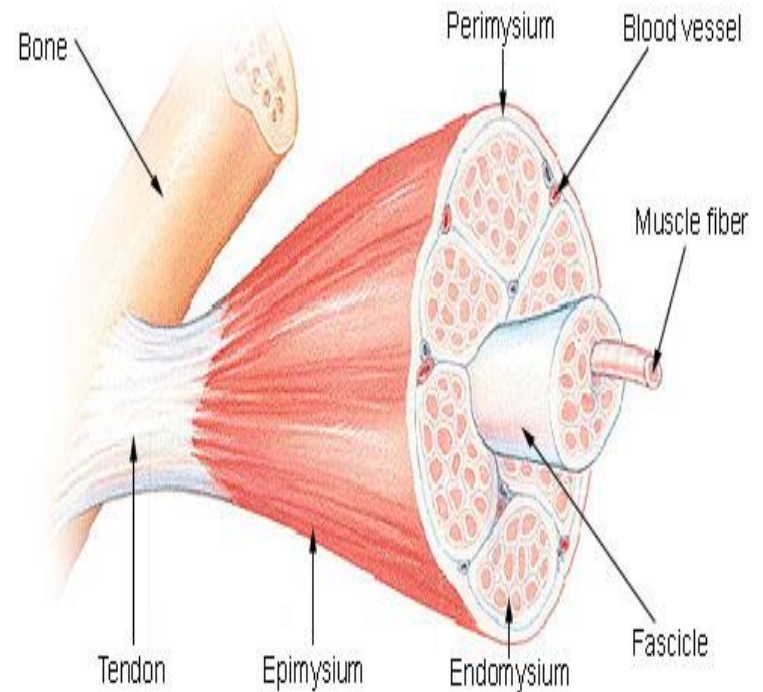


STRUCTURE OF SKELETAL MUSCLES

Muscle Mass

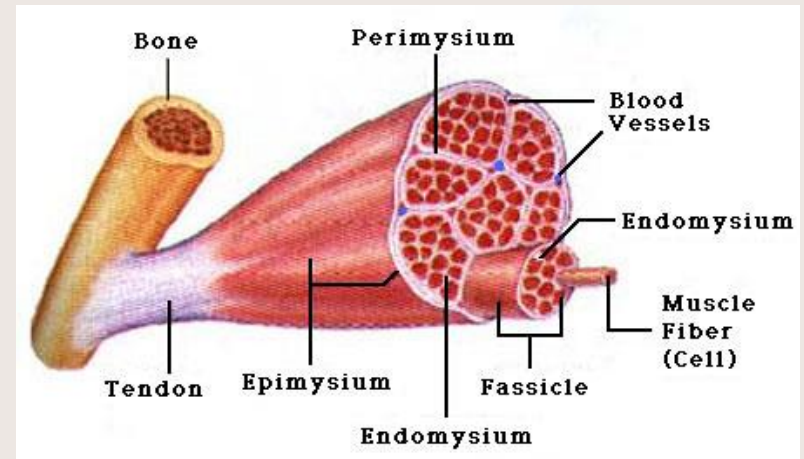
- The muscle cells (muscle fibers) are long and slender in appearance.
- The muscle cells are multinucleated arranged parallel to one another with some connective tissue in between.
- The muscle mass is separated from the neighboring tissue by the thick fibrous tissue layer known as **fascia**.
- Beneath the fascia, the connective tissue covering the muscle is called **epimysium**.

Structure of a Skeletal Muscle



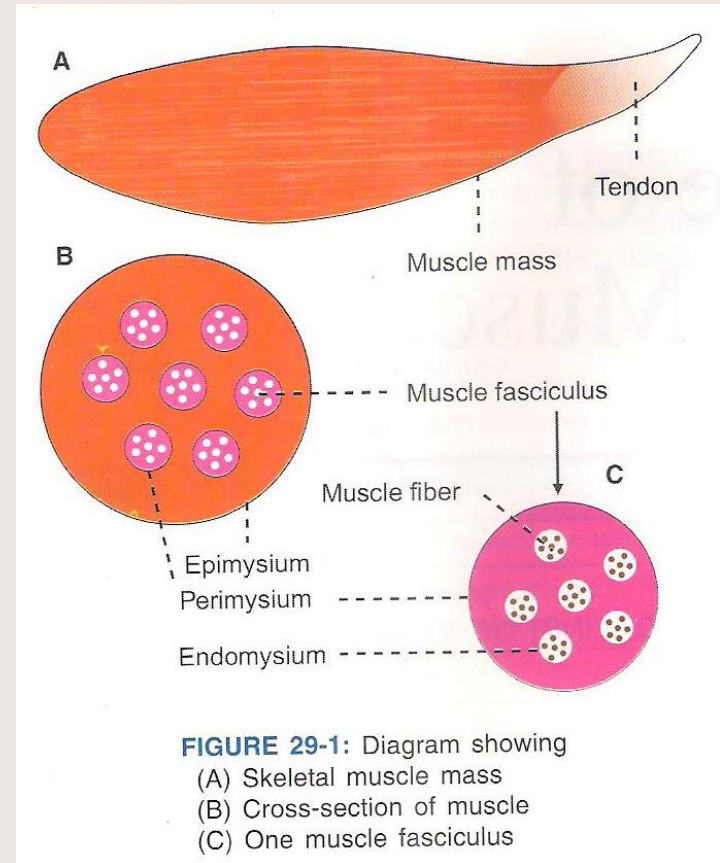
STRUCTURE OF SKELETAL MUSCLES (CONTINUED)

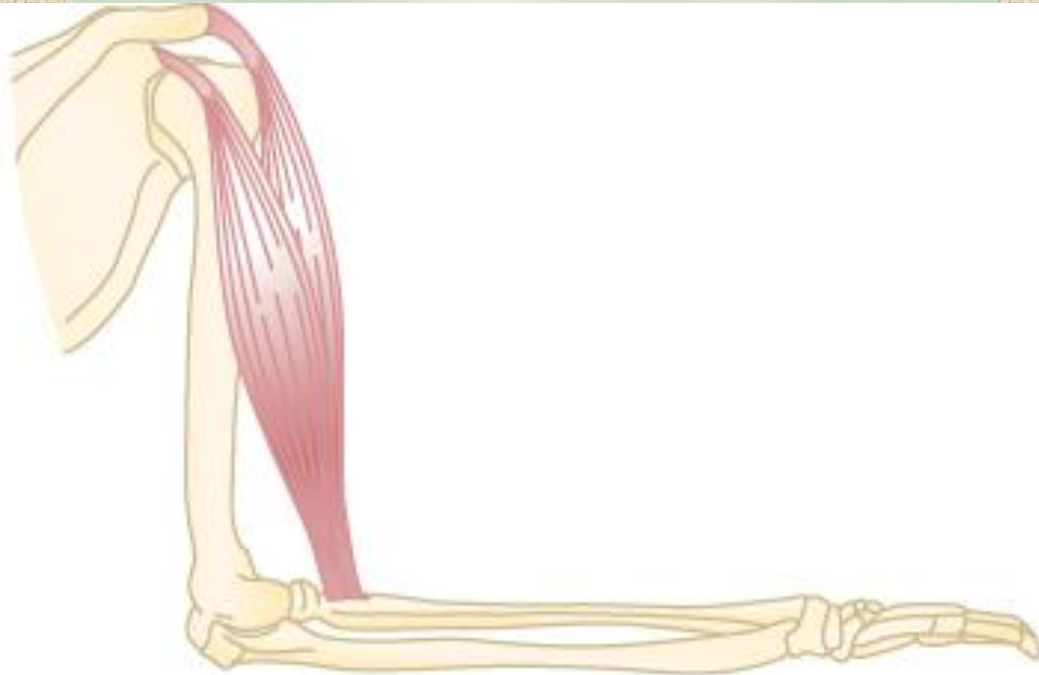
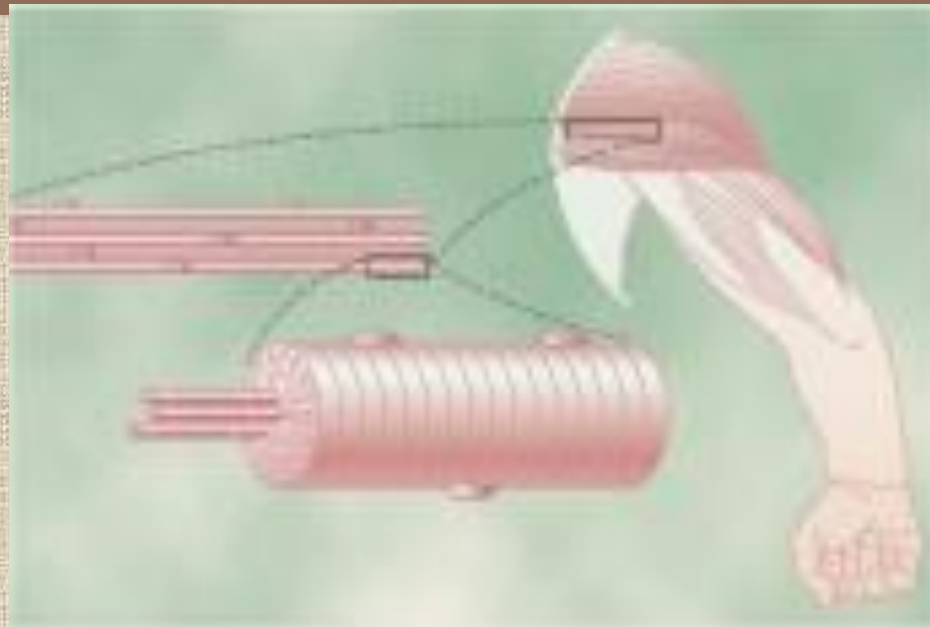
- In the muscle, the muscle fibers are arranged in various groups called the **bundles** or **fasciculi**.
- The Connective tissue sheath that covers each fasciculi is called **Perimysium**.
- Each muscle fiber is covered by the connective tissue layer called the **endomysium**.

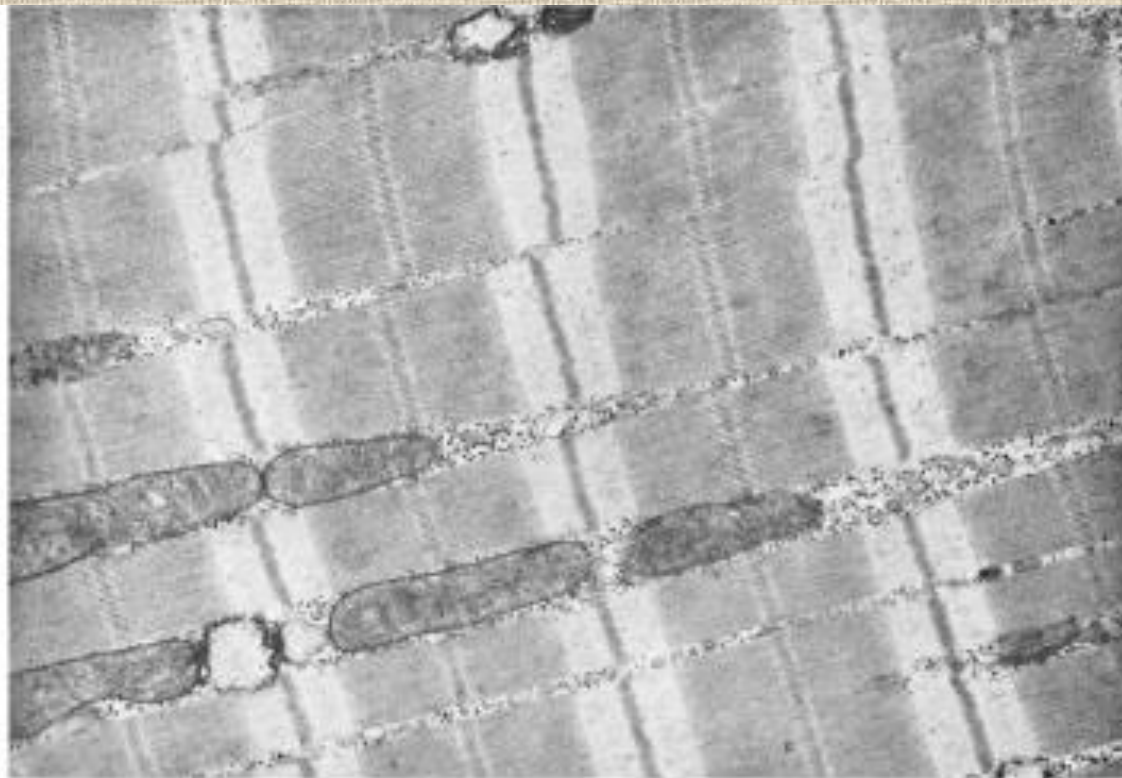


MUSCLE FIBER (CONTINUED)

- The structures embedded within the cytoplasm is nuclei, myofibril, golgi apparatus, mitochondria, sarcoplasmic reticulum, ribosomes, glycogen and occasional lipid droplets. There are one or more nuclei in each muscle fiber.
- In long muscle fibers many nuclei are seen.
- Nuclei are oval or elongated and situated beneath the sarcolemma.



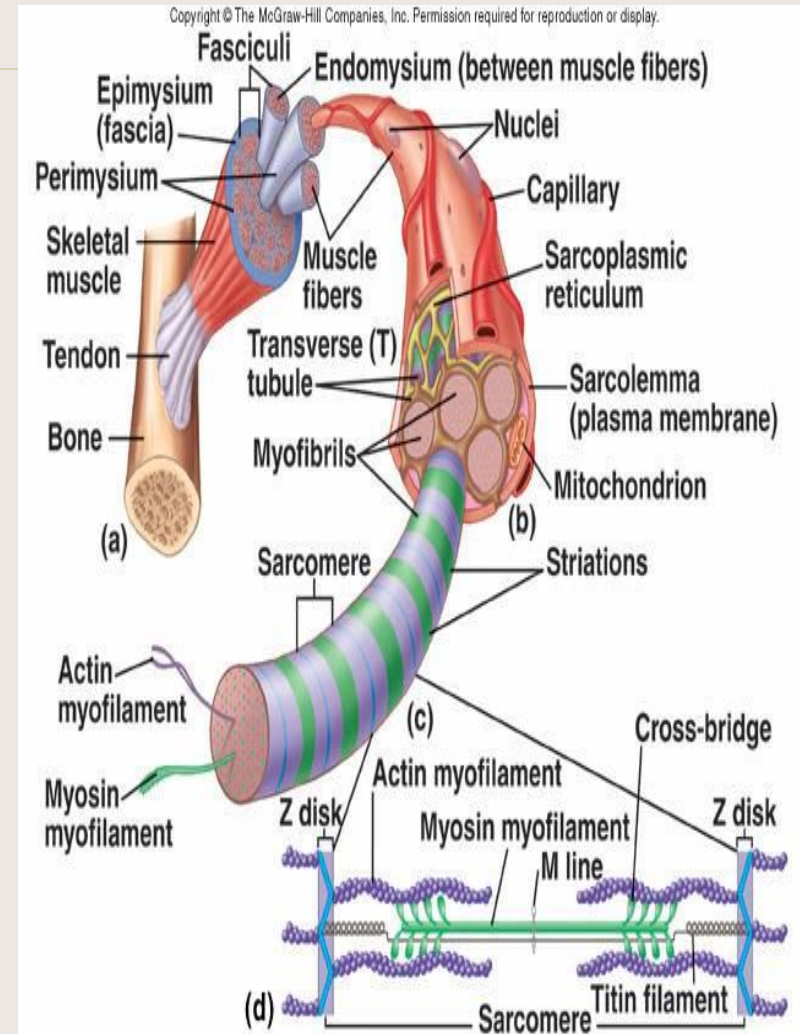




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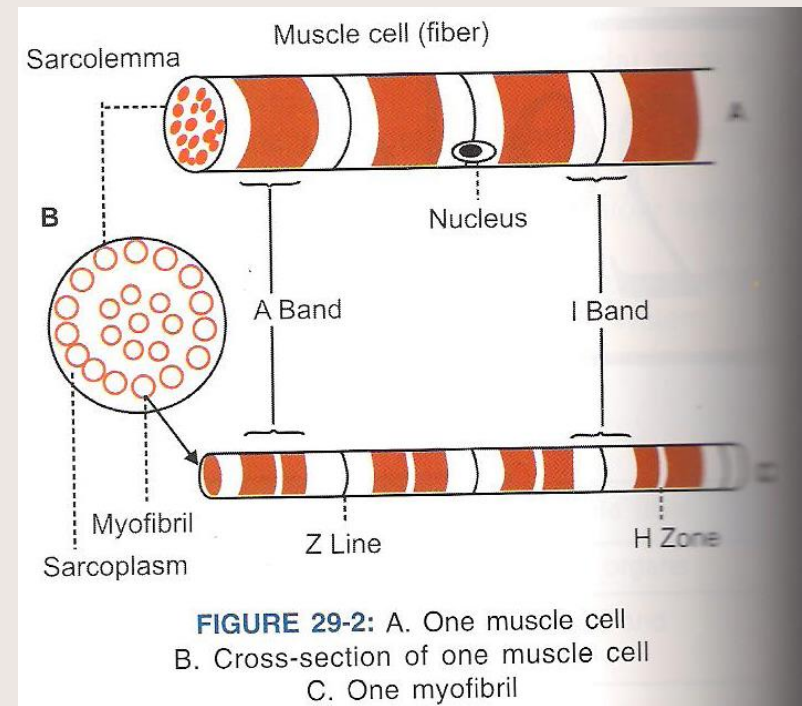
Myofibrils

- Myofibrils are fine parallel filaments present in sarcoplasm of the muscle cell.
- Myofibrils runs through the entire length of the muscle fiber.
- The myofibrils are separated from one another by sarcoplasm.
- Myofibrils are arranged in groups in some muscle fibers. These are called cohneims area. The dia is 0.2 to 2 micron and length varies between 1 to 4 cm depending upon the length of the muscle fiber.



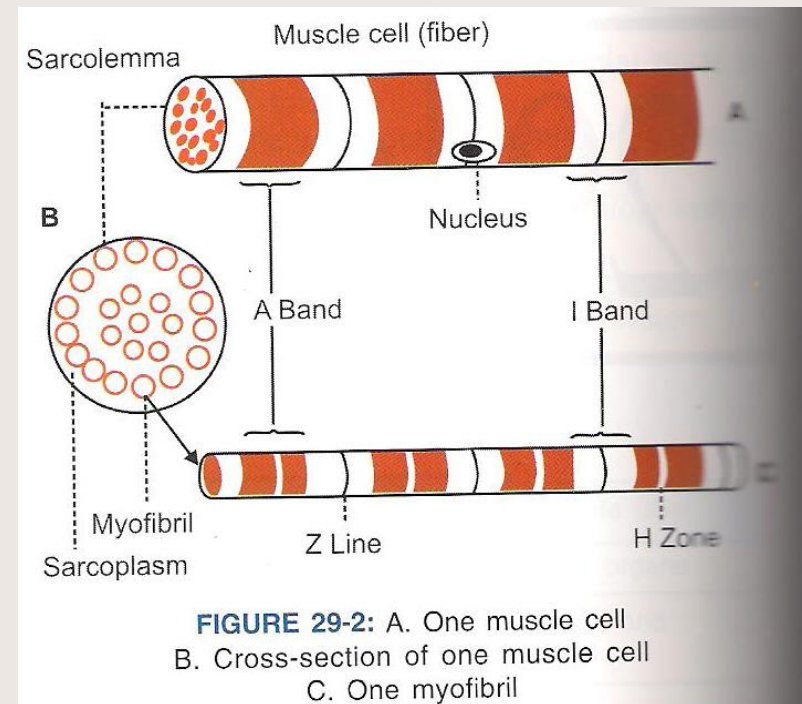
MICRO STRUCTURE OF MYOFIBRIL

- **LIGHT MICROSCOPIC STUDIES SHOW**
 - Myofibril consists of a number of alternating light and dark bands these bands are otherwise called the sections, segments or discs.
 - The light band is called **J band** and the dark band is called **Q disc** (Querscheibe = Cross disc).



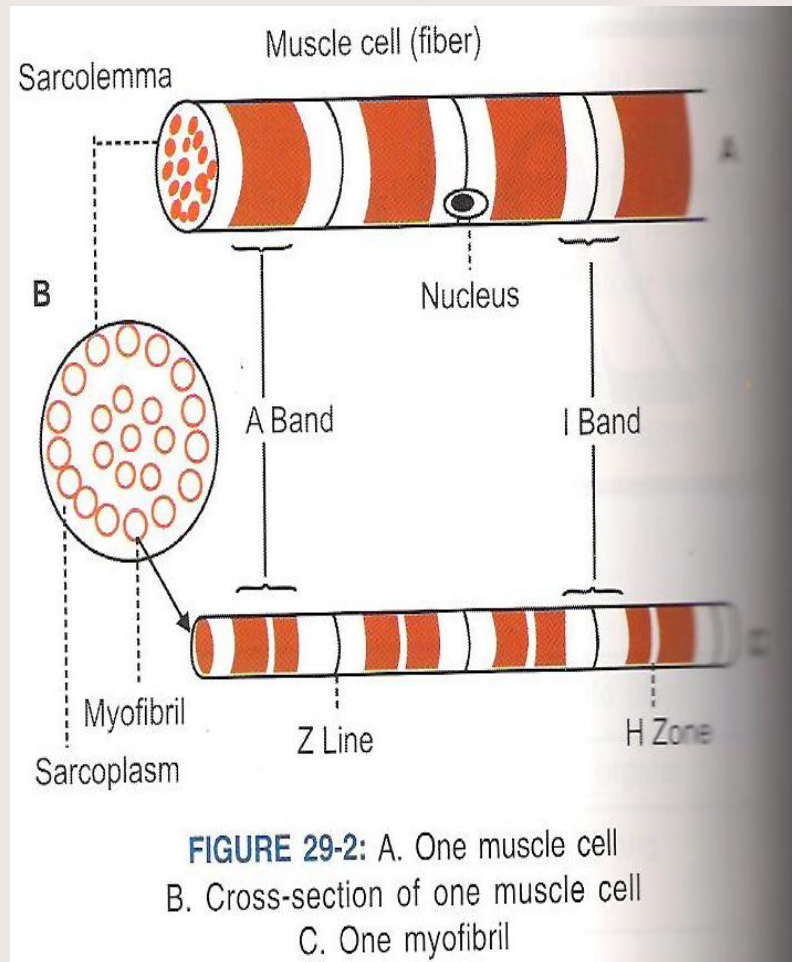
MICRO STRUCTURE OF MYOFIBRIL

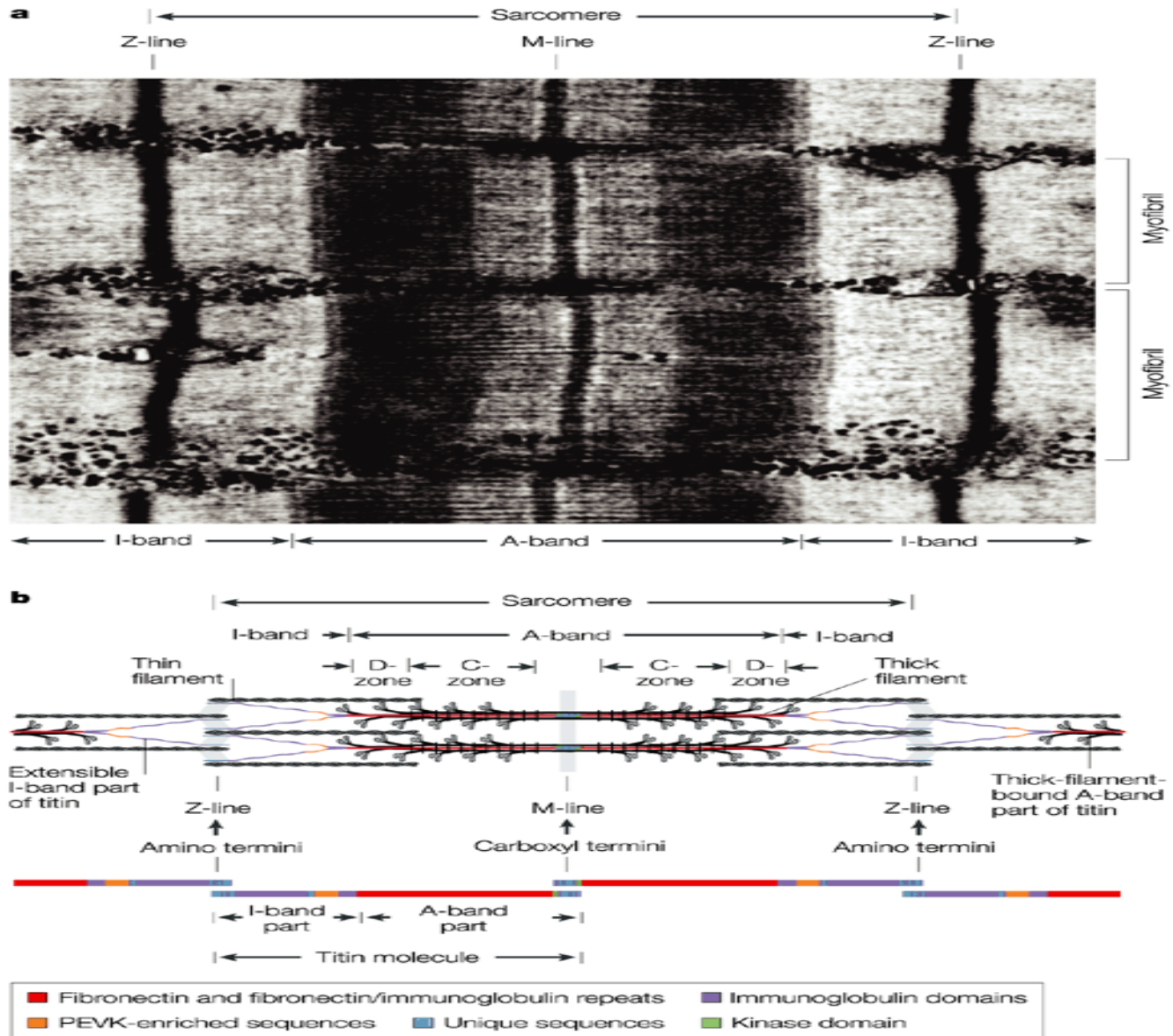
- The dark band is anisotropic if polarized light is passed through the muscle fiber at this area, the light rays are refracted at different directions (An = not; ISO = it; trop = turning) so this band is otherwise called “A” Band.
- The light band is isotropic. The rays of polarized light, passed through the muscle fiber at this area are refracted at the some angle. So this band is called “I” band.



MICRO STRUCTURE OF MYOFIBRIL (CONTINUED)

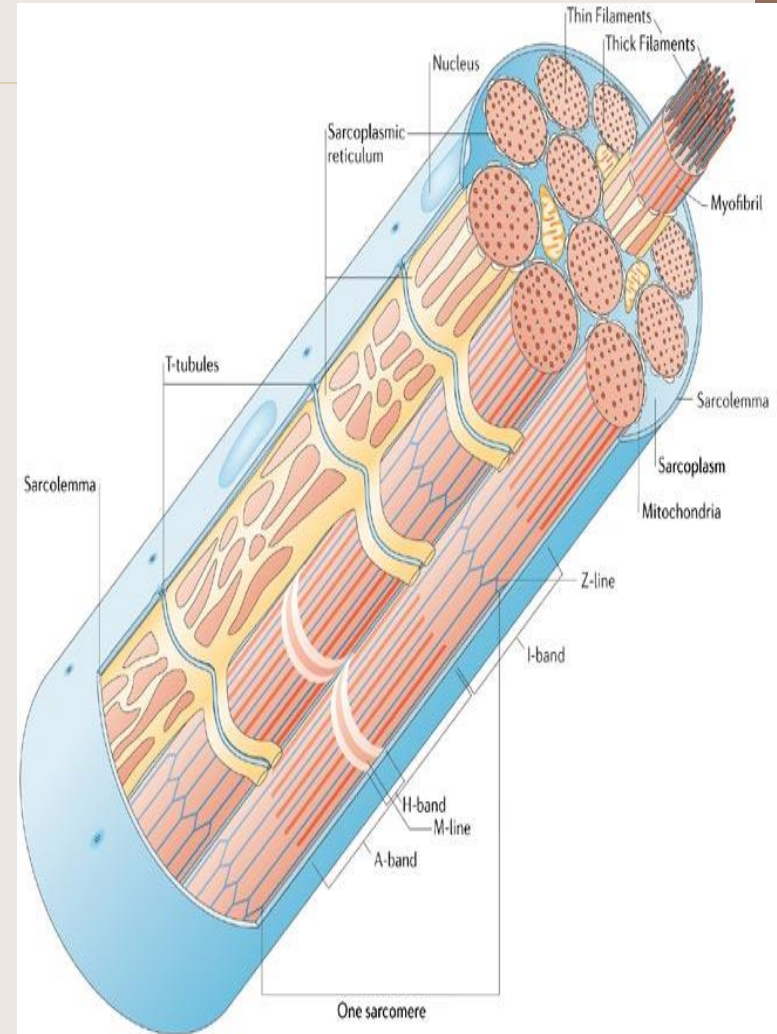
- In an intact muscle fiber “I” band and “A” band of the adjacent myofibrils are placed side by side. This gives the appearance of characteristic cross striations in the muscle fiber.
- A narrow lighter area called “H” zone (H = hell = light in German, H = Henson discover) is seen in the middle of A band.
- The I band is divided into two by an narrow line called Z line (a German Zwischenschelbe = between disc). The portion of myofibril in between two Z lines is called **Sarcomere**.



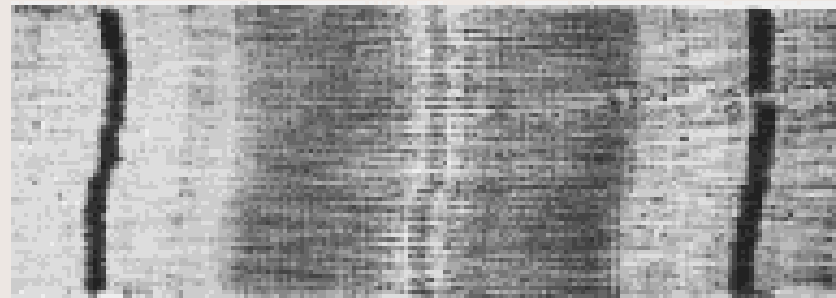


Sarcomere the structural and functional unit of the skeletal muscle.

- Sarcomere extends between the “Z” lines of myofibril.
- Each myofibril contains many sarcomeres arranged in series throughout the length of the myofibril.
- Each myofibril consists of alternate dark A band and light I band.
- In the middle of A band there is a light area called “H” zone.
- In the middle of H zone lies the middle part of myosin filament. This is called M line.
- Similarly the I band is divided into two equal portions by means of a narrow line called Z line.
- The part of myofibril between the two Z lines is the sarcomere.
- In relaxed state, the average length of each sarcomere is 2 to 3 microns.



