Human Physiology

Lecture 9 – Wednesday 9/3/2016

"Neuromuscular junction & Muscle contraction"

with Dr. Esraa' Kiwan

(Slides are on e-learning)

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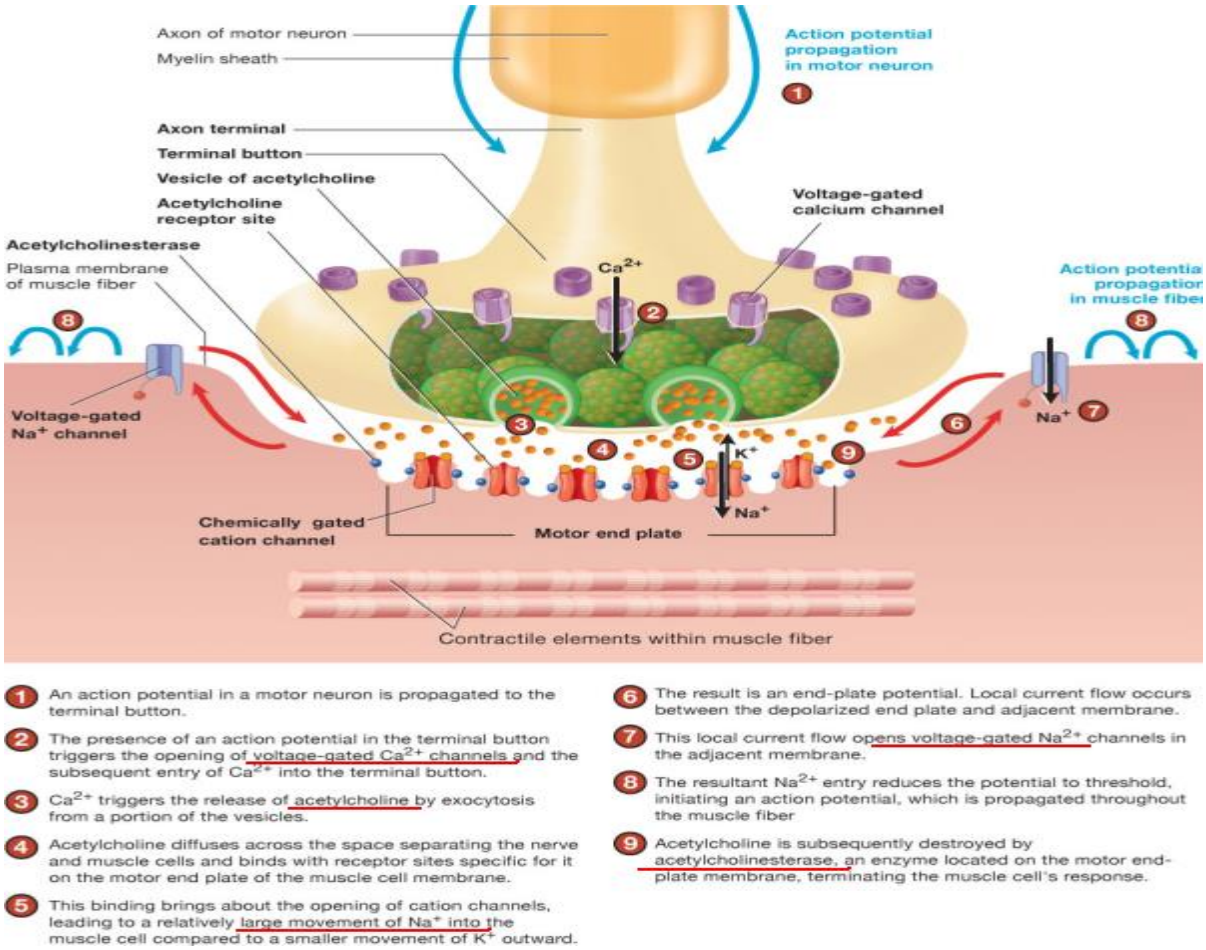
PSU

(F): Means a question that can come in the First exam

Reminder: A neuron may terminate (ينتهي) at a muscle, or a gland, or another neuron.



- This diagram shows a **neuromuscular junction** – which is a junction between a motor neuron & a skeletal muscle.
    - A "motor neuron" (العصبون الحركي) is a nerve cell that passes impulses/messages from the brain or spinal cord to a muscle/gland.
    - There is only one type of neurotransmitter here: **Acetylcholine**.
    - Acetylcholine is a neurotransmitter that activates muscles
    - The membrane that is below the synaptic knob (of the motor neuron) is called the end plate.
- This diagram shows us how muscle contraction (التقبض العضلي) happens
    - Action potential leads to the opening of voltage-gated Ca^{+2} channels.
    - The opening of the Ca^{+2} channels causes an influx of Ca^{+2} ions.

