Handout for lecture 2

Introduction

Three types of muscle are found in our body
- Skeletal
- Cardiac
- Smooth muscle cells

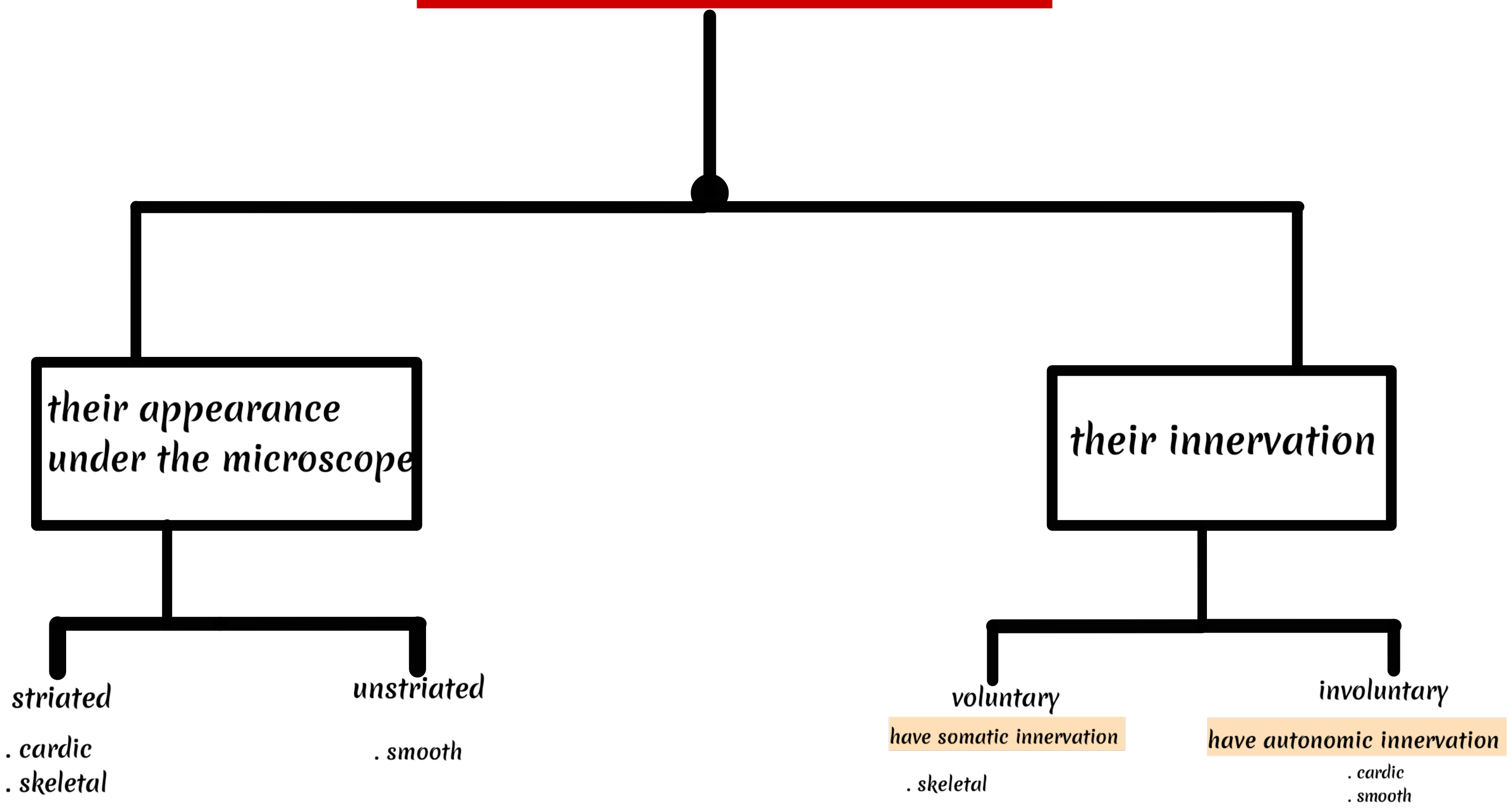
These cells are found where mechanical activity is needed

