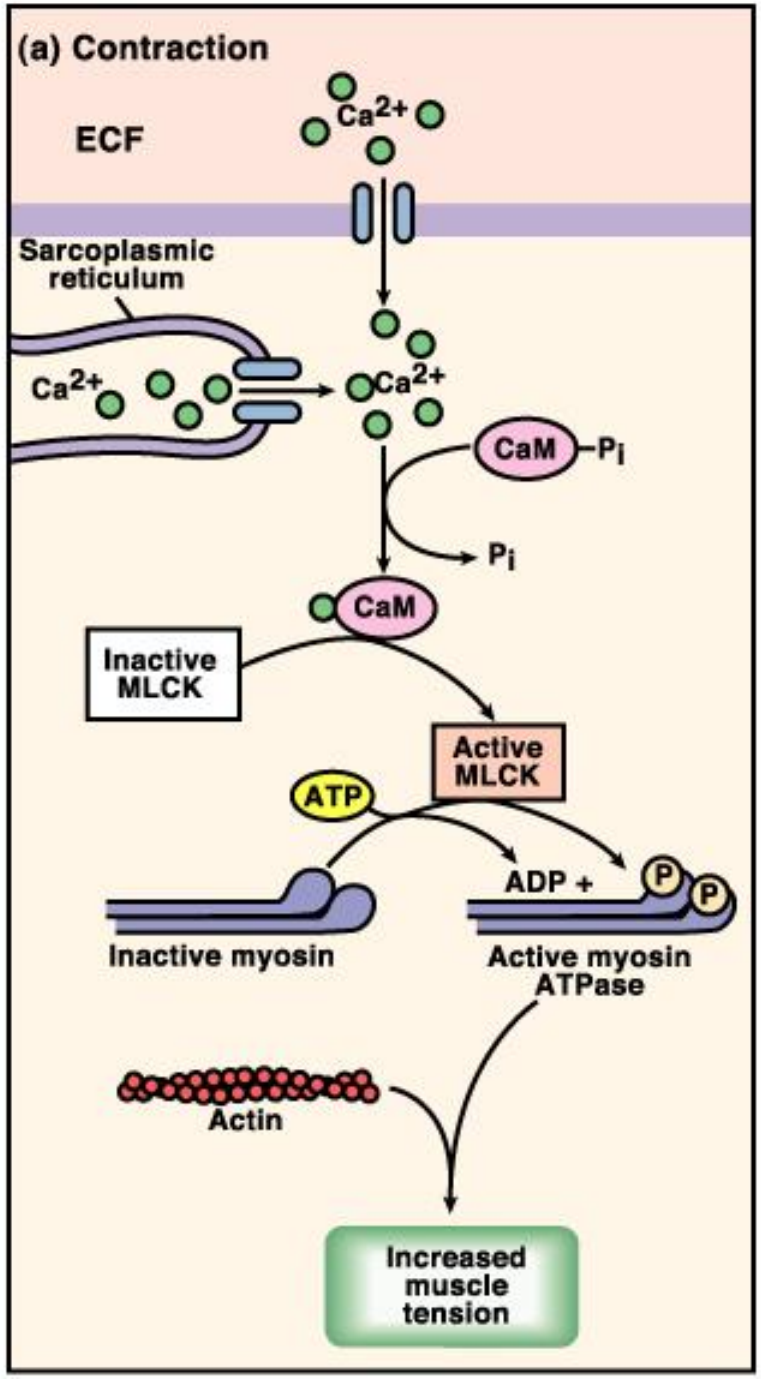
Smooth Muscle Contraction

- Begins with the opening of membrane channels. Channels may be ligand-gated (NTs, hormones, metabolites), voltage-gated, or mechanically-gated (stretch).
- Channels will allow significant calcium entry from the ECF. Remember smooth muscle has little SR.
- Calcium binds to a regulatory molecule called calmodulin and activates it.
- Activated calmodulin activates an enzyme called Myosin Light Chain Kinase.



Smooth Muscle Contraction

- Activated MLCK will add a phosphate group to the myosin of the thick filament. This enables the myosin to interact with actin.
  - Tropomyosin is present but not blocking actin's myosin binding sites
  - Troponin is not present
- Contraction then ensues.