- Ca^{+2} ions causes the vesicles in the synaptic knob to release Acetylcholine into the synaptic cleft.
- Acetylcholine binds to receptors in the end plate causes a change in the membrane permeability (نفاذية الغشاء)
- This change opens the Na^+ and K^+ ion channels, causing Na^+ to move inside & K^+ to move outside (however, more Na^+ moves inside due to the electrical gradient & this causes the membrane to become less negative)
- This decrease in negativity produces **end plate potential** (a type of graded potential – since there is no voltage gated ion channels in the end plate membrane, meaning threshold potential cannot be reached so no action potential happens)
- However, in the next area of junction (look at (7) in the picture) there are Na^+ channels, and these channels will open.
- The opening of Na+ channels causes an influx of Na+, making that area less negative (depolarization)
- This depolarization causes the area to reach threshold potential – action potential is produced

- Finally, Acetylcholine is broken down by its enzyme <u>acetylcholinesterase</u>

Factors that affect neuromuscular junction

- **Botulinum toxin:**
  - This toxin blocks the release of Acetylcholine from the synaptic knob, meaning it stops muscle contraction – causing **muscle paralysis** (شلل)
- **Black widow spider venom** (سم عنكبوت "الأرمل السوداء")
  - This venom causes explosive release of Acetylcholine, causing persistent/continuous muscle contraction.
- **Organophosphate**: A poisonous compound (it was used in war before)
  - This compound inhibits/stops Acetylcholinesterase, the enzyme that breaks down Acetylcholine. This leads to continuous contraction as there the acetylcholine is not destroyed & will keep producing its effect. Continuous

contraction does not allow the body to relax its muscles, and this causes respiratory failure

- **Curare**: A muscle relaxer, used in surgeries.
    - Curare binds with receptors in the end plate membrane, inhibiting the ability of Acetylcholine to bind (resulting in muscle paralysis).
      <يأخذ مكان الاسيتايل كولين و هذا يمنع ارتباط الاسيتايل كولين – يسبب شلل العضلات>
- **Myasthenia Gravis:** An autoimmune disease (مرض مناعي ذاتي)
    - The body starts to destroy Acetylcholine receptors, so Acetylcholine cannot bind // Myasthenia Gravis results in muscle paralysis.

What are the (S) similarities and (D) differences between NMJ (neuromuscular junction) & a synapse?

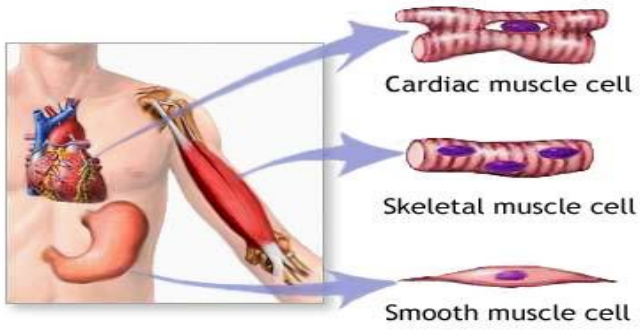
SIMILARITIES	DIFFERENCES
Both consist of two excitable cells separated by a narrow cleft that prevents direct transmission of electrical activity between them.	A synapse is a junction between two neurons. A neuromuscular junction exists between a motor neuron and a skeletal muscle fiber.
Axon terminals of both store chemical messengers (neurotransmitters) that are released by the Ca^{2+}-induced exocytosis of storage vesicles when an action potential reaches the terminal.	One-to-one transmission of action potentials occurs at a neuromuscular junction, whereas one action potential in a presynaptic neuron cannot by itself bring about an action potential in a postsynaptic neuron. An action potential in a postsynaptic neuron occurs only when summation of EPSPs brings the membrane to threshold.
In both, binding of the neurotransmitter with receptor sites in the membrane of the cell underlying the axon terminal opens specific channels in the membrane, permitting ionic movements that alter the membrane potential of the cell.	A neuromuscular junction is always excitatory (an EPP); a synapse may be either excitatory (an EPSP) or inhibitory (an IPSP).
The resultant change in membrane potential in both cases is a graded potential.	Inhibition of skeletal muscles cannot be accomplished at the neuromuscular junction; can occur only in CNS through IPSPs at dendrites and cell body of the motor neuron.

- (S) Both the NMJ & the synapse are a junction between excitable cells (reminder: the two types of excitable cells are nerve cells & muscle cells)
    - (D) However, a synapse is a junction between 2 neurons while a NMJ is a junction between a motor neuron and a skeletal muscle.
- (S) In both, action potential causes an influx of Ca^{+2}/release of neurotransmitters
    - (D) In NMJ, the neurotransmitter release is always Acetylcholine (Excitatory), while in a synapse there are many excitatory & inhibitory neurotransmitters.
- (S) In both, the change in membrane potential is graded.
    - (D) There is no inhibition in NMJ, so we do not have summation (جمع أو تحصيل) since there is only 1 input unlike the synapse.