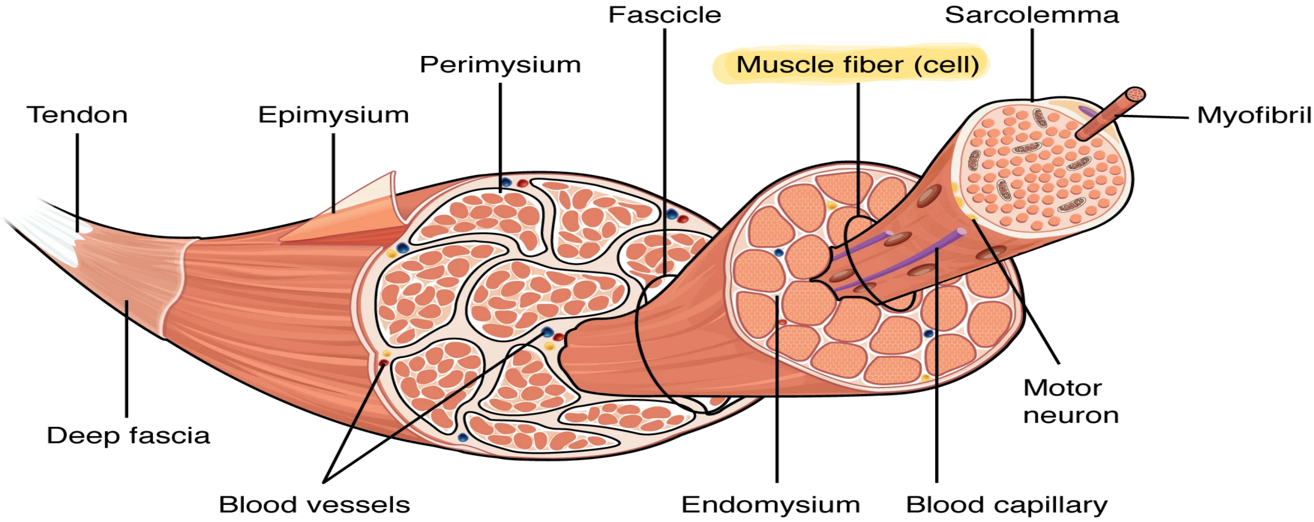
- contraction of skeletal muscles : Movements of the whole body or parts of it

- contraction of cardiac muscle: Pumping of blood in vessels

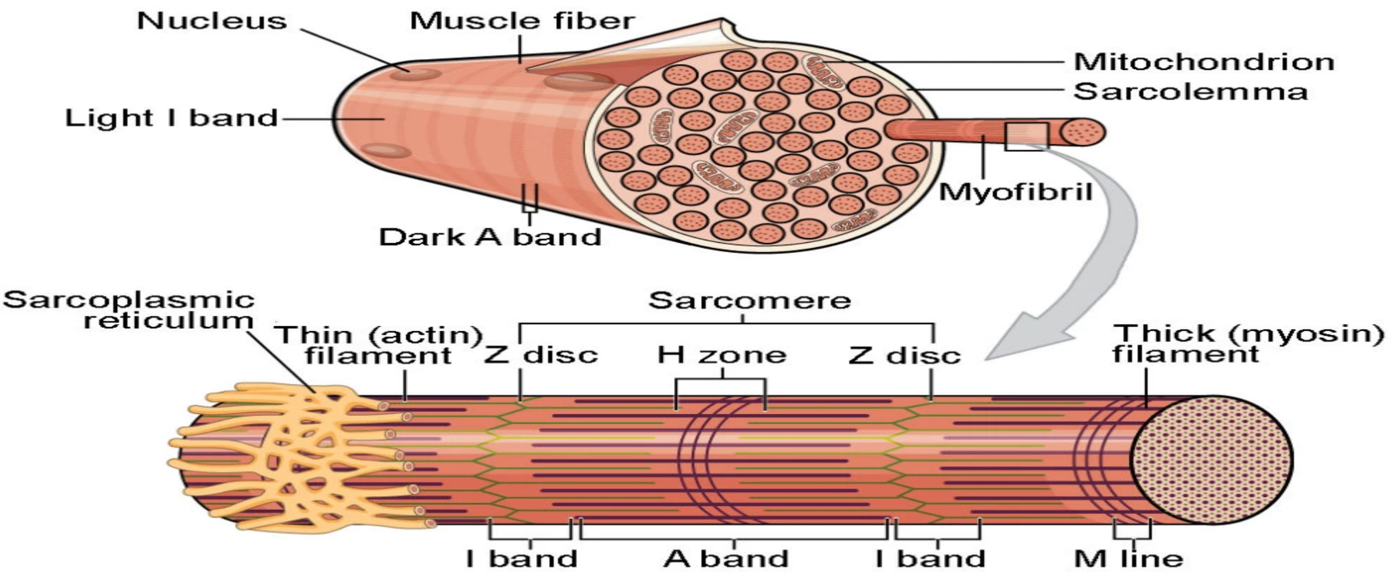
- Emptying the content of hollow organs requires contraction of smooth muscle in that particular organ