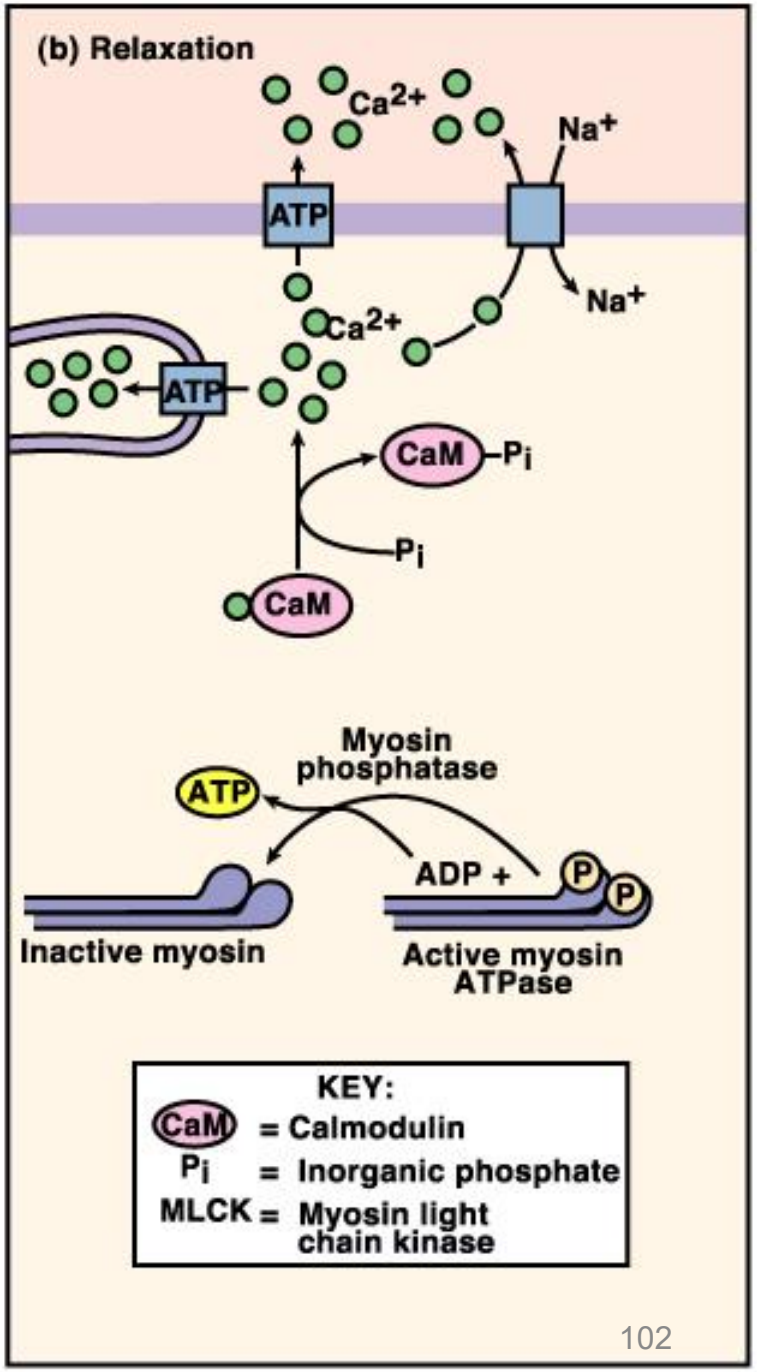


Smooth muscle relaxation:

Calcium is pumped out of the cell, which decreases the amount of active calmodulin which decreases the amount of active MLCK which decreases the number of crossbridges.

MLC phosphatase is required (removes phosphate from the myosin)

Relaxation can occur subsequent to contraction or at any time if anything causes a decrease in the calcium permeability of the smooth muscle cell.