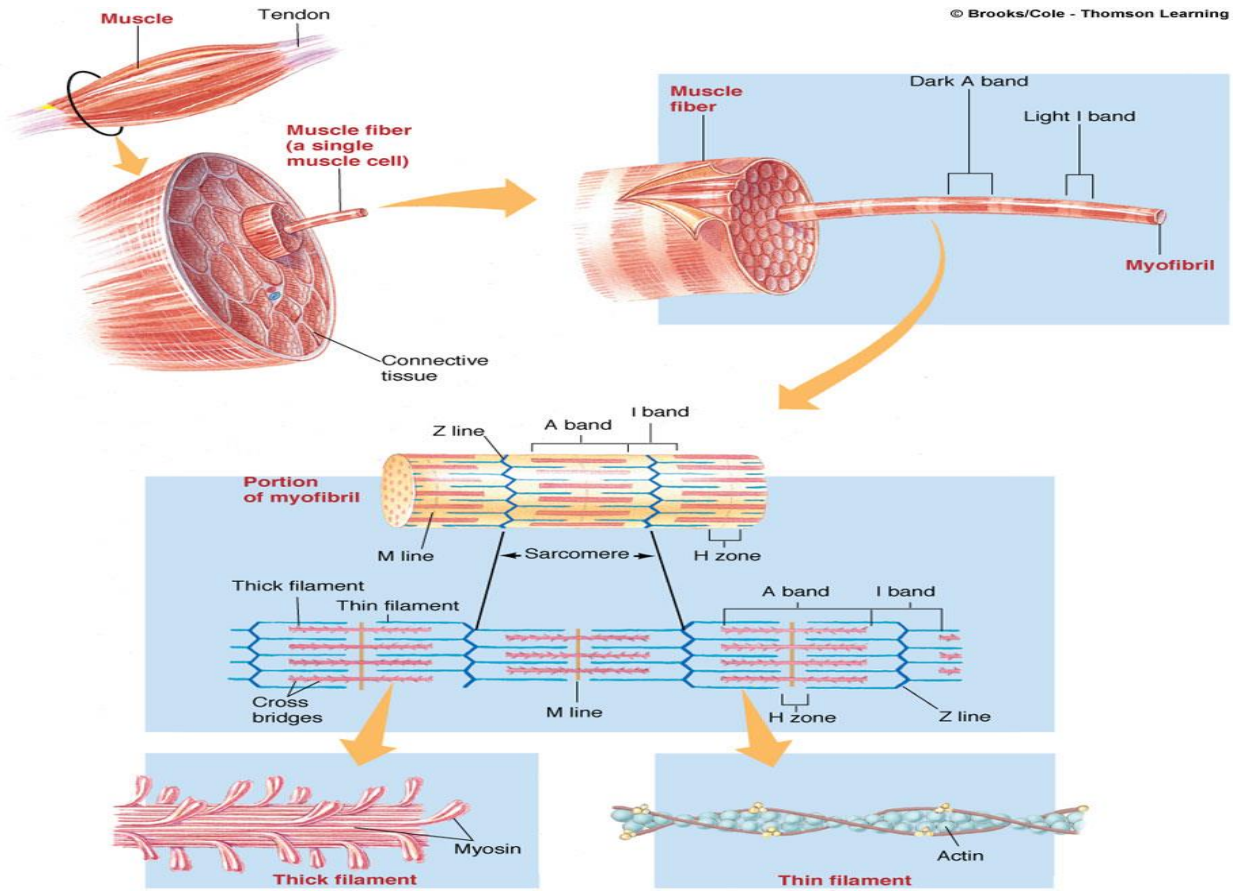
Muscles

What are the types of muscles?

- Smooth – Not striated, involuntary
- Skeletal – Striated, voluntary (we control it)
- Cardiac – Striated, involuntary (we do not consciously control it)

