1st Year Medical Students
Physiology (Lecture 15)
(Excitation-Contraction Coupling)

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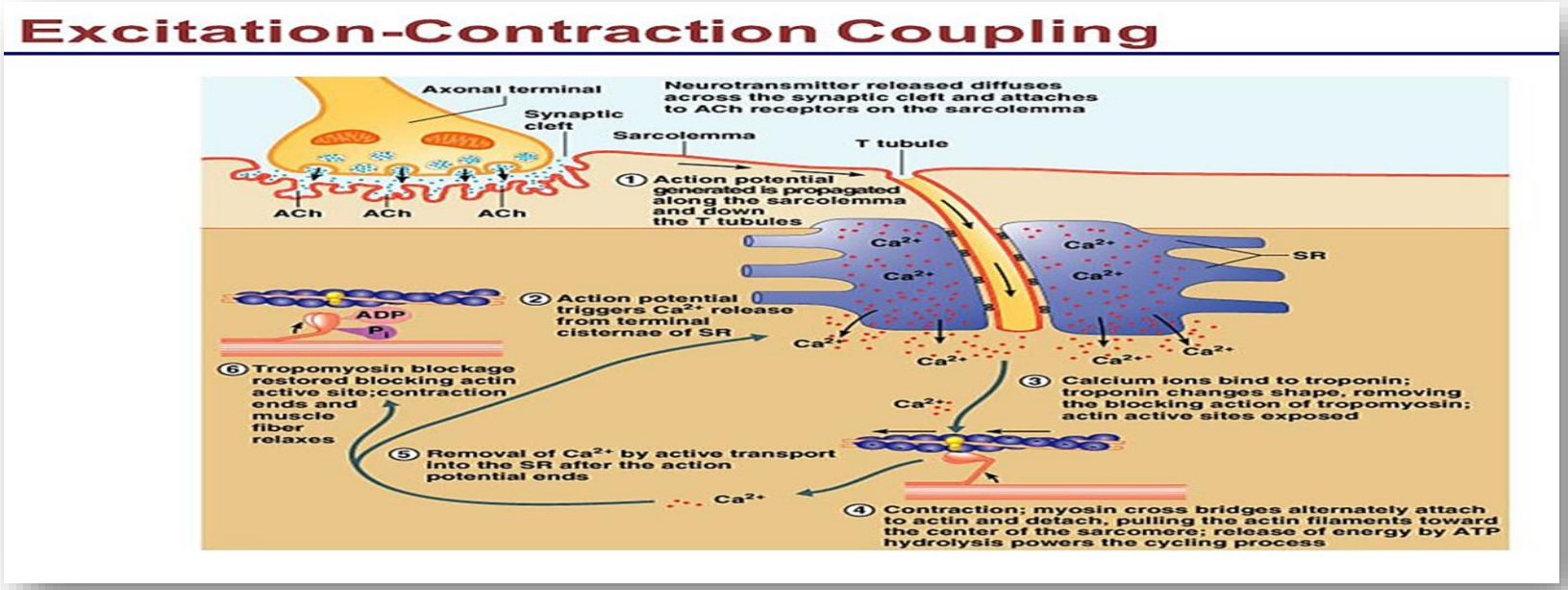


PHYSIOLOGY OF THE MUSCLE

- Muscle cells, like neurons, can be excited to produce an action potential that is transmitted along their cell membranes.
- Unlike neurons, they respond to stimuli by activating a contractile mechanism.
- The function of the muscle is to **CONTRACT** when stimulated.
- **Types of Muscles:**