Sarcomere



Z line

Z line

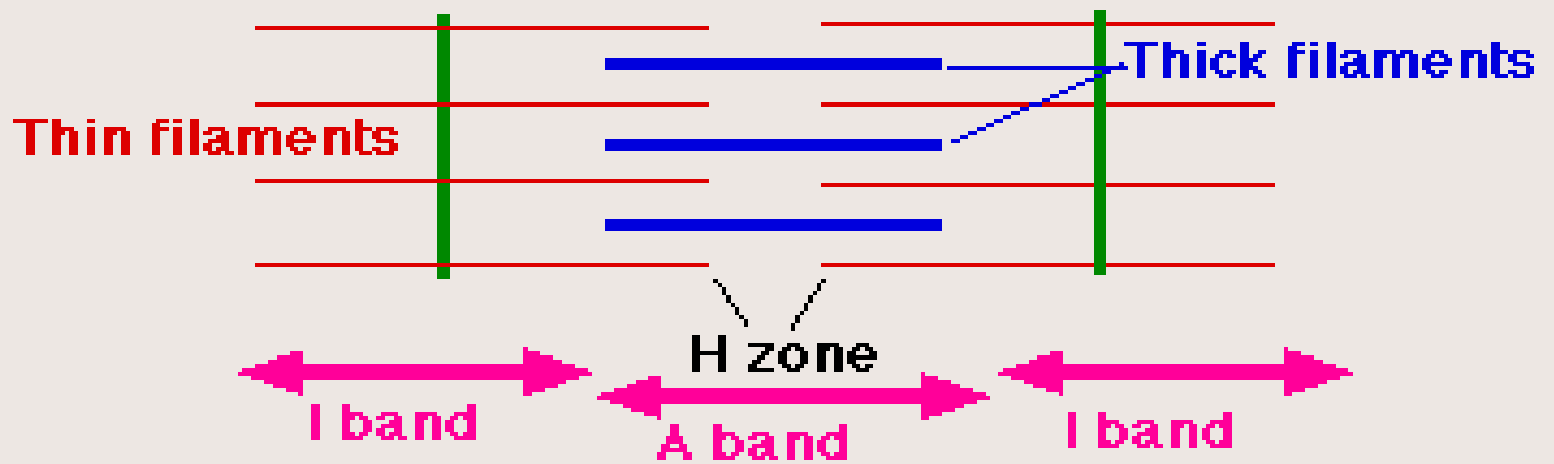
Thin filaments

Thick filaments

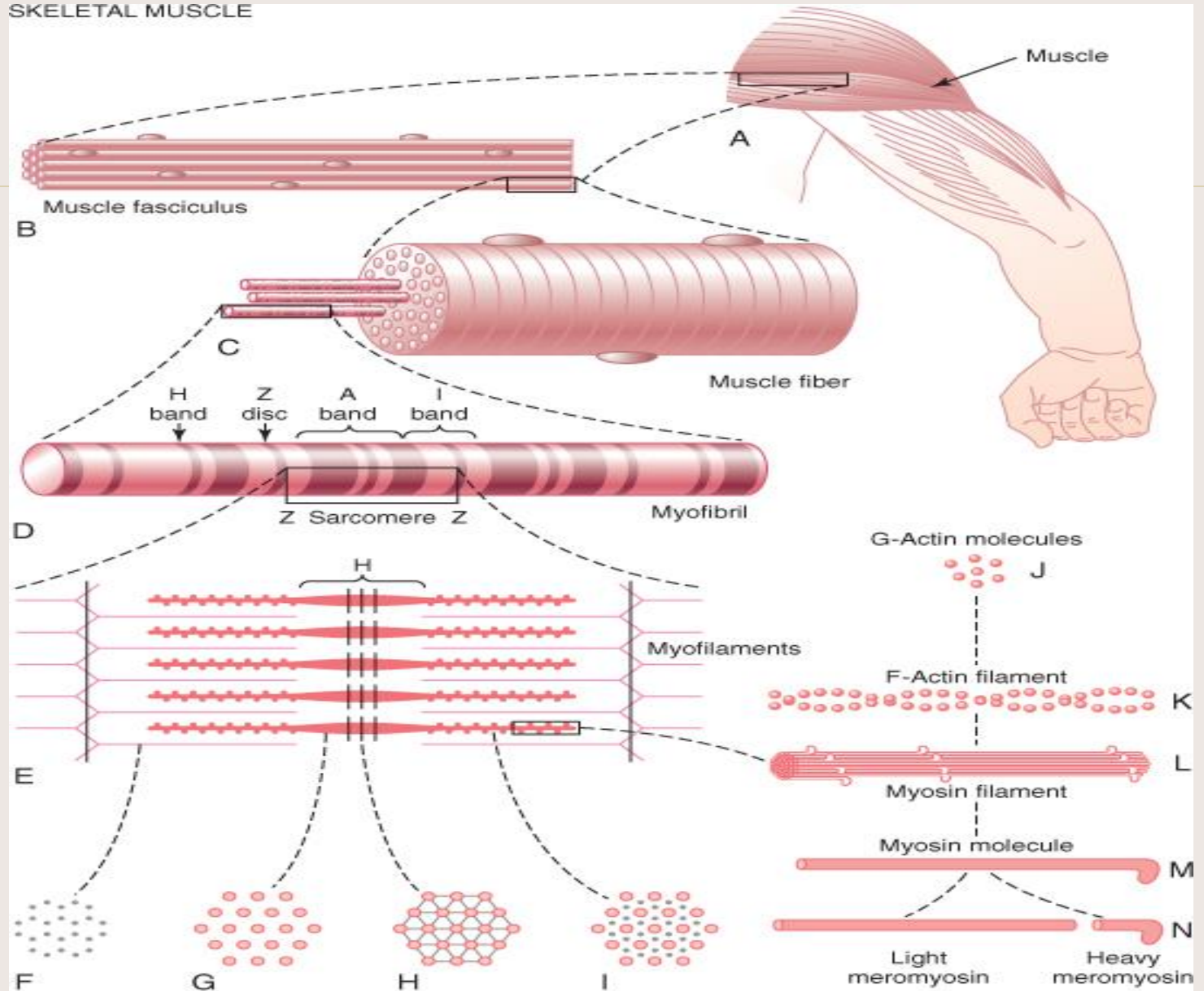
I band

H zone
A band

I band

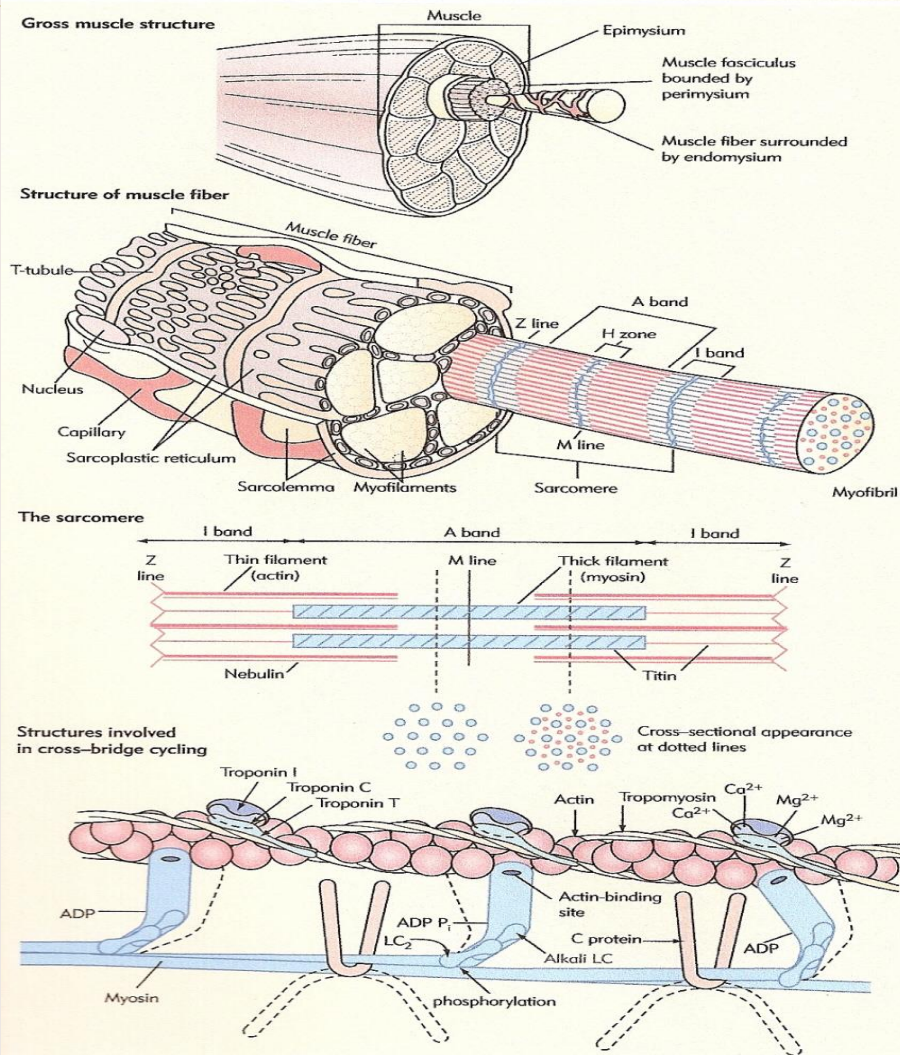


SKELETAL MUSCLE



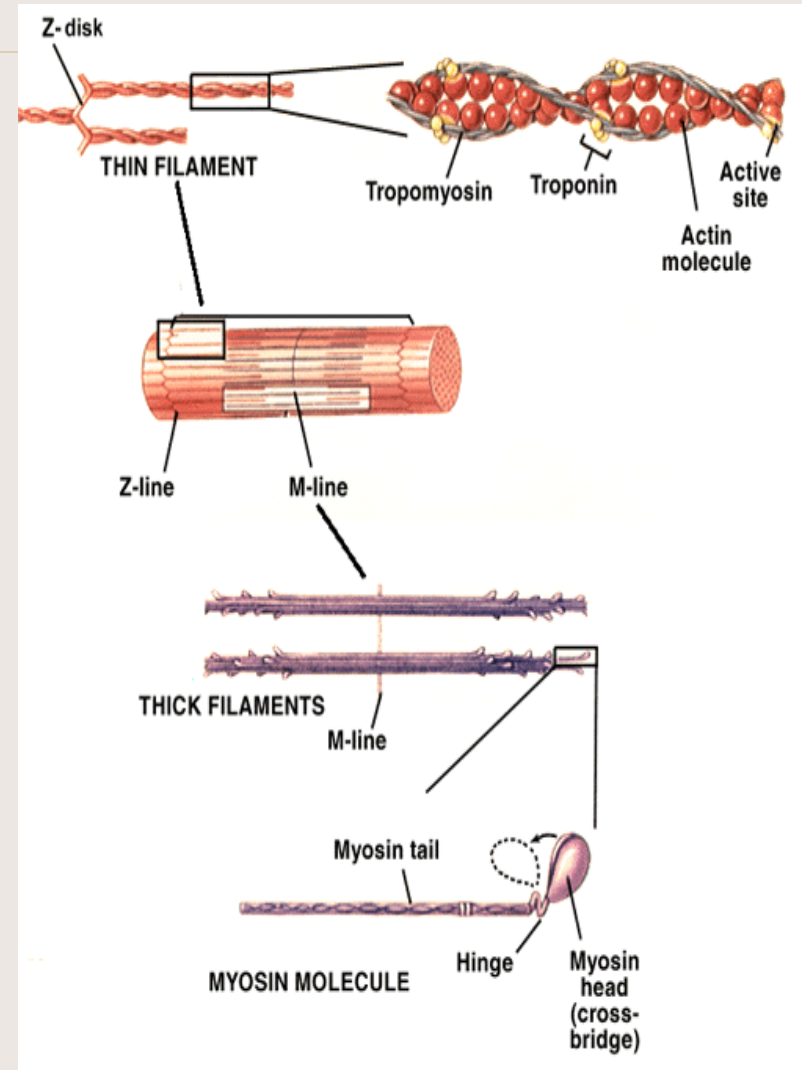
ELECTRON MICROSCOPIC STUDY OF SARCOMERE

- Myofilaments are thread like structures in the sarcomere.
- Two types of myofilaments are actin and myosine filaments.



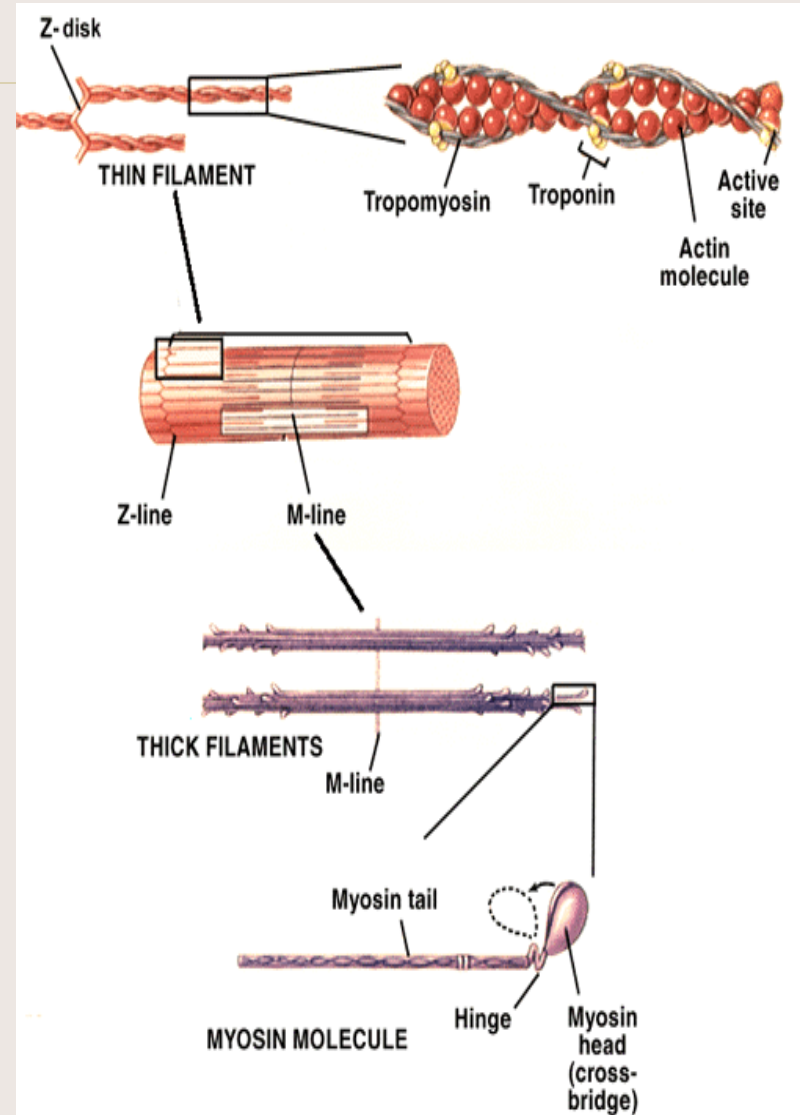
ACTIN FILAMENTS

- Are thin filaments extend from each side of the Z lines, runs across “I” band and enter into A band up to “H” zone.



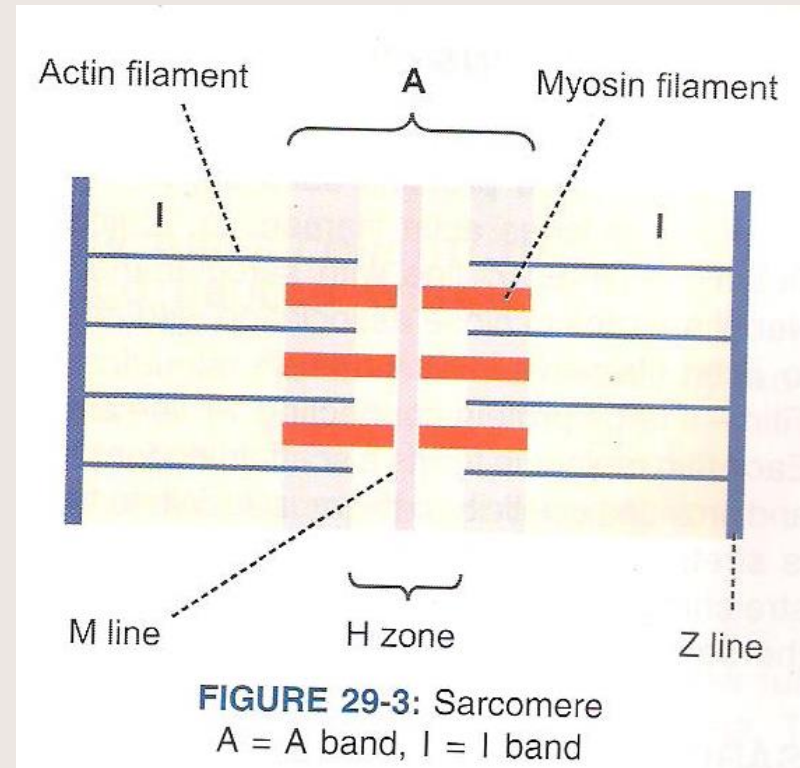
MYOSINE FILAMENTS

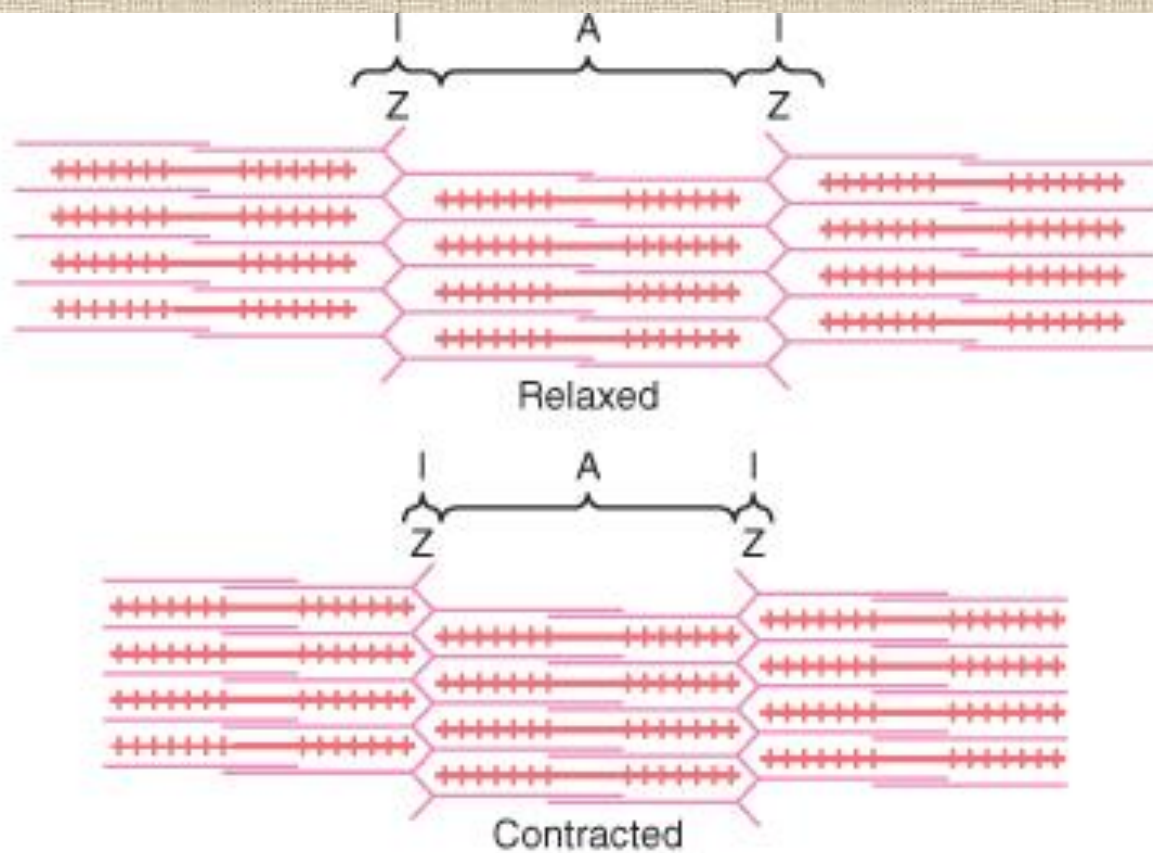
- Are thick filaments are situated in A band.
- From the myosine filaments there are some lateral processes (Projections) or cross bridges.
- Bridges have enlarged structures called myosine heads at their tips.
- The myosine heads attach themselves to actin filaments
- These heads pull the actin filaments during contraction of the muscles by means of a mechanism called sliding mechanism or ratchet mechanism.



CHANGES DURING CONTRACTION OF MUSCLE

- Contraction of the muscle, the actin filaments glide down between the myosin filaments towards the center of “H” zone and approach the corresponding actin filaments from the next “Z” line.
- The “Z” lines also approach the ends of myosine filaments, so that the “H” zone and “I” bands are shortened during contraction of the muscle.
- During the relaxation of the muscle the actin filaments and “Z” lines come back to the original position.





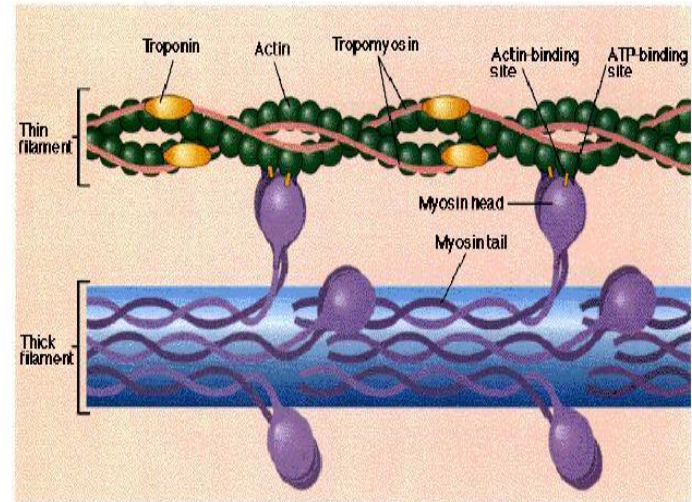
CONTRACTILE ELEMENTS (PROTEINS) OF MUSCLE

- Myosine filaments are formed by myosine molecules.
- The actin filaments are formed by three types of proteins called actin, tropomyosin and troponin.
- These four proteins together constitute the muscle protein or contractile elements of the muscle.

MYOSIN MOLECULE

- Myosin filaments consists of about 200 myosine molecules, each having molecular weight of about 480,000.
- Myosine molecule consist of two heavy chains and four light chains.
- Two heavy chains twist around each other to form a double helix which forms the tail portion of myosine molecule.
- At one end, the two chains remains twisted around one another whereas at the other end, both the chains turn away in opposite directions and form the globular head portion.

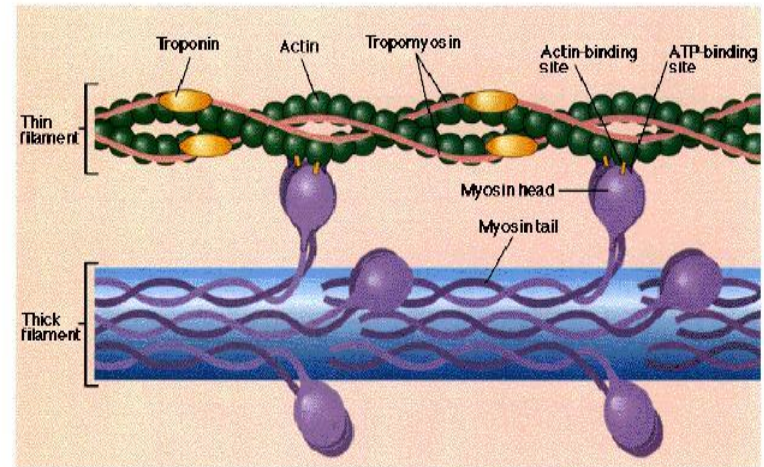
Myosin & the Thick Filament



MYOSIN MOLECULE

- Each part of head are attached to two light chains.
- Thus there are four light chains in each myosine molecule each myosine head has two attachment site.
- The four light chains are also part of myosin heads,two to each head.These light chains help control the function of the head during muscle contraction.

Myosin & the Thick Filament



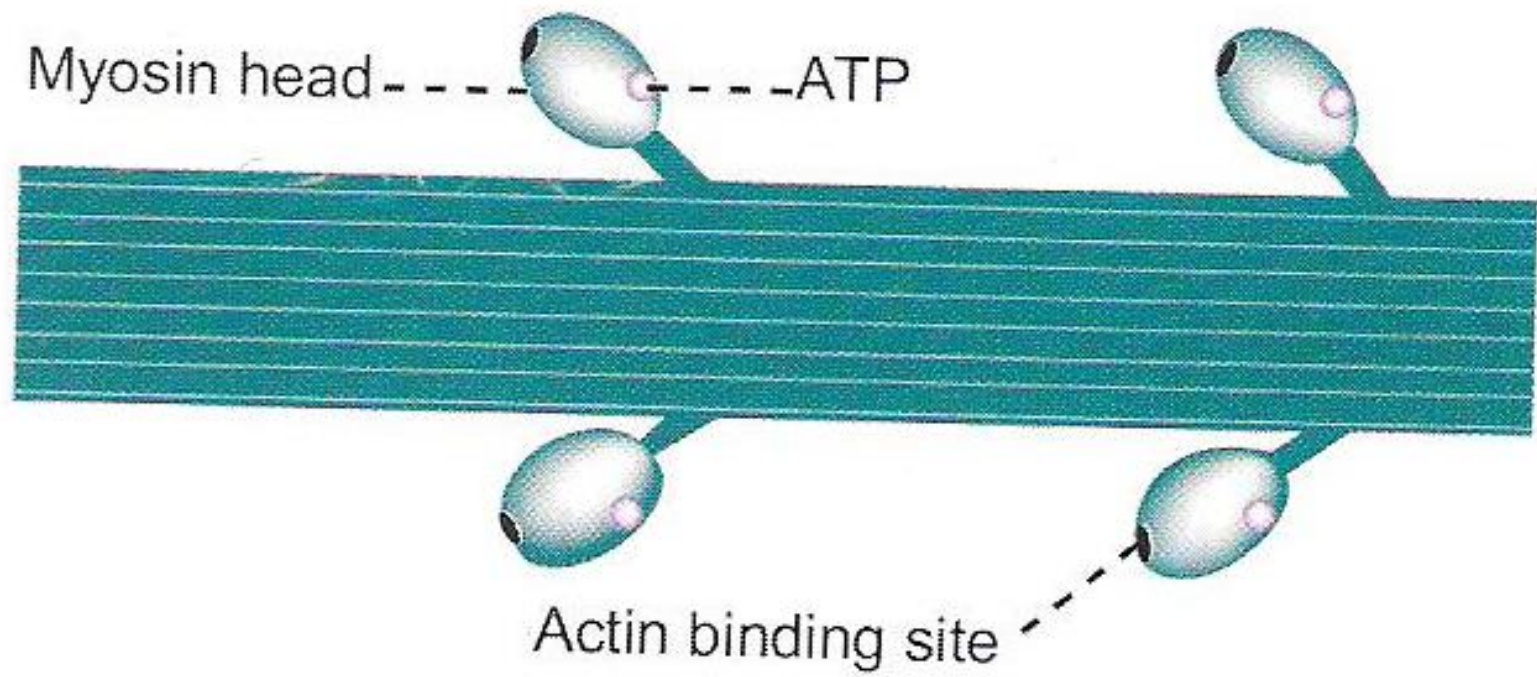
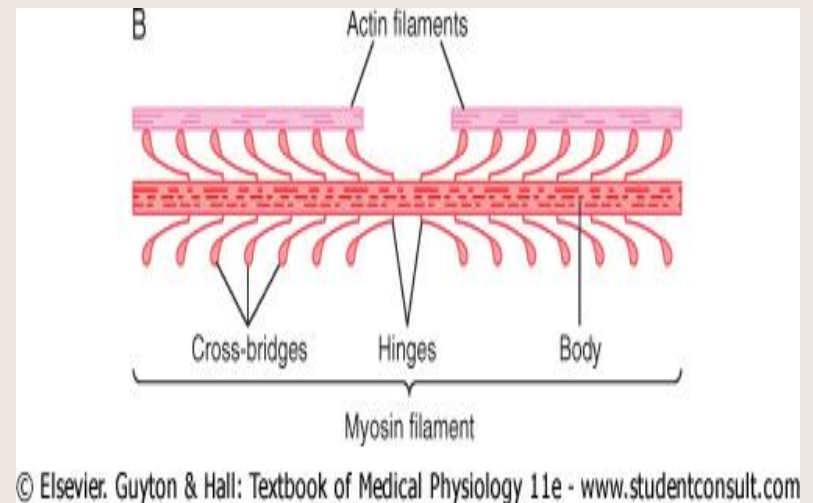
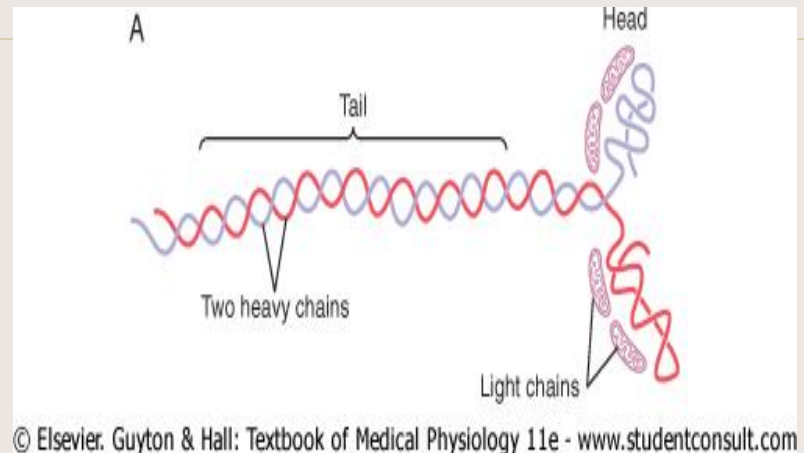


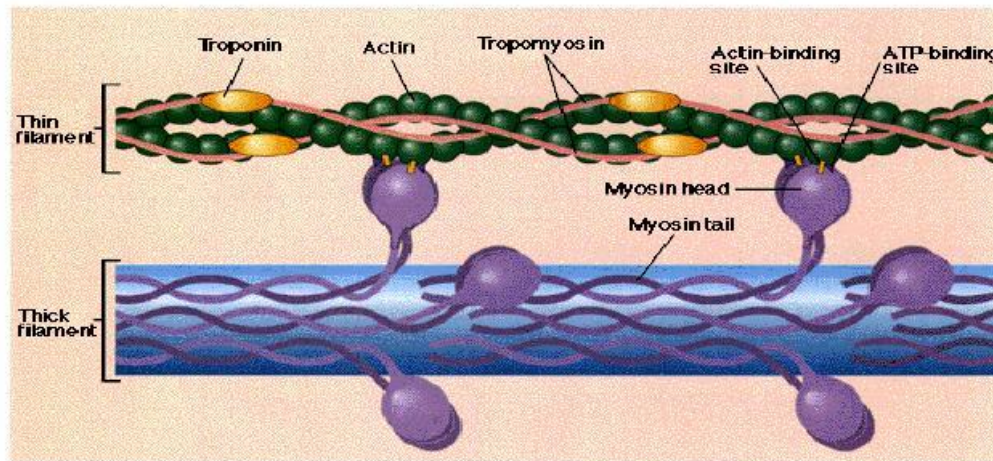
FIGURE 29-4: Diagram showing myosin filament

MYOSINE FILAMENT

- Is made up of 200 or more individual myosine molecules.
- The central portion are bundled together to form the body of the filament, from here the tails of myosin molecules are displaying, while many heads of the molecules hang outward to the sides of the body.
- Protruding arms and heads together are called cross bridges
- Each cross bridge is flexible at two points called hinges, one where the arm leaves the body of the myosine filament and the other where the head attaches to the arm.