the classification of muscles





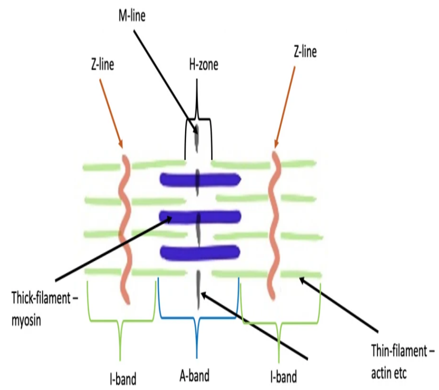
- One muscle is composed of many muscle fibers
- Muscle fibers lie parallel to each other
- Muscle fibers are bundled together by connective tissue



- The most dominant structure in muscle fibers is myofibrils
- Each myofibril consists of a regular arrangement of cytoskeletal elements known as thick and thin filaments
- Thick and thin filaments give the striated appearance in skeletal muscles.

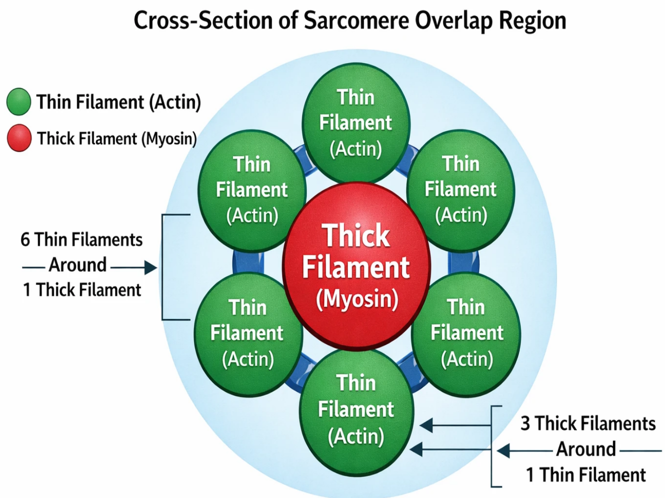
• Thick and thin filaments are arranged into lighter and darker bands
• I Band (light band): • Formed only from thin filaments
• A Band (dark band): • Formed from thick filaments with the portion of thin filaments that overlap on both ends on thick filaments.
• H Zone: • Area of thick filaments not overlapped by thin filaments

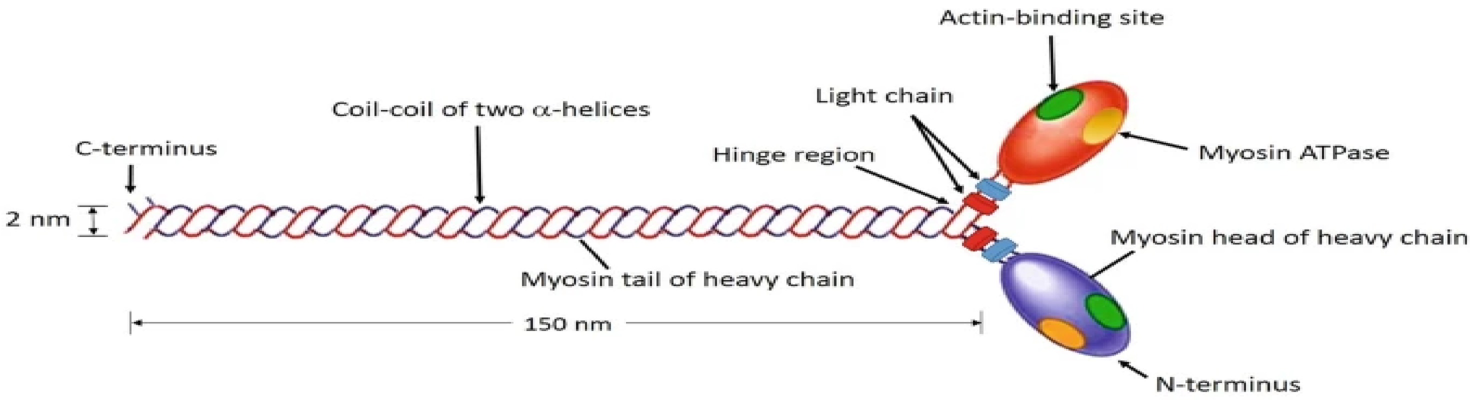
• In the middle of the I band → Z disc
• Z disc = dense vertical structure(flattened disc-like structure that hold thin filaments)
• The area between two Z discs → Sarcomere
• Sarcomere = functional unit of skeletal muscle contraction



