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جامعة بغداد
التقنيات الأحيائية

"Excitation-Contraction Coupling: How Nerve Signals Trigger Muscle Contraction"

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	المرحلة:
	الشعبة:
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The topics covered in this report are: -

1 \ Introduction

2 \ Mechanism of Muscle Contraction

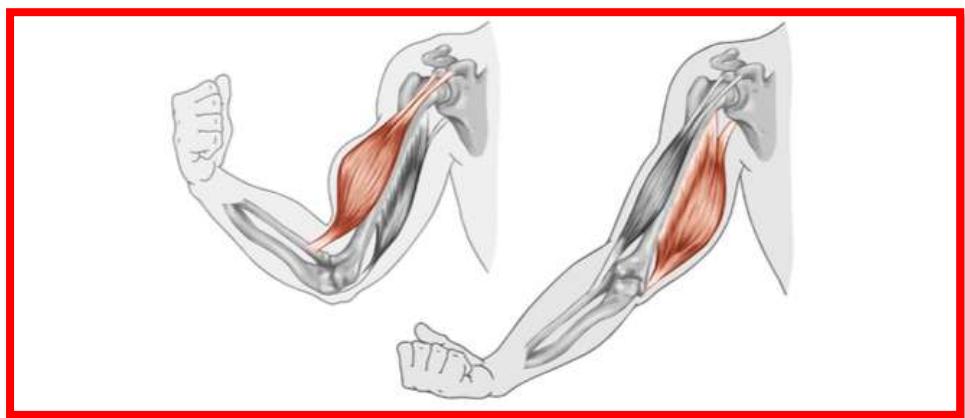
3 \ Skeletal Muscle Relaxation

4 \ The Importance of Muscles in the Body

Introduction :

The muscular system is one of the fundamental components of the human body, playing a crucial role in movement, stability, and essential physiological functions. Muscles are composed of specialized fibers capable of contraction and relaxation, allowing the body to respond to external stimuli and control movement with precision. The muscular system is divided into three main types: skeletal muscles, which control the movement of limbs and the body; smooth muscles, which line blood vessels and the digestive system; and cardiac muscle, which continuously pumps blood throughout the body.

The ability of muscles to contract relies on a complex process known as excitation-contraction coupling, which links neural signals to muscle fiber contraction. This process begins when the nervous system sends electrical signals to the muscles, triggering the release of calcium ions within muscle fibers. This, in turn, activates interactions between muscle proteins, leading to contraction. This mechanism is essential for movement, respiration, heartbeat, and various internal organ functions.

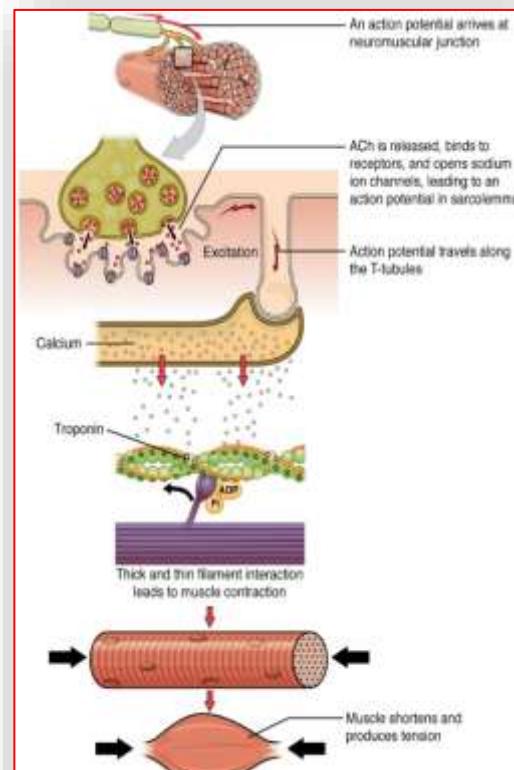


Mechanism of Muscle Contraction

Muscle contraction is a complex process in which actin and myosin filaments slide past each other, causing muscle fibers to contract. This process relies on calcium, troponin, and tropomyosin. Voluntary muscle contraction begins with electrical impulses occurring at the neuromuscular junction when nerve signals travel from the spinal cord to the nerve endings, leading to the opening of calcium channels and the release of calcium ions.