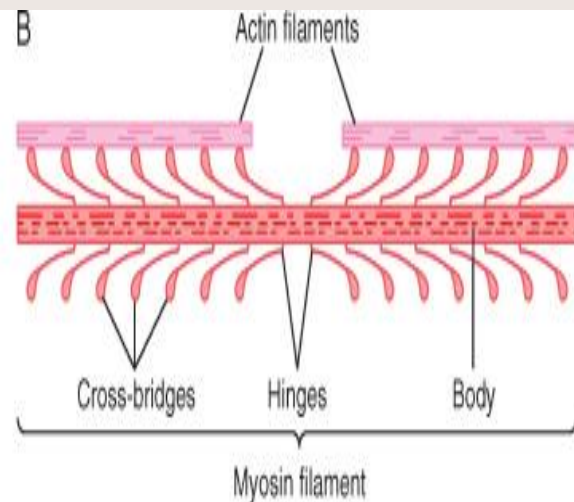
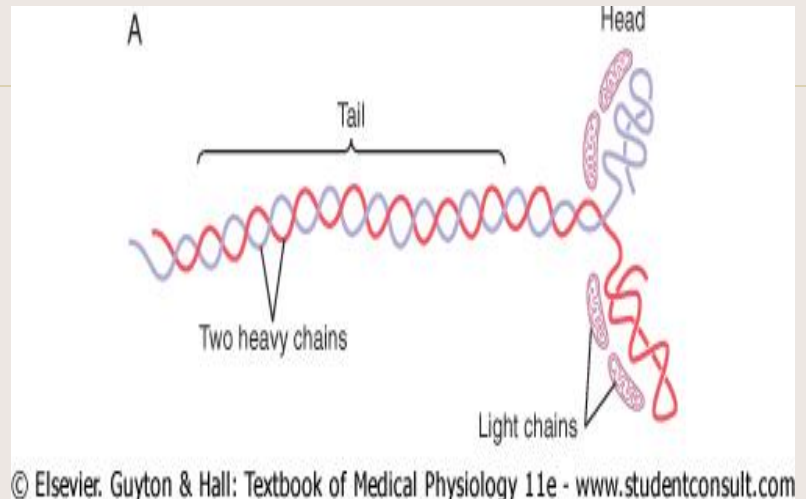


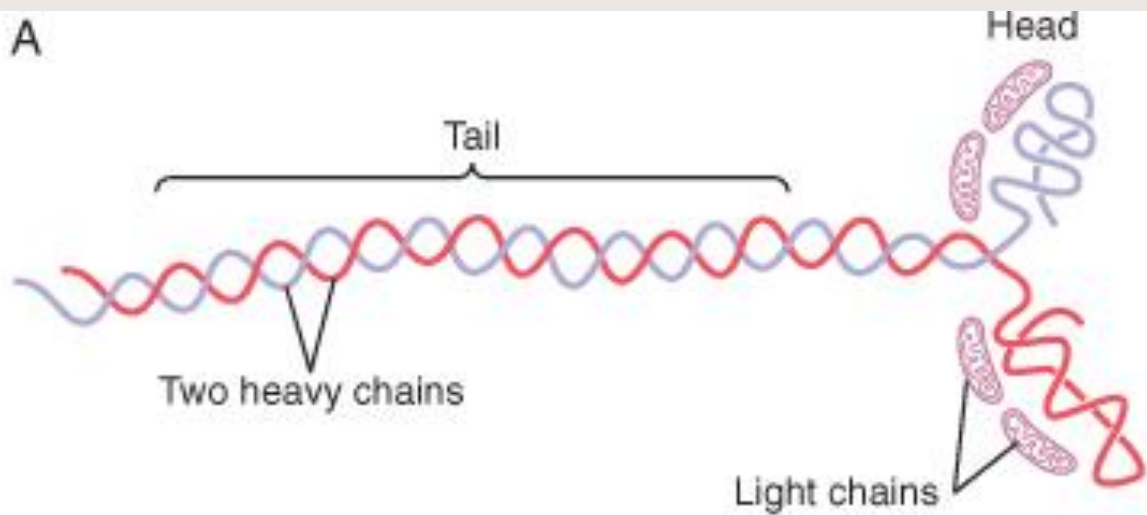
Myosin & the Thick Filament



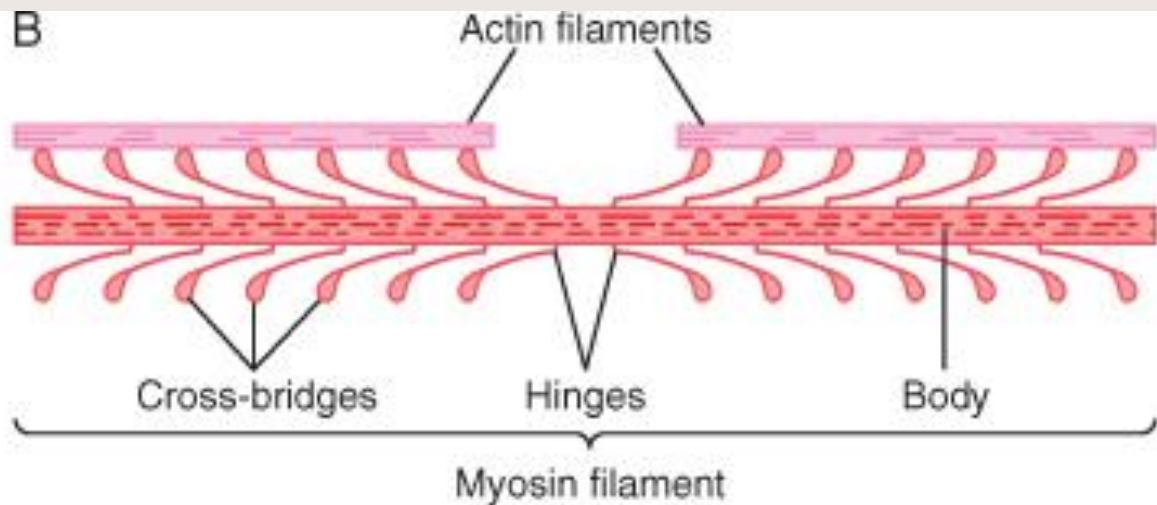
MYOSINE FILAMENT (Continued)

- The hinged arms allow the heads either to be extended far outward from the body of the myosine filament or to be brought close to the body.
- The hinged heads in turn participate in the actual contraction process.
- The total length of each myosine filament is uniform, almost exactly 1.6 micrometer.
- There is no cross bridge heads in the center of the myosine filament for a distance of about 0.2 micrometer because the hinged arms extend away from the center.
- Myosine filament itself is twisted so that successive pairs of cross bridges is axially displaced from the previous pair by 120 degrees.





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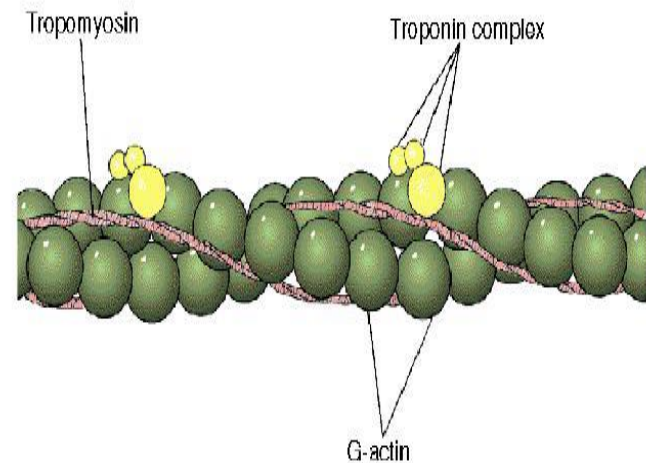
ATPASE ACTIVITY OF THE MYOSINE HEAD

- Myosine head is essential for muscle contraction is that its function as an ATPase enzyme.
- This property allows the head to cleave ATP and to use the energy derived from the ATP's high energy phosphate bond to energize the contraction process.

Actin filament also called Factin

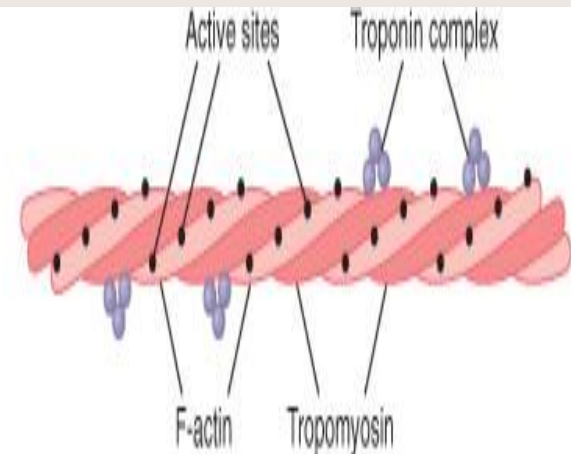
- Actin filament is composed of three protein component; Actin, troponin, and tropomyosine.
- It is 1 micrometer long.
- The bases of the actin filaments are inserted strongly into the Z disc; the ends of the filaments protrude in both direction to lie in the spaces between the myosine molecule.
- There are about 300 to 400 actin molecules in each actin filament.
- The actin molecule in the actin filament also are arranged in the form of double helix.

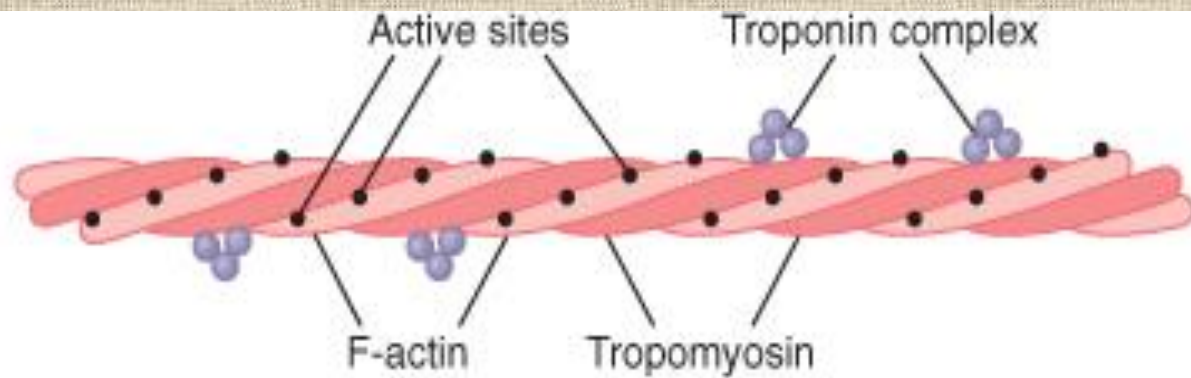
Thin Filament Structure



Actin filament

- Each strand of the double F-actin helix is composed of polymerized G-actin molecule, each having a molecular weight of about 42000.
- There are about 13 of these molecules in each revolution of each strand of helix.
- Attached to each one of the G-actin molecule is one molecule of ADP.
- Each F actin molecule has an active site (ADP molecules) to which myosine head is attached to cause muscle contraction.
- The active sites on the two F-actin strands of the double helix are staggered, giving one active site on the overall actin filament about every 2.7nanometer.





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summary

- ACTIN - when actin combines with MYOSIN HEAD the ATP associated with the head breaks down into ADP. This reaction released energy that causes the MYOSIN HEAD to SWIVEL.
- TROPOMYOSIN - In a relaxed muscle, the MYOSIN HEADS of the thick myofilament lie against TROPOMYOSIN molecules of the thin myofilament. As long as the MYOSIN HEADS remain in contact with TROPOMYOSIN nothing happens (i.e., a muscle remains relaxed).
- TROPONIN - Troponin molecules have binding sites for calcium ions. When a calcium ion fills this site it causes a change in the shape and position of TROPONIN. And, when TROPONIN shifts, it pulls the TROPOMYOSIN to which it is attached. When TROPOMYOSIN is moved, the MYOSIN HEAD that was touching the tropomyosin now comes in contact with an underlying ACTIN molecule.

TROPOMYOSINE

- There are about 40 to 60 tropomyosine molecule situated along the double helix strand of actin filament.
- Each molecule of tropomyosin has a molecular weight of 70,000 and a length of 40 nanometer.
- It is a long, thin molecule 40nm in length.
- In relaxed condition of the muscle, the tropomyosine molecules cover all the active sites of F actin molecules as they are wrapped spirally around the sides of the F-actin helix.
- In the relaxed state, the tropomyosine molecules lie on the top of the active sites of the actin strands, so that attraction cannot occur between the actin and myosine filaments to cause contraction.

TROPONIN

- Troponin has molecular weight of 18000-35000.
- Troponin muscle protein is formed by three subunits.
 1. Troponin I = attached to F actin, it inhibits actin myosin interaction.
 2. Troponin T = attached to strongly to tropomyosin
 3. Troponin C = attached to calcium on structures constituting the sarco-tubular system.

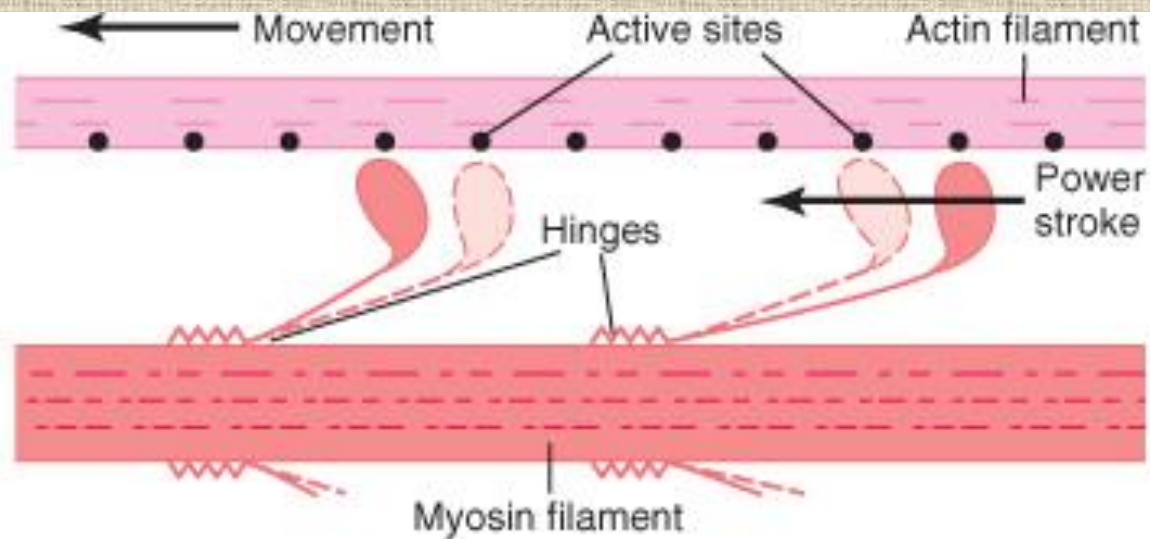
Sarco-tubular system is formed mainly of two types of structures.

1. T tubules
2. L Tubules or sarcoplasmic reticulum.

Attached along the sides of the tropomyosin molecules are still other protein molecules called troponin.

These are actually complexes of three loosely bound protein subunits, each of which plays a specific role in controlling muscle contraction.

The strong affinity of the troponin for calcium ions is believed to initiate the contraction process.



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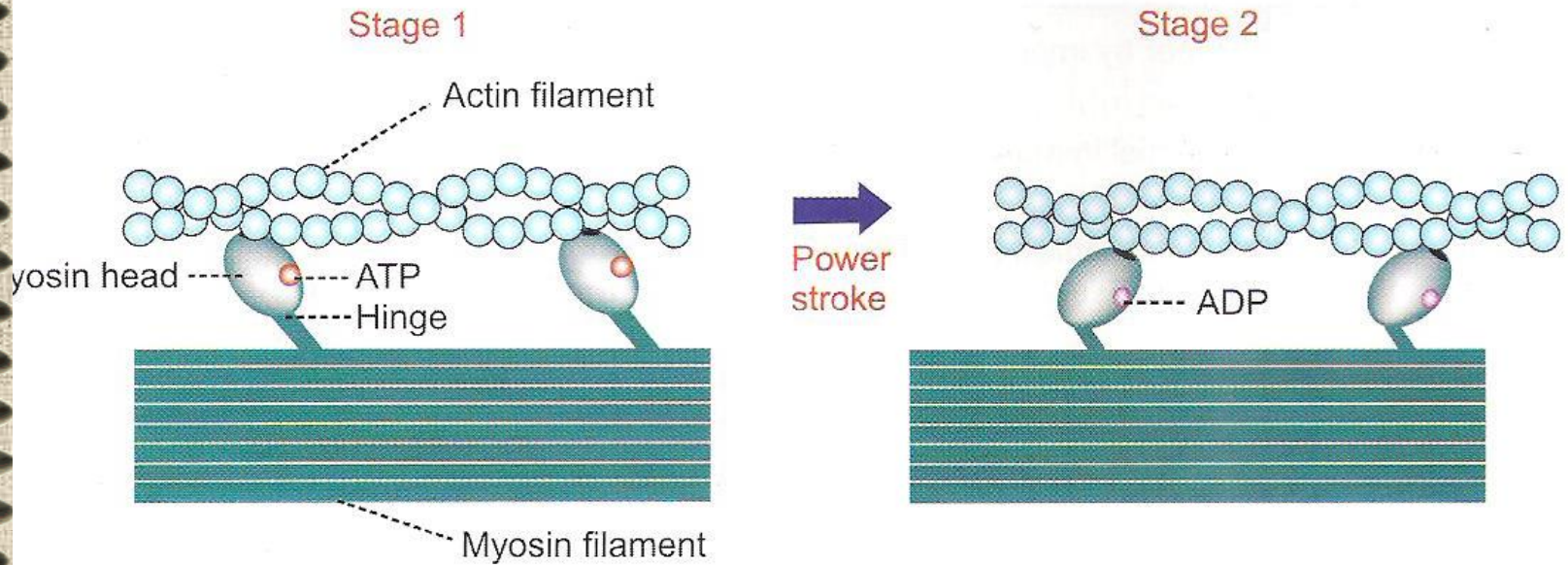


FIGURE 31-4: Diagram showing power stroke by myosin head. Stage 1: Myosin head binds with actin; Stage 2: Tilting of myosin head (power stroke) drags the actin filament

INTERACTION OF MYOSIN, ACTIN FILAMENTS, AND CALCIUM IONS TO CAUSE CONTRACTION

- A pure actin filament without the presence of troponin tropomyosine complex binds instantly and strongly with the heads of the myosine molecules in the presence of Mg ions and ATP, both of which are abundant in the myofibril
- If the troponin-tropomyosin complex is added to the actin filament, this binding does not take place
- Active sites on the normal actin filament of the relaxed muscle are inhibited or physically covered by the troponin tropomyosin complex.

INTERACTION OF MYOSIN, ACTIN FILAMENTS, AND CALCIUM IONS TO CAUSE CONTRACTION

- Consequently, the sites cannot attach to the heads of the myosine filaments to cause contraction.
- Before contraction can take place, the inhibitory effect of the troponin tropomyosin complex must itself be inhibited, especially in the presence of large amount of calcium ions.
- When Ca ions combine with troponin C each molecule of which can bind strongly with up to four Ca ions
- The troponin complex supposedly undergoes a conformational changes that in some way tugs on the tropomyosine molecule and supposedly moves it deeper into the grooves between the two actin strands.

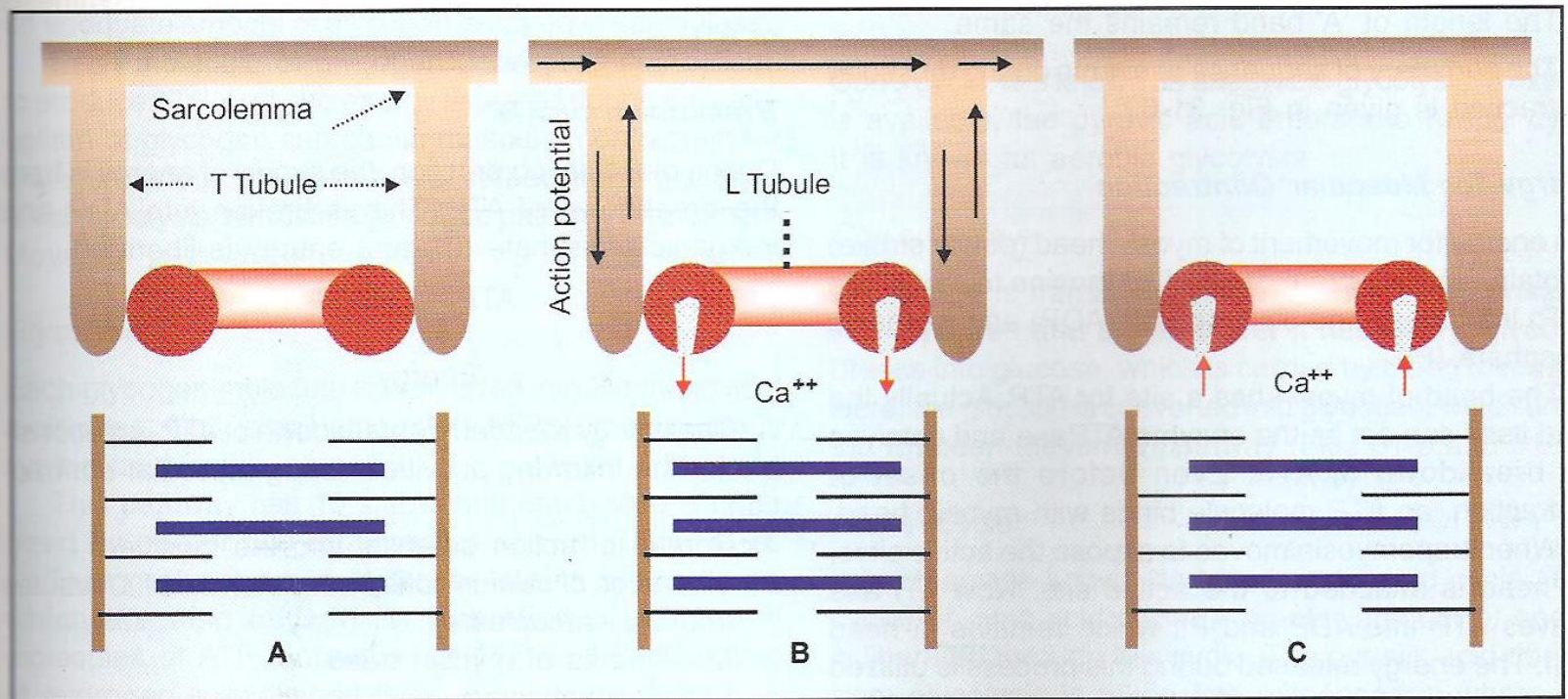


FIGURE 31-5: Changes in sarcomere during contraction. A = Sarcomere in resting condition. B = Contraction. Depolarization causes release of calcium ions from cisternae. Calcium ions bind with troponin resulting in shortening of sarcomere. Length of sarcomere, H zone, and I band is shortened. No change in the length of A band. C = Relaxation. During repolarization, calcium ions go back to cisternae resulting in relaxation of sarcomere

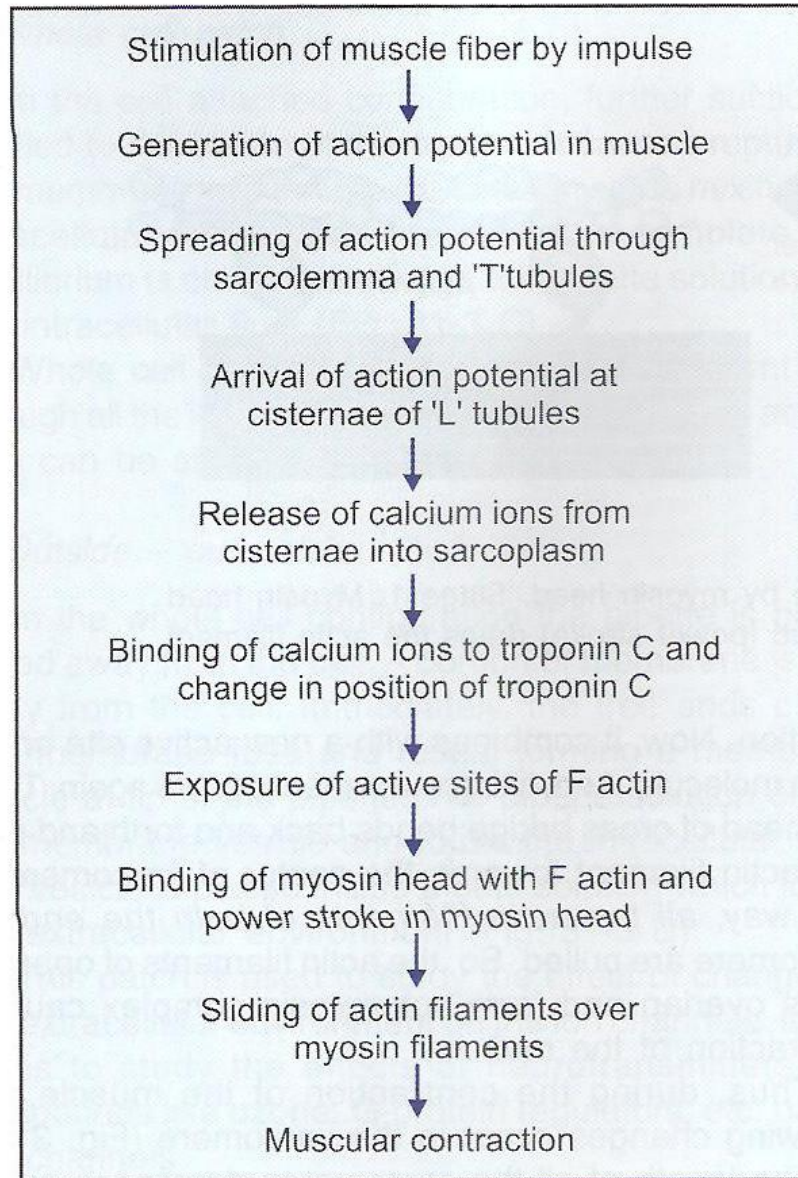


FIGURE 31-6: Sequence of events during muscular contraction

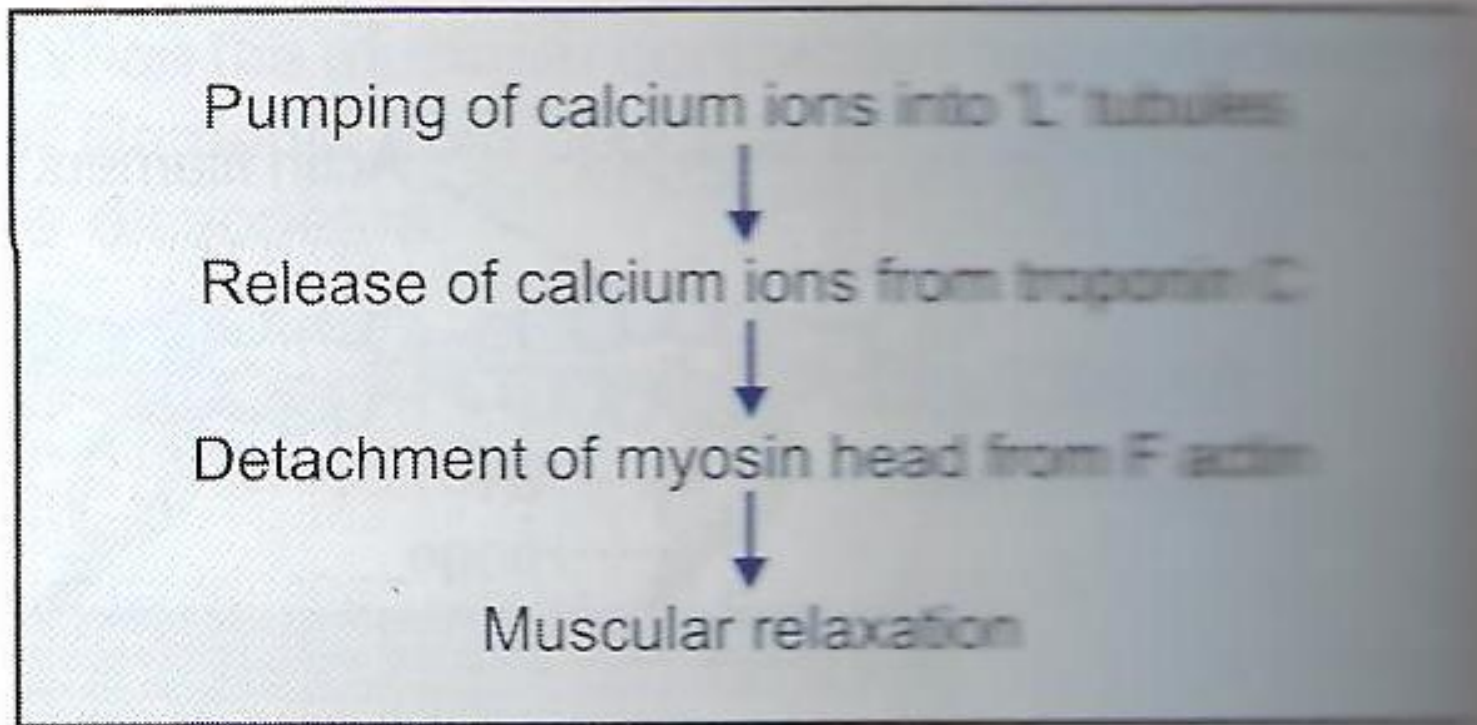


FIGURE 31-7: Sequence of events during muscular relaxation

INTERACTION OF MYOSIN, ACTIN FILAMENTS, AND CALCIUM IONS TO CAUSE CONTRACTION

- This uncovers the active sites of the actin, thus allowing these to attract the myosine heads and cause contraction to proceed. (hypothetical mechanism).
- Actin filaments become activated by Ca ions, the heads of the cross bridges from the myosine filaments become attracted to the active sites of the actin filament, and this, in some way, causes contraction to occur.

WALK ALONG MECHANISM OR RATCHET THEORY FOR CONTRACTION OF THE MUSCLE

- The heads of the two cross bridges attraction to and disengaging from active sites of an actin filament.
- When the head attracts to an active site, this attachment simultaneously causes profoundly changes in the intra molecular force between the head and arm of the cross bridges.

WALK ALONG MECHANISM FOR CONTRACTION OF THE MUSCLE

- The new alignment of forces causes the head to tilt towards the arm and to drag the actin filament along with it. This tilt of head is called the power stroke.
- Immediately after tilting the head automatically breaks away from the active site.

WALK ALONG MECHANISM FOR CONTRACTION OF THE MUSCLE

- Next, the head returns to its normal perpendicular direction.
- In this position it combines with a new active site farther down along the action filament, then the head tilts again to cause a new power stroke, and the actin filament moves another step.

WALK ALONG MECHANISM FOR CONTRACTION OF THE MUSCLE

- Thus the heads of the cross bridges bend back and forth and step by step walk along actin filament, pulling the ends of the actin filaments towards the centre of the myosin filaments.
- Each one of the cross bridges is believed to operate independently of all others, each attaching pulling in a continuous repeated cycle.

WALK ALONG MECHANISM FOR CONTRACTION OF THE MUSCLE

- Therefore the greater the number of cross bridges in contact with the actin filament at any time, the greater theoretically is the force of contraction.

ATP AS THE SOURCE OF ENERGY FOR CONTRACTION-CHEMICAL EVENTS IN THE MOTION OF THE MYOSINE HEADS

- When a muscle contracts, work is performed and energy is required.
- Large amount of ATPase cleaved to form ADP during the contraction process ,the greater the amount of work performed by the muscle ,the greater the amount of ATP that is cleaved, which is called the Fenn effect.

Summary of Muscle contraction

- 1 - Because skeletal muscle is voluntary muscle, contraction requires a nervous impulse. So, step 1 in contraction is when the impulse is transferred from a neuron to the SARCOLEMMA of a muscle cell.
- 2 - The impulse travels along the SARCOLEMMA and down the T-TUBULES. From the T-TUBULES, the impulse passes to the SARCOPLASMIC RETICULUM.
- 3 - As the impulse travels along the Sarcoplasmic Reticulum (SR), the calcium gates in the membrane of the SR open. As a result, CALCIUM diffuses out of the SR and among the myofilaments.
- 4 - Calcium fills the binding sites in the TROPONIN molecules. As noted previously, this alters the shape and position of the TROPONIN which in turn causes movement of the attached TROPOMYOSIN molecule

- 5 - Movement of TROPOMYOSIN permits the MYOSIN HEAD to contact ACTIN.
- 6 - Contact with ACTIN causes the MYOSIN HEAD to swivel.
- 7 - During the swivel, the MYOSIN HEAD is firmly attached to ACTIN. So, when the HEAD swivels it pulls the ACTIN (and, therefore, the entire thin myofilament) forward. (Obviously, one MYOSIN HEAD cannot pull the entire thin myofilament. Many MYOSIN HEADS are swivelling simultaneously, or nearly so, and their collective efforts are enough to pull the entire thin myofilament).

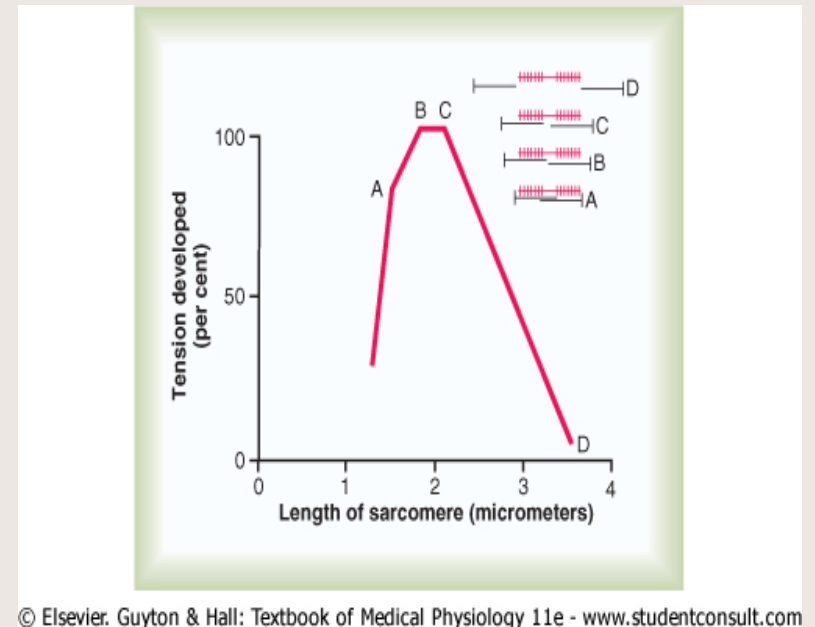
- 8 - At the end of the swivel, ATP fits into the binding site on the cross-bridge & this breaks the bond between the cross-bridge (myosin) and actin. The MYOSIN HEAD then swivels back. As it swivels back, the ATP breaks down to ADP & P and the cross-bridge again binds to an actin molecule.
- 9 - As a result, the HEAD is once again bound firmly to ACTIN. However, because the HEAD was not attached to actin when it swivelled back, the HEAD will bind to a different ACTIN molecule (i.e., one further back on the thin myofilament). Once the HEAD is attached to ACTIN, the cross-bridge again swivels, SO STEP 7 IS REPEATED.

- As long as calcium is present (attached to TROPONIN), steps 7 through 9 will continue. And, as they do, the thin myofilament is being "pulled" by the MYOSIN HEADS of the thick myofilament. Thus, the THICK & THIN myofilaments are actually sliding past each other. As this occurs, the distance between the Z-lines of the sarcomere decreases. As sarcomeres get shorter, the of course, gets shorter. And, obviously, the muscle fibers (and entire muscle) get shorter.myofibril,

- Skeletal muscle relaxes when the nervous impulse stops.
- No impulse means that the membrane of the **SARCOPLASMIC RETICULUM** is no longer permeable to calcium (i.e., no impulse means that the **CALCIUM GATES** close). So, calcium no longer diffuses out. The **CALCIUM PUMP** in the membrane will now transport the calcium back into the **SR**. As this occurs, calcium ions leave the binding sites on the **TROPONIN MOLECULES**.
- Without calcium, **TROPONIN** returns to its original shape and position as does the attached **TROPOMYOSIN**.
- This means that **TROPOMYOSIN** is now back in position, in contact with the **MYOSIN HEAD**. So, the **MYOSIN** head is no longer in contact with **ACTIN** and, therefore, the muscle stops contracting (i.e., relaxes).