In the A band → M line
• M line holds thick filaments

• Cross-sectional arrangement in the area where is an overlap between thin and thick filaments shows:
• 6 thin filaments around 1 thick filament
• 3 thick filaments around 1 thin filament





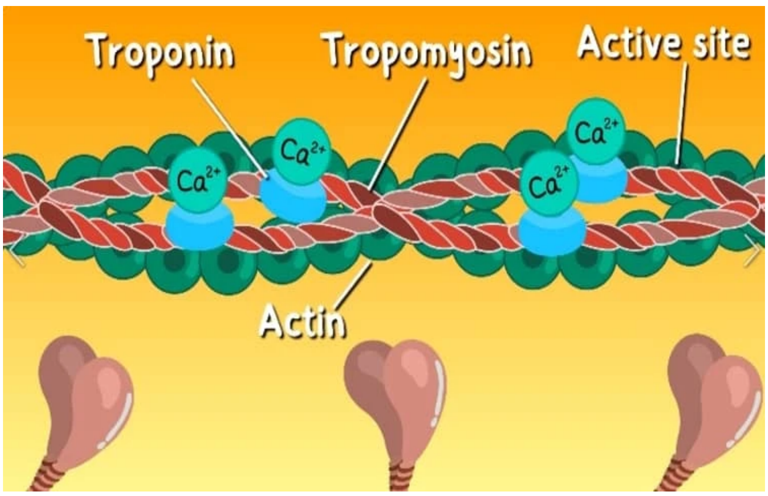
Thick Filament (1.6 μm length)
• Composed of several hundreds of myosin molecules that are held together in specific arrangement

• Myosin molecule:
• Composed of 2 identical subunits
• Each subunit has:
1- Globular head that projects out to one end
2- Tail that is intertwined with the tail of the other molecule

• Each Myosin head contains 2 binding sites:
1- One can interact with thin filaments
2-the other is Myosin ATP-ase site

The heads and the portions of the tail that are protruding from thick filaments are known as cross bridges.

Thin Filament (1.0 μm length)
• Composed of three proteins:
• Actin
• Tropomyosin
• Troponin



Actin

- F-Actin helix forms backbone of a double-stranded structure of the thin filaments
- Each strand is formed of polymerized G-actin
- Actin contains myosin binding site
- On actin molecules, there is a site that can interact with myosin head (myosin binding site). It is believed that this site is an ADP molecule bound to G-actin.
- The bases are inserted to Z disc.
- The ends lie in the space between thick filaments.

Tropomyosin

- Protein molecules wrapping around F-actin helix
- In resting state this protein:
- Covers the active site (myosin binding site) on actin
- Prevents interaction of actin with myosin head.