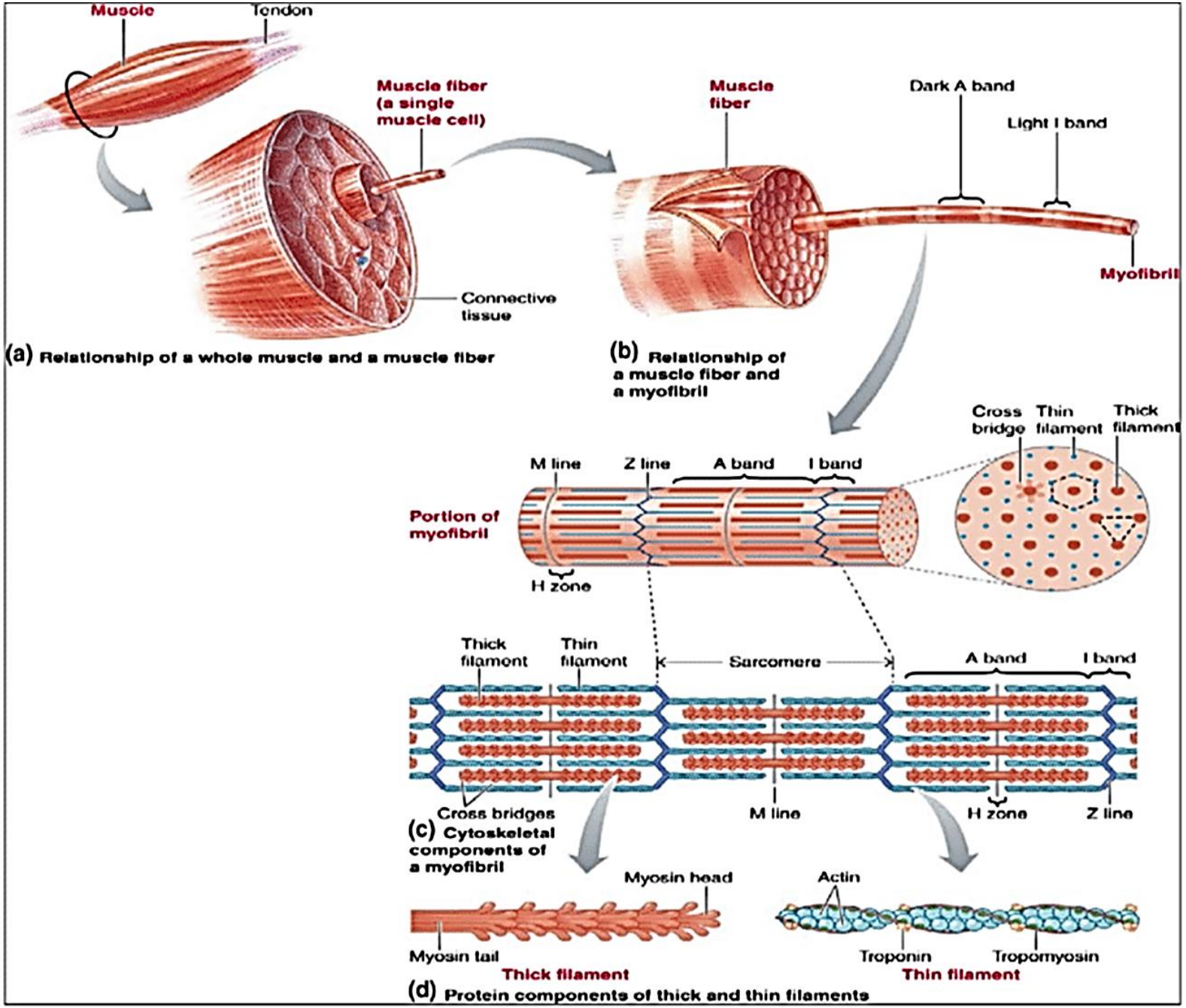
1. Skeletal (striated) Muscles.
2. Cardiac (striated) Muscle.
3. Smooth (non-striated) Muscles.

The Skeletal Muscle

- Skeletal muscles are **voluntary** and controlled by somatic motor nerves.
- They are formed of parallel individual **muscle fibers** **completely separated from each other**.
- **Muscle fiber or cell:**
  - **It is the structural unit of skeletal muscle**.
  - Most of the cytoplasm of a fiber is filled with **fibrils (myofibrils)** formed of **filaments formed of contractile proteins (myofilaments)**.
  - Skeletal muscle has **regular arrangement of A bands and I bands giving it a striated appearance**.

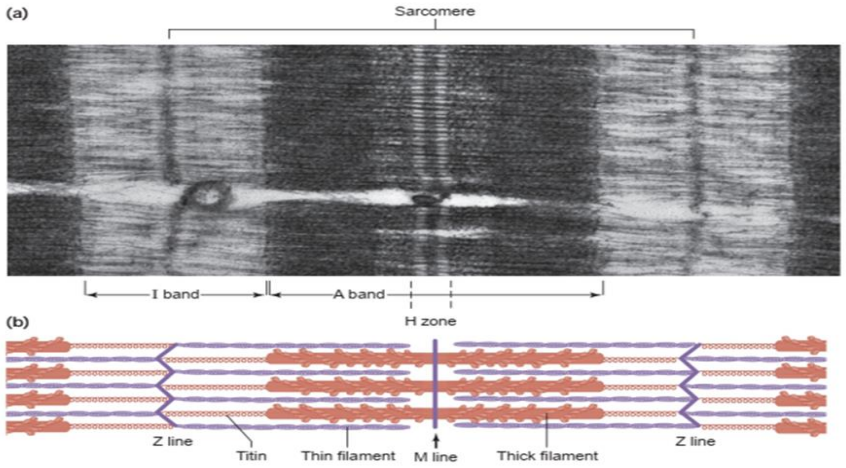
The Muscle Fibril (Myofibril)