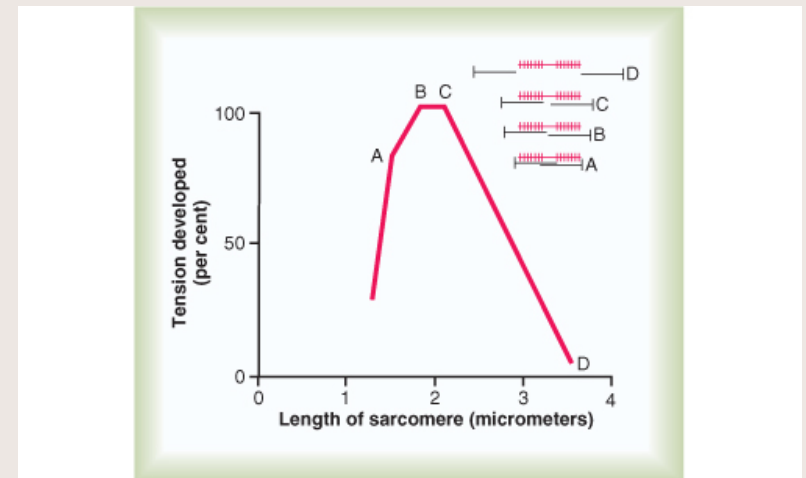
EFFECT OF ACTIN AND MYOSINE FILAMENTS OVERLAP ON TENSION DEVELOPED BY THE CONTRACTING MUSCLE

- The figure shows the effect of sarcomere length and of myosine actin filament overlap on the active tension developed by the contracting muscle fiber.



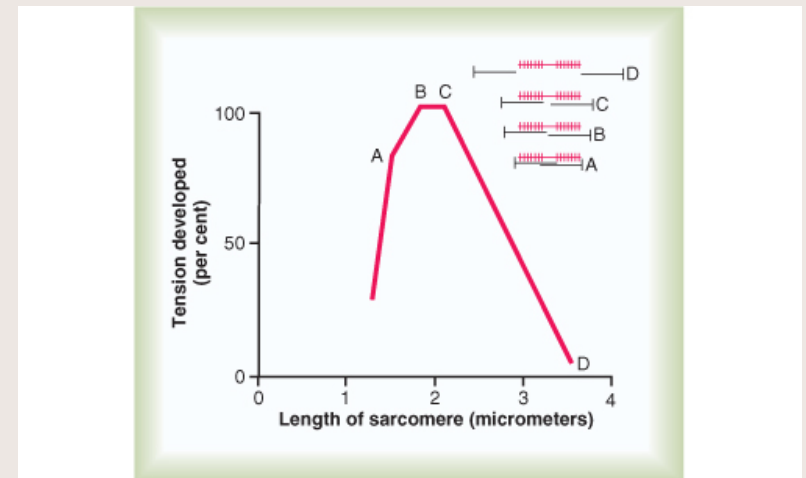
EFFECT OF ACTIN AND MYOSINE FILAMENTS OVERLAP ON TENSION DEVELOPED BY THE CONTRACTING MUSCLE

- At point D, on the diagram, the actin filament has pulled all the way out to the end of the myosine filament with no actin myosine overlap.
- At this point the tension developed by the activated muscle is zero



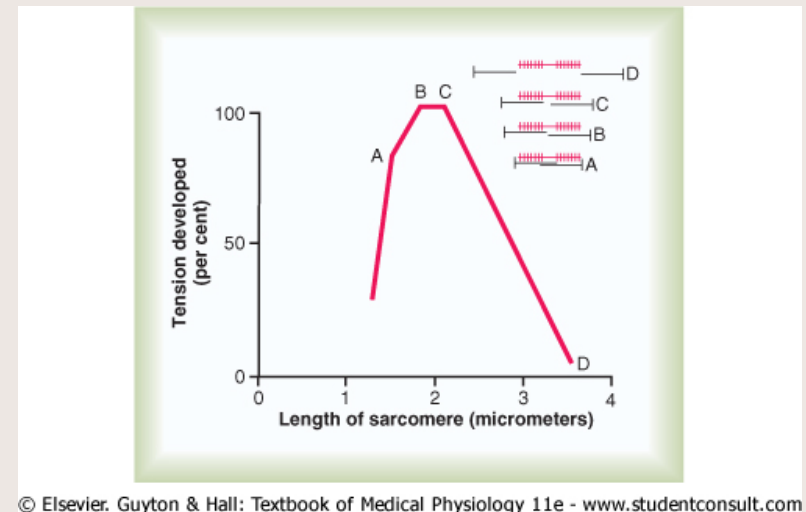
EFFECT OF ACTIN AND MYOSINE FILAMENTS OVERLAP ON TENSION DEVELOPED BY THE CONTRACTING MUSCLE

- Then as the sarcomere shortens the actin filament begins to overlap the myosine filament, the tension increases progressively until the sarcomere length decreases to about 2.2micrometer.
- At this point,the actin filament has already overlapped all the cross bridges of the myosine filament but has not yet reached the centre of the myosine filament.



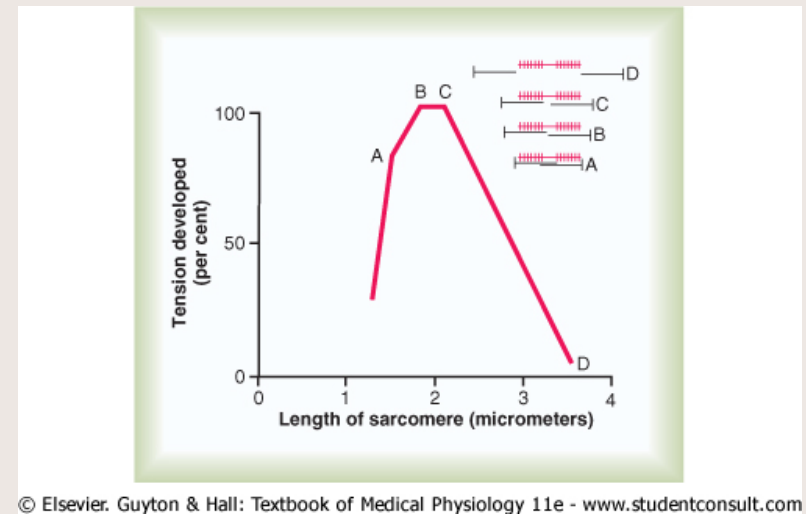
EFFECT OF ACTIN AND MYOSINE FILAMENTS OVERLAP ON TENSION DEVELOPED BY THE CONTRACTING MUSCLE

- On further shortening the sarcomere length of about 2.0 micrometer.
- At this point, the ends of the two actin filaments begin to overlap each other, in addition to overlapping the myosine filaments



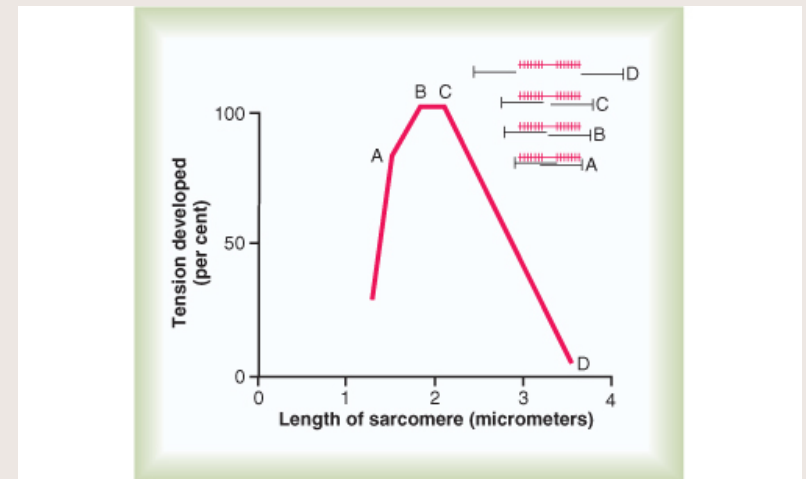
EFFECT OF ACTIN AND MYOSINE FILAMENTS OVERLAP ON TENSION DEVELOPED BY THE CONTRACTING MUSCLE

- As the sarcomere length falls 2 micrometer down to about 1.65 micrometer at point A, the strength of contraction decreases.
- At this point the two Z discs of the sarcomere abut the ends of the myosine filaments



EFFECT OF ACTIN AND MYOSINE FILAMENTS OVERLAP ON TENSION DEVELOPED BY THE CONTRACTING MUSCLE

- This diagram demonstrates the maximum contraction occurs when there is maximum overlap between the actin filaments and the cross bridges of the myosine filaments, and it supports the idea **that the greater the number of cross bridges pulling the actin filament, the greater the strength of contraction.**



Tension and sarcomere length relationship

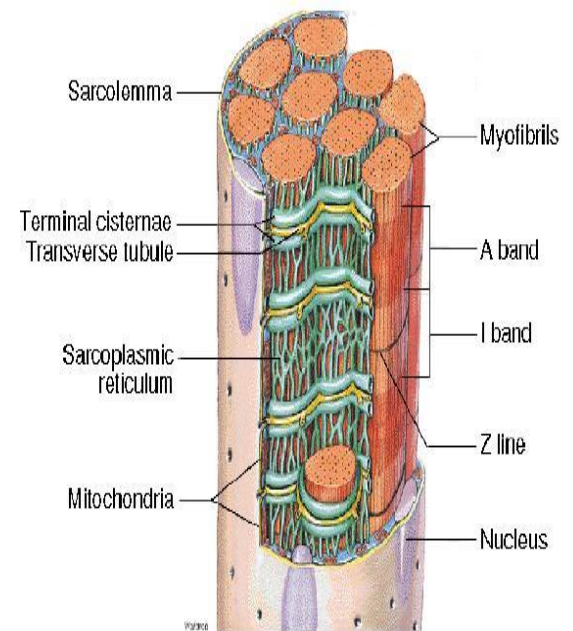
The tension decline at sarcomere length less than 1.65micrometer due to several factors

- The overlapping sets of thin filaments from opposite ends of the sarcomere may interfere with the cross bridges ability to bind and exert force.
- At very short length, the Z lines collide with the ends of the relatively rigid thick filaments, causing an internal resistance to sarcomere shortening.

T TUBULES

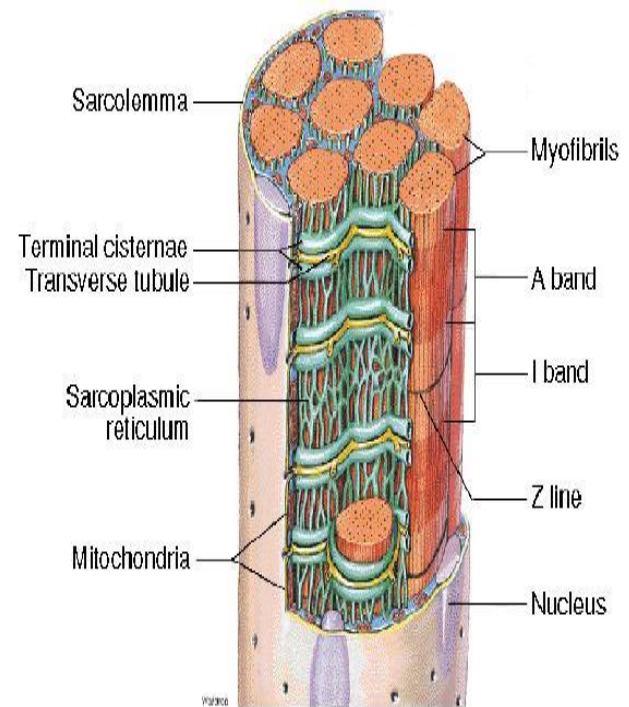
- The SARCOLEMMA has a unique feature: it has holes in it. These "holes" lead into tubes called TRANSVERSE TUBULES (or T-TUBULES for short).
- These tubules pass down into the muscle cell and go around the MYOFIBRILS.
- However, these tubules DO NOT open into the interior of the muscle cell; they pass completely through and open somewhere else on the sarcolemma (i.e., these tubules are not used to get things into and out of the muscle cell).

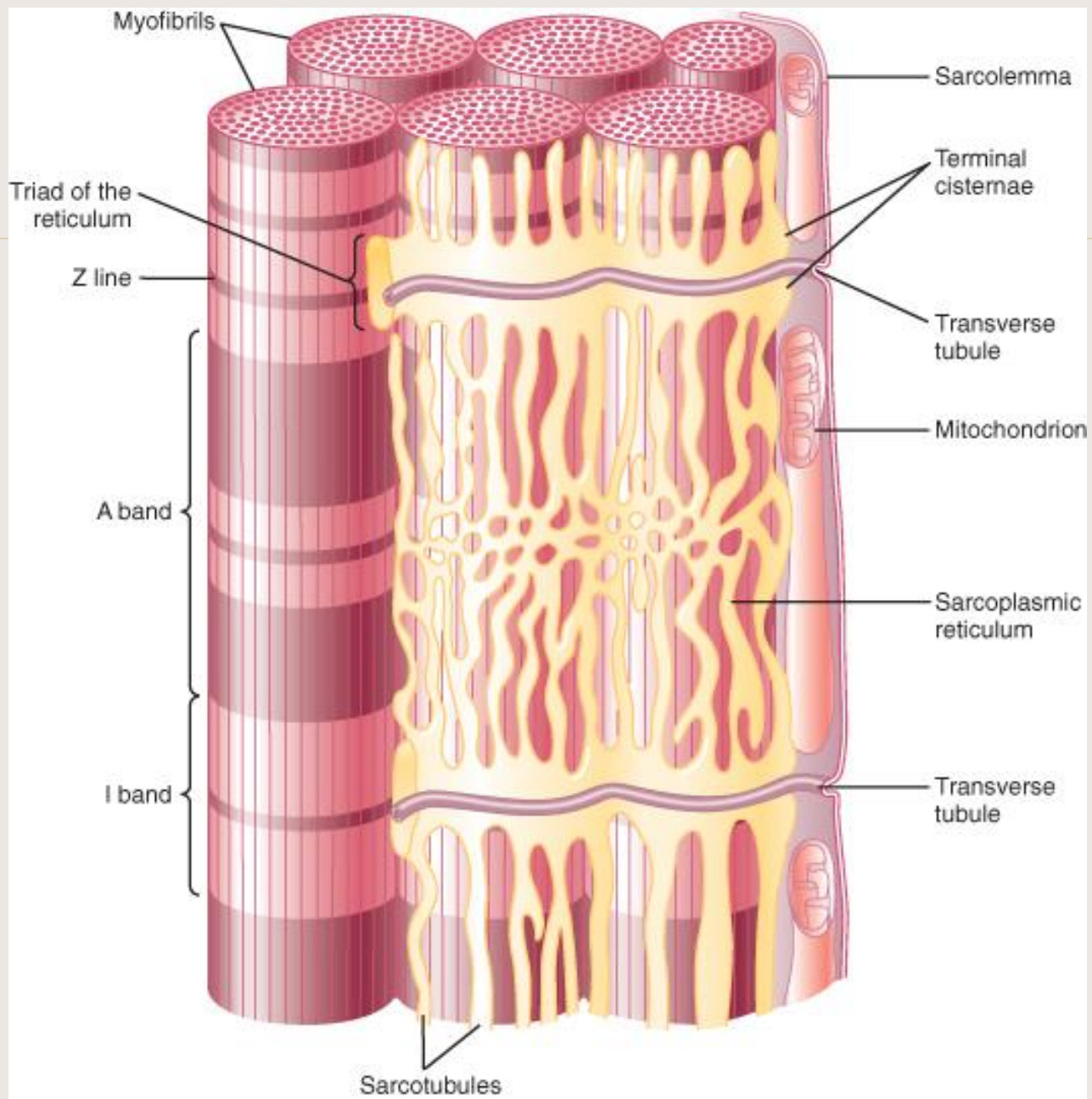
Sarcoplasmic Reticulum



- The function of T-TUBULES is to conduct impulses from the surface of the cell (SARCOLEMMA) down into the cell and, specifically, to another structure in the cell called the SARCOPLASMIC RETICULUM.
- As they open to the exterior, the extracellular fluid runs through their lumen.

Sarcoplasmic Reticulum





L TUBULES – SARCOPLASMIC RETICULUM

- Extend throughout the sarcoplasm.
- Together called sarcoplasmic Reticulum.
- Runs in long axes of the muscle fiber and hence called longitudinal tubules or “L tubules”.
- Form a closed tubular system around each myofibril.
- They do not open to exterior like T tubules.
- It connects to the endoplasmic reticulum of other cells regular intervals, throughout the length of the myofibrils, the L tubules dilate to form a pair of lateral sacs called terminal cisternae.
- Each pair of terminal cisternal is in close contact with T tubule. (The T tubule along with cisternae on either side is called the triad of skeletal muscle).

FUNCTIONS OF T TUBULES

- Responsible for rapid transmission of impulse in the form of action potential to the myofibrils.

FUNCTION OF L TUBULES

- Store a large quantity of calcium ions.
- When the action potential reaches the cisternal of “L” tubule, these calcium ions are released into the sarcoplasm, which trigger the processes involved in the contraction of the muscle this process is called excitation contraction coupling.

Sarcoplasmic and Endoplasmic reticulum.

- Sarcoplasmic Reticulum is from the greek sarx 'flesh' is a special type of smooth endoplasmic reticulum found in smooth, striated muscles.
 - SR is greyish blue in colour and wrapped around the myofibril.
 - Terminal cisternae is a part of the SR
 - S R stores and pumps Ca ions.
- E R synthesizes protein molecules.
 - ER causes facilitation of protein folding and transport of synthesized proteins in sacs called Cisternae.

Sarcoplasmic reticulum

- Sarcoplasmic reticulum is very abundant in skeletal muscle cells and is closely associated with the MYOFIBRILS (and, therefore, the MYOFILAMENTS).
- The membrane of the SR is well-equipped to handle calcium: there are "pumps" (active transport) for calcium so that calcium is constantly being "pumped" into the SR from the cytoplasm of the muscle cell (called the SARCOPLASM).
- As a result, in a relaxed muscle, there is a very high concentration of calcium in the SR and a very low concentration in the sarcoplasm (and, therefore, among the myofibrils & myofilaments).
- In addition, the membrane has special openings, or "gates", for calcium.
- In a relaxed muscle, these gates are closed and calcium cannot pass through the membrane. So, the calcium remains in the SR.
- However, if an impulse travels along the membrane of the SR, the calcium "gates" open &, therefore, calcium diffuses rapidly out of the SR & into the sarcoplasm where the myofibrils & myofilaments are located.

COMPOSITION OF MUSCLE

➤ Skeletal muscle is formed by 75% of water, 20% of proteins and 5% of organic substances other than proteins and some inorganic substances.

MUSCLE PROTEINS

➤ Following are the protein present in the muscle.

1. Myosine
2. Actin
3. Tropomyosin
4. Troponin
5. Actinin
6. Titin
7. Desmin
8. Myogen (Sarcoplasm of the muscle cell).
9. Myoglobin (Sarcoplasm)

This myoglobin is also called myohemoglobin. Its function is similar to haemoglobin that is to carry O₂.

SKELETAL MUSCLES

- Skeletal muscle has Cross Striations
- Skeletal muscle are the Voluntary muscles.
- Skeletal muscles are in Association with bones forming the skeletal system.
- Skeletal muscles form 40 to 50% of body mass.
- Skeletal muscles are Supplied by somatic nerves.

PROPERTIES OF SKELETAL MUSCLES EXCITABILITY

- Is defined as the reaction or response of a tissue to the irritation or stimulation.
- The muscle can be excited by both **direct stimulation** and **indirect (through its nerve) stimulation**.
- Four types of stimulus, which can excite a living tissue.
 - ✓ Mechanical stimulus (Prnching)
 - ✓ Electrical stimulus (Electric Shock)
 - ✓ Thermal stimulus (by applying heated glass rod or wire)
 - ✓ Chemical Stimulus (acids)
- The stimulus whose strength (or voltage) is sufficient to excite the tissue is called threshold or minimal stimulus.
- For a weak stimulus, the duration be longer and for a stronger stimulus the duration is short.

EXCITABILITY CURVE OR STRENGTH DURATION CURVE

- In this curve, the strength of the stimulus is plotted (in volts) vertically and the duration in (milliseconds) horizontally.
- To start with a stimulus with higher strength or voltage (4 to 5) is applied. The minimum duration during which the stimulus must be applied to excite the tissue is determined.
- Strength of the stimulus is reduced and the duration is found.
- **Rheobase:** This is the least possible i.e. *minimum strength* (voltage) which can excite the tissue, whatever may be the duration of stimulus.
- **Utilization time:** Is the **minimum time** required to excite the tissue.
- **Chronaxic:** It is the minimum time, at which a stimulus with double the rheobasic strength (voltage) can excite the tissue.

IMPORTANCE OF CHRONAXIE

- Is used to compare the excitability in different tissues.
- Longer the chronaxie, lesser is the excitability.
- Chronaxie in human Skeletal muscle varies from 0.8 millisecon to 0.32 milli seconds and 10 times more in skeletal muscle of infants than in the skeletal muscles of adults.
- Chronaxie is longer in paralyzed muscles than the normal muscle.
- In the neural diseases it is prolonged gradually.
- Chronaxie is shortened in increased temperature and shorter in red muscles than in white muscle.

CONTRACTILITY

- Skeletal muscle gives response to a stimulus in the form of contraction.
- **Contraction:** Can be defined as the interval events of the muscle, which are manifested by change in either the length of the muscle fibers or the tension.
- **Isotonic Contraction:** In this type of contraction the tension remains the same whereas the change occurs in the length of the muscle fiber (ISO = same tonic = tension)
- Example is simple flexion of arm
- **Isometric contraction:** In this type, the length of muscle fibers remains the same and the tension is increased. Example is pulling any heavy object.

Isometric contraction

- The force exerted on an object by contracting muscle is known as muscle tension, and the force exerted on the muscle by an object (usually its weight) is the load.
- Muscle tension and load are opposing forces.
- When a muscle develops tension but does not shorten (or lengthen), the contraction is called isometric (constant length)

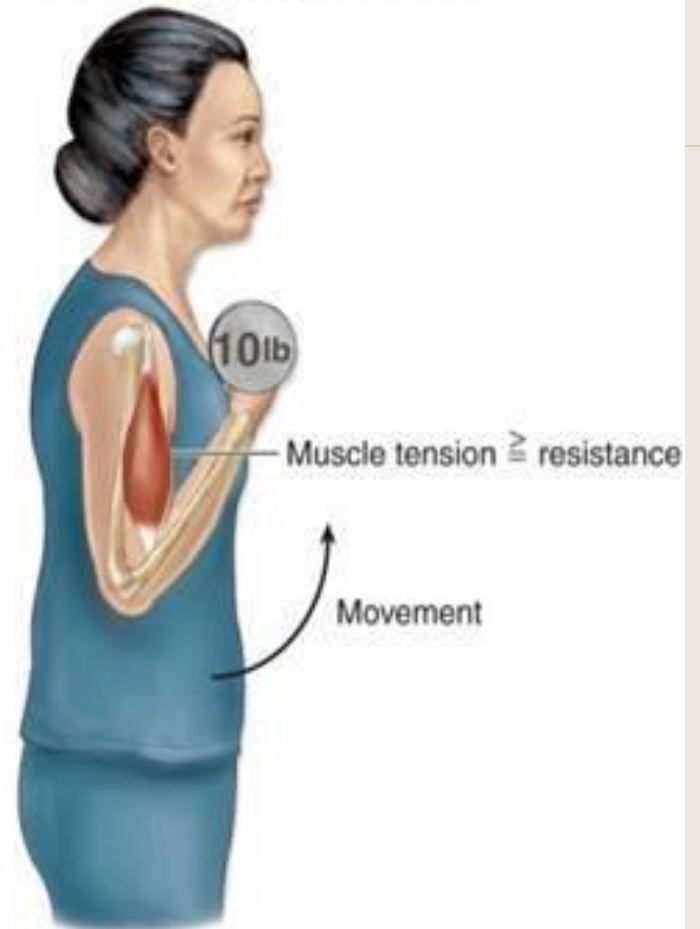
Isometric contraction(continued)

- Isometric Contractions, on the other hand, are situations where the muscle TRIES to contract, but cannot. An example of this is if you tried to lift an immovable object. Holding a weight at arm's length would be another.
- An **isometric contraction** of a muscle generates force without changing length. An example can be found when the muscles of the hand and forearm grip an object; the joints of the hand do not move, but muscles generate sufficient force to prevent the object from being dropped.



(a) Isometric contraction

Muscle tension is less than the resistance. Although tension is generated, the muscle does not shorten, and no movement occurs.



(b) Isotonic contraction

Muscle tension equals or is greater than the resistance. The muscle shortens, and movement occurs.

Isometric exercise

- Isometric exercise, is a strength training activity in which your muscle length and joint angles do not change.
- Isometric exercises strengthen and condition muscles, and increase muscle size. Isometrics are often performed in yoga workouts. They are also used in rehabilitation and for sport-specific training.





EXERCISE A IS AN ISOTONIC
CONTRACTION, EXERCISE B IS
ISOMETRIC

Isotonic contraction

- A contraction in which the muscle changes length, while the load on the muscle remain constant is isotonic(constant tension)
- Exercises which utilize isotonic contractions are, Swinging a bat, throwing a ball or lifting a weight are all isotonic movements.
- Anatomy wise, an isotonic movement is one in which a muscle is shortened and the body part it is attached to moves as well.
- If you perform a bicep curl, the process of shortening the bicep is what moves the arm
- isotonic contraction can be associated with either shortening or lengthening of a muscle when tension exceeds a load, shortening occurs and it is referred to as **concentric contraction**

Isotonic contraction

- On the other hand if an unsupported load is greater than the tension generated by cross bridges the result is a lengthening contraction (**eccentric contraction**).
- In this situation, the load pulls the muscle to a longer length in spite of the opposing force produced by the cross bridges.

Difference between isometric and isotonic contraction

- Isometric contraction occurs when a muscle contracts against an immovable load
- Actin filaments are unable to slide on myosin filaments
- Tension rises during contraction
- No shortening occurs ,hence no external work is done
- Isotonic contraction occurs when a muscle contracts against zero load.
- Actin filaments easily slide on myosine filaments.
- Tension remains unchanged during contraction.
- Shortening occurs and external work is done.

Difference between isometric and isotonic contraction.

- Occurs at the beginning and end of all contraction.
- Isometric contraction increases when load increases.
- Heat released is less hence, more energy-efficient.
- An isometric twitch has a shorter latent period. The tension peaks quickly and relaxation is slow.
- Occurs in the middle of a contraction.
- Isotonic contraction decreases when load increases.
- Heat released is more hence, less energy-efficient.
- An isotonic twitch has a longer latent period. The shortening peaks somewhat later and relaxation is quicker.

Isometric-Isotonic contractions have their benefits .

- Isotonic movements typically are much **more vigorous**, which is better for the heart.
- Due to their **vigorous nature, isotonic exercises are usually better at burning calories** and therefore **greatly aid in weight reduction.**
-
- Isometrics only work the heart indirectly.
- Isometric exercises **are static position exercises** that don't require the worked muscle to move.
- isometrics, you **merely contract muscles while keeping a particular body part still.**
- Isometric exercises **are not great for strength development but are ideal for aiding in rehabilitation.**
- It help the **entire body and help maintain your strength.**

Isometric exercise



Comparison

Anaerobic exercises

- Use fast twitch fibres
- Weight lifting, push up exercises.
- Depletes Oxygen reserve in the muscle cells quickly.
- To repay the oxygen Debt human breath quickly which restores oxygen level.
- Creates excess of Lactic acid(a waste product) increase oxygen intake the liver cells can convert the excess lactic acid into glucose used in cellular metabolism.

Aerobic exercises

- Uses slow twitch muscle
- Include activities that are prolonged and requires constant energy
- Long distance running and cycling are examples of aerobic exercise.
- The muscle cell requires the same amount of oxygen that the body supplies. The oxygen debt is slashed and lactic acid is not formed.

LATENT PERIOD

- Is the time taken for the impulse to travel along the nerve from the place of stimulation to the muscle.
- It is the time taken for initial chemical changes in the muscle to start with.
- Latent period is not constant. It decreases in high temperature and increases in low temperatures.

CONTRACTION TIME (Total Twitch Period)

- Based on the contraction time, the skeletal muscles are classified into two types, the red muscles and white muscles.
- Similarly, depending upon contraction time and myosin ATPase activity the muscle fibers are also divided into two types.
- Type 1 fibers (slow twitch fibers) having small diameters.
- Type 2 fibers (fast twitch fibers) having Large diameter.

TABLE 30-1: Features of red and white muscles

Red (slow) muscle	White (fast) muscle
1. Myoglobin content is more. So, it is red	Myoglobin content is less. So, it is pale
2. Sarcoplasmic reticulum is less extensive	Sarcoplasmic reticulum is more extensive
3. Blood vessels are more extensive	Blood vessels are less extensive
4. Mitochondria are more in number	Mitochondria are less in number
5. Response is slow with long latent period	Response is rapid with short latent period
6. Contraction is less powerful	Contraction is more powerful
7. This muscle is involved in prolonged and continued activity as it undergoes sustained contraction	This muscle is not involved in prolonged and continued activity as it relaxes immediately
8. Fatigue occurs slowly	Fatigue occurs quickly
9. Depends upon cellular respiration for ATP production	Depends upon glycolysis for ATP production

Red and white muscle fibers

- red muscle fibers initiate all movement while white fibers activate only when intensity surpasses a given level
- White muscle fibers create high-intensity actions lasting fewer than 30 seconds, such as jumping and lifting loads greater than 70 percent of your maximal ability.

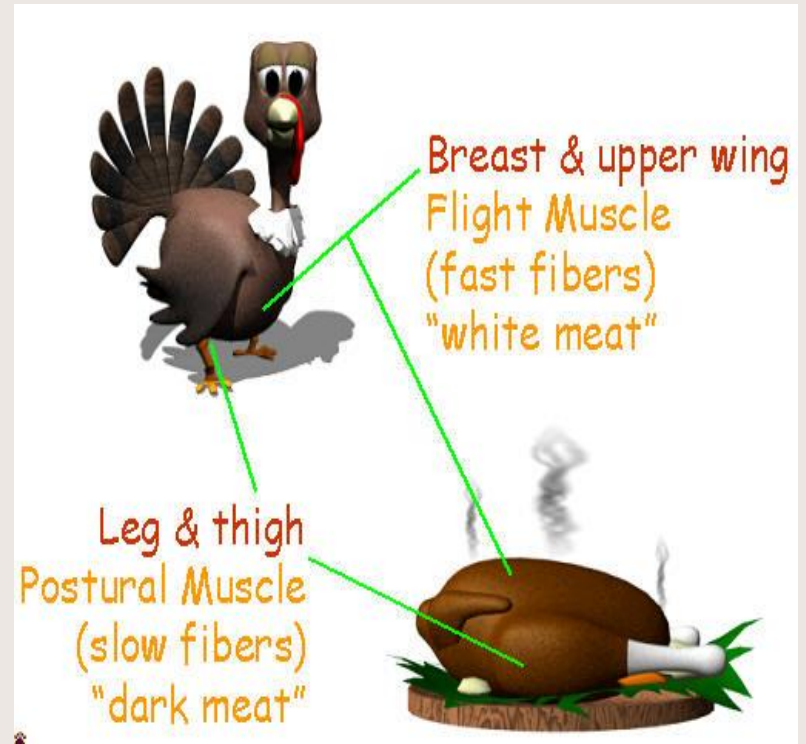
Red and white muscle fibers

- red muscle fibers specialize in long-duration, low-intensity movement, such as walking, standing or lifting loads below 70 percent of your maximal ability.
- Red fibers fatigue slowly
- dominate muscle composition in the human body.
- red fibers contribute to all muscular contractions, they are easier to target with exercise. For example, any repetitive, weight-bearing action
- Designed for quick movements (like the muscles in your hands & for moving your eyes)
- More SR in these fibers, so they are better equipped for quick release and re-uptake of calcium ions
- Myosin heads have a slight molecular difference that makes them faster and more efficient at hydrolyzing ATP.
- Because of this, they can run through the cross-bridge cycle faster. More likely to fatigue (due to lactic acid build up)

Red and white muscle fibers

- More mitochondria & myoglobin
 - better blood supply. Two major advantages of this: rather than making ATP and having lactic acid build up, the pyruvate is better able to enter the mitochondria and be broken down further there... all you need is plenty of mitochondria and plenty of myoglobin. slow muscle fibers are less likely to fatigue (because of a slower build-up of lactic acid)
 - Note that since myoglobin is a red pigment molecule (like hemoglobin is), these fibers tend to look redder (or darker) than fast muscle fibers
- The red muscles are aerobic while the white muscle is mostly anaerobic.