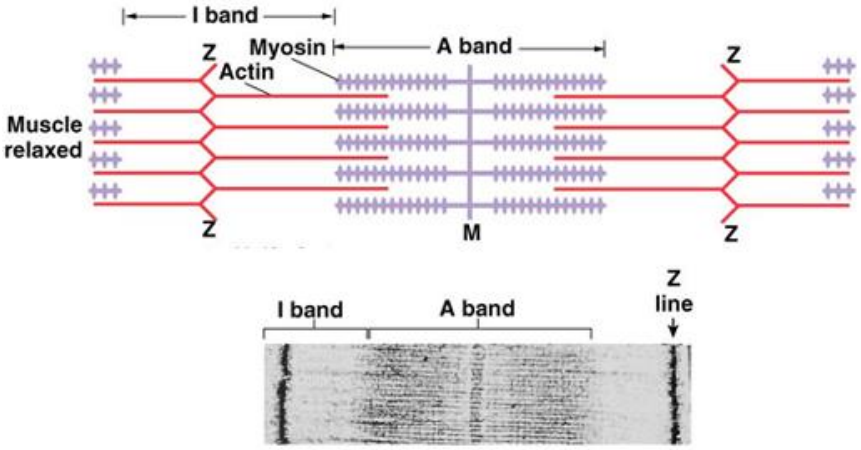


Structure of (skeletal) muscles

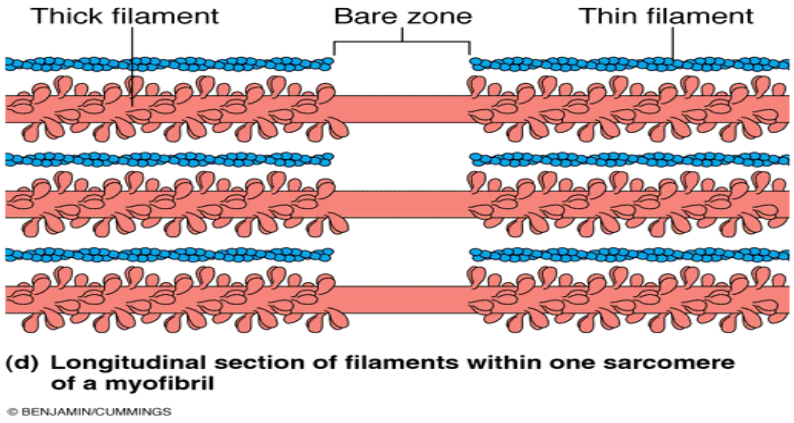


- Inside a muscle (organ) -> there is a cell called **muscle fiber.**
- Inside the muscle fiber -> there is an intracellular structure called **Myofibril**
- Inside the myofibril -> there are thick and thin filaments ("خيوط")
    - The dark/thick filaments are made of the protein myosin
    - The light/thin filaments are made of the protein actin

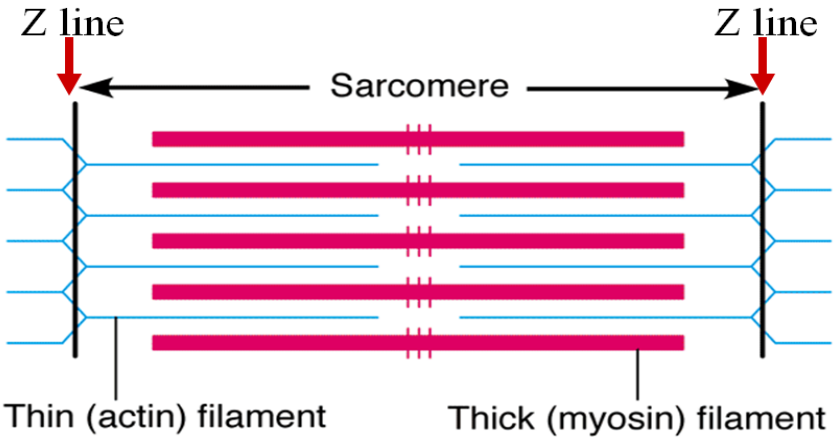
Thin and thick filaments



- **A Band (شريط):** The area where thick filaments overlap thin filaments (تداخل)
- **I Band:** Thin filament that did not overlap with thick filament // the I band is the area of the thin filament that did not reach the A band.
- **M line:** The M line is found at the center of the thick filaments, and it binds the thick filaments together vertically (خط عامودي)
- **Z line:** The Z line binds the thin filaments vertically with each other.

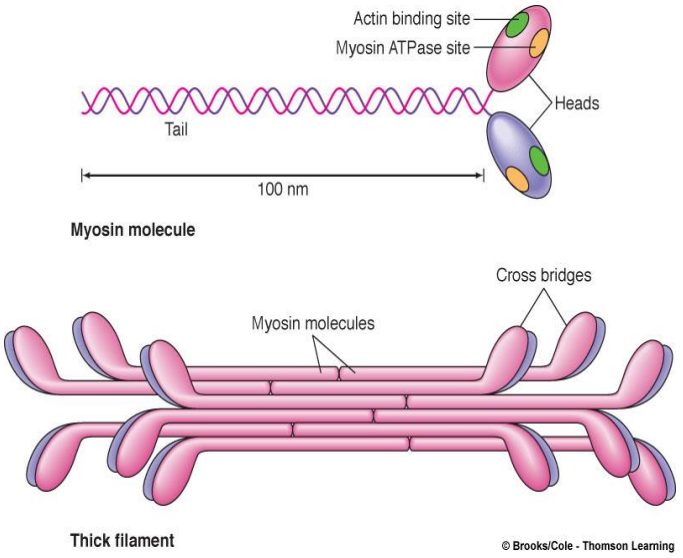


- **H zone:** There is an area (bare zone) in the thick filaments that has no thin filaments