Vesicles at the end of the neuron fuse with the membrane to release the neurotransmitter acetylcholine (ACh), which binds to its receptors on muscle cells. This binding opens sodium channels, causing electrical changes that spread across the muscle membrane. The sequence of events leading to the contraction of an individual muscle fiber starts with a signal from the motor neuron. The entry of positively charged sodium ions (Na^+) depolarizes the local membrane, generating an action potential that propagates along the membrane, including the transverse tubules (T-tubules).

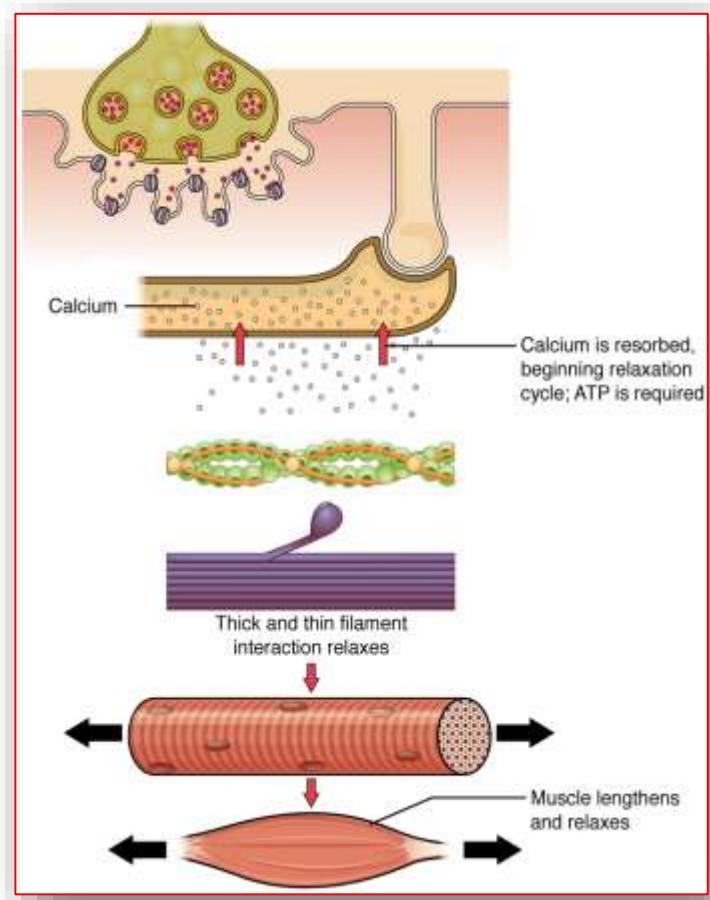
This triggers the release of calcium ions (Ca^{2+}) from storage in the sarcoplasmic reticulum (SR). The released Ca^{2+} initiates muscle contraction, which is powered by ATP. As long as Ca^{2+} remains in the sarcoplasm and binds to troponin, actin binding sites remain exposed, allowing the cross-bridge cycle to continue. Myosin pulls the actin filaments, causing the muscle fibers to contract until reaching a physiological limit.



A cross-bridge forms between actin and myosin heads, triggering contraction. As long as calcium ions (Ca^{2+}) remain in the sarcoplasm to bind with troponin and ATP is available, the muscle fiber will continue to contract.

Muscle contraction typically stops when signals from the motor neuron endings reach the muscle, leading to the repolarization of the sarcolemma and transverse tubules. This action closes the voltage-gated calcium channels in the muscle fiber. Calcium ions (Ca^{2+}) are then pumped back into the sarcoplasmic reticulum, causing tropomyosin to re-cover the binding sites on the actin filaments. Muscle contraction may also stop when ATP is depleted and the muscle becomes fatigued (see Figure).