Red and white muscle fibers



SOURCES OF ENERGY FOR MUSCLE CONTRACTION

- Muscle contraction depends on energy supplied by ATP.
- Energy is required to activate the walk along mechanism by which the cross bridges pull the actin filaments.
- Small amounts are required for pumping calcium from the sarcoplasm into the sarcoplasmic reticulum after the contraction is over.
- Pumping sodium and potassium ions through the muscle fiber membrane to maintain an appropriate ionic environment for propagation of muscle fiber action potential.

Energy sources

- Energy is converted from fuel molecules in the mitochondria
- Muscle fibers have many mitochondria to provide their high energy needs
- Muscle fibers are specialized for producing energy efficiently



SOURCES OF ENERGY FOR MUSCLE CONTRACTION

- The concentration of ATP in the muscle fiber, about 4 millimolar, is sufficient to maintain full contraction for only 1 to 2 seconds at most.
- After this, ATP is split to form ADP.
- The ADP is rephosphorylated to form new ATP within another fraction of a second, which allows the muscle to continue its contraction.

SOURCES OF ENERGY FOR MUSCLE CONTRACTION

- The first source of energy that is used to reconstitute the ATP is the substance **phosphocreatine**, which carries a high energy phosphate bond similar to the bond of ATP.
- The high energy phosphate bond of phosphocreatine has a slightly higher amount of free energy than that of the ATP bond.
- Therefore phosphocreatine is instantly cleaved, and the released energy causes bonding of a new phosphate ions to ADP to reconstitute the ATP.

SOURCES OF ENERGY FOR MUSCLE CONTRACTION

- Total amount of phosphocreatine in the muscle fiber is also very little, only five times as great as the ATP.
- Therefore, the combined energy of both the **stored ATP** and the **phosphocreatine** in the muscle is still capable of causing maximal muscle contraction for only 5 to 8 seconds.

SOURCES OF ENERGY FOR MUSCLE CONTRACTION

- The second important source of energy, which is used to reconstitute both ATP and phosphocreatine, is glycogen previously stored in the muscle cells
- Rapid enzymatic breakdown of the glycogen to pyruvic acid and lactic acid liberates energy that is used to convert ADP to ATP can then be used directly to energize muscle contraction or to reform the stores of phosphocreatine.

IMPORTANCE OF GLYCOLYSIS MECHANISM

- Can occur in the absence of oxygen
- The rate of formation of ATP by glycolytic process is 2 and a half times as rapid as ATP formation when cellular food stuffs react with oxygen.
- After about 1 min glycolysis loses the capacity to sustain maximum muscle contraction because the end products of glycolysis accumulate in the muscle cells

FINAL THIRD SOURCE OF ENERGY

- Is oxidative metabolism. this means the combining of oxygen with various cellular foodstuffs to liberate ATP.

Functional characteristics of muscle fibers

- Excitable
- Contractile
- Extensible
- Elastic



TABLE 28-1: Features of skeletal, cardiac and smooth muscle fibers

Features	Skeletal muscle fiber	Cardiac muscle fiber	Smooth muscle fiber
Location	In association with bones	In the heart	In the visceral organs
Shape	Cylindrical and unbranched	Branched	Spindle shaped and unbranched
Length	1-4 cm	80-100 μ	50-200 μ
Diameter	10-100 μ	15-20 μ	2-5 μ
No. of nucleus	One or more	One	One
Cross striations	Present	Present	Absent
Myofibrils	Present	Present	Absent
Sarcomere	Present	Present	Absent
Troponin	Present	Present	Absent
Sarcotubular system	Well developed	Well developed	Poorly developed
'T' tubules	Long and thin	Short and broad	Absent
Depolarization	Upon stimulation	Spontaneous	Spontaneous
Fatigue	Possible	Not possible	Not possible

TABLE 28-1: Features of skeletal, cardiac and smooth muscle fibers

Summation	Possible	Not possible	Possible
Tetanus	Possible	Not possible	Possible
Resting membrane potential	Stable	Stable	Unstable
For trigger of contraction, calcium binds with	Troponin	Troponin	Calmodulin
Source of calcium	Sarcoplasmic reticulum	Sarcoplasmic reticulum	Extracellular
Speed of contraction	Fast	Intermediate	Slow
Neuromuscular junction	Well defined	Not well defined	Not well defined
Action	Voluntary action	Involuntary action	Involuntary action
Control	Only neurogenic	Myogenic	Neurogenic and myogenic
Nerve supply	Somatic nerves	Autonomic nerves	Autonomic nerves
Starling's law	Applicable	Applicable	Not applicable

Muscle fatigue

- When a skeletal muscle fiber is repeatedly stimulated, the tension the fiber develops eventually decreases even though the stimulation continues.
- This decline in muscle tension as a result of previous contractile activity is known as muscle fatigue.

Characteristics of fatigued muscle are

- A decreased shortening velocity and slower rate of relaxation.

Factors involved in skeletal muscle fatigue

- **Conduction failure:** The muscle action potential can fail to be conducted into the fiber.
- Conduction failure results from the buildup of potassium ions in the T tubules during the repolarization of repetitive action potential.
- Elevated external K concentration leads to a persistent depolarization of the membrane potential and eventually cause a failure to produce action potential in the T tubular membrane (due to inactivation of sodium channels)

Factors involved in skeletal muscle fatigue

- **Lactic acid buildup: Elevated H ions concentration alters protein confirmation and activity.**
- **Thus acidification of muscle by lactic acid may alters a number of muscle protein including actin and myosin as well as proteins involved in calcium release.**

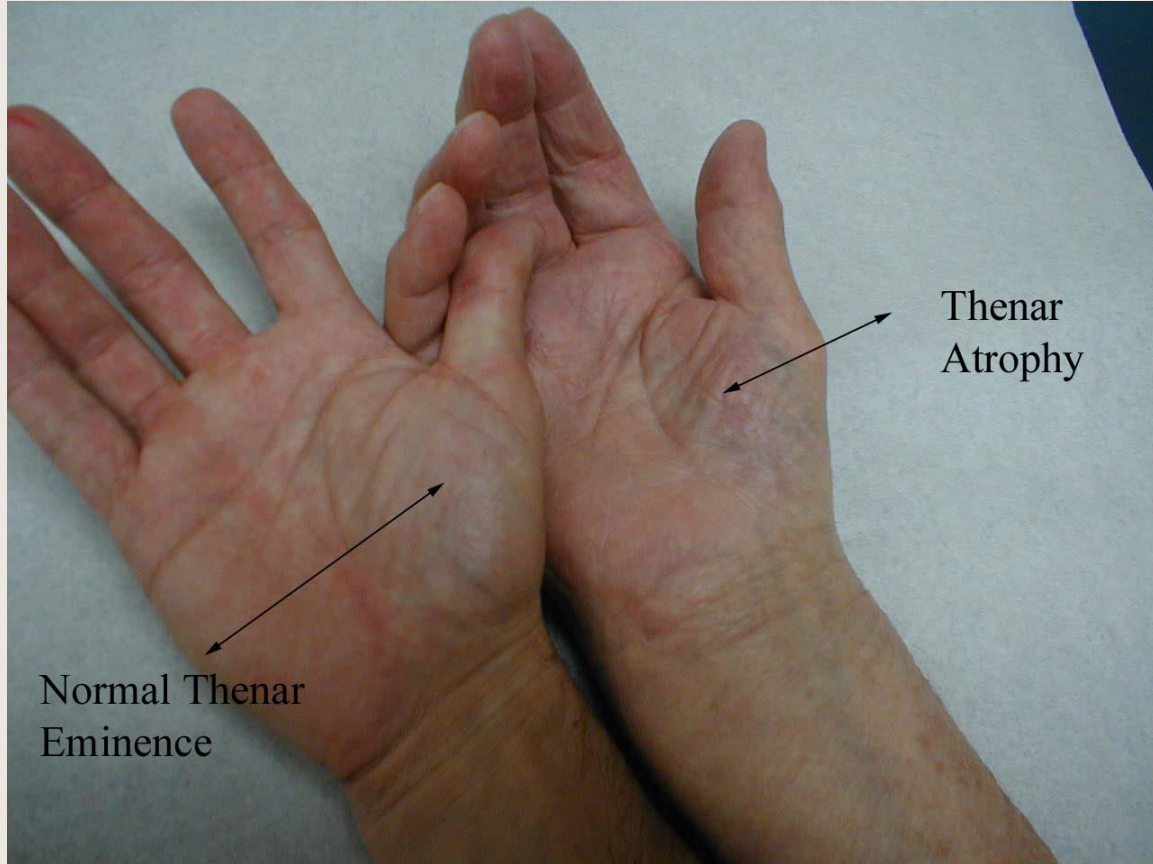
Factors involved in skeletal muscle fatigue

- **Inhibition of cross bridge cycling:** high intensity exercise cause impaired relaxation observed in muscles as a result there is delay with cross bridge detachment from actin filaments.
- **ATP depletion is not a cause of fatigue.**
- The decrease in muscle glycogen which supplied fuel for contraction correlates closely with the fatigue on set.
- Low blood glucose and dehydration have been demonstrated to increase fatigue.

Atrophy of the skeletal muscles

Atrophy is are of two types

1. **DENERVATION ATROPHY**: If the neurons to a skeletal muscle are destroyed or the neuromuscular junctions become nonfunctional, the denervated muscle fibers will progressively smaller in diameter, and the amount of contractile proteins they contain will decrease. This condition is known as denervation atrophy.



Normal Thenar
Eminence

Thenar
Atrophy

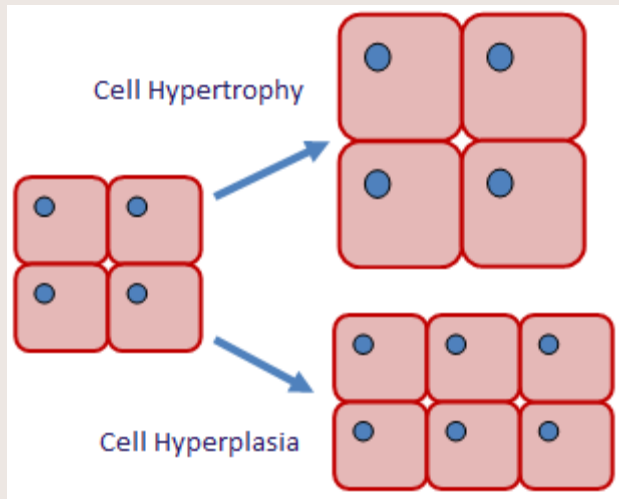
Atrophy of the skeletal muscles

DISUSE ATROPHY: A muscle can also atrophy with the nerve supply intact, if the muscle is not used for a long period of time as when a broken arm or leg is immobilized in a cast. This condition is known as disuse atrophy.

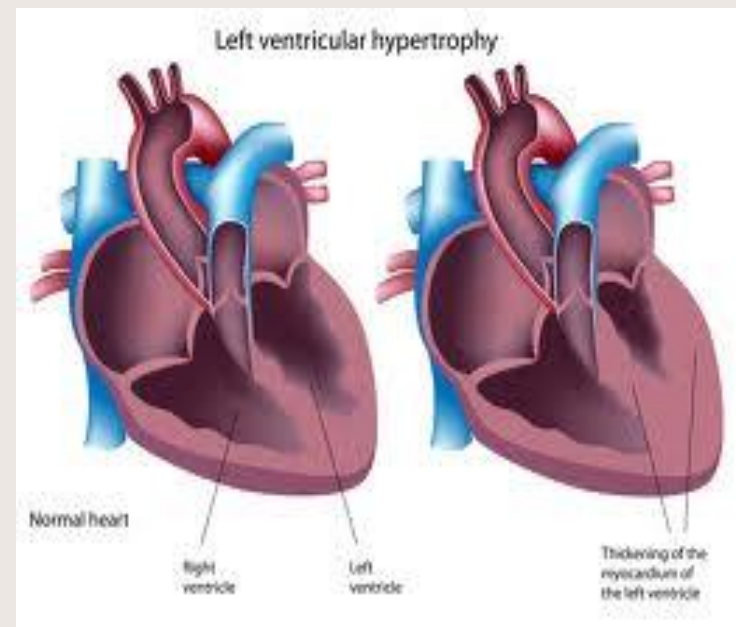
Muscle Hypertrophy

- Increase muscle size due to forceful muscular activity for a long period of time, is called muscle hypertrophy.
- Cause are increase in diameter of muscle fiber.
- Increase in number of muscle fiber(hyperplasia).

Difference between Hyperplasia and hypertrophy



Difference between physiological and pathological hypertrophy



Effect of exercise on skeletal muscles

- An increase in the size(hypertrophy) of muscle fibers as well as changes in their capacity for ATP production.
- Exercise of relatively low intensity but longer duration(popularly called Aerobic exercise) such as running or swimming produce increase in the number of Mitochondria in the fibers that are recruited in this type of activity.

Effect of exercise on skeletal muscles

- **The number of capillaries around these fibers** also increases.
- **Exercise increases the capacity for endurance activity with a minimum of fatigue.**(Endurance means the power to withstand hardship)
- **Exercise improves the delivery of oxygen and fuel molecules to the muscle.**

Muscle Cramps

- Involuntary tetanic contraction of the skeletal muscles produces muscle cramps.
- During cramping, action potentials fire at abnormally high rates, a much greater rate than occurs during maximum voluntary contraction.

Summation of muscle contraction

- Adding together of individual muscle contraction to give a strong muscle contraction, is called summation.

There are two types of summation

- **Multiple motor unit summation:** In this number of motor units contracting simultaneously is increased
- **Wave summation:** In this frequency of contraction of individual motor is increased .

Hypocalcemic Tetany

- Is involuntary tetanic contraction of skeletal muscle that occurs when the extracellular calcium concentration falls to about 40% of its normal value.
- Hypocalcemia opens the Na channels in excitable membranes ,leading to membrane depolarization and spontaneous firing of action potential causing increase muscle contraction

EXAMINATION TIP



Recognizing carpopedal spasm

In the hand, carpopedal spasm involves adduction of the thumb over the palm, followed by flexion of the metacarpophalangeal joints, extension of the interphalangeal joints (fingers together), adduction of the hyperextended fingers, and flexion of the wrist and elbow joints. Similar effects occur in the joints of the feet.



Muscular Dystrophy

- Genetic disease.
- Affecting one in every 3500 males (but many fewer females)
- It is associated with the progressive degeneration of skeletal and cardiac muscle fibers, weakening the muscles and leading to death from respiratory and cardiac failure.
- The symptoms become evident at about 2 to 6 years of age.
- Most affected individuals do not survive far beyond age of 20.

*Muscular dystrophy
is a disease in
which muscles of
the body get
weaker and weaker
and may slowly
stop working.*

faulty
gene
carrier
mother



non
carrier
father



LEGEND: X^r =
recessive faulty gene
on X chromosome

X or Y =
correct gene

eggs



sperm



faulty gene carrier



non carrier

GIRLS

1 OUT OF 4 CHANCE
25%

1 OUT OF 4 CHANCE
25%



affected



non carrier

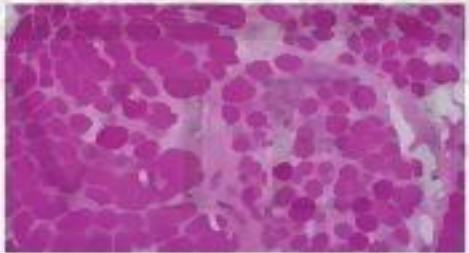
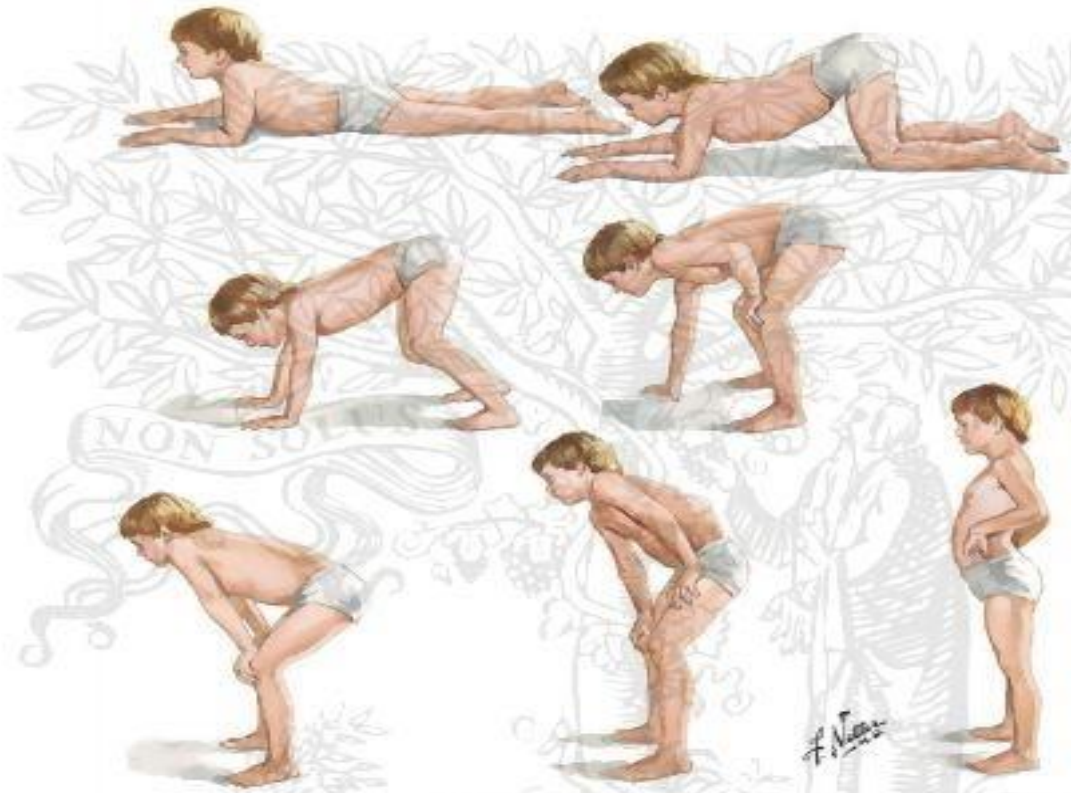
BOYS

1 OUT OF 4 CHANCE
25%

1 OUT OF 4 CHANCE
25%

Muscular Dystrophy

- The recessive gene responsible for a major form of muscular dystrophy (Duchenne muscular dystrophy) has been identified on the X chromosome.
- It is thus a sex-linked recessive disease, girls have two X chromosomes and boys only have one.
- Consequently, with one abnormal X chromosome and one normal one, they will not generally develop the disease. This is why the disease is more common in boys.
- This gene codes for a protein known as dystrophin, which is present in a non-functional form or absent in patients with the disease.

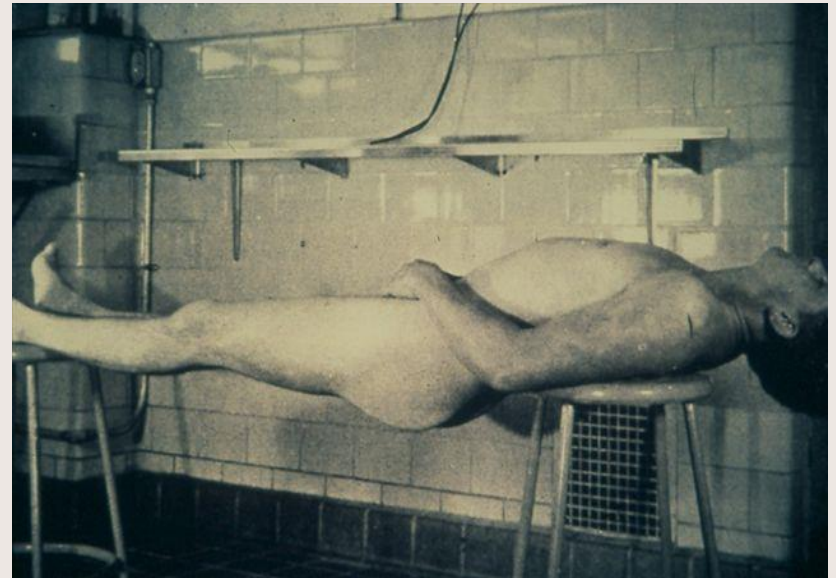


Muscular Dystrophy

- Dystrophin is a large protein that links Cytoskeletal proteins to membrane Glycoproteins
- It resemble other known cytoskeletal proteins and may be involved in maintaining the structural integrity of the plasma membrane, or of elements within the membrane, such as ion channels.
- In its absence ,fibers subjected to repeated structural deformation during contraction and susceptible to membrane rupture and cell death.

Rigor mortis

- After death muscle contract and become rigid ,this is called rigor mortis.
- Cause of rigor mortis is loss of ATP which is needed for separation of cross bridges from actin filament



Neuromuscular Junction

- The skeletal muscle fibers are innervated by a large, myelinated nerve fiber that originates from large motor neurons in the anterior horns of spinal cord.
- Each nerve fiber, before entering the muscle, normally branches and stimulates from three to several hundred muscle fibers.

Motor end plate

- Each terminal branch of nerve fiber(axon terminal) when comes close to the muscle fiber it loses the myelin sheath ,and innervates into the surface fiber,this portion is expanded.This entire structure is called motor end plate .It is covered by one or more schwann cells that insulate it from the surrounding fluid.

Neuro muscular junction

- Each nerve ending makes a junction called the neuromuscular junction with the muscle fiber near its midpoint.

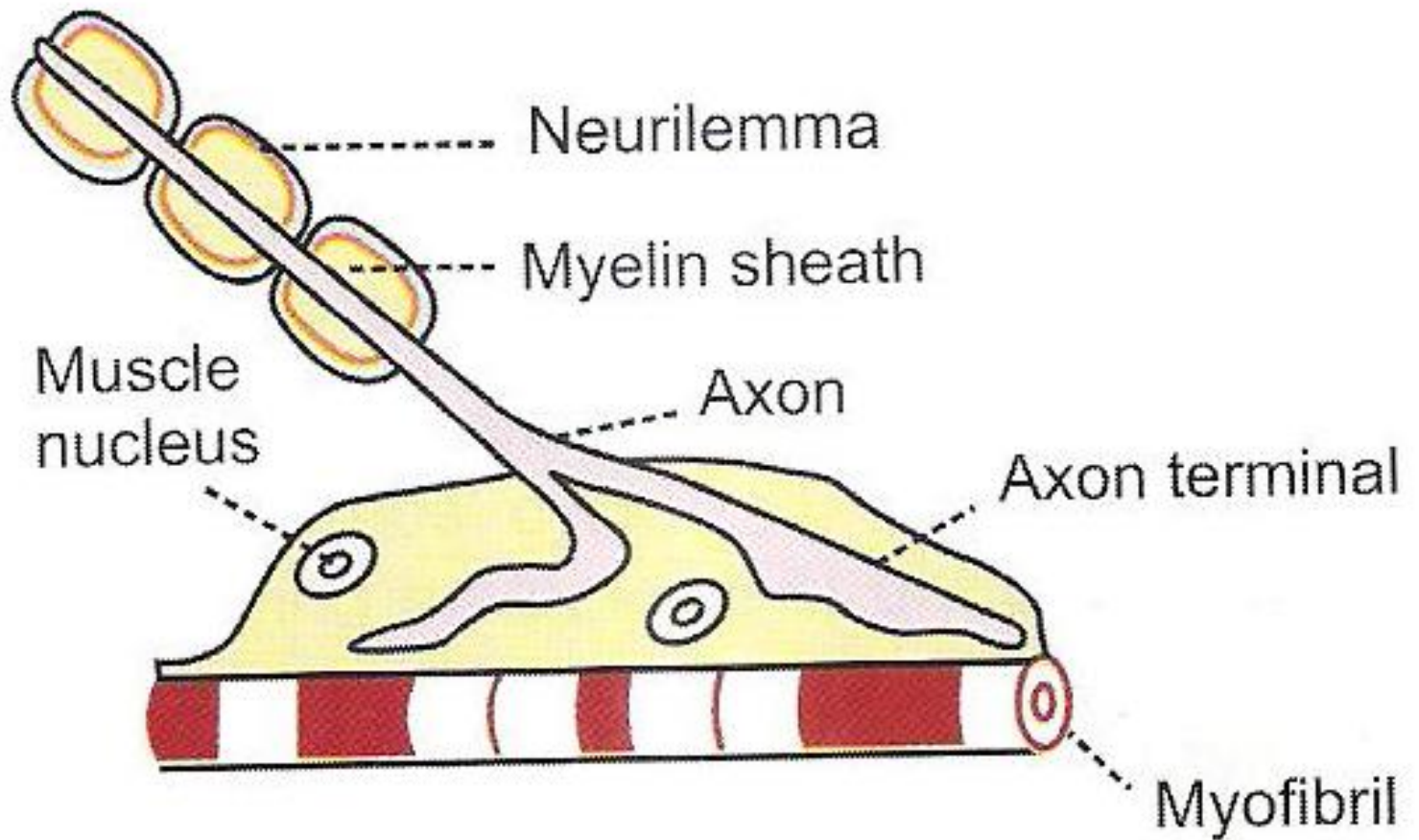


FIGURE 32-1: Longitudinal section of neuromuscular junction

Synaptic gutter or synaptic trough

- The motor end plate invaginates inside the muscle fiber and forms a depression which is known as synaptic trough or synaptic gutter.

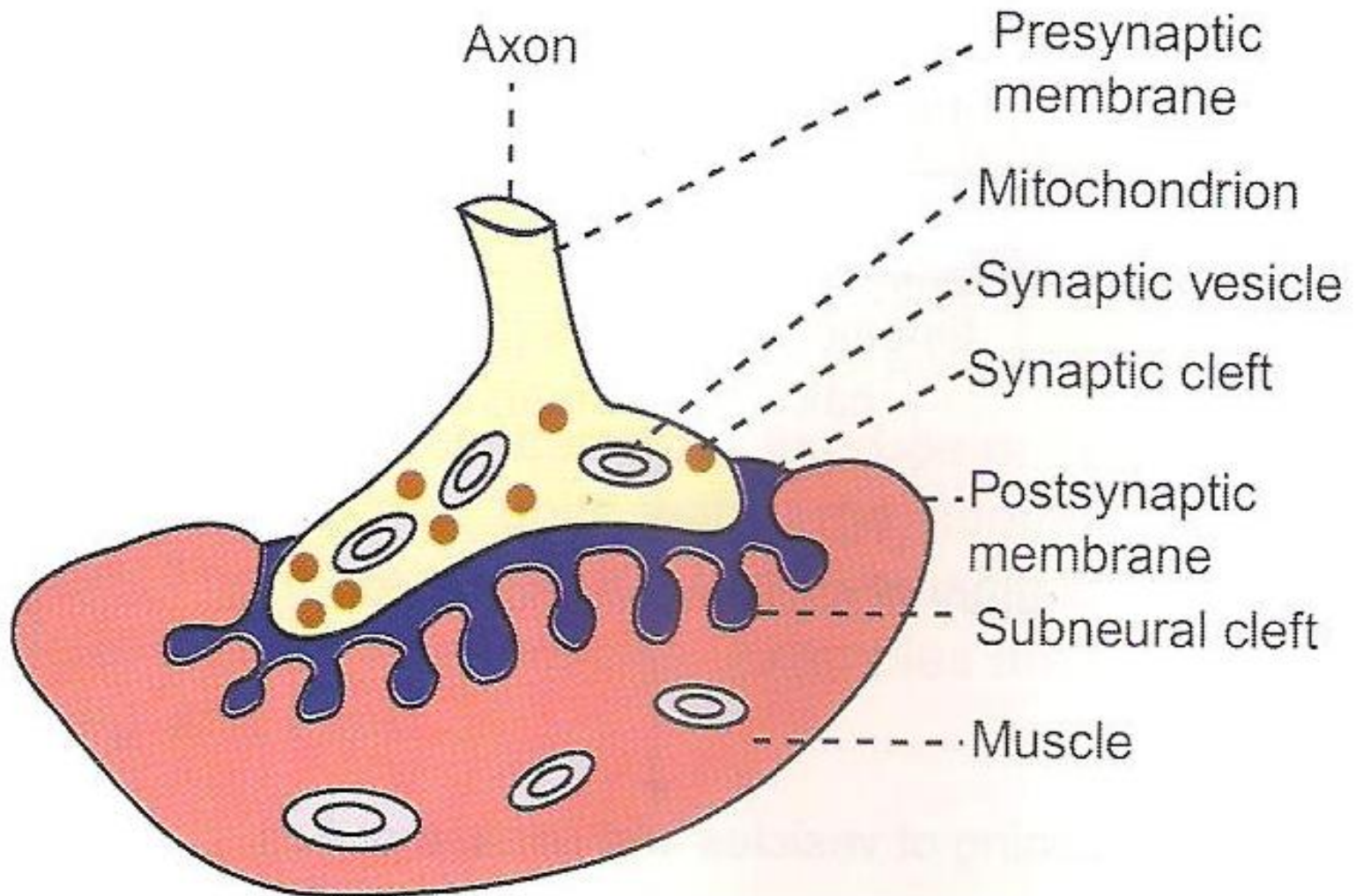
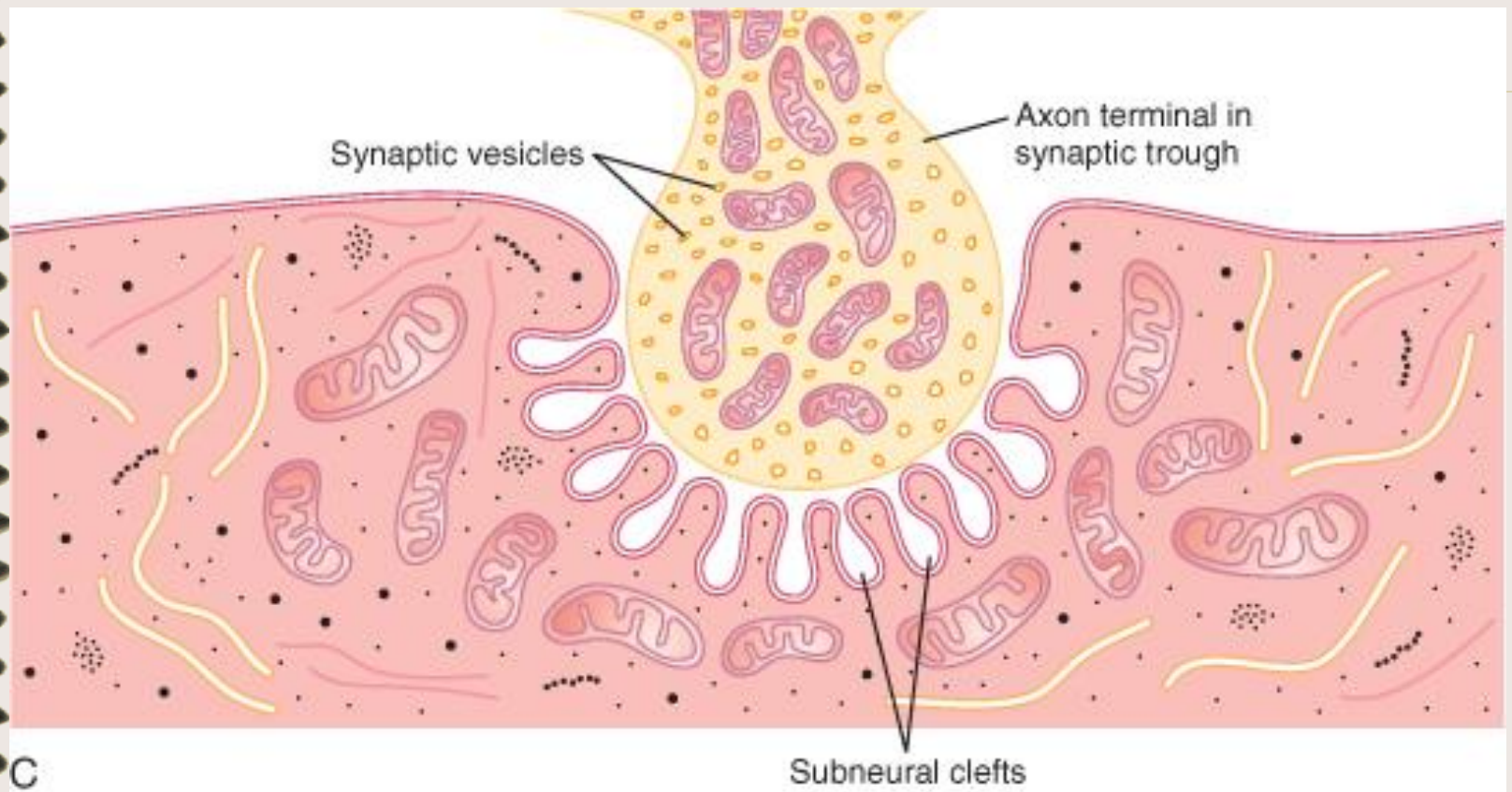


FIGURE 32-2: Structure of neuromuscular junction



C

Synaptic cleft

- The membrane of the nerve ending is called the presynaptic membrane.
- The membrane of the muscle fiber is called postsynaptic membrane.
- The space between these two is called synaptic cleft.
- The space is 20-30 nanometer wide.
- The axon terminal contain mitochondria and synaptic vesicles.
- The synaptic vesicles contain the neuromuscular substance, acetylcholine.