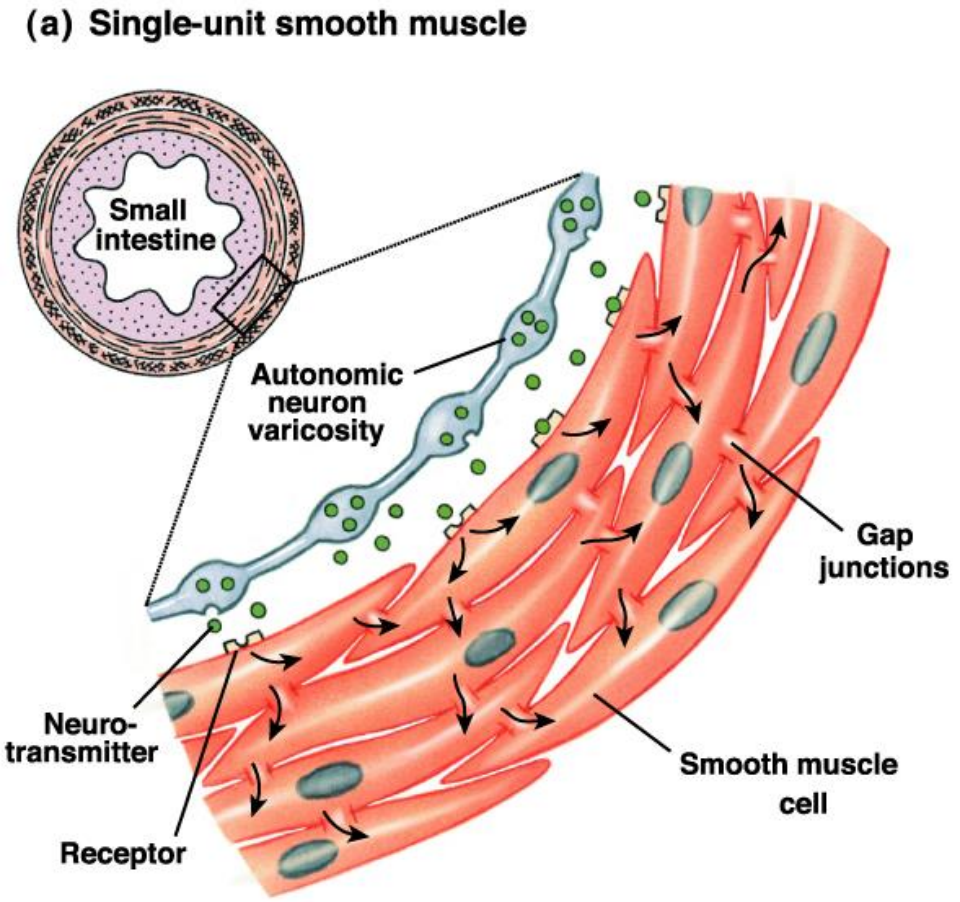


Types of Smooth Muscle

- Smooth muscle varies widely from organ to organ in terms of:
  - Fiber arrangement
  - Responsiveness to certain stimuli
- Broad types of smooth muscle:
  - Single unit (visceral)
  - Multi unit