Figure . Muscle Fiber Relaxation. Calcium ions (Ca^{2+}) are pumped back into the muscle fiber, causing tropomyosin to re-cover the binding sites on the actin filaments. The muscle may also stop contracting when ATP is depleted and it becomes fatigued.¹



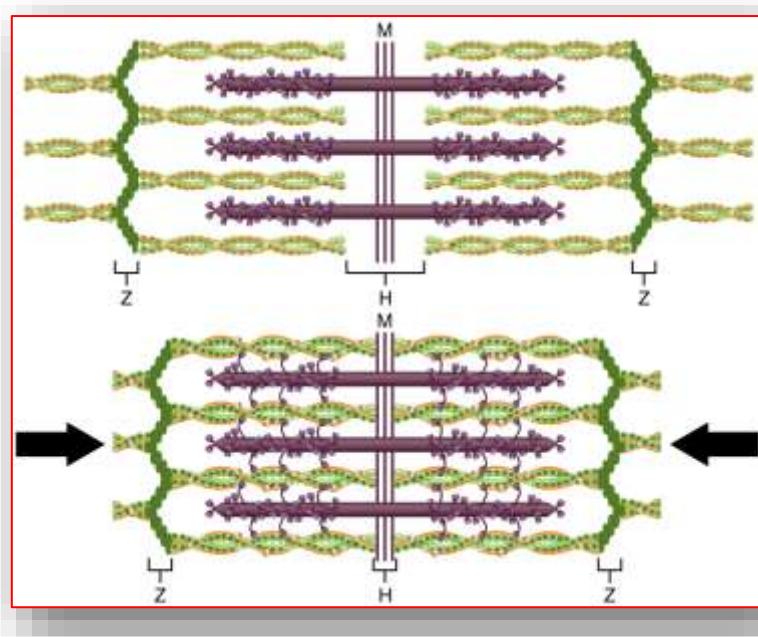
The molecular events of muscle fiber shortening occur within the sarcomeres of the fibers. Skeletal muscle fiber contraction happens when the sarcomeres, arranged linearly within the myofibrils, shorten as the myosin heads pull on the actin filaments.

¹ <https://www.youtube.com/watch?v=CepeYFvqmk4>

The region where the thick and thin filaments overlap appears dense due to the narrow space between them. This region is crucial for muscle contraction, as it is where the filament movement begins. The thin filaments, anchored at their ends by Z-discs, do not extend fully into the central region, which contains only thick filaments, anchored at their bases at a point called the M-line. A myofibril consists of many sarcomeres extending along its length; thus, the myofibrils and muscle cells contract as the sarcomeres shorten.

When a signal is sent from a motor neuron, a skeletal muscle fiber contracts by pulling the thin filaments, which then slide past the thick filaments within the sarcomeres of the fiber. This process is known as the sliding filament model of muscle contraction. The sliding only occurs when the binding sites for myosin on the actin filaments are exposed through a series of steps that begin with the entry of calcium ions into the sarcoplasm (see Figure).

The Sliding Filament Model of Muscle Contraction. When the sarcomere contracts, the Z-lines move closer together, and the I band decreases in size. The A band remains the same width. During full contraction, the thin and thick filaments overlap.



Tropomyosin is a protein that wraps around the actin filaments, covering the myosin binding sites and preventing actin from binding to myosin. Tropomyosin binds to troponin to form the troponin-tropomyosin complex. This complex prevents the myosin heads from attaching to the active sites on the thin actin filaments. Troponin also has a binding site for calcium ions.

To initiate muscle contraction, tropomyosin must uncover its binding site for myosin on the actin filament, allowing a cross-bridge to form between the actin and myosin filaments. The first step in the contraction process is the binding of calcium ions to troponin, which allows tropomyosin to shift away from the binding sites on the actin filaments. This enables the myosin heads to bind to the exposed sites and form cross-bridges. After that, the myosin heads pull the thin filaments past the thick filaments toward the center of the sarcomere. However, each head can only pull a very short distance before it reaches its limit, and it must reset before it can pull again, a step that requires ATP.