Synaptic cleft(continued)

- The acetylcholine is synthesized by mitochondria present in the axon terminal and stored in the vesicle.
- The mitochondria contain ATP which is the source of energy for the synthesis of acetylcholine.

Synaptic cleft(continued)

- The synaptic cleft contain layer of spongy reticular matrix,which contain large quantities of acetylcholinesterase.
- Post synaptic membrane is the membrane of the muscle fiber.It is thrown into numerous folds called subneural cleft.The post synaptic membrane contain the receptors called **NICOTINE ACETYLCHOLINE RECEPTORS**

Synaptic cleft(continued)

- In the axon terminal there are many mitochondria that supply the ATP, the energy source that is used for synthesis of the excitatory neurotransmitter Acetylcholine.
- Acetylcholine in turn excites the muscle fiber membrane.
- Acetylcholine is synthesized in the cytoplasm of the terminal but is absorbed into many small vesicles, about 300,000 are normally in the terminals of a single end plate

Synaptic cleft(continued)

- In the synaptic space are large quantities of the enzyme acetylcholinesterase which destroy acetylcholine a few milliseconds after it has been released from the synaptic vesicles

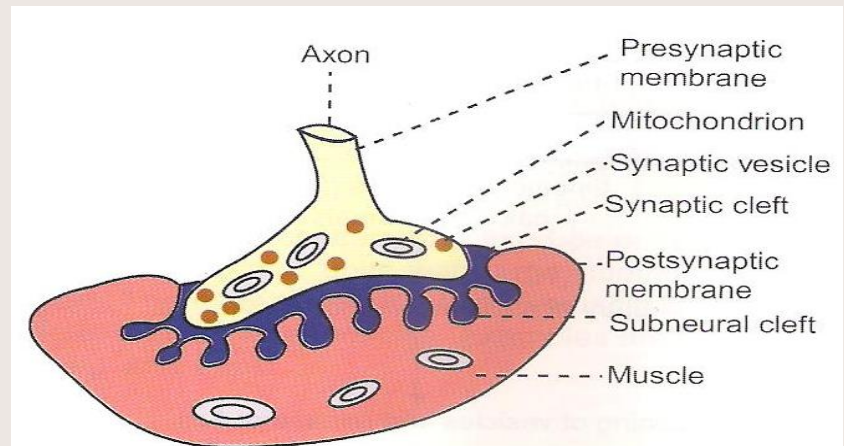
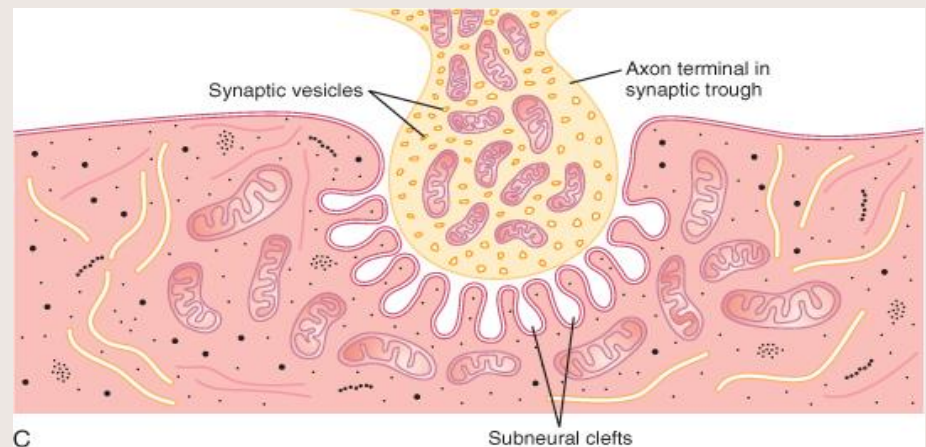


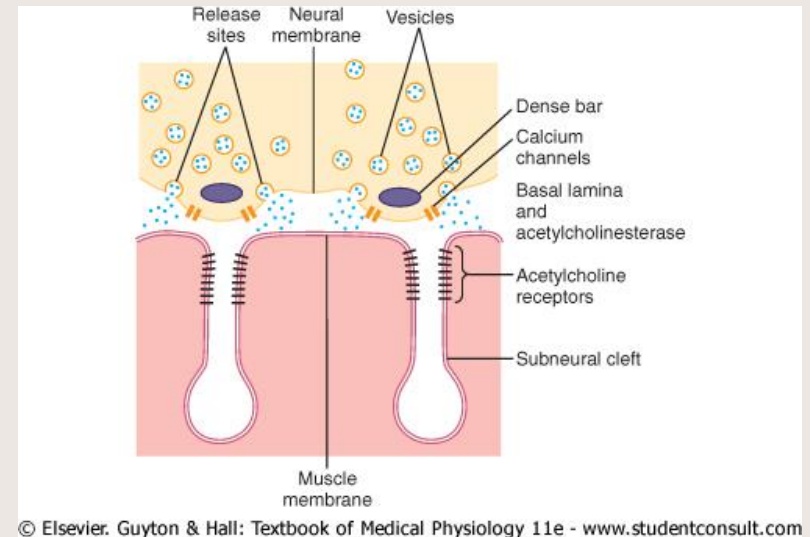
FIGURE 32-2: Structure of neuromuscular junction



C

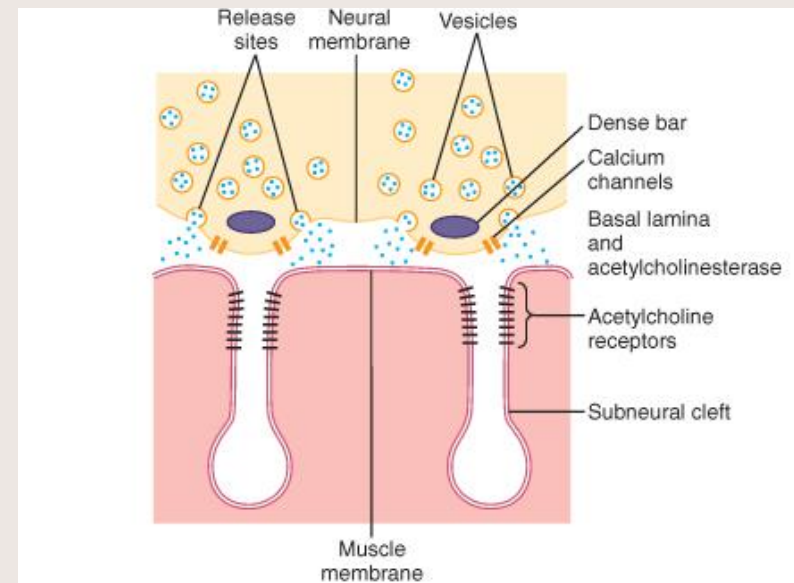
Release of Acetylcholine

- When a nerve impulse reaches the neuromuscular junction about 125 vesicles of acetylcholine are released from the terminal into the synaptic space.



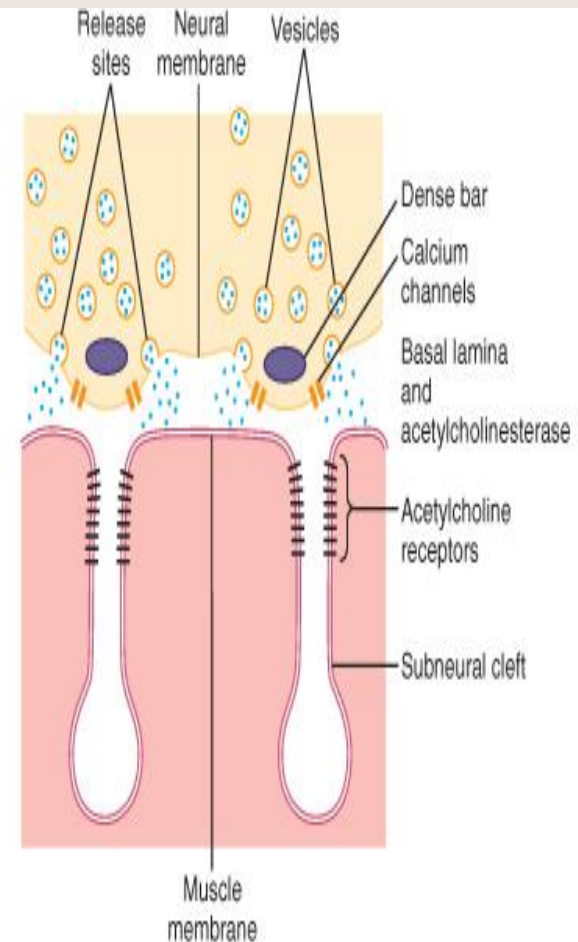
Release of Acetylcholine

- On the inside of the neural membrane are linear dense bars.
- To each side of each dense bar are protein particles that penetrate the neural membrane these are voltage gated calcium channels



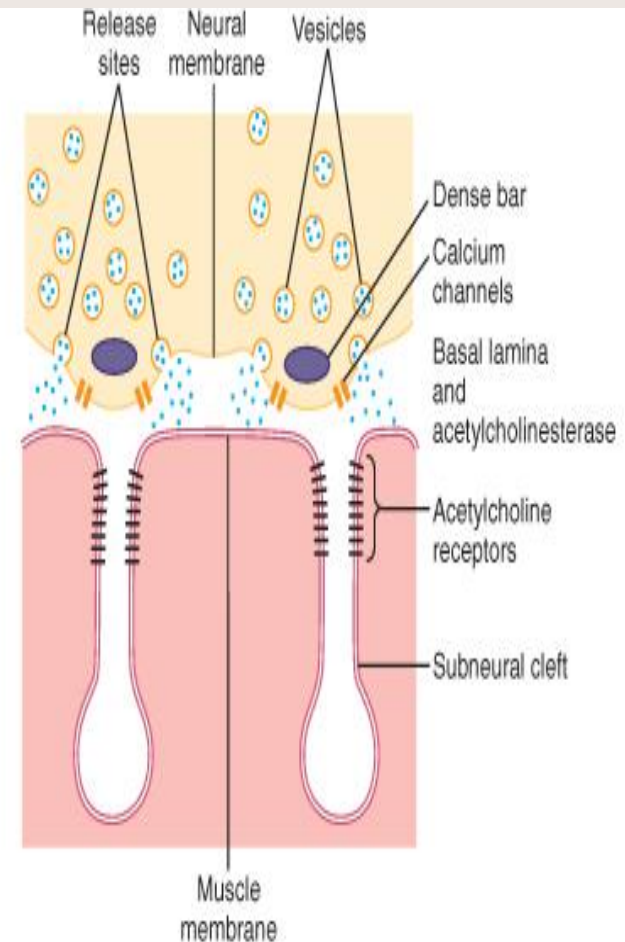
Release of Acetylcholine

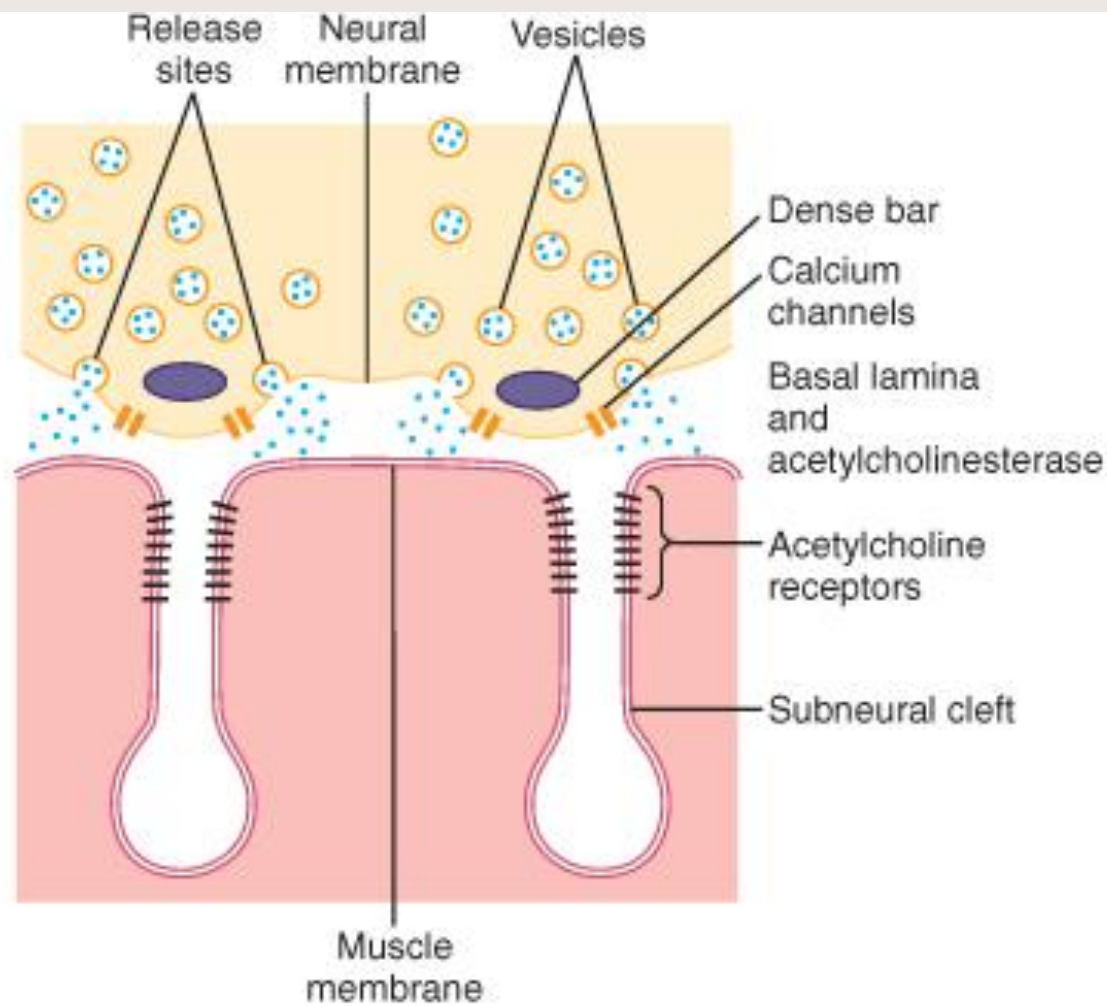
- When the action potential spread over the terminal these channels open and allow calcium ions to diffuse from the synaptic space to the interior of the nerve terminal.
- The Ca ions exert an attractive influence on the acetylcholine vesicles drawing them to the neural membrane adjacent to the dense bars.



Release of Acetylcholine

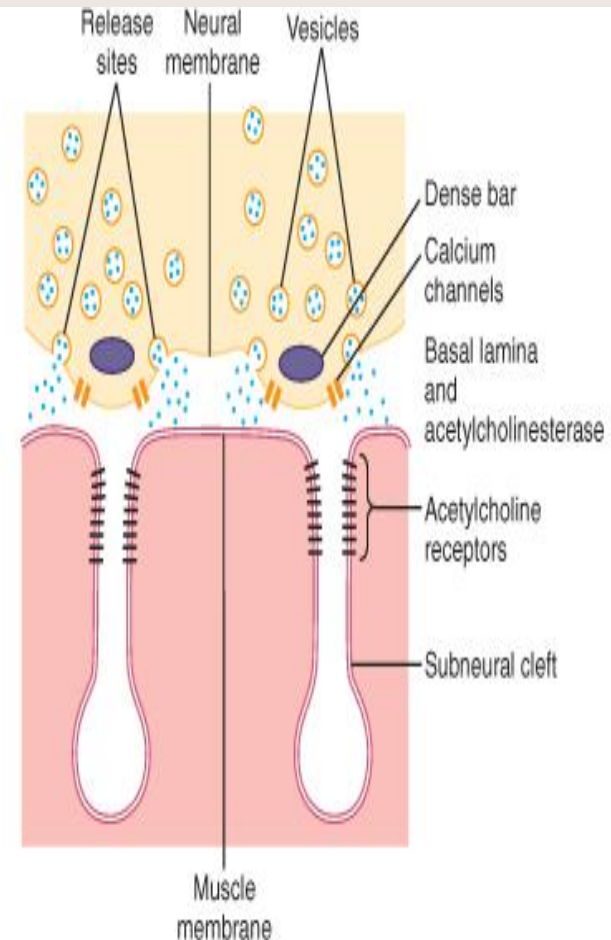
- The vesicles then fuse with the neural membrane and empty their acetylcholine into the synaptic space by the process of Exocytosis.





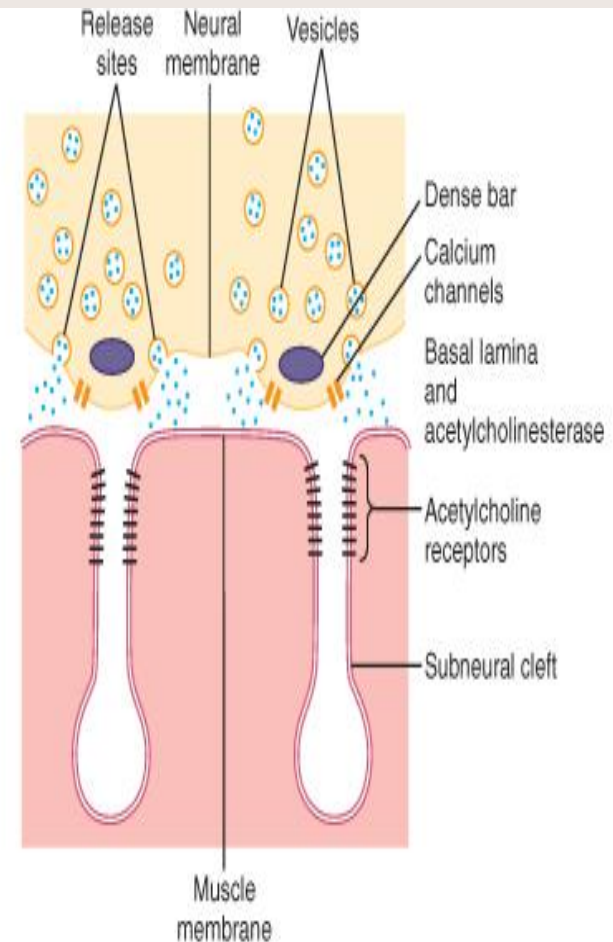
Effect of Acetylcholine on the post synaptic muscle fiber membrane to open the ion channels

- Acetylcholine receptors or acetylcholine gated ion channels are located almost entirely near the mouths of the subneural cleft, where the acetylcholine is emptied into the synaptic space.
- Each receptor is a protein complex that has a total molecular weight of 275000.



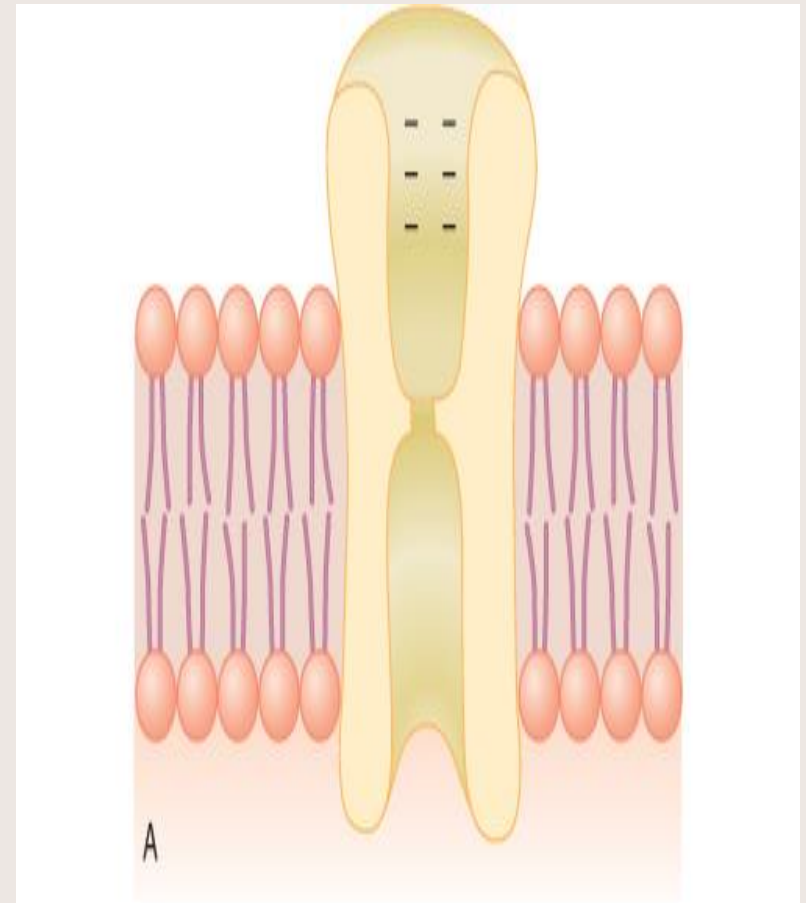
Effect of Acetylcholine on the post synaptic muscle fiber membrane to open the ion channels

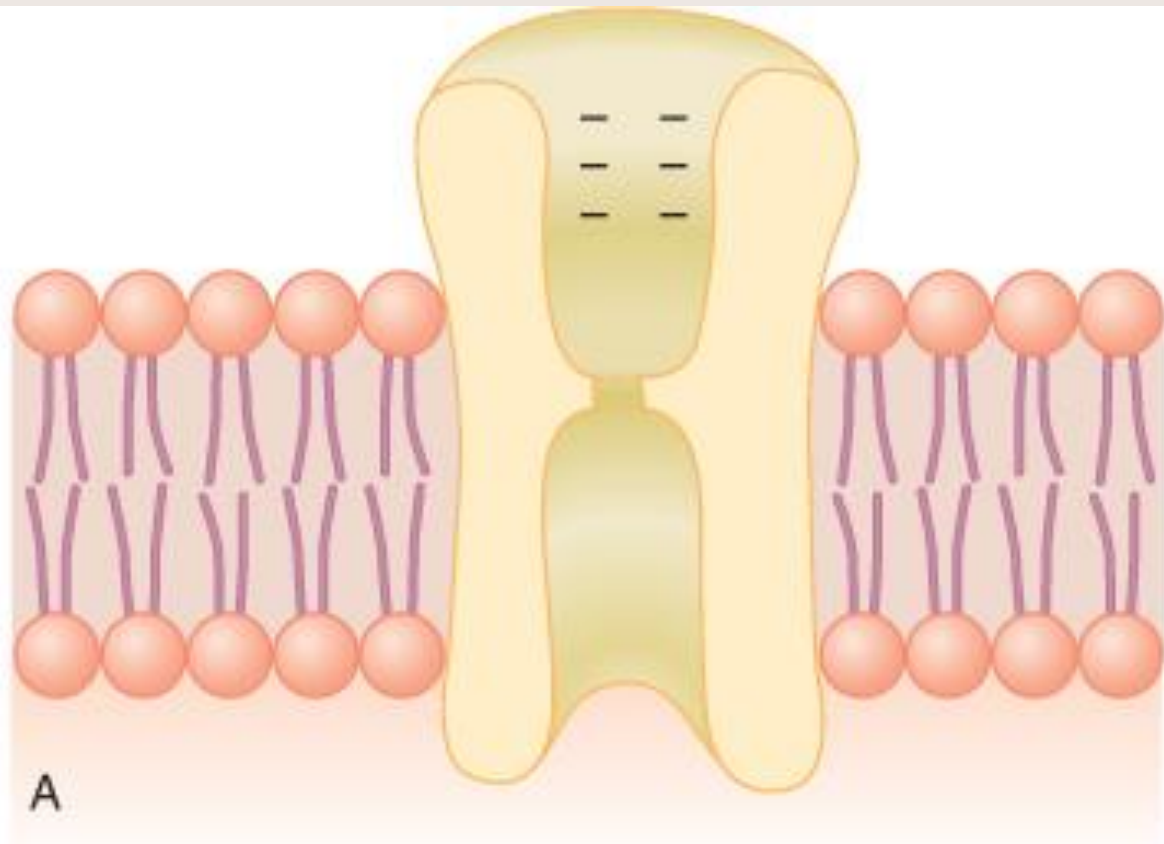
- After entering the synaptic cleft the acetylcholine molecules bind with receptors present in the post synaptic membrane and form the acetylcholine receptors complex.
- The complex is composed of five subunit proteins, two alpha proteins and one of beta, delta and gamma proteins.

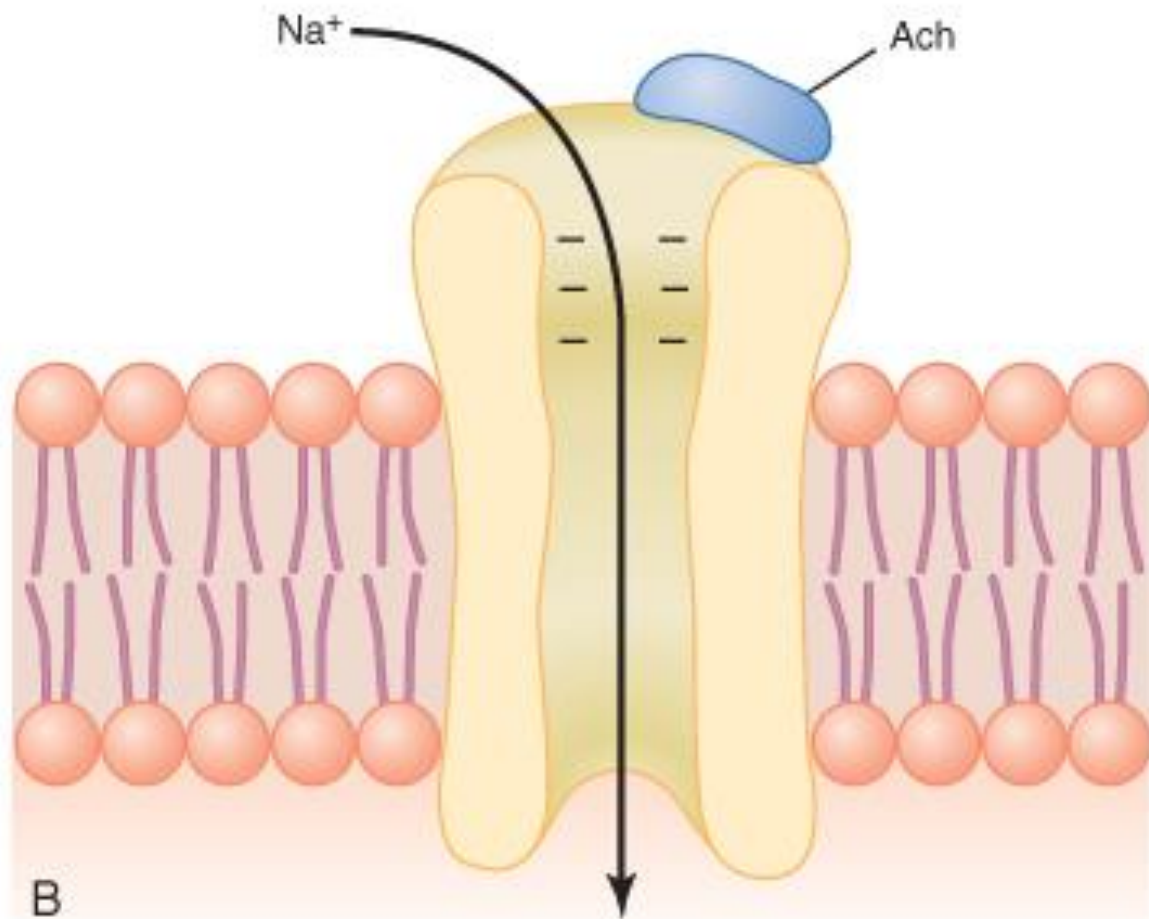


Effect of Acetylcholine on the post synaptic muscle fiber membrane to open the ion channels

- These protein molecules penetrate all the way through the membrane lying side by side in a circle to form a tubular channel.
- The channel remain constricted as shown in figure A. Until two acetylcholine molecules attach respectively to the two alpha subunit proteins.
- This causes a conformational change that opens the channels as shown in figure B .







Effect of Acetylcholine on the post synaptic muscle fiber membrane to open the ion channels

- The opened acetylcholine channels has a diameter of about 0.65nanometer which is large enough to allow Na^+ , k^+ , Ca^+ to move easily through the opening.
- Cl^- ions due to negative charge in the mouth of channels are repelled.
- More Na ions flow through the acetylcholine channels then any other ions.

Principal effect of opening the acetylcholine gated channels

- First there are only two positive ions in large concentration Na ions in the extracellular fluid and K ions in the intracellular fluid.
- The very negative potential on the inside of the muscle membrane -80 to -90 mV, pulls the +ve charged Na^+ ions to the inside of the fiber, while simultaneously efflux of the positively charged K ions when they attempt to pass outward.
- This creates a local positive potential charge inside the muscle fiber membrane, called the **end plate potential**.
- This end plate potential initiates an action potential that spreads along the muscle membrane and thus causes muscle contraction.

Destruction of the released Acetylcholine by acetylcholinesterase

- The acetylcholine ,once released into the synaptic space, continues to activate the acetylcholine receptors as long as the acetylcholine persists in the space.
- Acetylcholine is removed rapidly by two means. Most of the acetylcholine is destroyed by the enzyme acetylcholinesterase which is attached mainly to the spongy layer of connective tissue that fills the synaptic space and between the presynaptic nerve terminal and the post synaptic muscle membrane.

Destruction of the released Acetylcholine by acetylcholinesterase

- A small amount of acetylcholine diffuses out of the synaptic space and is then no longer available to act on the muscle fiber membrane.
- The short time that the acetylcholine remains in the synaptic space a few milliseconds at most normally is sufficient to excite the muscle fiber.



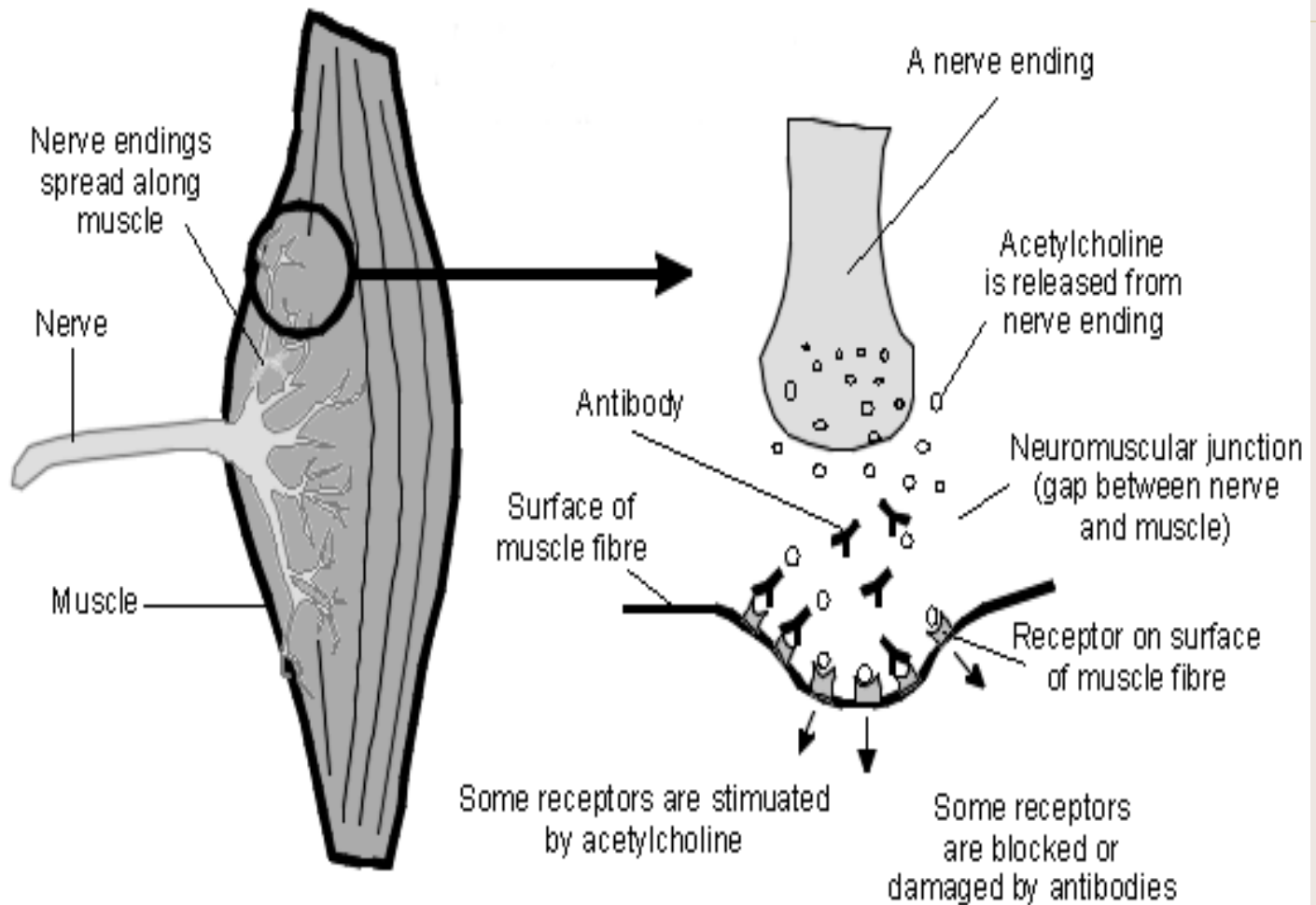


Myasthenia Gravis

- Neuromuscular disease
- Autoimmune mechanism: antibodies block acetylcholine receptors
- Prevalence: 85 - 125 per million
- Incidence: 2 - 4 million per year
- Age of onset:
 - 20 - 40 (women)
 - 60 - 80 (men = women)
- Females 3:2
- Symptoms:
 - Muscle weakness
 - Marked fatigability of skeletal muscles
 - Improves with rest

MYSTHENIA GRAVIS

- Is an autoimmune disease in which antibodies attack the acetylcholine receptors on the motor end plate region of the muscle cell.
- The symptoms are due to both the activation of the **acetylcholine receptors** and to the **disruption of the histology** of the motor end plate region.