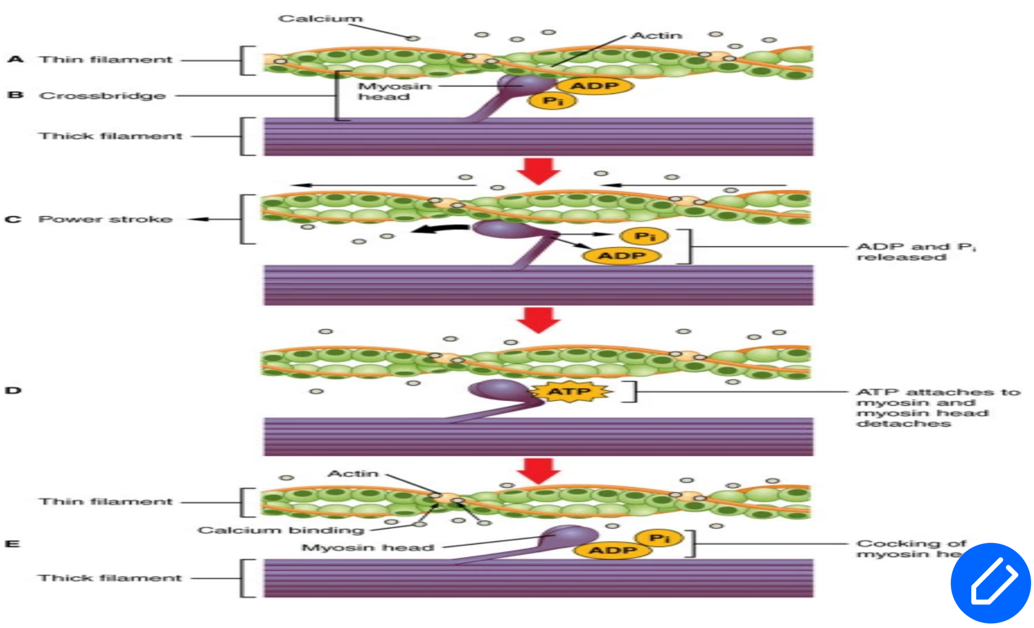
Troponin

plays a role in controlling muscle contraction

.is a complex structure of 3 subunits:

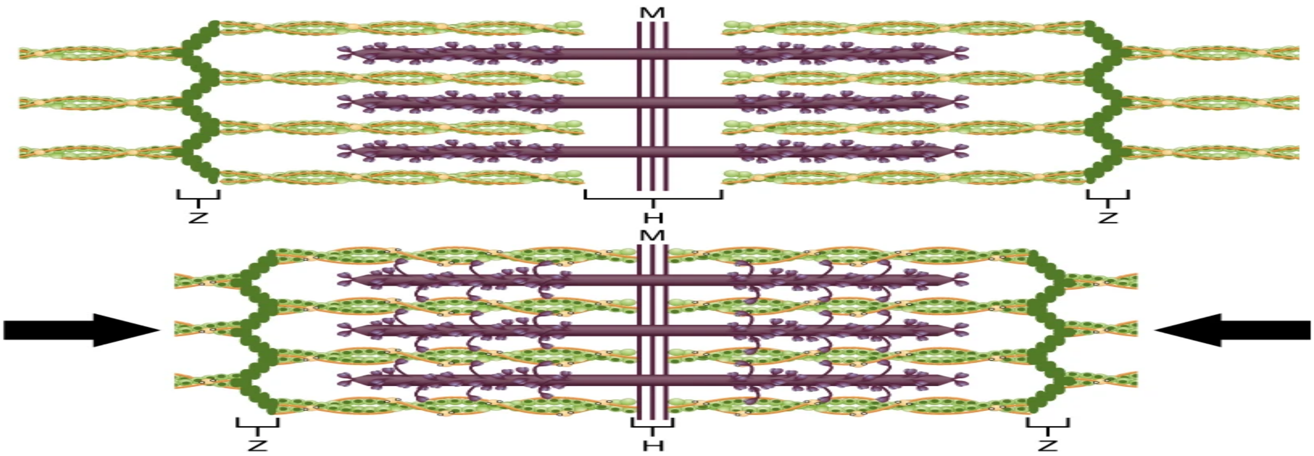
- Troponin I → Affinity for actin
- Troponin T → Affinity for tropomyosin
- Troponin C → Affinity for Ca++

Interaction of thick and thin filaments to induce contraction, and the role of Ca++



• The myosin binding site on actin is the place where myosin heads bind to actin
• In the absence of troponin –tropomyosin complex, myosin can bind strongly to actin in the presence of ATP and Mg++
• When troponin-tropomyosin complex is added, the binding is inhibited
• From these it was suggested that in relaxed muscle, troponin-tropomyosin complex inhibits or physically covers the binding site on actin and prevents the interaction between myosin heads and actin