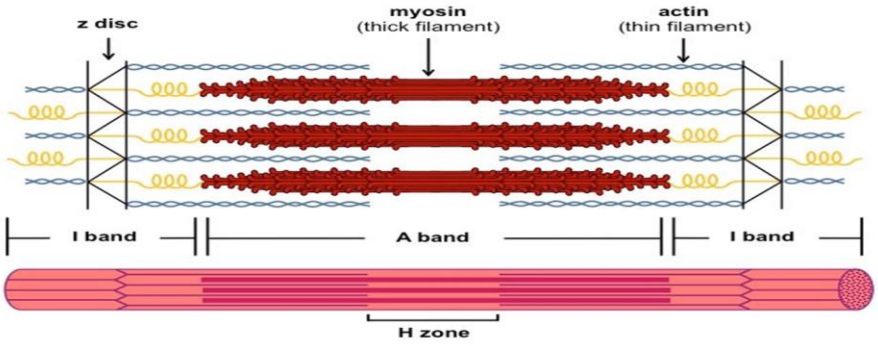
- Each myofibril shows alternating dark (A) and light (I) bands.
- In the **middle** of the **I band**, there is a **dark Z line.**
- In the **middle** of the **A band** there is a **light (H) band** in the **middle** of which a transverse **(M) line** is seen.
- The **contractile proteins** that make the myofibril are:
    1. **Myosin (thick filaments).**
    2. **Actin (thin filaments).**
- The **thick myosin** filaments extend along the whole length of the **dark (A)** band **only**.
- The **thin actin** filaments extend from the (**Z) line** to the **H band.**
- The **dark (A)** band contains **both** actin and myosin, while **the light (I)** band contains **only** actin.


Muscle
Tendon
Muscle fiber (a single muscle cell)
Connective tissue
(a) Relationship of a whole muscle and a muscle fiber
Muscle fiber
Dark A band
Light I band
Myofibril
(b) Relationship of a muscle fiber and a myofibril
Cross bridge
Thin filament
Thick filament
M line
Z line
A band
I band
Portion of myofibril
H zone
Thick filament
Thin filament
Sarcomere
A band
I band
Cross bridges
M line
H zone
Z line
(c) Cytoskeletal components of a myofibril
Myosin head
Myosin tail
Thick filament
Actin
Troponin
Tropomyosin
Thin filament
(d) Protein components of thick and thin filaments

The SARCOMERE:

- ✓ It is the functional and contractile unit of the skeletal muscle fiber.
- ✓ It is the area between 2 adjacent (successive) Z lines.
- ✓ The two myofilaments (thin and thick filaments) are present in sarcomere.





The Myofilaments

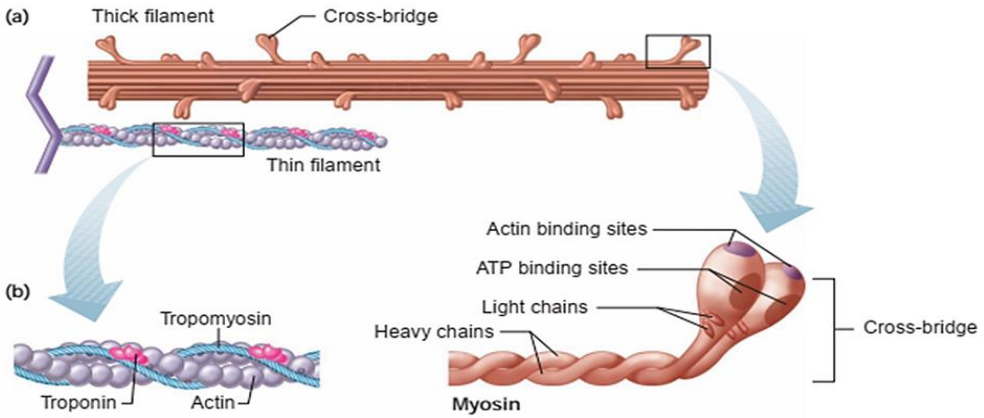
(1)The Thick Filaments (Myosin Filaments)