Patho physiology of Myasthenia Gravis.

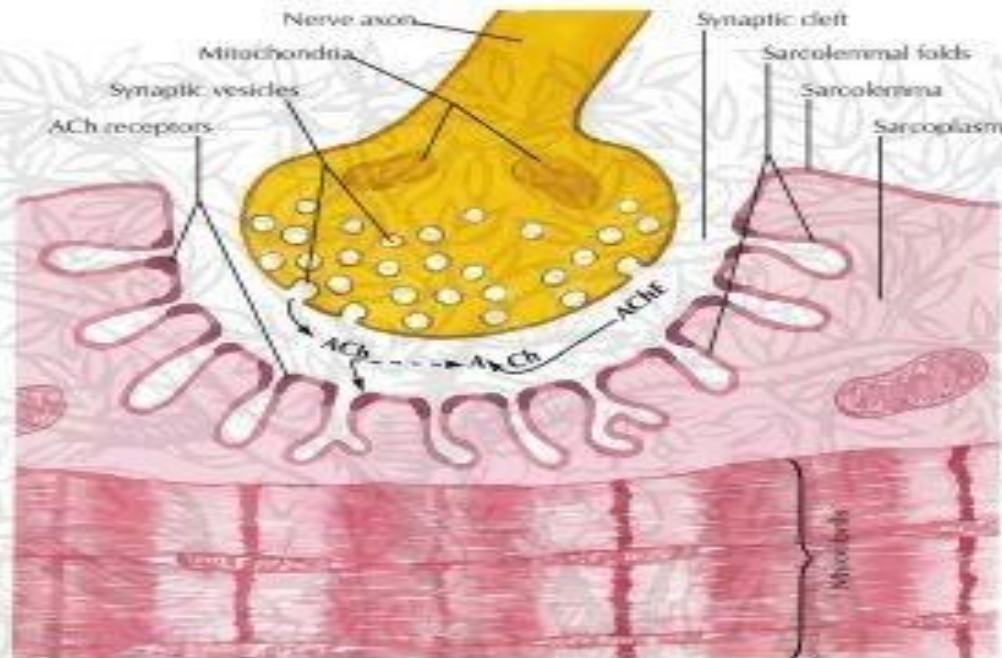
- Neuromuscular transmission requires the release of an appropriate amount of acetylcholine into the synaptic cleft
- The diffusion of the acetylcholine across the cleft
- Binding of the acetylcholine to the receptors opens a channel that is equally selective for Na^+ and K^+ and there is selective depolarization of the end plate region to -15mV .
- The depolarization generates an action potential that spreads along the skeletal muscle cell, causing the release from the sarcoplasmic reticulum and inducing a contraction.

Patho physiology of Myasthenia Gravis.

- Myasthenia gravis is a chronic autoimmune disease leading to destruction of the acetylcholine receptors(**approximately 70%**) on the motor end plate region of muscle cells.
- Acetylcholine release is normal ,**the absence of functional receptors on the motor end plate region of the muscle cell means that biological response is diminished.**
- Normally acetylcholine is degraded in the synaptic cleft by the activity of the enzyme acetylcholinesterase

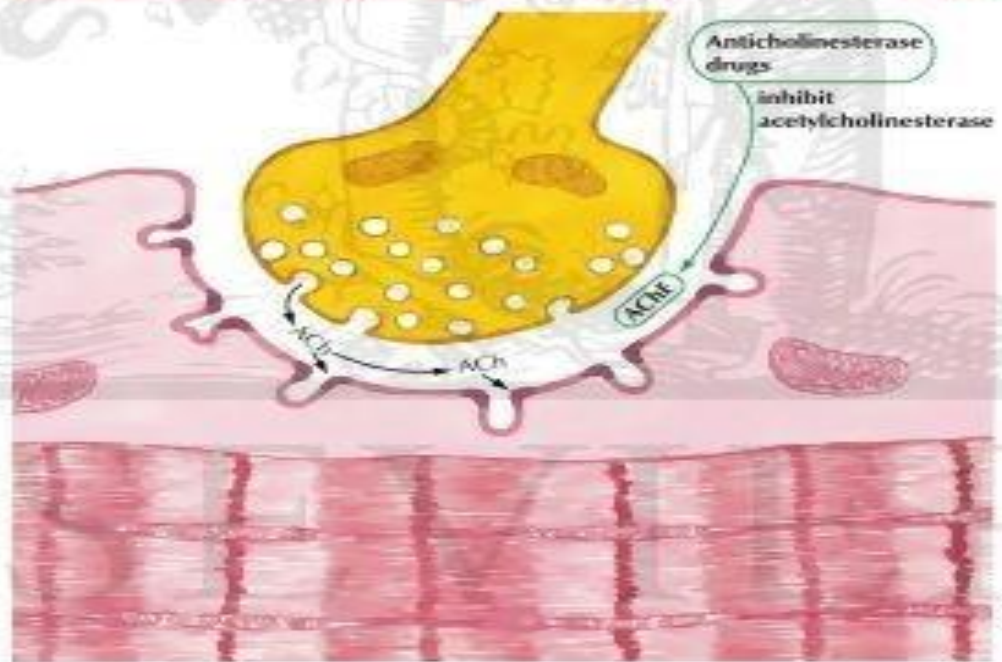
Normal neuromuscular junction

Synaptic vesicles containing acetylcholine (ACh) form in nerve terminal. In response to nerve impulse, vesicles discharge ACh into synaptic cleft. ACh binds to receptor sites on muscle sarcolemma to initiate muscle contraction. Acetylcholinesterase (AChE) hydrolyzes ACh, thus limiting effect and duration of its action.

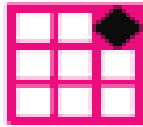


Myasthenia gravis

Marked reduction in number and length of subneural sarcolemmal folds indicates that underlying defect lies in neuromuscular junction. Anticholinesterase drugs increase effectiveness and duration of ACh action by slowing its destruction by AChE.



F. Netter M.D.



PATHOPHYSIOLOGY

IMPAIRED TRANSMISSION IN MYASTHENIA GRAVIS

NORMAL NEUROMUSCULAR TRANSMISSION

Motor nerve impulses travel to motor nerve terminal.



Acetylcholine (ACh) is released.



ACh diffuses across synapse.



ACh receptor sites in motor end plates depolarize muscle fiber.



Depolarization spreads, causing muscle contraction.

NEUROMUSCULAR TRANSMISSION IN MYASTHENIA GRAVIS

Motor nerve impulses travel to motor nerve terminal.



ACh is released.



ACh diffuses across synapse.

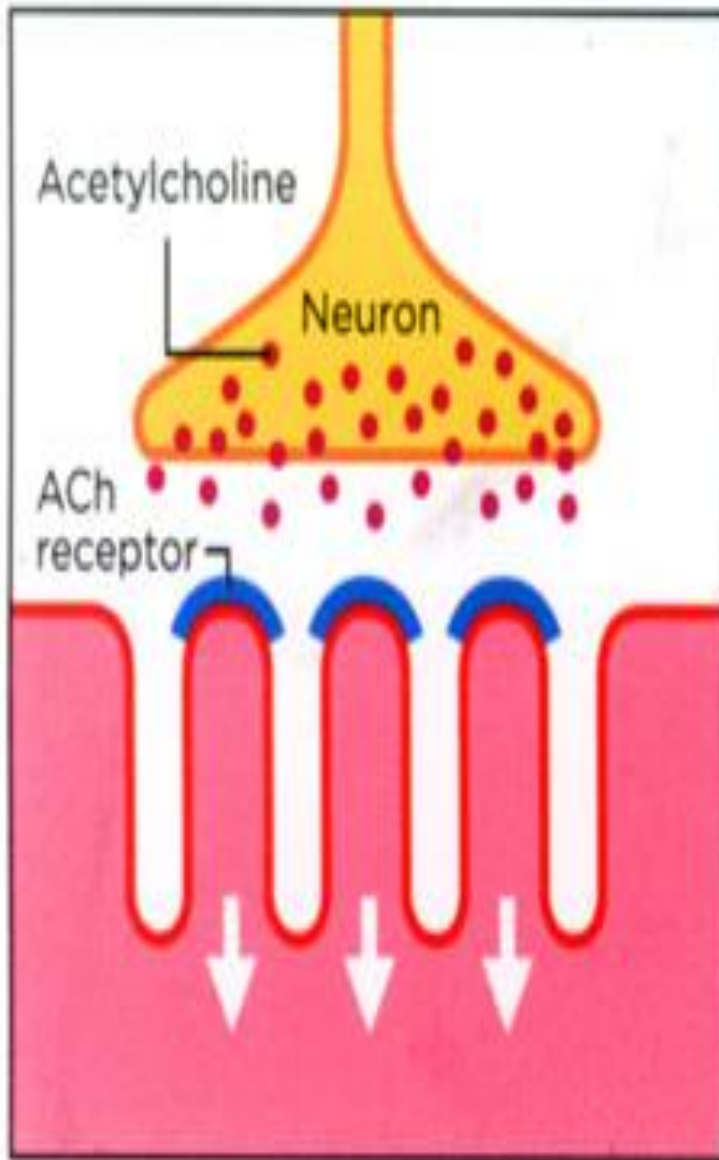


ACh receptor sites, weakened or destroyed by attached antibodies, block ACh reception.

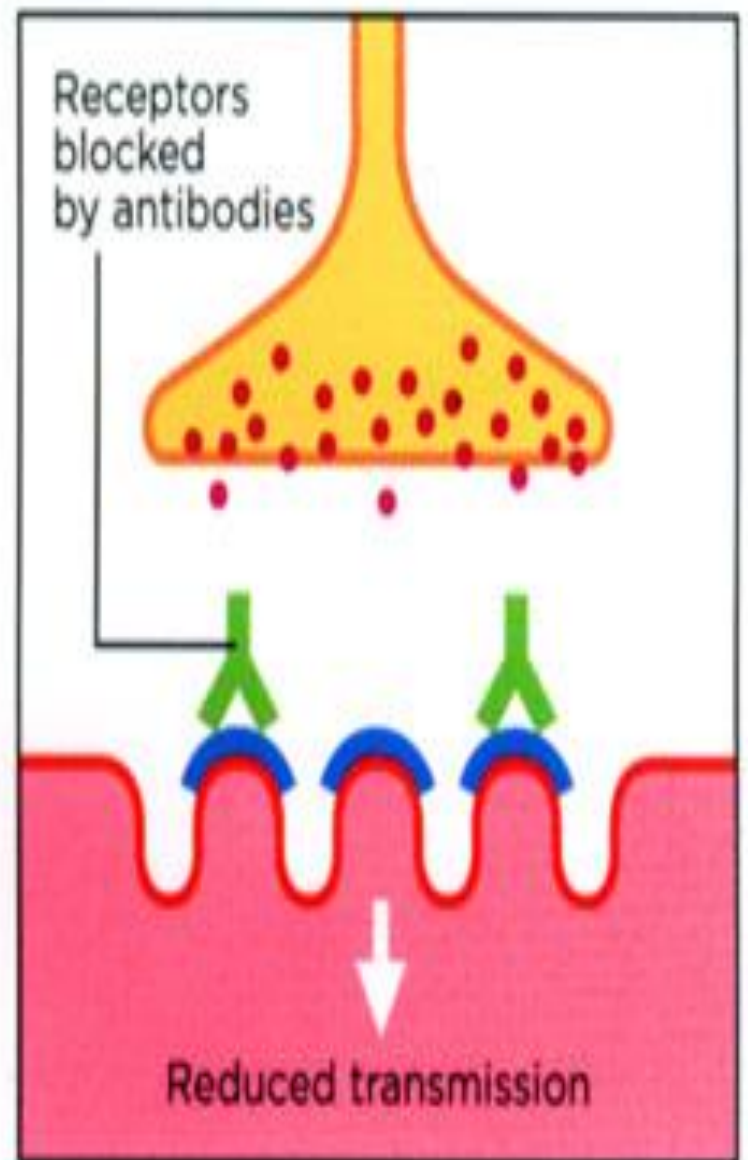


Depolarization and muscle contraction don't occur. Neuromuscular transmission is blocked.





Normal neuromuscular junction



Neuromuscular junction in myasthenia gravis

Ptosis (drooping of the eyelid)



Mysthenia gravis



Normal neuromuscular transmission begins with action potential traveling down the motor neuron

Action potential reaches the nerve terminal and activates Ca⁺ channels

↑ Calcium causes synaptic vesicles containing ACh to be released into synaptic cleft

Unknown initiating event

Associated Risk Factors include:

- Autoimmune disease
- Thymus abnormalities
- Genetic Link

T cell process produces **ACh receptor antibodies** which reduce normal neurotransmission: **MYASTHENIA GRAVIS**

- 3 mechanisms:
1. Directly alters function of receptor by blocking ACh binding and ACh receptor activation
 2. Promote endocytosis of Ach resulting to degradation of ACh R
 3. Destroys post synaptic surface leading to ↓ number of Ach R

↓neuromuscular transmission to skeletal muscle

Muscle weakness and fatigue with repetitive use = **myasthenic fatigue** due to continuous muscle contraction

Clinical Presentation of MG:

- Diplopia
- Ptosis
- “Snarling Expression”
- Dysphagia
- Nasal Speech
- Proximal Limb Weakness
- Respiratory Muscle Weakness

Outcome of myasthenia gravis

- Symptoms can be diminished by increasing the amount of acetylcholine in the synaptic cleft.
- This is done by administering Pyridostigmine, an acetylcholinesterase inhibitor.
- **Blocking the degradation of acetylcholine acts to increase the effective concentration of acetylcholine in the synapse and therefore activates a greater percentage of the remaining functional acetylcholine.**
- Plasma testing: Presence of antibodies directed against the acetylcholine receptors (normal $< 0.03 \text{ mmol/L}$)

Excitation contraction coupling

- Action potential comes down the neuron---Axon terminal—stimulates Ca to enter axon terminal---Ca causes the vesicles to releases—Acetylcholine—Acetylcholine are ion channels which causes the flow of ions which is responsible for the change in potential.
- When the membrane depolarizes voltage gated Ca channels present in the sarcolemma open up and Ca moves into the sarcoplasm from the extracellular fluid.
- This Ca from the Sarcoplasmic Reticulum stimulates the release of more Calcium called as Calcium induced calcium release(CICR)
- Increased Ca bind to Troponin move the Tropomyosin out of the way thus it help in muscle contraction.

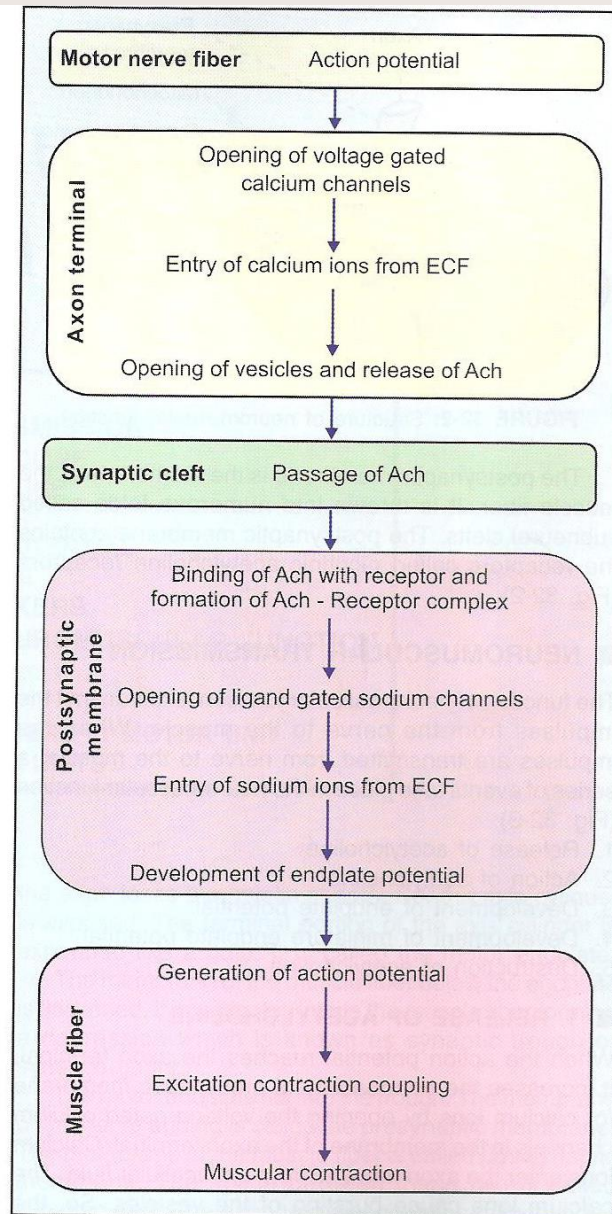


FIGURE 32-3: Sequence of events during neuromuscular transmission. Ach = Acetylcholine. ECF = Extracellular fluid

CARDIAC MUSCLES HEART MUSCLE CELLS OR MYOCARDIAL CELLS

- Striated, involuntary effectors regulated by autonomic by motor neurons.
- Contain actin and myosine filaments arranged in the form of sarcomeres.
- Nucleus is in the center of the cell.
- Contract by means of the sliding filament mechanism.
- Myocardial cells are short, branched and interconnected.
- The gap junctions are fluid filled channels through the plasma membrane of adjacent cells that permit the conduction of impulses from one cell to the next.
- Gap junction is composed of connexin proteins
- The gap junctions are concentrated at the ends of each myocardial cells, which permits electrical impulses to be conducted primarily along the long axis from cell to cell.
- Gap junctions in cardiac muscle have an affinity for stain that makes them appear as dark lines between adjacent cells when viewed in the light microscope. These dark staining lines are known as intercalated discs.

Cardiac muscles.

- The muscle fibers are 10-100um in diameter and their length varies with length of the muscle cell.
- Each muscle is composed of small fibrous structure called myofibrils lying parallel to the long axis of the cells.
- The myofibrils are separated by small amount of sarcoplasm containing row of mitochondria
- The mitochondria are of great amount showing great cardiac activity and contain abundant oxidative enzyme.
- In fact heart is not one syncytium but it consists of two syncytia. two atria form one syncytium and two ventricles form the other syncytium.
- The bundle of His is the only connection between the atria and ventricles.

Cardiac muscles

- Intercalated discs form tight junction between the muscle fibers and do not permit any ion to pass through.
- Intercalated disc play an important role during contraction of the muscle by pulling the muscle fibers with one another(functional syncytium).
- The resting membrane potential is about -85 to-95mv.

Functions of intercalated disc

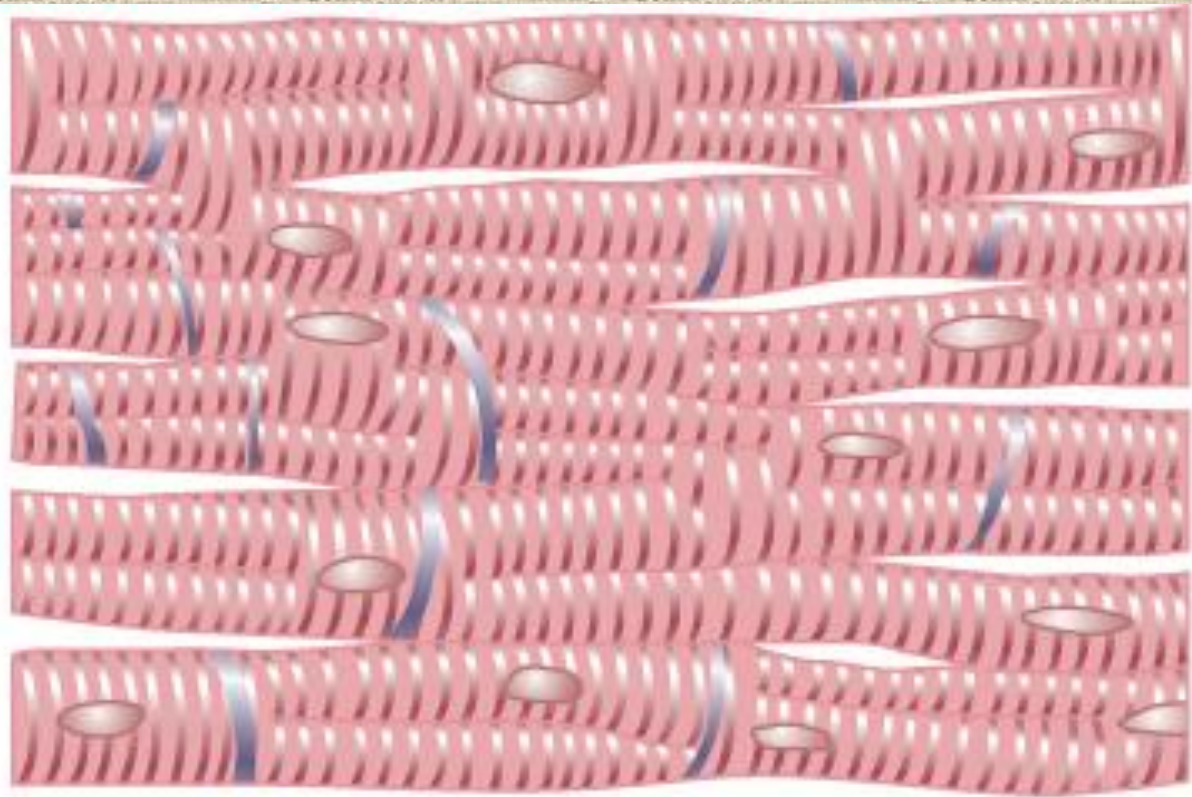
- The intercalated disc always coincides with the Z line
- The intercalated disk binds the cells.
- It transmits the force of contraction.
- It provides area of low electrical resistance for rapid spread of excitation throughout the myocardium
- It is an interdigitating junction.

CARDIAC MUSCLES HEART MUSCLE CELLS OR MYOCARDIAL CELLS (CONTINUED)

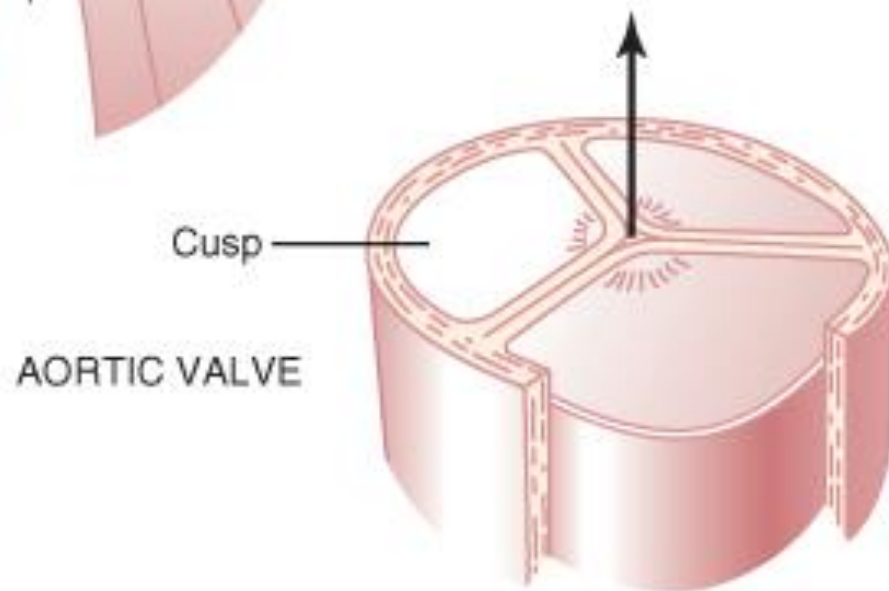
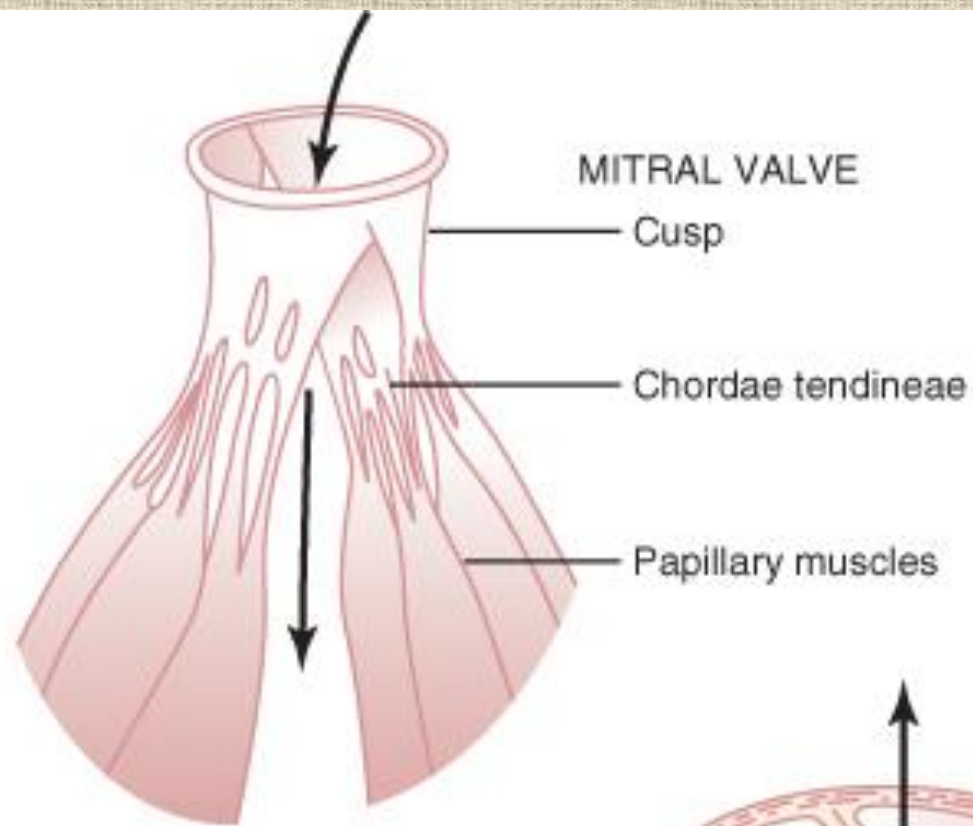
- Electrical impulses that originate at any point in a mass of myocardial cells called a myocardium, can spread to all cells in the mass that are joined by gap junction.
- Due to gap junction, the myocardium are electrically joined and behaves as a single functional unit.
- Cardiac muscle is able to produce action potential autonomically.
- Cardiac action potentials normally originate in a specialized group of cells called the pace maker.
- The rate of this spontaneous depolarization and thus the rate of the heart beat are regulated by autonomic enervation.
- Cardiac muscle are striated actin and myosine arranged in sarcomeres.
- T tubular system is more numerous and is formed by the sarcolemma (plasma membrane of the muscle cell) extending transversely.

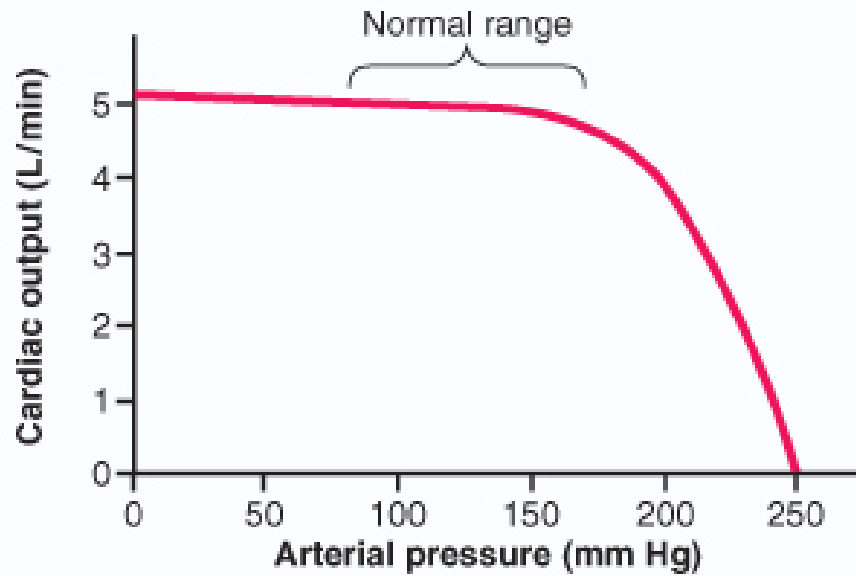
CARDIAC MUSCLES HEART MUSCLE CELLS OR MYOCARDIAL CELLS (CONTINUED)

- Contain troponin in the thin filaments.
- Ca enters cytoplasm from sarcoplasmic reticulum and extracellular fluid.
- Ca entry originate action potential in pace maker cells of heart
- Long plateau in action potential the contraction time is longer in cardiac muscle by about 5 to 15 times than in skeletal muscle.
- The action potential spreads through the cardiac muscle very rapidly this is because of the presence of gap junction in the cardiac muscle fibers, which allows the free movements of ions.
- If the stimulus is applied, whatever may be the strength, the muscle responds to a maximum or does not give response at all. This is called all or none law



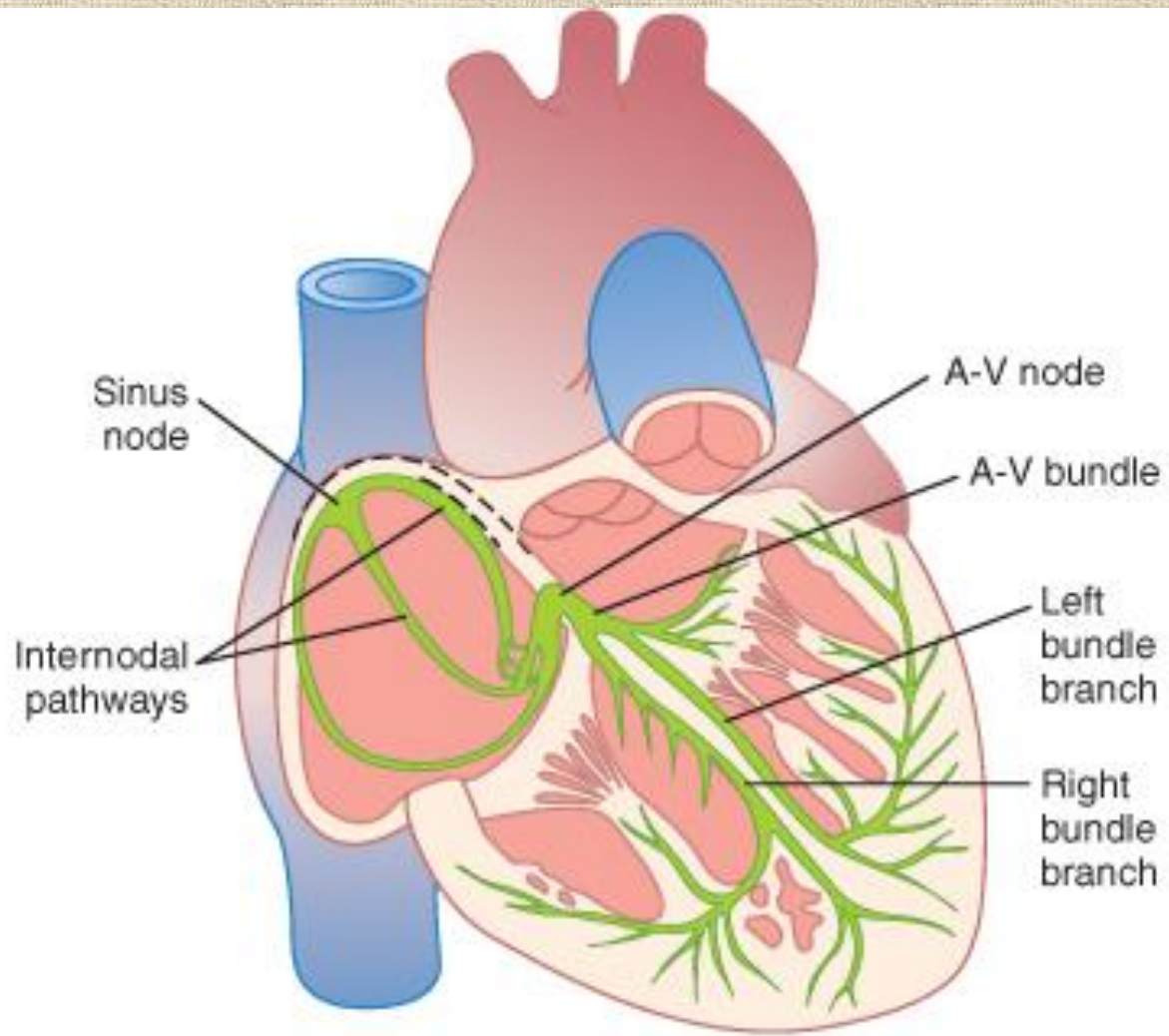
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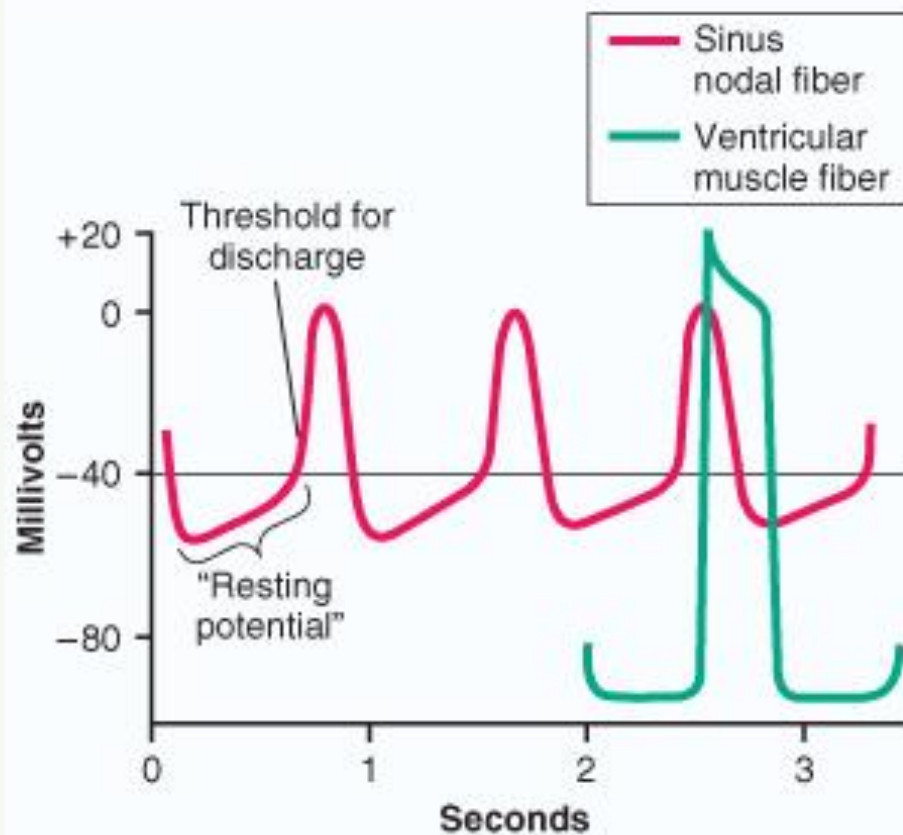