For the thin filaments to continue sliding over the thick filaments during muscle contraction, the myosin heads must pull actin at binding sites, then detach, reattach, pull again, detach again, and so on. This repetitive movement is known as the cross-bridge cycle. The movement of the myosin heads is similar to the action of paddles when an individual rows a boat: the myosin heads pull, then are lifted out of the water (detach), pulled back to their position (reattach), and then immersed again to pull. Each cycle requires energy, and the work done by the myosin heads in the sarcomeres, which repeatedly pull the thin filaments, also requires energy, which is provided by ATP.

The cross-bridge formation occurs when the myosin head binds to actin while ADP (adenosine diphosphate) and inorganic phosphate (Pi) are still bound to the myosin (Figures 4A, B). Then, Pi is released, which causes the myosin-actin binding to become stronger, and the myosin head moves toward the M line, pulling actin with it. As the actin is pulled, the filaments move approximately 10 nanometers toward the M line. This movement is called the power stroke, during which the thin filament moves (Figure 4C). In the absence of ATP, the myosin head will not detach from actin.

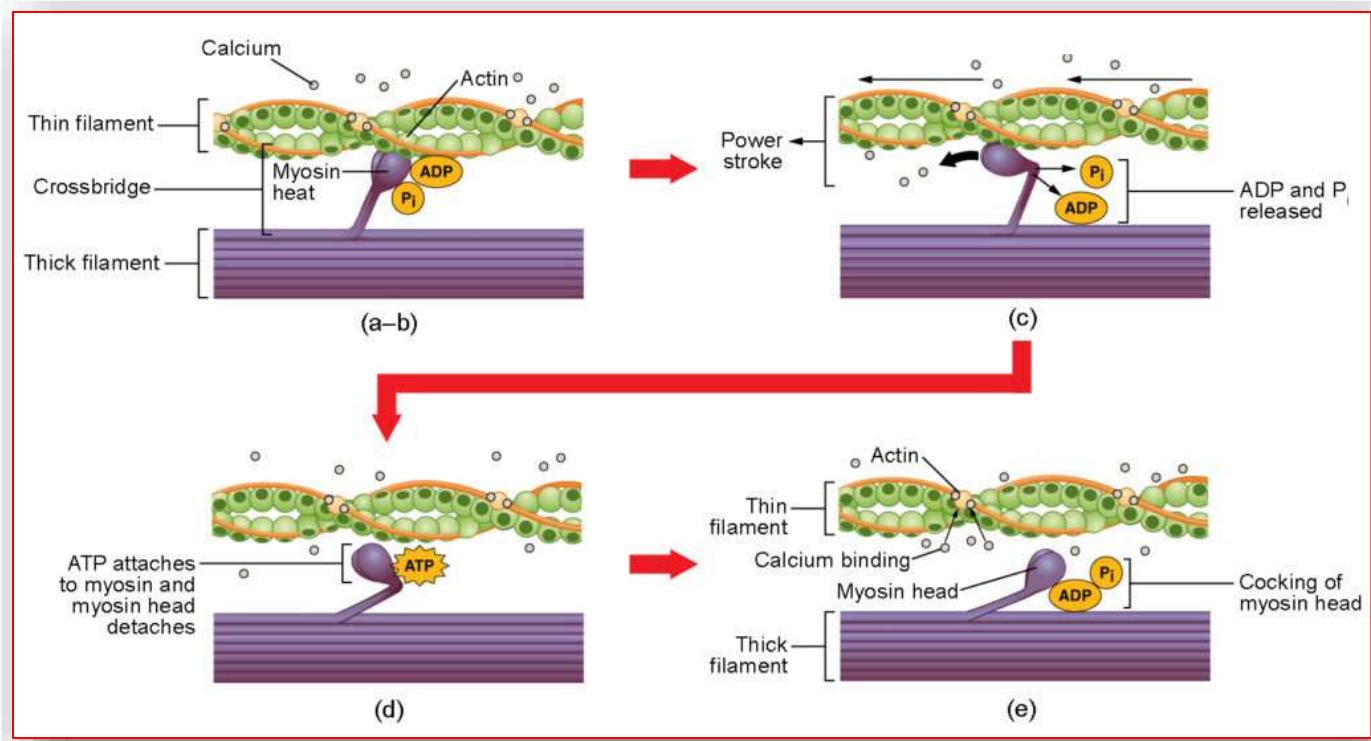


Figure 4. Skeletal Muscle Contraction.