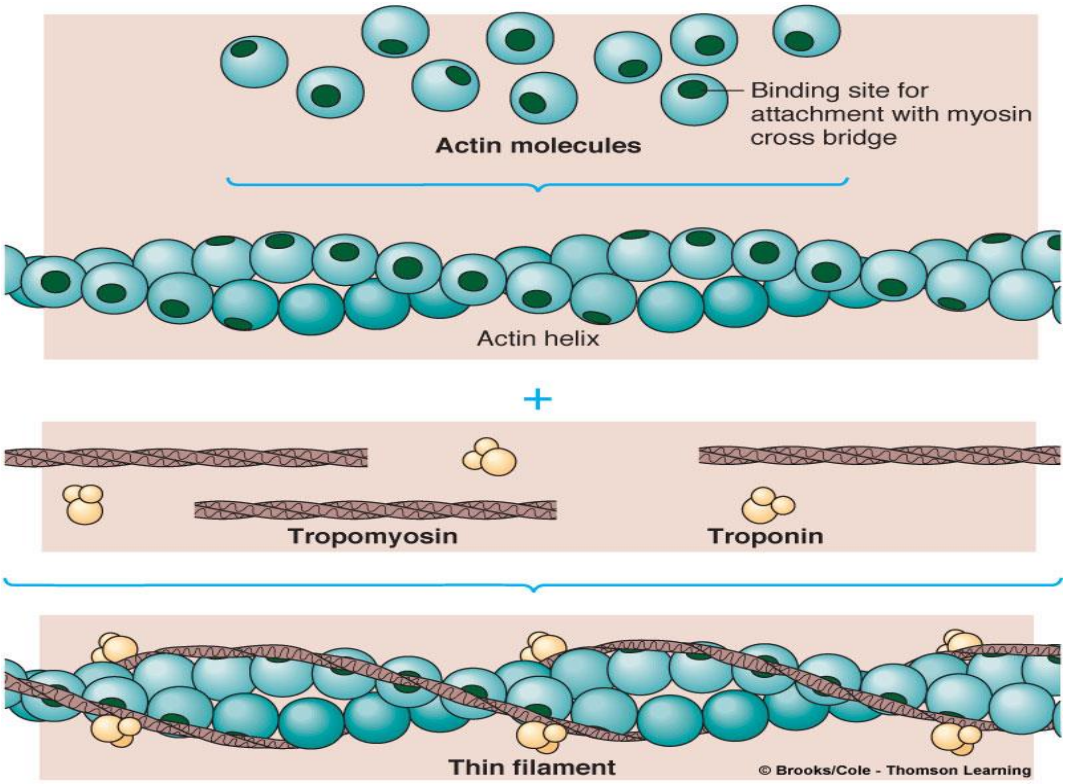
- **Sarcomere:** It is the functional unit (the smallest unit that is able to perform the function) of the muscle, and it is the area in between two Z lines.

Thick filament



- Composed of myosin protein – and myosin is made of two identical subunits
- Each myosin subunit is composed of a head that points outward, and a tail oriented towards the center.
- As you can see in the picture above, each head has two binding sites (مناطق للارتباط)
    - Actin binding site (to bind with actin)
    - Myosin ATPase / charging site (to bind with ATP, to provide the head with energy)

Thin filaments



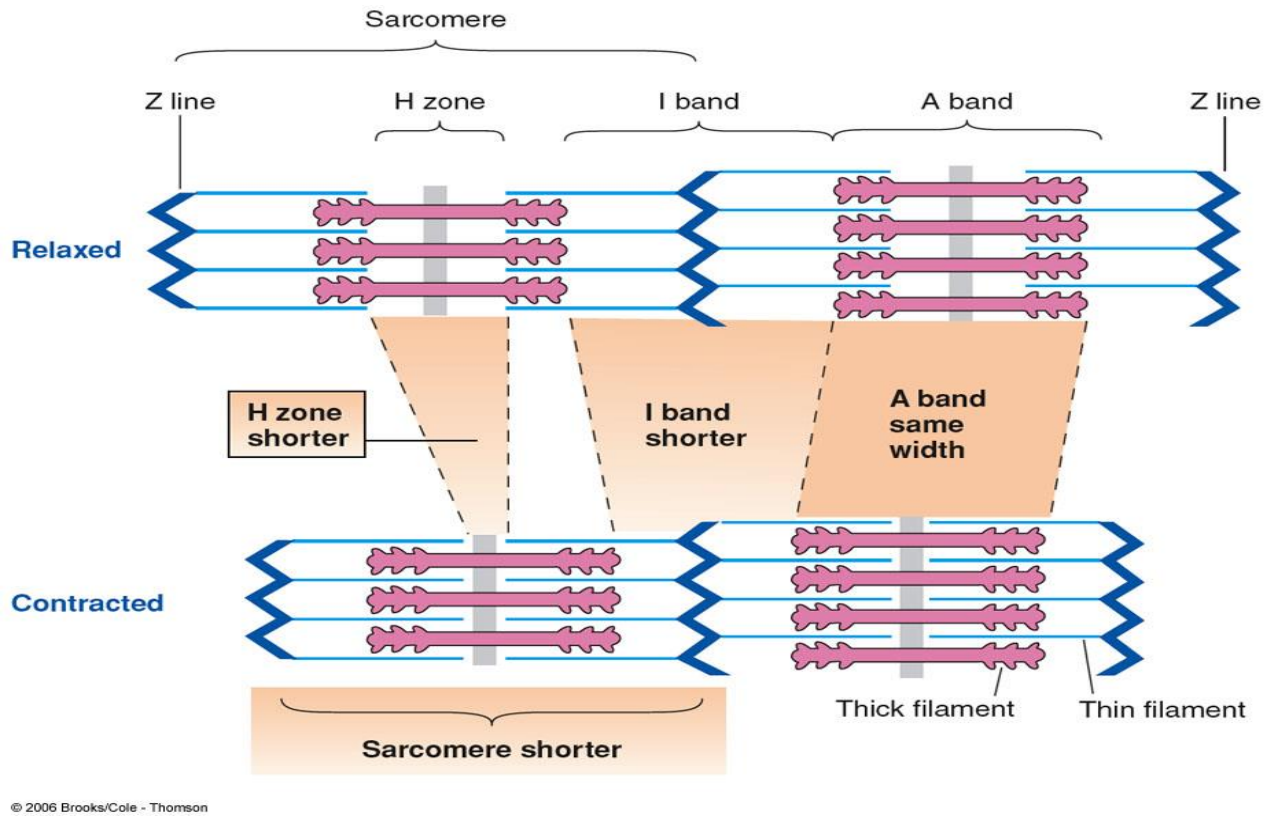
- It is composed of 3 proteins – actin, tropomyosin, and troponin.
  - **Actin**: spherical in shape, and is twisted (ملفوف) & has a special binding site for myosin.
  - **Tropomyosin**: thread-like structure that covers the myosin binding site on the actin, in order to prevent myosin from attaching to actin (in other words, in prevents muscle contraction)
  - **Troponin**: found at the end of tropomyosin – they hold the tropomyosin in its place. It has 3 subunits:
    - **Troponin T:** binds to tropomyosin
    - **Troponin I:** binds to actin
    - **Troponin C:** binds to Ca^{+2}, which results in a change in the shape of the protein. This causes it to slide off of Tropomyosin, which allows actin and myosin to attach to each other (muscle contraction).