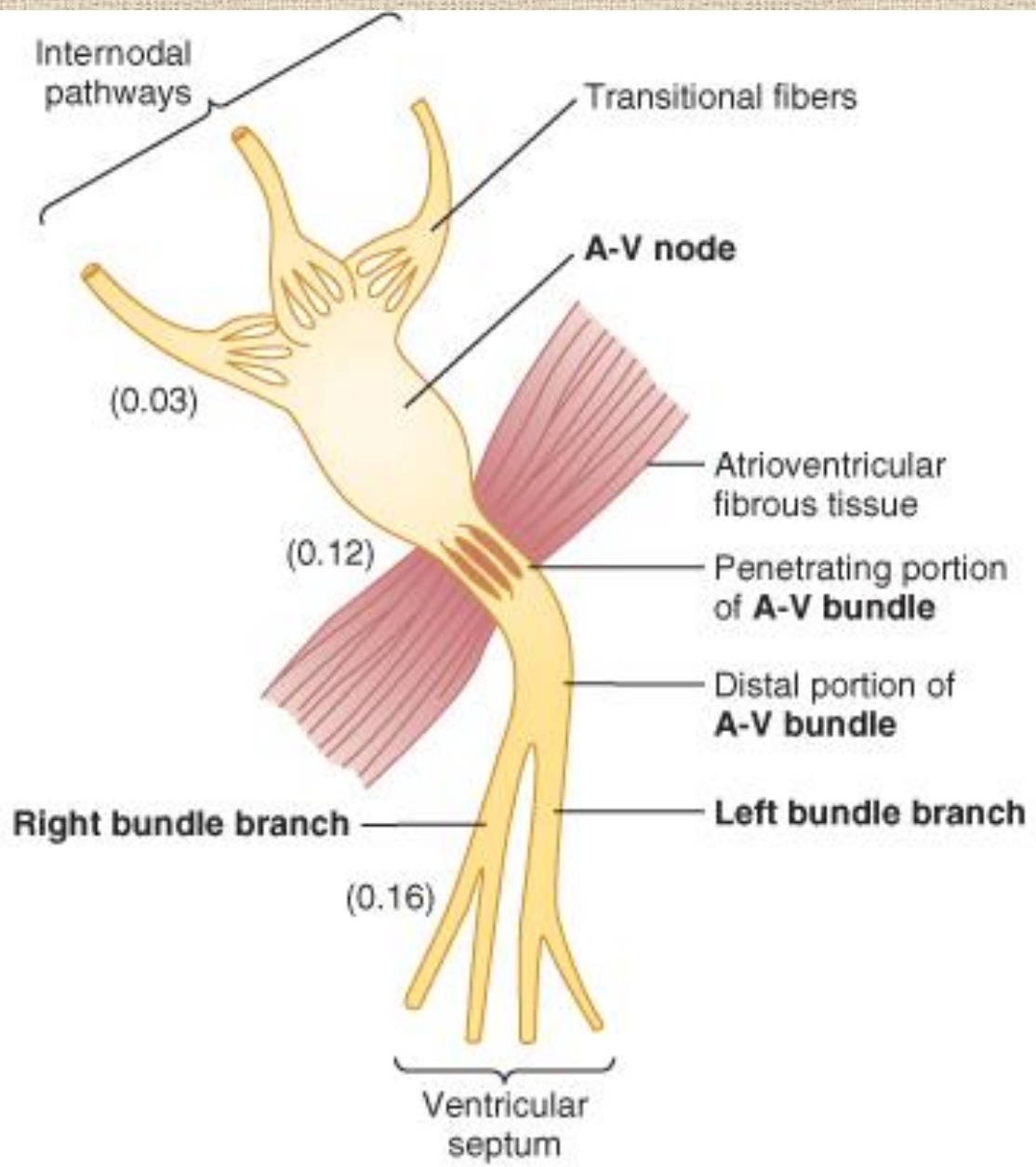


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CARDIAC MUSCLE

➤ Cardiac muscle like skeletal muscle, contains the troponin complex of three proteins.

Troponin I: Helps inhibit the binding of the myosin cross bridges to actin.

Troponin T: Binds to troponin myosin in the thin filaments.

Troponin C: Binds to calcium for muscle contraction.

Thus troponins T and I are slightly different in cardiac muscle than in skeletal muscle thus troponins T and I released by damaged myocardial cells can be distinguished and measured by laboratory tests using specific antibodies.

➤ Smooth muscles are nonstriated (plain) involuntary muscle.

➤ Smooth muscle fibers are fusiform or elongated cells of different length.

➤ The nucleus is single and elongated and it is centrally placed. containing two or more nuclei in the centre.

Properties of cardiac muscle

1. Functional syncytium
2. Rhythmicity
3. Refractory period is further subdivided into absolute refractory period and relative refractory period
4. Conductivity
5. Contractility

Properties of cardiac muscle

6. Stair case phenomenon.

7. Tone.

8. All or Nothing principle

9. Peculiar action potential in cardiac muscle

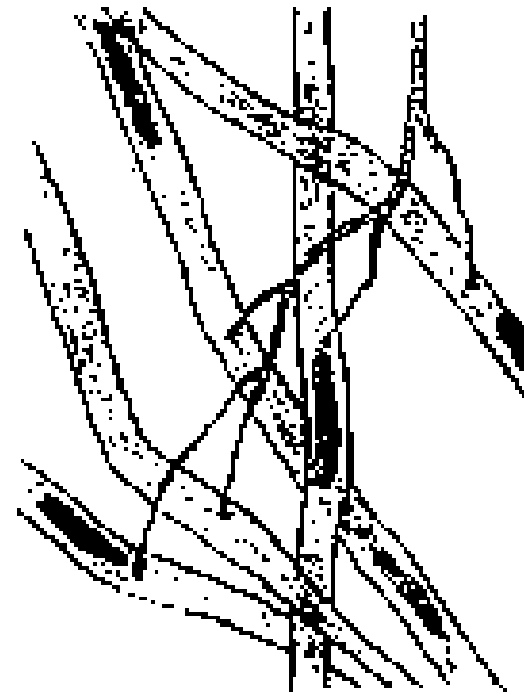
10. Excitability.

Smooth muscle

- Non striated.
- Involuntary.
- Elongated cells of different length.
- Nucleus is single and elongated and it is centrally placed. Normally two or more nucleoli are present in the nucleus
- Smooth muscle fibers are generally small, 2 to 5 micron in diameter and 50 to 200 micron in length.
- The muscle fiber contain myofibrils.
- The smooth muscle fiber contain actin, myosin and tropomyosin components.
- In the smooth muscle **troponin is absent** and **sarcoplasmic reticulum is poorly developed**.
- Ca ions combines with **calmodulin** leading to initiation of contraction.



Single-



Multi-unit

Smooth muscle

COMPARISON

Single unit smooth muscle

Multi unit smooth muscle

- Single-unit muscle are gathered into dense sheets or bands.
- The fibres run roughly parallel, they are densely and irregularly packed together, most often so that the narrower portion of one fibre lies against the wider portion of its neighbour

- The multi-unit smooth muscle fibres have no interconnecting bridges. They are mingled with connective tissue fibres.

• **Single unit smooth muscle**

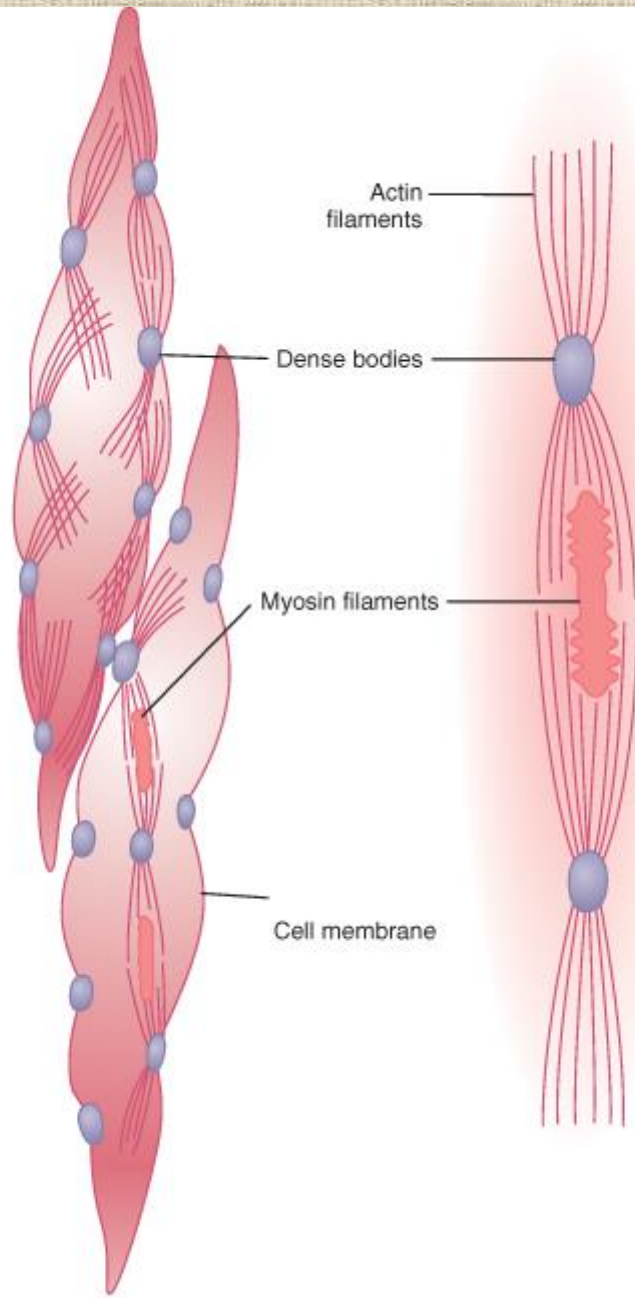
- These fibres have connections, the plasma membranes of two neighbouring fibres form gap junctions that act as low resistance pathway for the rapid spread of electrical signals throughout the tissue
- Single-unit smooth muscle has pacemaker regions where contractions are spontaneously and rhythmically generated. The fibres contract in unison, that is the single unit of smooth muscle is syncytial.

Multi unit smooth muscle

- The fibres of multi-unit smooth muscle are innervated by sympathetic and parasympathetic nerve fibres and respond independently from each other upon nerve stimulation.

SMOOTH CELLS

- Smooth (visceral) muscles are arranged in circular layers in the walls of blood vessels and bronchioles.
- Both circular and longitudinal smooth muscle layers occur in the tubular digestive tract, the ureters and it helps in peristaltic waves.
- Smooth muscle cells **do not contain sarcomeres** (which produce striations in skeletal and cardiac muscle).
- The ratio of thin (Actin) to thick (myosine) filaments is about **16 to 1** (in striated muscle the ratio is 2 to 1).
- Unlike striated muscles, in which the thin filaments are relatively short (extending from a z disc into a sarcomer), **the thin filaments of smooth muscle cells are quite long.**
- The thin filament are attached either to regions of the plasma membrane of the smooth muscle cell or to cytoplasmic protein structure called **dense bodies which are analogous to the Z discs of striated muscle.**



SMOOTH CELLS (CONTINUED)

- In smooth muscle, the myosine proteins of the thick filaments are stacked vertically so that their long axis is perpendicular to the long axis of the filament.
- The myosine head conform cross bridges with actin all along the length of the thick filament.
- **Dense bodies are round, amorphous bodies scattered through the cytoplasm of smooth muscle fibers; they appear to be points of attachment for myofilaments.**
- In general, smooth muscle contains much less protein (~110 mg/g muscle) than skeletal muscle (~200 mg/g). Notable is the decreased myosin content, ~20 mg/g in smooth muscle versus ~80 mg/g in skeletal muscle. On the other hand, the amounts of actin and tropomyosin are the same in both types of muscle

Smooth muscle

- The resting membrane potential of smooth muscle is -50 to -60mV

Smooth muscle

Smooth muscle are divided as multiunit smooth muscle and unitary(or single unit)smooth muscle

Multi unit smooth muscle: This type of smooth muscle is composed of discrete smooth muscle fiber.

Each fiber operates independently of the others and often **is innervated by a single nerve ending**, as occurs for skeletal muscle fibers.

The outer surface of these fibers are covered by thin layer of basement membrane like substance, a mixture of fine collagen and glycoprotein fibrillae and helps to insulate the separate fibers from one another. **These smooth muscle fibers do not exhibit spontaneous contractions**

Example of multiunit smooth muscle are the ciliary muscle of the eye. Walls of large blood vessels, Large airways of the lungs,Iris of the eye,At the base of the hair.

Unitary Smooth muscle

- Whole mass is composed of hundred to thousands of smooth muscle fibers that contract together as a single unit.
- The fibers are aggregated into sheets or bundles, and their cell membrane are adherent to one another at multiple points so that force generated in one muscle fiber can be transmitted to the next.

Unitary Smooth muscle

- The cell membrane are joined by many gap junctions through which ions can flow freely from one cell to the next and cause the muscle fibers to contract together. This type of smooth muscle also is known as syncytial smooth muscle because of its syncytial interconnections among fibers.
- Example are gut, bileducts, uterus, blood vessels often called visceral smooth muscle.

VISCERAL SMOOTH MUSCLE FIBER (SINGLE UNIT)

- The electrical changes leading to **contraction of multiunit smooth muscle occur in response to nervous stimuli**. The neurotransmitter like acetylcholine and nor adrenaline secreted by the nerve ending are responsible for the electrical changes leading to contraction.
- Action potential is not caused by the neurotransmitters in the multiunit smooth muscles. Rather a slight depolarization called local junctional potential occurs.
- Single unit smooth muscle also display **intrinsic, or myogenic electrical activity and contraction in response to stretch**. These smooth muscle fibers do not exhibit spontaneous contractions



Action potential in smooth muscle

- It is about 100mV as on rising from very negative membrane potential of -60mV to a slightly positive value of 40mV.
- The action potential in smooth muscles may be generated by electric excitation hormones, stimulators or as a result of spontaneous generation of impulse in smooth muscle fiber itself
- In case of spike potential duration of action potential is 0.01-0.05 second. Action potential with plateau 1 second.

Slow wave potential

- The instability of the resting membrane potential is caused by the appearance of some wave like fluctuations called slow waves.
- The slow waves occur in a rhythmic fashion that a frequency of 4 to 10 per minute with the amplitude of 10 to 15mV.
- The cause of the slow rhythm is not known.
- The slow wave is not action potential and it **cannot cause contraction** of the muscle but it can initiate action potential.

Action potential

- Three types of action potential occur in visceral smooth muscle.
 1. Spike potential.
 2. Spike potential initiated by slow wave rhythm.
 3. Action potential with plateau.

Spike potential

- The spike potential in visceral smooth muscle appears similar to that of skeletal muscle, but it is different from the spike potential in skeletal muscles in many ways.
- In smooth muscle, the average duration of spike potential varies between 30 and 50 millisecond, its amplitude is very slow and it does not reach the isoelectric base.
- Sometimes the spike potential rise above the isoelectric base(overshoot).
- The spike potential is due to nervous and other stimuli and it leads to contraction f the muscle.

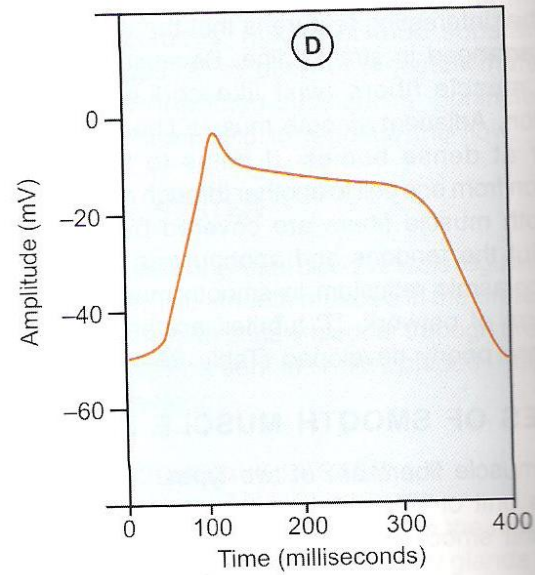
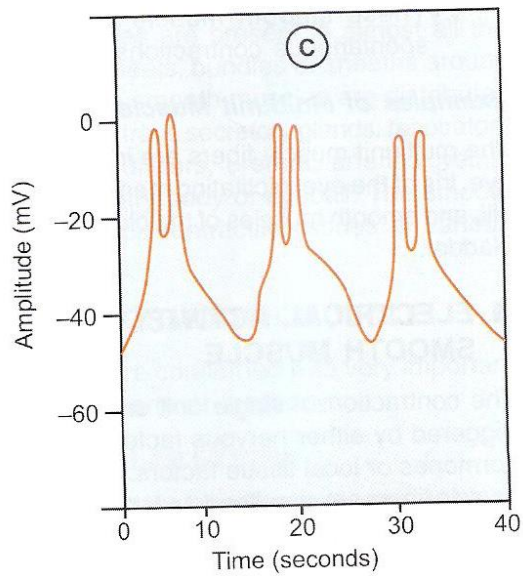
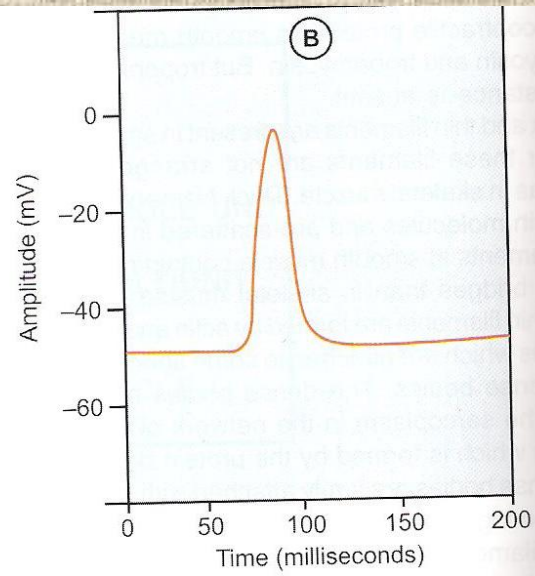
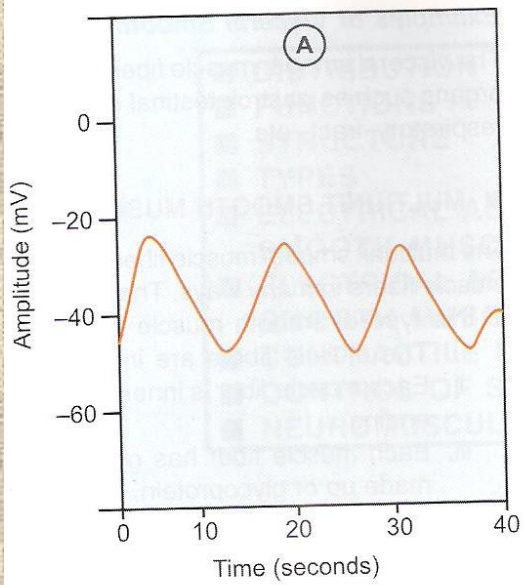


FIGURE 33-1: Electrical activities in smooth muscle

- A = Slow wave rhythm of resting membrane potential
- B = Spike potential
- C = Spike potential initiated by slow wave rhythm
- D = Action potential with plateau

Spike potential initiated by slow rhythm(pacemaker waves)

- The slow wave rhythm of resting membrane potential initiates the spike potentials ,which lead to contraction of the muscle.
- The spike potential appear rhythmically at a rate of about one or two spikes at the peak of each slow wave.
- The spike potentials initiated by the slow wave rhythm cause rhythmic contractions of smooth muscles.
- They are self excitatory and contract themselves without any external stimuli.
- The smooth muscles showing rhythmic contractions are present in some of the visceral organs such as intestine.

Action potential with plateau

- This type of action potential starts with rapid depolarization as in case of skeletal muscles.
- But repolarization does not occur immediately.
- The muscle remains depolarized for long periods of about 100 to 1000 milliseconds.
- This type of action potential is responsible for sustained contraction of smooth muscle fibers.
- After the long depolarized state, slow repolarization occurs.

Tonic contraction of smooth muscle without action potential.

- The smooth muscles of some visceral organs maintain a state of partial contraction called tonus or tone.
- Tonic contraction of the muscle occurs without any action potential or any stimulus.

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Ionic basis of action potential

- In skeletal muscle, the depolarization occurs due to opening of sodium channels and entry of sodium ions from extracellular fluid into the muscle fiber.
- Fast sodium that open and close rapidly
- In smooth muscle, the depolarization is due to entry of calcium ions rather than sodium ions.
- The calcium channels open and close slowly.(it is responsible for the prolonged action potential with plateau in smooth muscles)
- The calcium ions play an important role during the contraction of the muscle.

Contraction process

- In smooth muscles the contraction and relaxation process are slow.
- It is because of poor development of L tubules(sarcoplasmic reticulum) in smooth muscle fibers.
- So the Ca^+ ions, are responsible for excitation contraction coupling, must be obtained from the extracellular fluid. it makes the process of excitation contraction coupling slow.
- Thus the total twitch period is very long and it is about 1to3 seconds. A muscle twitch is an involuntary contraction of a muscle group without conscious effort
- **three phases of a muscle twitch**

Latent, contraction, and relaxation

-

- In skeletal muscle the total twitch period is 0.01second.

EXCITATION CONTROL

COUPLING IN SMOOTH MUSCLE

- As in striated muscle, the **contraction of smooth muscles is triggered by a sharp rise in the Ca^+ concentration** within the cytoplasm of the muscle cells.
- **Sarcoplasmic reticulum is less developed in smooth muscle**, and Ca released from this organelle may account for only the initial phase of smooth muscle contraction.
- Extra cellular Ca diffusing into the smooth muscle cells through its plasma membrane is responsible for sustained contraction.
- This Ca enters primarily through voltage regulated calcium channels in the plasma membrane.
- The opening of these channels is graded by the amount of depolarization, the greater the depolarization, the more Ca^+ will enter the cell and the stronger will be the smooth muscle contraction.
- In striated muscle, Ca^+ combines with troponin.

EXCITATION CONTROL COUPLING IN SMOOTH MUSCLE (CONTINUED)

- Troponin is not present in smooth muscle cells. In smooth muscle Ca^{+} combines with a protein in the cytoplasm called calmodulin (which is structurally similar to troponin).
- The Calmodulin Ca^{+} complex.



Activates myosin light chain kinase (MLCK) an enzyme



one of the light chains of each myosine head, called the regulatory chain, becomes phosphorylated in response to this myosine kinase.

- When this chain is not phosphorylated, the attachment detachment cycling of the myosin head with the actin filament does not occur.
- but when the regulatory chain is phosphorylated (means the addition of phosphate group to an organic molecule) the head has the capability of binding repetitively with the actin filament the same as occurs for skeletal muscles, thus causing muscle contraction.

Latch phenomenon

- **A smooth muscle contractile response proceeds at a more leisurely pace than does a skeletal muscle twitch. A single smooth muscle contraction may last as long as 3 seconds, compared to 100 msec required for a single contractile response in skeletal muscle.**
- **The rate of ATP splitting by myosine ATPase is much slower in smooth muscle, so cross bridge activity and filament sliding occurs more slowly.**
- **Smooth muscle also relaxes more slowly because of a slower rate of Ca removal.**
- **Slowness should not be equated with weakness, however smooth muscle is able to generate the same contractile tension but it does so more slowly and at considerably less energy expense it is responsible for the sustained contraction of the muscle without fatigue. It is called latch bridge mechanism.**
- **The relaxation of the muscle occurs due to the dissociation of calcium calmodulin complex.**

EXCITATION CONTROL COUPLING IN SMOOTH MUSCLE (CONTINUED)

- Unlike the situation in striated muscle cell, which produces all or none action potential, smooth muscle cells can produce graded depolarizations and contractions without producing action potentials.
- Graded depolarization are conducted from cell to cell in many smooth muscles. The greater the depolarization of a smooth muscle cells, the more Ca^{+} will enter and the more MLCK enzymes will be activated, more cross bridges will become phosphorylated and able to bind to actin.

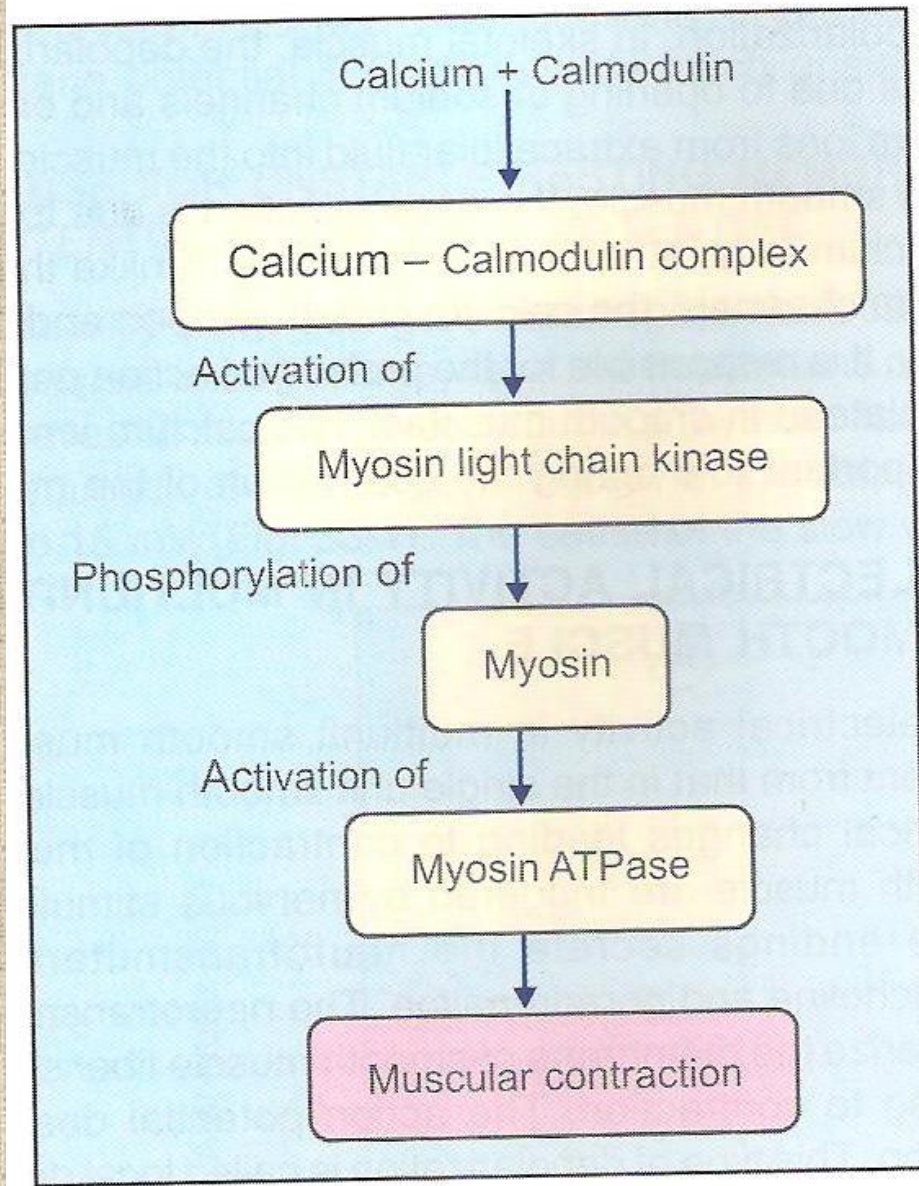


FIGURE 33-2: Molecular basis of smooth muscle contraction

Length tension relationship- plasticity

- Smooth muscle fibers have the property of plasticity.
- If the smooth muscle fibers is stretched ,it adapts to this new length and contracts when stimulated
- This adaptability to a wide range of lengths is called plasticity
- Because of this property,tension produced in the muscle fiber is not directly proportional to resting length of the muscle fiber.
- In skeletal and cardiac muscles,the tension or force of contraction is directly proportional to initial length of the muscle fibers.
- In spite of plasticity,smooth muscle fibers contract powerfully like the skeletal muscles fibers,
- Example is digestive organs like stomach which undergo remarkable changes in volume.

Control of smooth muscle

- Smooth muscle fibers are controlled by:
 1. Nervous factors
 2. Humoral factors

Nervous factors

- Smooth muscles are supplied by both sympathetic and parasympathetic nerves.
- These nerves are not responsible for the initiation of any activity in smooth muscle.
- Tone of the muscle is also independent of nervous control.

Neuromuscular junction in smooth muscle.

- Well defined neuromuscular junction is absent in smooth muscle
- The nerve fibers (axons) do not end as branches or motor end plate.
- These nerve fibers end on smooth muscles fibers in three different ways.

NEUROMUSCULAR JUNCTION IN SMOOTH MUSCLE

1. The nerve fibers diffuse on the sheet of smooth muscle fibers without making any direct contact with the muscle.
2. The diffused nerve fibers form diffuse junctions which contain neurotransmitters.
3. The neurotransmitters are released into the matrix which coats the smooth muscle fiber. From here the neurotransmitters enter the muscle fiber.

Neuromuscular junction in smooth muscle.

- In some smooth muscle fibers, the terminal part of the axon divides into many branches called varicosities.
- These varicosities have vesicles which contain the neurotransmitters.
- The neurotransmitters is released from varicosities through their wall into the muscle fiber.

Neuromuscular junction in smooth muscle

- In some of the multiunit smooth muscle fibers, a gap is present between varicosities and the membrane of smooth muscle fibers which resembles the synaptic cleft in skeletal muscle.
- The width of this gap is 30-40nm.
- This gap is called contact junction and it function as neurotransmitter junction of skeletal muscles.

Humoral factors

- The activity of smooth muscle is also controlled by humoral factors which include hormones, neurotransmitters and other humoral factors.
- The action of hormones and neurotransmitter depends upon the type of receptors present in the membrane of smooth muscle fibers in particular area.
- If excitatory receptors are present, the hormones or the neurotransmitters contract the muscle by producing depolarization.

Humoral factors.

- If inhibitory receptors are present the hormones or neurotransmitters relax the muscles by producing hyperpolarization.
- The hormones and neurotransmitters which act on the smooth muscles are: Acetylcholine, ADH, Adrenalin, Angiotensin 2, 3, 4, Endothelin, Histamine, Noradrenaline, oxytocin, serotonin.

Other humoral factors

- The humoral factors other than the hormones cause relaxation of the smooth muscle fibers. Humoral factors which act on smooth muscle are lack of oxygen, increase in hydrogen ion concentration, Lactic acid, decrease in Ca^+ ion.