(A) The active site on actin is exposed when calcium binds to troponin. (B) The myosin head is attracted to actin and binds to actin at the actin binding site, forming the cross-bridge. (C) During the power stroke, phosphate released from the previous contraction cycle causes the myosin head to rotate toward the center of the sarcomere, after which the attached ADP and phosphate are released. (D) A new ATP molecule binds to the myosin head, causing the cross-bridge to detach. (E) The myosin head hydrolyzes ATP to ADP and phosphate, returning myosin to the cocked position.

Part of the myosin head binds to a site on the actin, but the head has another binding site for ATP. The binding of ATP leads to the detachment of the myosin head from the actin (Figure 4D). Afterward, ATP is converted to ADP and Pi through the internal activity of ATPase in myosin. The energy released during ATP hydrolysis changes the angle of the myosin head to a bent position (Figure 4E). The myosin head is now in a position favorable for further movement.

When the myosin head is cocked, the myosin is in a high-energy state. This energy is used up during the power stroke, and at the end, the myosin head is in a low-energy state. After the power stroke, ADP is released; however, the cross-bridge remains in place, and actin and myosin remain bound together. As long as ATP is available, it will bind to myosin easily, and the cross-bridge cycle can repeat, allowing muscle contraction to continue.

Note that each thick filament, composed of about 300 myosin molecules, contains multiple myosin heads, and numerous cross-bridges are formed and broken continuously during muscle contraction. Multiply this by the number of sarcomeres in a single muscle fiber, and then by the number of myofibrils in a single muscle fiber, and by the number of muscle fibers in a skeletal muscle, and you'll understand why so much ATP is required to maintain skeletal muscle activity. In fact, the depletion of ATP is what leads to rigor mortis observed shortly after death. Without the ability to produce more ATP, ATP is not available for myosin heads to detach from actin binding sites, thus the cross-bridges remain in place, causing skeletal muscle stiffness.

Skeletal Muscle Relaxation:

The relaxation of skeletal muscle fibers, and ultimately the muscle itself, begins with the motor neuron, which stops releasing its chemical signal, acetylcholine (ACh), at the synapse at the neuromuscular junction. The muscle fibers are repolarized, causing the gates at the synapse, where calcium ions were previously released, to close. Calcium ions are pumped back from the sarcoplasm to the neuromuscular junction by ATP-driven pumps. This leads to the "reblocking" of actin binding sites on the thin filaments. Without the ability to form cross-bridges between the thin and thick filaments, the muscle fibers lose their tension and relax.

The Importance of Muscles in the Body :

Muscles play a crucial role in the body, contributing to various essential functions. Their importance can be highlighted in the following points:

- 1. Movement:** Movement is the primary function of the muscular system. Muscles enable activities such as walking, swimming, writing, speaking, and facial expressions.
- 2. Stability and Posture:** Tendons of muscles over the knee and shoulder joints help stabilize the body, providing stability and supporting posture.
- 3. Circulation:** The heart muscle is responsible for pumping blood throughout the body. Additionally, smooth muscles in arteries and veins play a key role in maintaining blood pressure and overall circulation.
- 4. Breathing:** The diaphragm muscle is responsible for the breathing process, facilitating inhalation and exhalation.
- 5. Digestion:** Smooth muscles extending from the mouth to the anus control the digestion process, allowing the movement of food and waste through the digestive tract.
- 6. Urination:** Smooth and skeletal muscles in the bladder, kidneys, prostate, ureter, urethra, and vagina work in coordination with nerves to complete the process of urination.
- 7. Childbirth:** Smooth muscles in the uterus contract and expand to assist in the delivery process during childbirth.
- 8. Vision:** Six skeletal muscles surrounding the eye control its movement, maintaining image stability and enabling the tracking of moving objects.
- 9. Temperature Regulation:** Approximately 85% of the heat generated in the body comes from muscle contractions, contributing to temperature regulation.
- 10. Body Protection:** The muscles of the trunk provide protection for the internal organs, acting as a shield against injury.

" Sources "

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