• In the presence of high Ca++ concentration, the inhibitory effect of tropomyosin-troponin complex on myosin and actin binding was inhibited (so, binding was induced)
• From this it was suggested that during muscle contraction Ca++ binds to troponin C (up to 4 Ca++ bind to one molecule of troponin C)
• This produce conformational changes that results in the displacement of tropomyosin away from the active sites on thin filaments
• The uncovered active sites can interact with myosin and induce contraction in the muscle
• This theory shows the relation between contractile and regulatory proteins (troponin and tropomyosin), and explains the role of Ca++ on muscle contraction



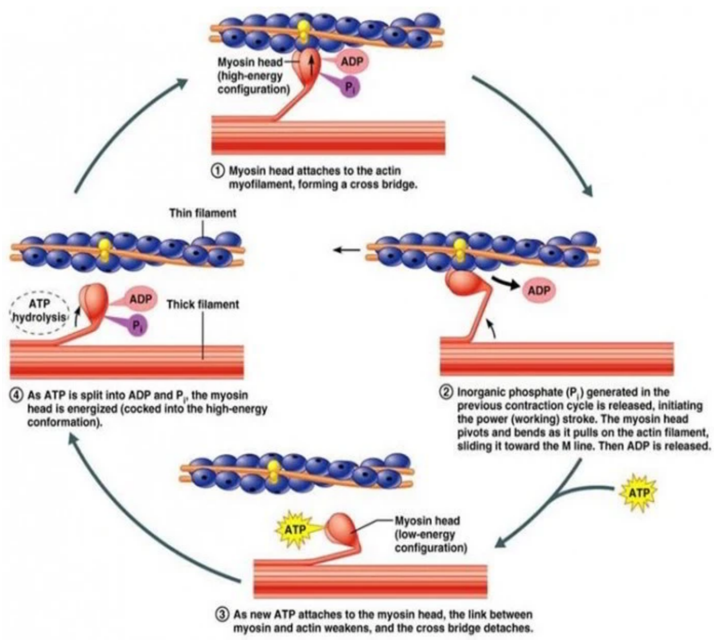
During contraction, the two Z lines become closer. This results by pulling thin filaments inward toward the center of the sarcomere. This will result in a decrease in the H zone, I band and the whole sarcomere length. This happens after binding of myosin heads to the active site on actin. After this binding, myosin bends between the head and the arm of cross bridges, which pulling the thin filament toward the center of the sarcomere. Bending (tilting) of myosin head is known as power stroke. Then the head detach from the actin and bind to another active site on actin, which located closer to the base of the thin filament, and the cycle is repeated many times. The result of this mechanism is more overlap will be obtained between thick and thin filaments by pulling thin filaments inside. This theory is known as "sliding theory" or "walk-along" theory.

According to this theory, after many cycles of (binding, power stroke, detachment, then binding again) that are taking place between cross bridges and actin, a shortening of the sarcomere will be induced in the muscle by sliding thin filaments toward the sarcomere center.

💥 Requirement of energy for contraction

- We have mentioned that myosin head has an ATP-ase site.
- At this site, ATP binds, where it splits into ADP and Pi.
- This needs Mg++ to attach the ATP before ATP-ase can split the ATP molecule.
- The breakdown of ATP occurs before the head links to actin.
- The resulted ADP and Pi remain bound to myosin (becomes phosphorylated).
- The generated energy from splitting is stored within the cross bridge.
- During relaxation of the muscle, the head is energized.
- When the muscle fiber is excited → the increase in Ca++ concentration in the sarcoplasm:
    - pulls tropmyosin-troponin complex out of their blocking position
- This will enable myosin head to attach to actin.
- When attached → the myosin head undergoes conformational changes and bends.
- After this power stroke:
    - the head releases ADP
    - the site is dephosphorylated
- Detachment of myosin head will take place ONLY when another ATP molecule binds to myosin head.
- After detachment:
    - the new molecule is cleaved
    - the head returns to its position
    - energized by splitting ATP
- The cycle continues as long as:
    - high Ca++ concentration inside the sarcoplasm (cytosol) to keep active sites on actin ready for interaction with myosin

ATP is necessary for the detachment of cross bridges from actin.
Not enough ATP will cause muscle to stiff because of the inability cross
bridges to detach from actin. This phenomenon is called rigor mortis (a stiffness of skeletal muscle after 3-4 hours of death).