Muscle proteins

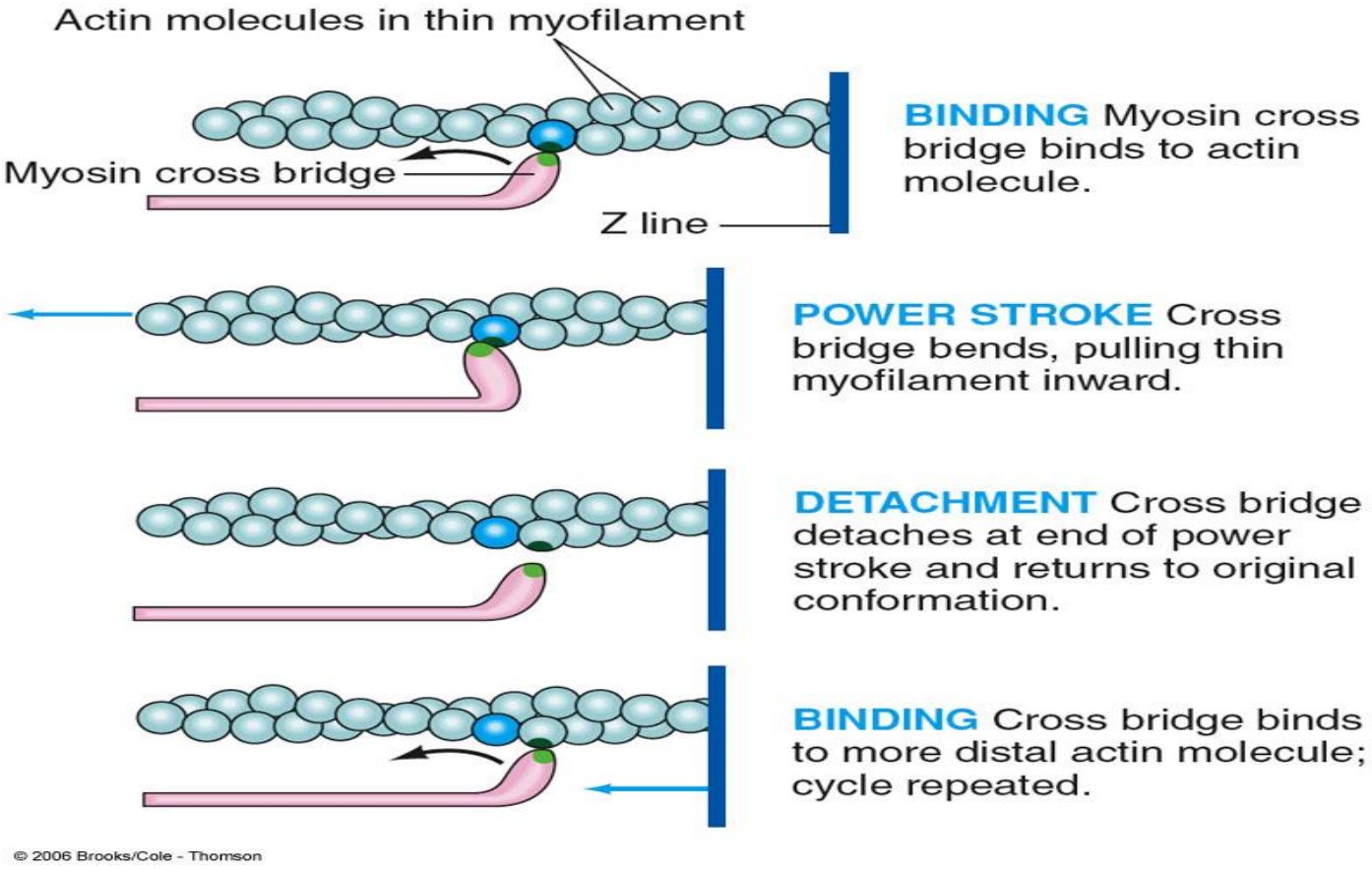
- **Contractile proteins:** actin and myosin. It is called "contractile" because when actin and myosin bind they cause muscle contraction.
- **Regulatory proteins:** tropomyosin and troponin. They are called "regulatory" because they regulate/control muscle contraction either by:
    - Covering the binding-site (stopping contraction)
    - Exposing the binding-site (allowing contraction)

