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Muscle physiology and the basis of contraction

Ref: Textbook of Medical Physiology, by Guyton, 13th and Jordan Edition: Chapts. 6, 7, 8,

Introduction:

Three types of muscle are found in our body. Skeletal, cardiac, and smooth muscle cells. These cells are found where mechanical activity is needed. Movements of the whole body or parts of it need contraction of skeletal muscles. Pumping of blood in vessels need contraction of cardiac muscle. Emptying the content of hollow organs requires contraction of smooth muscle in that particular organ.

Muscle cells have been classified according to their characteristics, first (according to their appearance under the microscope) in **striated** (cardiac and skeletal muscle) and **unstriated** (smooth muscle) fibers. Second, (according to their innervation): **voluntary** (have somatic innervation), an example: skeletal muscle, and **involuntary** (have autonomic innervation), example: cardiac and smooth muscle.

Structure of skeletal muscle:

One muscle is composed of many **muscle fibers** that are lying parallel to each other and bundled together by a connective tissue, (each fiber extends the entire length of the muscle. Except for about 2 percent of the fibers, each fiber is usually innervated by only one nerve ending, located near the middle of the fiber.). The most dominant structure in muscle fibers is the presence of **myofibrils**. Each myofibril consists of regular arrangement of cytoskeletal elements known as **thick and thin filaments.** Which give the striated appearance in skeletal muscle and are responsible for the actual muscle contraction.

The special arrangement of thick and thin filaments is alternated in lighter and darker (I and A) bands (because of the partial interdigitation between them), gives the striated

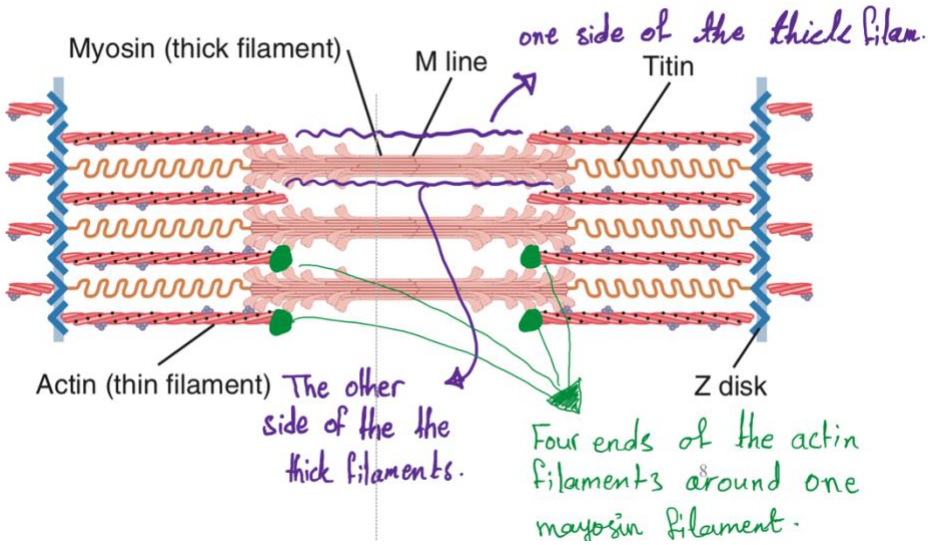
appearance in skeletal muscle. The **I** band is formed only from thin filaments (they are named *I bands* because they are *isotropic* to polarized light). While the **A** band is formed from thick filaments with the portion of thin filaments that overlap on both ends on thick filaments (they are named *A bands* because they are *anisotropic* to polarized light). The area of thick filaments that is not overlapped by thin filaments is known as **H zone**.

In the middle of I band, there is a dense vertical structure (flattened disc-like structure that hold thin filaments) known as **Z disc** (The Z disk, which is composed of filamentous proteins different from the actin and myosin filaments, passes crosswise across the myofibril and also crosswise from myofibril to myofibril, attaching the myofibrils to one another all the way across the muscle fiber. Therefore, the entire muscle fiber has light and dark bands, as do the individual myofibrils). The area between 2 Z discs is known as **sarcomere**, which represents the functional unit in skeletal muscle contraction (when the actin filaments completely overlap the myosin filaments, and the tips of the actin filaments are just beginning to overlap one another, the muscle is capable of generating its greatest force of contraction). In the A band a similar system holds thick filaments known as **M line**.

The cross sectional arrangement in the area where is an overlap between thin and thick filaments shows 6 thin filaments around one thick filament and 3 thick filaments around one thin filament.