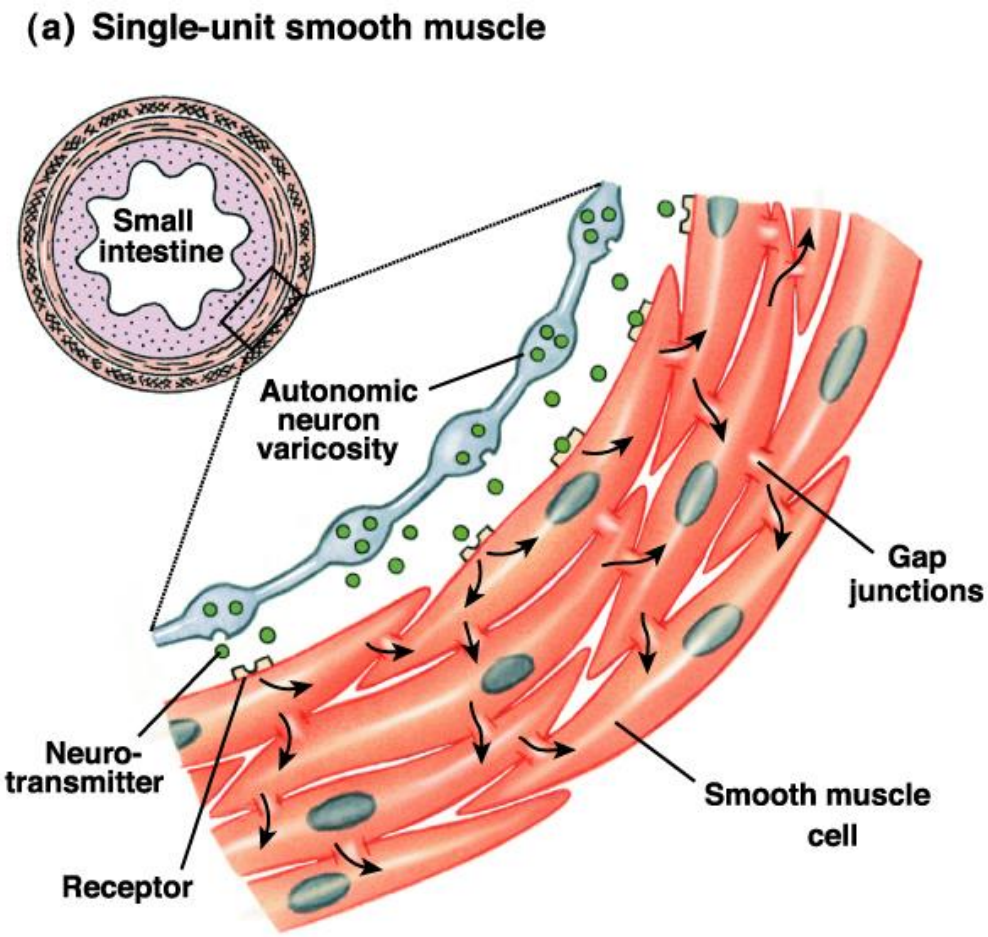
Single Unit Smooth Muscle

- More common
- Cells contract as a unit because they are all connected by gap junctions - protein complexes that span the PM's of 2 cells allowing the passage of ions between them, i.e., allowing the depolarization of one to cause the depolarization of another.
- Some will contract rhythmically due to pacemaker cells that have a spontaneous rate of depolarization.



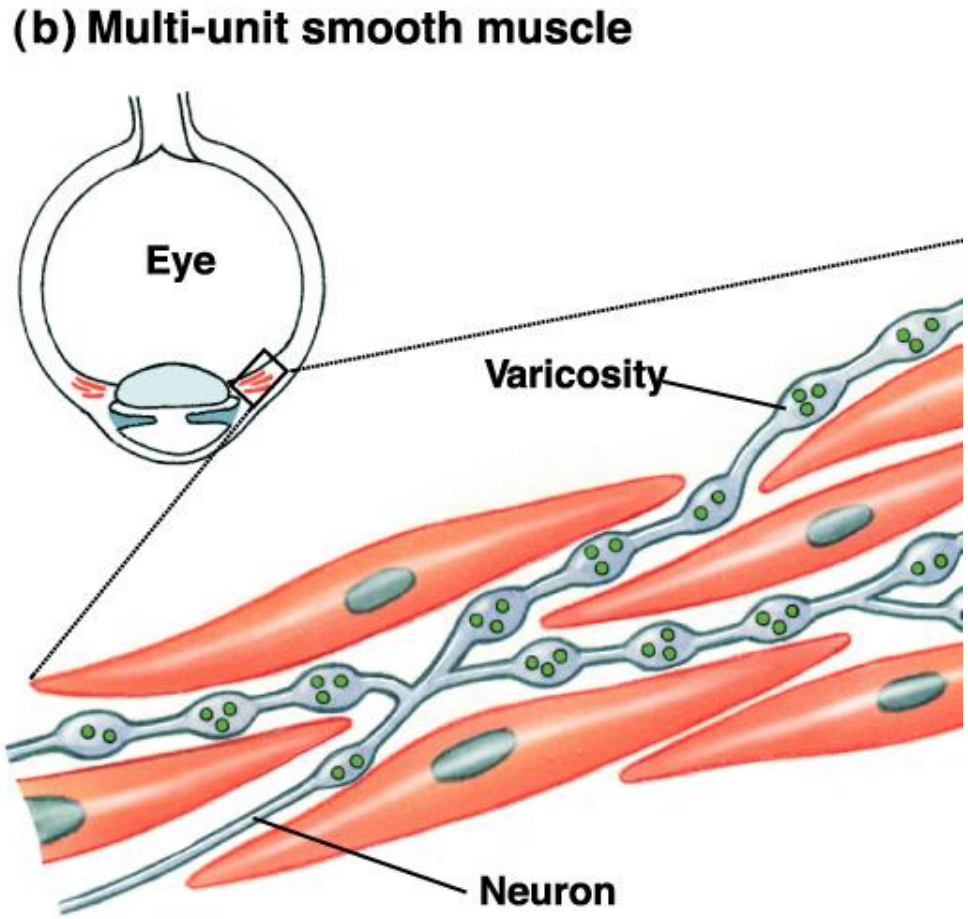
Single Unit Smooth Muscle

- Not directly innervated. Diffuse release of neurotransmitters at varicosities (swellings along an axon).
- Responsive to variety of stimuli including stretch and concentration changes of various chemicals
- Found in the walls of the digestive tract, urinary bladder, and other organs