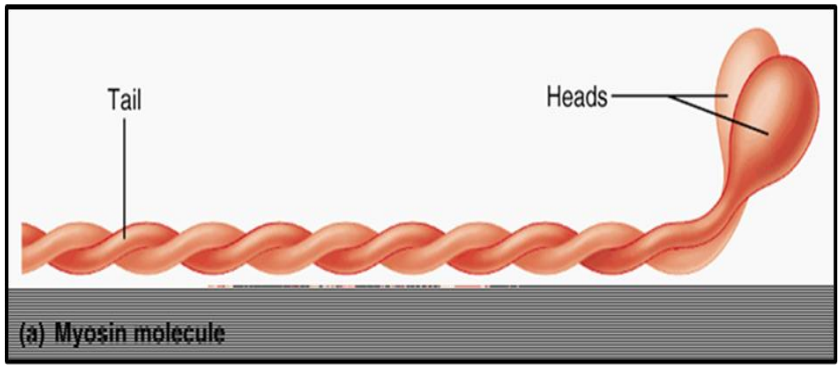
- Each myosin filament is formed of nearly 200 myosin molecules.
- Each myosin molecule consists of **two globular heads** and **a long tail**.
- The two **globular heads** extend out to the sides, forming **cross-bridges**, which make contact with the thin filament and exert force during muscle contraction.
- **Each globular head contains two binding sites:**
  - One for **attaching to the thin filament (actin binding site).**
  - One for **ATP (ATP binding site)**. **The ATP binding site also serves as an enzyme—an ATPase** that hydrolyzes the bound ATP; energy for contraction.

(2) The thin (actin) filaments:

The thin filaments are principally composed of:

- **The protein actin**.
- Each actin molecule contains a binding site for myosin **(myosin-binding site)**.
- As well as **two other proteins—troponin and tropomyosin**—that play important roles in regulating contraction **(regulatory proteins)**.
- **Troponin is composed of three subunits: I (inhibitory), T (tropomyosin - binding) and C (Ca^{2+} - binding)**.





SARCOTUBULAR SYSTEM

It is formed of a **transverse (T)-tubular system and the sarcoplasmic reticulum (SR)**.

(1) THE T-TUBULAR SYSTEM:

- It is an internal invagination of the cell membrane.
- It is present at the junction of the dark (A) and light (I) bands in the skeletal muscles.
- The lumen of the T-tubule is continuous with the extracellular fluid surrounding the muscle fiber.
- **Function:**

Rapid conduction of the action potential from the surface of the muscle to all muscle fibrils inside.

(2) THE SACROPLASMIC RETICULUM (SR):

- It forms long longitudinal tubules that surround the myofibrils.
- It ends in large chambers called terminal cisternae.
- **Function:**

The sarcoplasmic reticulum is concerned with Ca^{2+} storage and release.

- The arrangement of the T-tubules with the terminal cisternae one on either sides is called **Triad**.