Thick filament (1.6 micrometer length) is composed of several hundreds of **myosin** molecules that are held together in a specific arrangement. A myosin molecule is composed of 2 identical subunits. Each has a globular head that projects out to one end and a tail that is intertwined with the tail of the other molecule. Each myosin head has 2 binding sites. One can interact with thin filaments and the other is myosin ATP-ase site. The heads and the portions of tail that are protruding from thick filaments are known as **cross bridges**. The myosin filament interacts on one side with the ends of two actin filaments.

لمّا نحكي one side يعني قصده ال filament من فوق بس أو من تحت بس، هو فعليًا على ال two sides بيعمل interaction مع 4 ends of actin filaments.



Thin filament (1.0 micrometer length) is composed of three proteins, actin, tropomyosin and troponin. **F-Actin** helix forms the backbone of a double stranded structure of the thin filaments. Each strand is formed of polymerized G-actin. 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 (Attached to each one of the G-actin molecules is one molecule of ADP. These ADP molecules are believed to be the active sites on the actin filaments with which the cross-bridges of the myosin filaments interact to cause muscle contraction). The bases are inserted to Z disc. The ends lie in the space between thick filaments.

Tropomyosin is protein molecules that wrap around the F-actin helix. In resting state this protein covers the active site (myosin binding site) on actin and prevents interaction of actin with myosin head.

Troponin is a complex structure of 3 subunits, which plays a role in controlling muscle contraction. One subunit has affinity for actin (troponin I), the other has affinity for tropomyosin (troponin T), and the third has affinity for Ca++ (troponin C), (the strong affinity of the troponin for calcium ions is believed to initiate the contraction process).

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

The myosin binding sites 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, before contraction can take place, the inhibitory effect of the troponin-tropomyosin complex must itself be inhibited.

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 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*. (Next, the head returns to its extended direction. In this position, it combines with a new active site farther down along the actin filament) the head detaches from the actin and bind to another active site on actin, which located closer to the base of thin filament (the base that is inserted in the z disc) 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" (or *"ratchet"*) theory.

Thus, the heads of the cross-bridges bend back and forth and step by step walk along the actin filament, pulling the ends of two successive actin filaments toward the center of the myosin filament. Each one of the cross-bridges is believed to operate independently of all others, each attaching and pulling in a continuous repeated cycle. Therefore, the greater the number of cross-bridges in contact with the actin filament at any given time, the greater the force of contraction.

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.

https://www.youtube.com/watch?v=GneonFlcZG8

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 ATP molecule. This breakdown of ATP occurs before the head links to actin. The resulted ADP and Pi remain bound to myosin and 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 tropomyosin-troponin complex out of their blocking position. This will enable myosin head to attach to actin. When attached, myosin head can use stored energy to bend. After this power stroke, the head releases ADP and Pi from their site. At this point, the 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 and energized by splitting ATP. The cycle continues as long as we have 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).

- هدول الخطوات حسب نصّ الكتاب حسّيتهم أوضح شوي وأرتب من الفقرة الّي فوق، فهيهم:

- Large amounts of ATP are cleaved to form ADP during the contraction process, and the greater the amount of work performed by the muscle, the greater the amount of ATP that is cleaved; this phenomenon is called the *Fenn effect*. The following sequence of events is believed to be the means by which this effect occurs:

1- Before contraction begins, the heads of the crossbridges bind with ATP. The ATPase activity of the myosin head immediately cleaves the ATP but leaves the cleavage products, ADP plus phosphate ion, bound to the head. In this state, the conformation of the head is such that it extends perpendicularly toward the actin filament but is not yet attached to the actin.
2- When the troponin-tropomyosin complex binds with calcium ions, active sites on the actin filament are uncovered and the myosin heads then bind with these sites.
3- The bond between the head of the cross-bridge and the active site of the actin filament causes a conformational change in the head, prompting the head to tilt toward the arm of the cross-bridge and providing the power stroke for pulling the actin filament. The energy that activates the power stroke is the energy already stored, like a “cocked” spring, by the conformational change that occurred in the head when the ATP molecule was cleaved earlier.
4- Once the head of the cross-bridge tilts, release of the ADP and phosphate ion that were previously attached to the head is allowed. At the site of release of the ADP, a

new molecule of ATP binds. This binding of new ATP causes detachment of the head from the actin.

5- After the head has detached from the actin, the new molecule of ATP is cleaved to begin the next cycle, leading to a new power stroke. That is, the energy again "cocks" the head back to its perpendicular condition, ready to begin the new power stroke cycle.

6- When the cocked head (with its stored energy derived from the cleaved ATP) binds with a new active site on the actin filament, it becomes uncocked and once again provides a new power stroke.