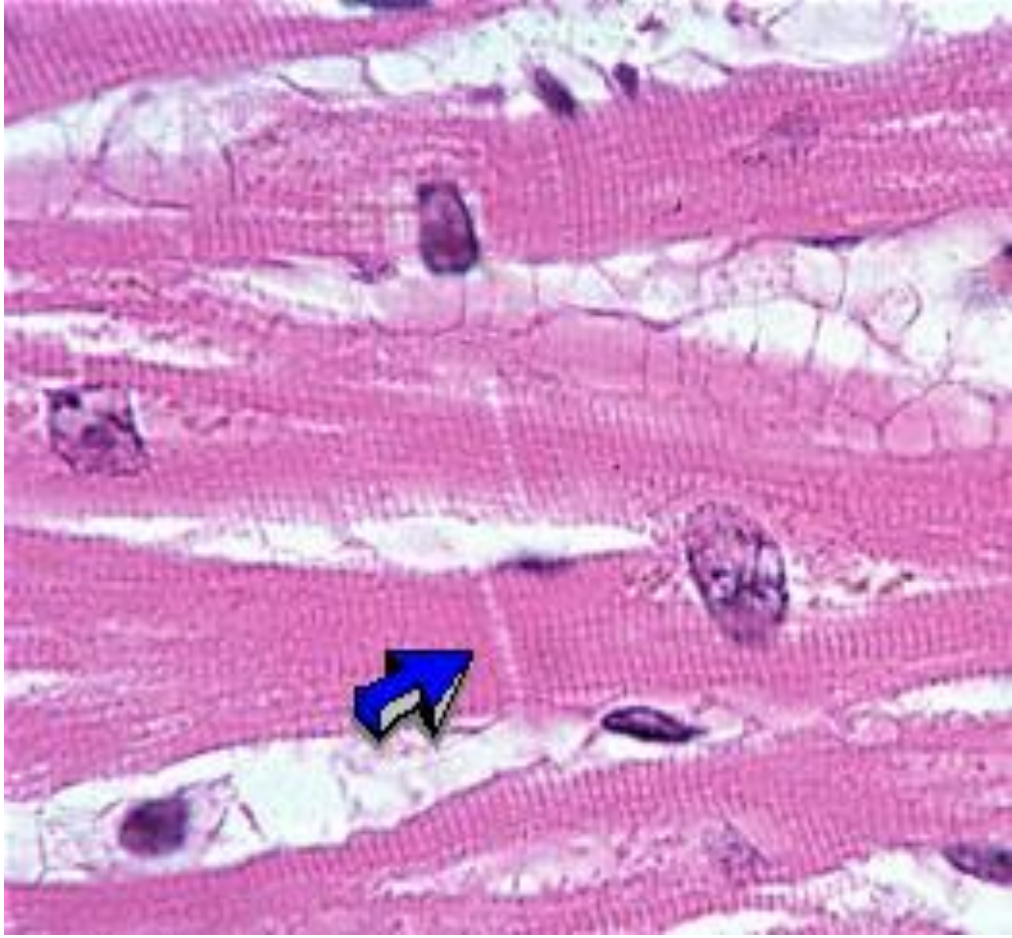
Multi-Unit Smooth Muscle

- Innervated in motor units comparable to those of skeletal muscles
- No gap junctions. Each fiber is independent of all the others.
- Responsible to neural & hormonal controls
- No pacemaker cells
- Less common
- Found in large airways to the lungs, large arteries, arrector pili, internal eye muscles (e.g., the muscles that cause dilation of the pupil)



Cardiac Muscle

- Striated, involuntary muscle
- Found in walls of the heart
- Consists of branching chains of stocky muscle cells. Uni- or binucleate.
- Has sarcomeres & T-tubules
- Cardiac muscle cells are joined by structures called intercalated discs – which consist of desmosomes and gap junctions.



Notice the branching and the intercalated disc, indicated by the blue arrow.