Mechanisms of contraction

- **Sliding (انزلاق) filament mechanism:** sliding of thin filaments ([F] I band, sarcomere, H zone becomes shorter but the A band stays the same) towards the M line.



- **Cross activity:** (1) binding of myosin to actin (we need Ca^{+2}) -> (2) "power stroke"

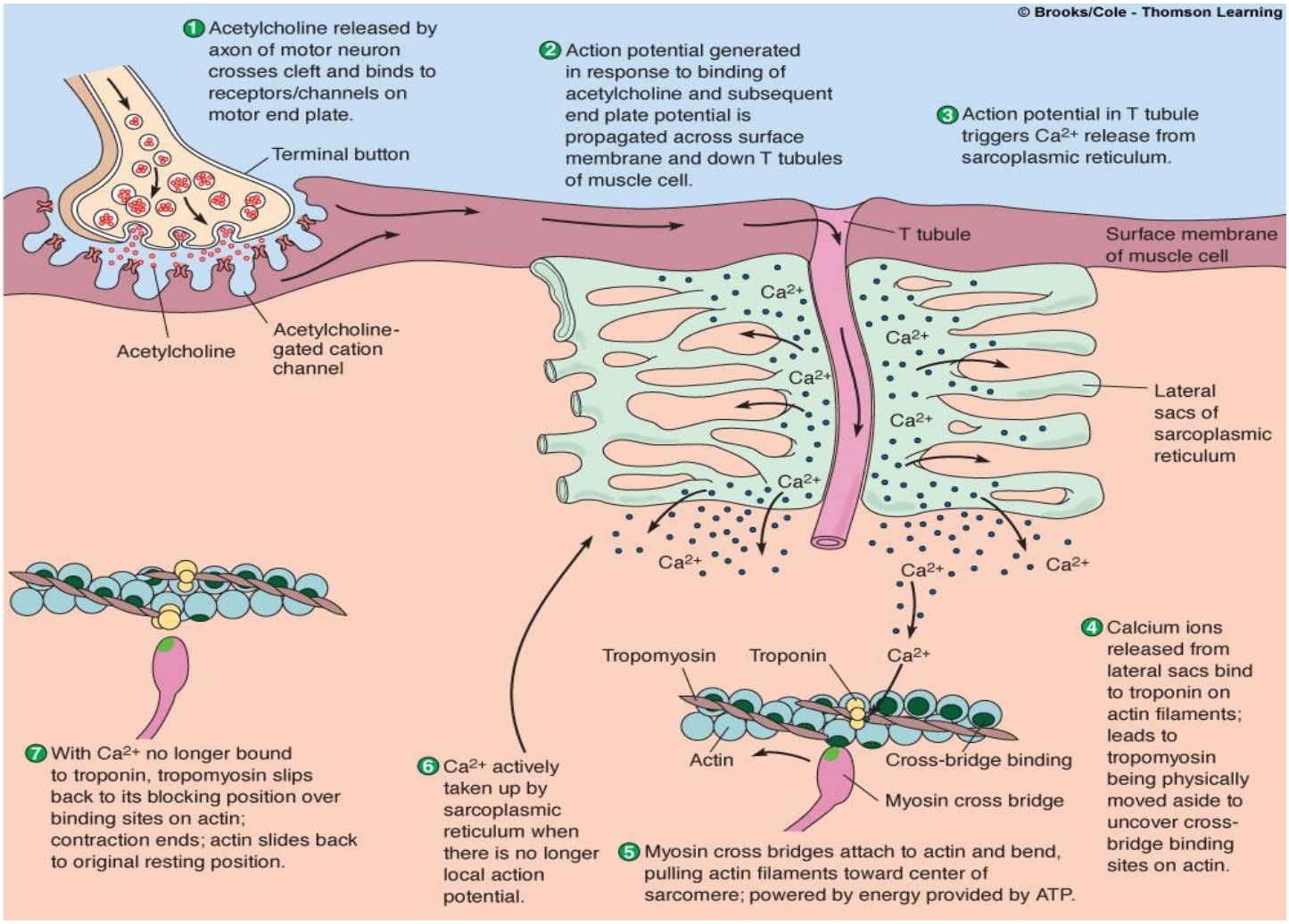


or "bending" of the head of myosin, which causes the actin part to move inward -> (3) detachment of the myosin, and this myosin binds with another actin. This keeps repeating.