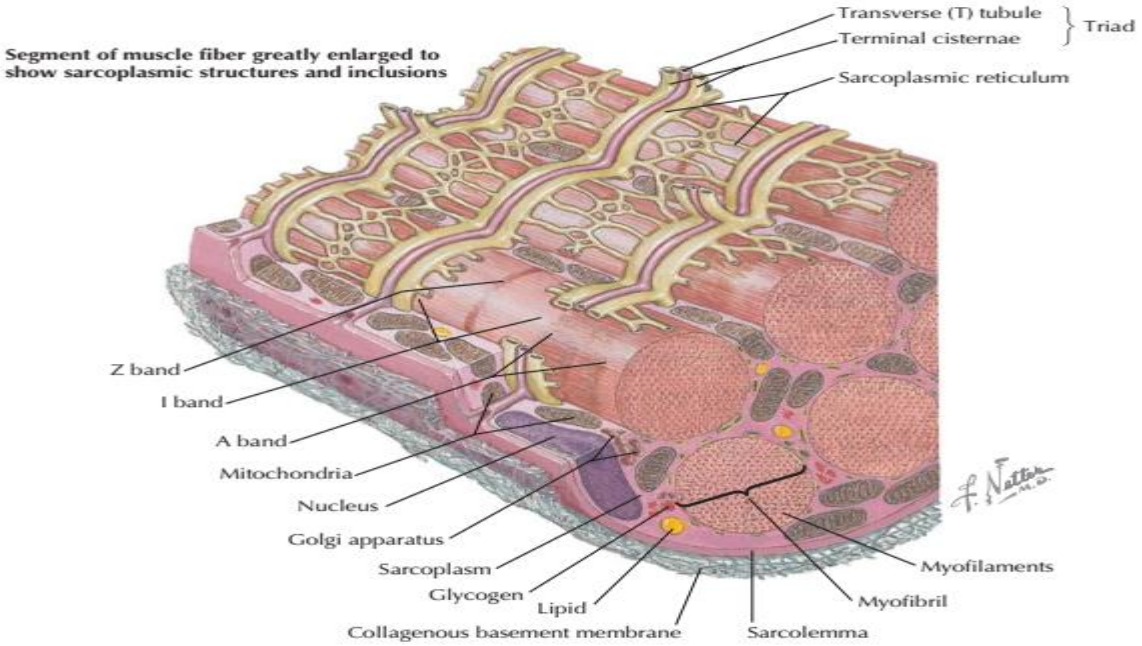
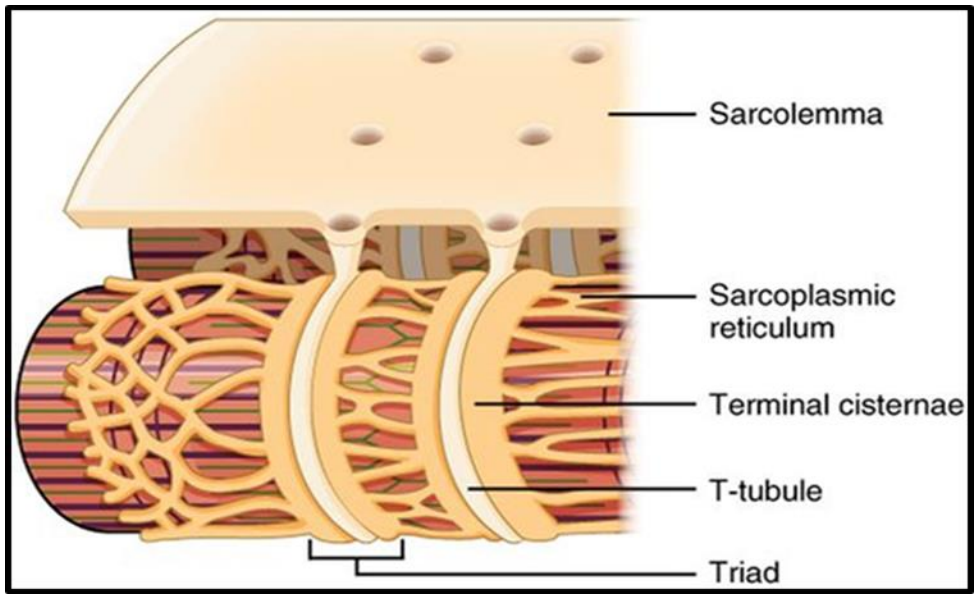


Figure 3.12 **Sarcoplasmic Reticulum** The sarcoplasmic reticulum is a complex network surrounding the myofibrils and storing high concentrations of Ca^{2+}, sequestered from the sarcoplasm. The membrane of the sarcoplasmic reticulum contains Ca^{2+}-ATPase, which is essential for this sequestration. The transverse tubules are deep invaginations of the sarcolemma and form triads with the terminal cisternae of the sarcoplasmic reticulum. These transverse tubules conduct the action potential from the sarcolemma to the cisternae, causing release of Ca^{2+}.



SKELETAL MUSCLE EXCITATION CONTRACTION COUPLING (ECC)

- Skeletal muscle can **contract** either:
  a. In response to a **nerve impulse (AP)** in the somatic motor nerve supplying the muscle (inside the body, i.e. Natural mechanism).
  b. Or by **direct stimulation** of the muscle (e.g. experimentally or during physiotherapy).

Contraction of skeletal muscle is accompanied by:

- ✓ Electric changes.
- ✓ **Mechanical** changes……..Muscle Contraction.
- ✓ Excitability changes.
- ✓ Metabolic changes.
- ✓ Thermal changes.