Source of energy for muscle contraction:

During muscle activity, ATP is needed to provide energy for the power stroke. In addition to that, Ca++ is pumped into the sarcoplasmic reticulum by the activity of the Ca++ pump. This pump needs ATP for its operation. Pumping of Na+ and K+ through sarcolema maintains the ionic composition of cytosol and permits optimal activity of muscle cells. All these activities need a direct use of ATP. In muscle, the amount of ATP is sufficient for only few seconds.
3 ways by which muscle cells supply additional ATP as needed:

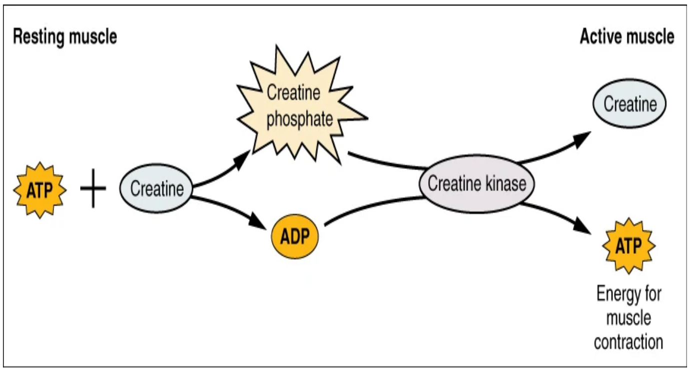
✅ Transfer of high energy phosphate from creatine phosphate to ADP

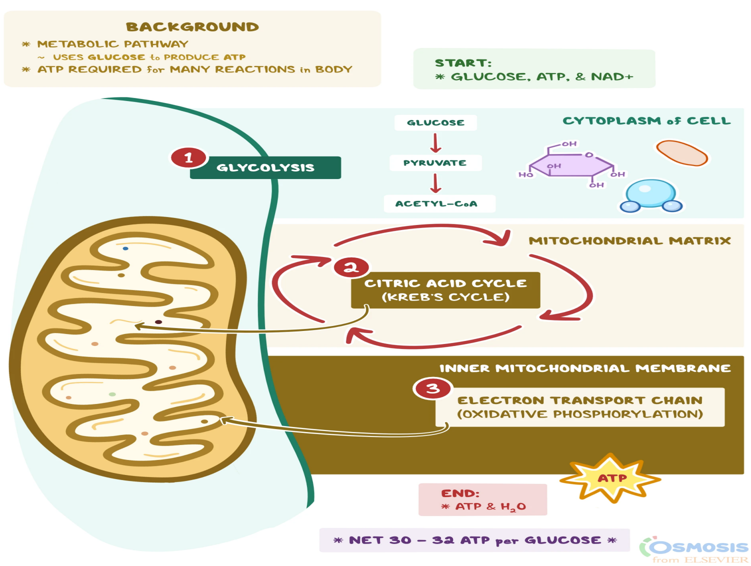
→ Creatine phosphate contains a high-energy phosphate bond.

→ This bond can be transferred to an ADP molecule to form an ATP by the activity of an enzyme known as creatine kinase.

→ The amount of creatine phosphate in muscle is 5 times that of ATP.

→ For that, the muscle needs more efficient supply for longer activities of muscle.





✅ Oxidative phosphorylation

→ This takes place in the muscle when a sufficient supply of O2 is present.

→ This pathway provides a rich supply of ATP (from one glucose molecule processed by oxidative phosphorylation, 36 ATP molecules are yielded).

→ This source is slow and needs constant supply of O2.

→ This way can be sufficient for ATP supply when there is a moderate demand for ATP, such as during light and moderate exercise (walking, jogging, or swimming).

✅ Glycolysis

→ high amount of glycogen are stored in muscle cells.

→ The breakdown of glycogen to glucose, which can be broken down by glycolysis into two pyruvic acid molecules to yield 2 ATP molecules.

→ Pyruvic acid can undergo further degradation by oxidative phosphorylation.

→ Glycolytic pathway is much faster than oxidative phosphorylation in generating ATP molecules.

→ And it is operating anaerobically (there is no need for O2).

→ On this process, fast muscles are depending on for energy supply.

Although it is very useful during intense exercise when the O2 supply is reduced, but it can lead to a muscle fatigue because of accumulation of lactic acid in muscle which results in inhibition of enzymes (involved in energy-producing pathways or excitationcontraction coupling) and depletion of e[illegible]gy reserves.