*Note: In order to start bending, the myosin needs to be charged with ATP & in order to detach we need to have fresh ATP in order to bind with the myosin head

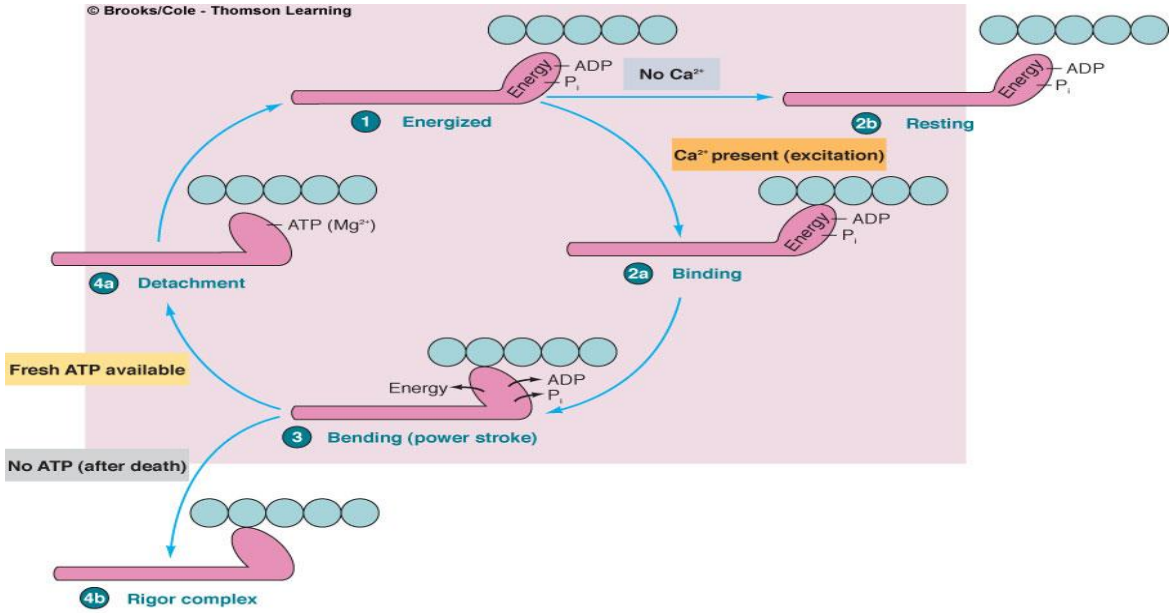
*Note: The myosin head is also called a "cross bridge"

Overview of muscle contraction



1. Influx of Calcium ions causes the release of Acetylcholine, and the Acetylcholine binds to specific receptors in the end plate.
2. This causes ion channels like Na^+ & K^+ to open, causing Na^+ to move inside & K^+ to move outside – but due to the electrical gradient more Na^+ moves inside. This causes depolarization of the membrane, leading to end plate potential which results in reaching threshold (producing action potential).
3. Action potential reaches T tubule of muscle cell, which causes the release of Calcium ions from "sarcoplasmic reticulum"
4. The free Calcium ions start to bind to troponin (found on the actin filaments), and this leads to troponin sliding off of tropomyosin. Tropomyosin covers actin & since it moved off due to Calcium ions, this results in actin cross-binding sites being open.
5. Myosin attaches to actin and starts to perform the **cross-activity mechanism**, which results in muscle contraction.

Last slide regarding muscle contraction:



1. Reminder: The myosin head is charged, meaning it has energy stored inside. The energy comes from splitting ATP into ADP & P_i.
2. We need Ca^{+2} ions in order to start the cross-activity mechanism.
    a. If it is present: it binds to troponin which leads to actin being exposed (مكشوف) – enabling actin to bind with the cross bridge
    b. If it isn't present: muscle remains at rest because actin and myosin don't bind.
3. Bending/Power stroke (the ADP & P_i are released)
4. We need fresh ATP in order for the myosin head to detach
    a. If it is present: the link between actin & myosin is broken
    b. If it is not present: actin & myosin remain attached in <u>rigor complex</u>.

Rigor mortis/stiffness of death (التصلب بعد الوفاة) that happens 3 hours after death:

- This happens because the cell membrane becomes permeable to Ca^{+2}, causing an influx of Ca^{+2}.
- The influx of Ca^{+2} causes <u>binding</u> of actin and myosin, then the power stroke takes place.
- However, detachment (إنفصال) cannot take place since there is no fresh of ATP.