1. THE ELECRTIC CHANGES

- Resting membrane potential (RMP) in skeletal muscle fibers is about –90 mV (the same as in large myelinated nerve fibers).
- Initiation of muscle contraction begins with AP in the muscle fiber that is conducted from the surface to the interior of the muscle fiber along the T-tubule.

2. THE MECHANICAL CHANGES

- The mechanical changes mean the **contractile response** itself.
- It **follows the electric change (AP)** and the link between them is called **Excitation-Contraction Coupling (ECC)**.

Steps of Excitation Contraction Coupling (ECC)

1. DISCHARGE of the motor neuron and arrival of the nerve impulse (AP) to the axon terminal.

2. DEPOLARIZATION of the axon terminal allows the entry of Ca^{2+} from the ECF (through voltage gated Ca^{2+} channels) and rupture of the vesicles releasing their contents of ACh.

3. GENERATION OF THE END PLATE POTENTIAL (EPP):

- **ACh crosses synaptic cleft and binds** with its receptors (nicotinic receptors) on the surface of the muscle.
- The binding of ACh to its receptors opens an ion channel in each receptor protein → **ligand-gated Na^+ channels** → Na^+ influx → local depolarization at MEP called **End-Plate Potential (EPP)**.
- When the **EPP reaches the threshold potential, an action potential is generated at the MEP** and **propagates on either sides of the sarcolemma,** as well as to the **interior of the muscle fiber** along the **T-tubules**.

4. RELEASE OF Ca^{2+} FROM THE SR:

- When the **AP reaches** the terminal cisternae of **SR** along the T-tubules → opens **Ca^{2+} channels** → **release** of **Ca^{2+}** from its stores in SR into the **sarcoplasm**.
- Ca^{2+} diffuses to adjacent myofibrils to **bind** with **troponin C.**

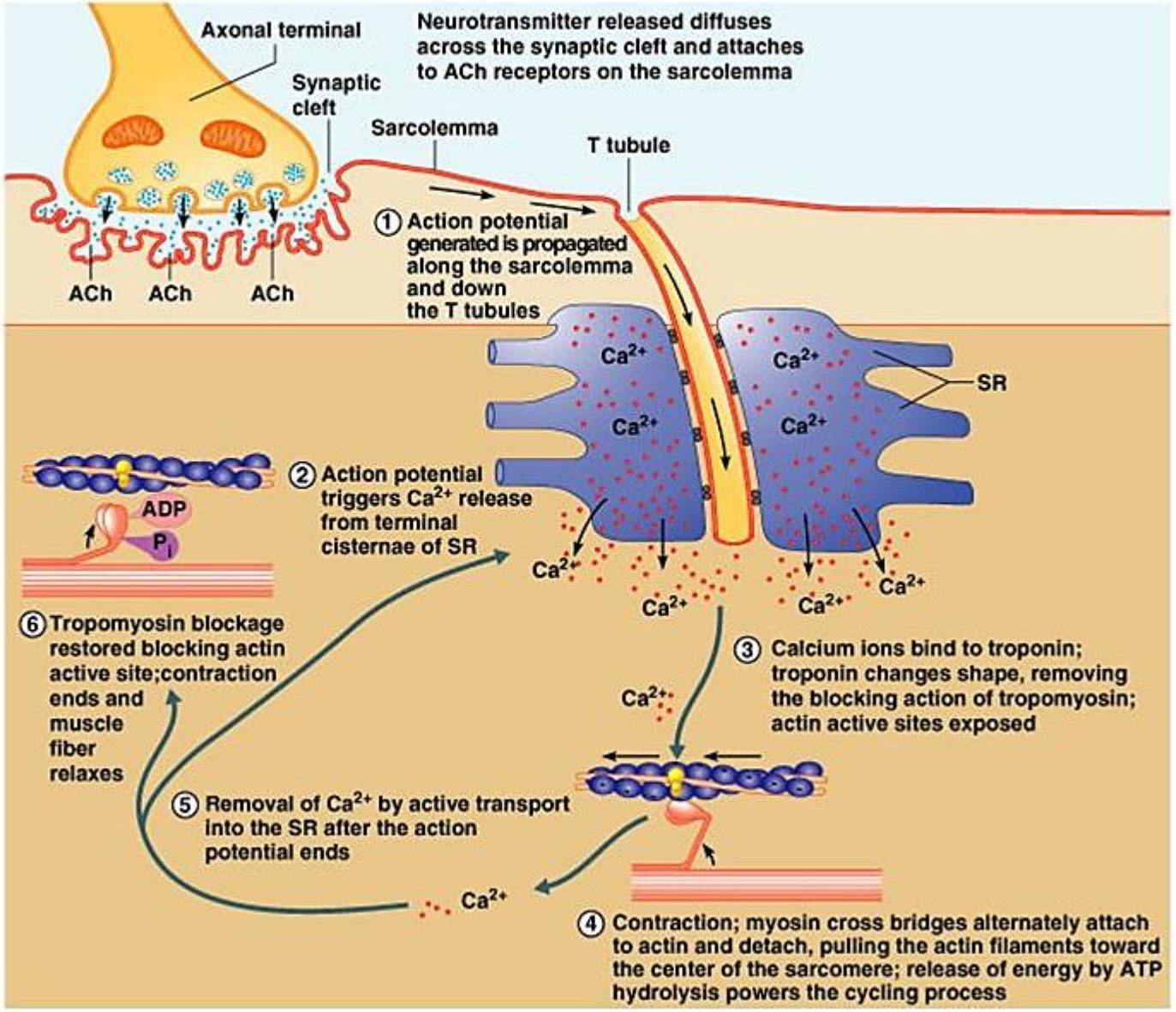
5. THE ROLE OF Ca^{2+}:

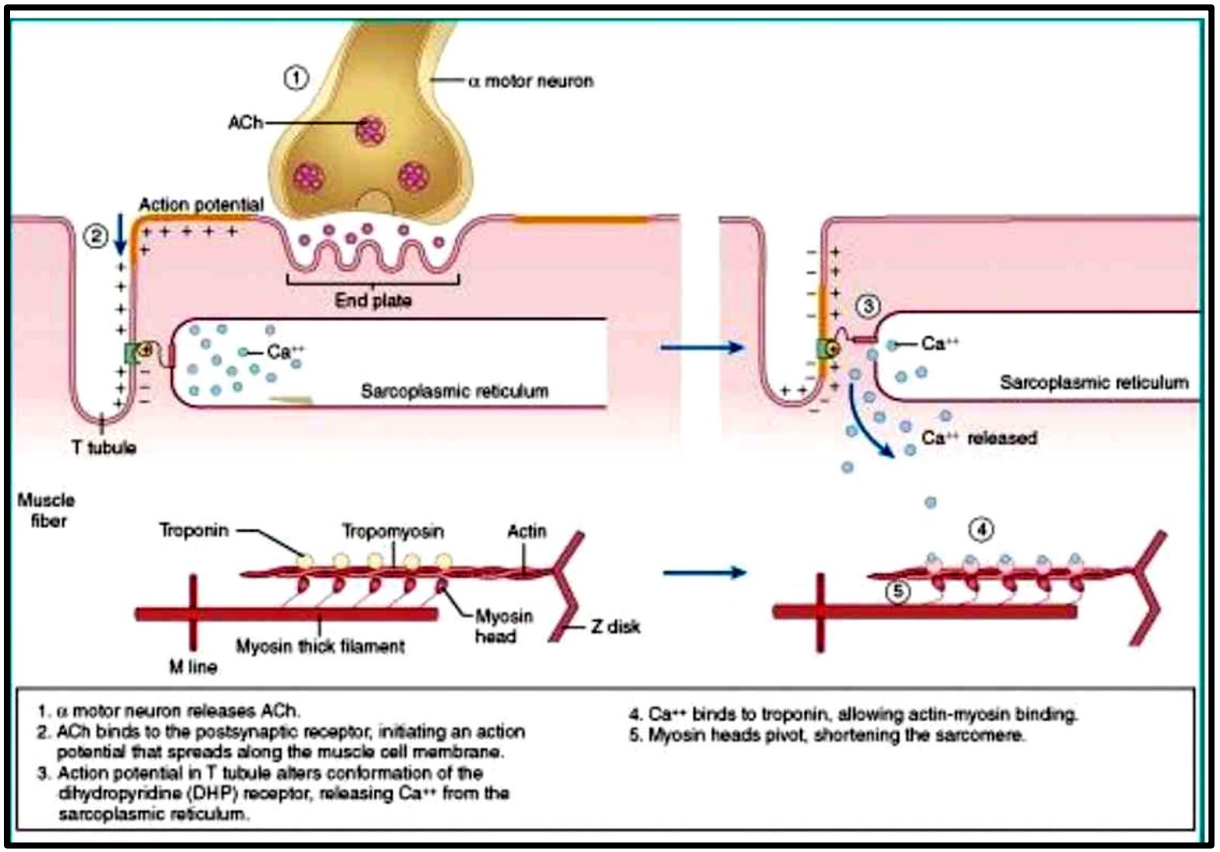
- **DURING RELAXATION OF THE MUSCLE,** troponin **I** is **tightly** bound to **actin**, and **tropomyosin covers** the **myosin-binding sites** on **actin**, thus, **preventing** the interaction of myosin heads with actin to cause contraction.
- Thus, **troponin and tropomyosin block the interaction of myosin cross-bridges with actin**.
- **WHEN Ca^{2+} BINDS TO TROPONIN C** → the binding of troponin I to actin is **weakened** and tropomyosin is **moved laterally** to **uncover** the **myosin-binding sites** of actin.