Thus, the process proceeds again and again until the actin *filaments pull the Z membrane up against the ends of the myosin filaments* OR until *the load on the muscle becomes too great for further pulling to occur.*

Source of energy for muscle contraction:

- Most of the energy required for muscle contraction is used to actuate the walk-along mechanism by which the cross-bridges pull the actin filaments, but small amounts are required for (1) pumping calcium ions from the sarcoplasm into the sarcoplasmic reticulum after the con- traction is over and (2) pumping sodium and potassium ions through the muscle fiber membrane to maintain an appropriate ionic environment for propagation of muscle fiber action potentials.

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 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:

1. Transfer of high energy phosphate from **creatine phosphate *(phosphocreatine)*** 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.

- However, the total amount of phosphocreatine in the muscle fiber is also small—only about five times as great as the ATP (remember that the amount of ATP is already small, and five times as great as it stills small amount). Therefore, the combined energy of both the stored ATP and the phosphocreatine in the muscle is capable of causing maximal muscle contraction for only 5 to 8 seconds.

2. Oxidative phosphorylation: This takes place in the muscle when a sufficient supply for O2 is present. This pathway provides 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 demands for ATP, such as during light and moderate exercise (walking, jogging, or swimming).

- More than 95 percent of all energy used by the muscles for sustained, long-term contraction is derived from oxidative metabolism.

3. 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 (the ATP can then be used directly to energize additional muscle contraction and also to re-form the stores of phosphocreatine). 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 excitation contraction coupling) and depletion of energy 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 electronic force transducer to measure tension).

Tension and sarcomere length relation:

The tension that can develop on muscle depends on the length of sarcomere and the length of the muscle (the length of the sarcomere depends on the overlapping degree between the filaments, and the length of the muscle depends on the length of its sarcomeres). When sarcomere length is more than 3.6 micrometer (length of one thick filaments and 2 thin filaments without any overlapping, and here the tension is zero), the tension that can develop is almost zero. When the sarcomere length decreases, the tension increases as the overlap increases and cross bridges that can be recruited for muscle contraction increases. This increase reaches a maximum after which more overlap will reduce developed tension. The *maximum tension* that can develop is at the sarcomere length of 2.0-2.2 micrometer (this known as optimal length). Below this length (from 2.0-1.6 □m) an interaction between thin filaments and cross bridges from the other half of sarcomere may result in a decrease in tension.

- As the sarcomere length decreases from 2 micrometers down to about 1.65 micrometers, the strength of contraction decreases rapidly. At this point, the two Z disks of the sarcomere abut the ends of the myosin filaments. Then, as contraction proceeds to still shorter sarcomere lengths, the ends of the myosin filaments are crumpled and, the strength of contraction approaches zero, but the sarcomere has now contracted to its shortest length. And because of this it's below the optimality.

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 filaments (increasing overlap with the other side).

Tension and whole muscle length relation:

We have seen that maximum tension develops at a sarcomere length of 2.0 –2.2 □m. This corresponds with the resting length of the muscle. At its normal length, the muscle also responded with the maximum *active tension* (tension induced by stimulation). By stretching muscle (increasing its length) (However, the increase in tension that occurs during contraction, called active tension, decreases as the muscle is stretched beyond its normal length—that is, to a sarcomere length greater than about 2.2 micrometers), 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□m.

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.

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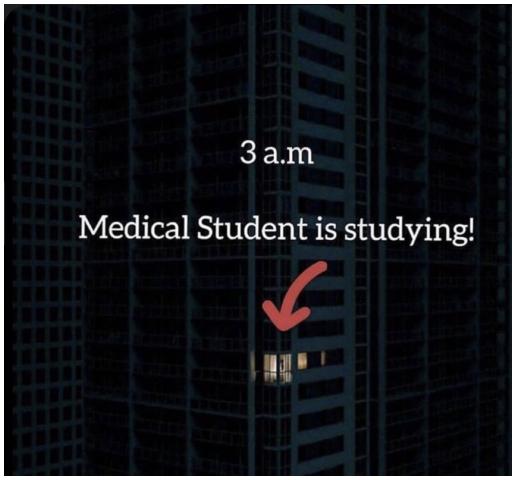
Challenge yourself !!!

1) The binding sites for the cross-bridges are located on :
A) actin
B) myosin
C) troponin



2)When muscle contracts upon stimulation, calcium ions bind to which exposes the binding sites for the myosin cross-bridges to attach to.
A) actin
B) myosin
C) troponin

3) ATP is required for muscles to contract. Which of the following statements is FALSE?
A) ATP is used to get the cross-bridges to bind to actin.
B) ATP is used to get the cross-bridges to disconnect from actin.
C) ATP is used to get the troponin-tropomyosin complex to move in such a manner to expose the binding sites.

Answers : A \ C \ C