Muscle mechanics

We have seen that muscle contraction induces shortening in the sarcomere, which results by pulling thin filaments toward the center of the sarcomere. This contraction is seen in the whole muscle as a change in length. When a muscle contracts by changing its length without changing its tension, the contraction is said to be isotonic. If a muscle develops tension without changing its length, the contraction is said to be isometric (which can be recorded by using an electronic force transducer to measure tension).

Tension and sarcomere length relation:

⚡ Length-Tension Relationship

- The tension that can develop on muscle depends on the length of the sarcomere and the length of the muscle .

✅ Very Long Sarcomere

- When sarcomere length is more than 3.6 micro meter(length of one thick filaments and 2 thin filaments), the tension that can develop is almost zero.

✅ Decreasing Sarcomere Length

- When the sarcomere length decreases, the tension increases as:
    - the overlap increases
    - cross bridges that can be recruited for muscle contraction increases
- This increase reaches a maximum, after which more overlap will reduce developed tension

✅ Optimal Length

- The maximum tension that can develop is at the sarcomere length of 2.0-2.2 micro meter (this known as optimal length).

✅ Excessive Shortening

- Below this length (from 2.0-1.6 micro meter):
    - an interaction between thin filaments and cross bridges from the other half of the sarcomere is suggested
    - which may result in a decrease in tension

✅ Key Conclusion

- From this, we can conclude that:
    - more overlap between thin and thick filaments located in the same half of sarcomere will induce more tension.
    - This tension is reduced by:
        - decreasing the overlap in the same side
        - or increase in the interaction of thin filaments with cross bridges from the other side of thick fila[illegible]s (increasing overlap with the other side)

Tension and whole muscle length relation:

⚡ Maximum Tension & Resting Length

- We have seen that maximum tension develops at a sarcomere length of 2.0 -2.2 micro meter.
- This corresponds with the resting length of the muscle.

✅ Normal Muscle Length

- At its normal length, the muscle also responded with the maximum active tension (tension induced by stimulation).

✅ Effect of Stretching

- By stretching muscle (increasing its length):
  - before stimulation → we increase the inactive (passive) tension (due to elastic property) in the muscle.
- When the muscle stimulated at this new length will develop less active tension.That corresponds to the increase in sarcomere length beyond 2.2 micro meter .

Velocity of contraction and load:

Skeletal muscle contracts with maximum velocity when it is not loaded. By loading the muscle, the velocity of contraction decreases as the load increases.

Muscle twitches and characteristics:

Once a nerve of a nerve and muscle preparation is electrically stimulated, the muscle will respond by a contraction then followed by relaxation. The whole recordings from the beginning of stimulation until the end of muscle relaxation is known as simple muscle twitch.

The simple muscle twitch can take:

- Less time → in muscles composed of fast fibers such as ocular muscle
- Longer time → in muscles composed of slow fibers such a soleus muscle

Differences Between Fast & Slow Fibers

(These muscles not only differ in their speed of contraction but also in their color and composition)

Fast fibers

- Large fibers
- Have extensive sarcoplasmic reticulum
- Contain large amount of glycolytic enzymes
- Fewer mitochondria
- Less extensive blood supply

Slow fibers

- Smaller
- More extensive blood supply
- Contain more mitochondria
- Contain a larger amount of myoglobin

Myoglobin:

(an iron containing molecule similar to hemoglobin that can combine with O_2)

Function:

Stores O_2 until needed by fibers for oxidative phosphorylation

Appearance:

The presence of large amounts of myoglobin gives the slow fibers a reddish appearance . For this reason, slow muscles are known as red muscles while the muscles containing fast fibers are white muscle.

Innervation of Skeletal Muscles

Skeletal muscles are innervated by motor neurons that originate from the central nervous system (CNS).
Each neuron innervates a certain number of muscle fibers.

Motor Unit

Muscle fibers that are innervated by a single nerve fiber are called motor unit.
The number of muscle fibers in a motor unit depends on the function of the muscle.

Examples

Fine movements
Such as laryngeal muscles
- Only two or three muscle fibers in a motor unit

Less precise movements
Movements that do not need fine control of muscle contraction
- May contain up to 100 muscle fibers in one unit