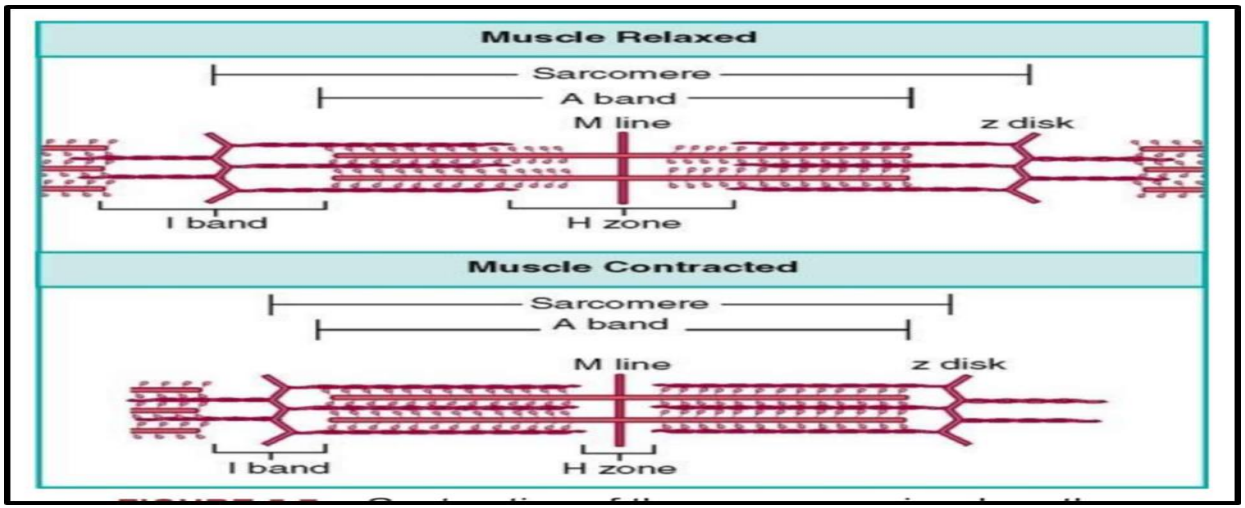
6. CROSS BRIDGE CYCLING :

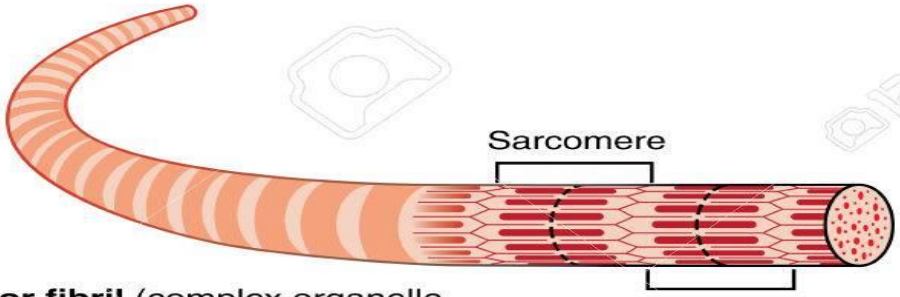
- Once the **myosin-binding sites** on actin are exposed, the myosin heads (**cross bridges**) become **attached** to them, thus **allowing sliding of actin on myosin**.
- The actin filaments move towards the center of myosin filaments and shortening of sarcomere occurs by cycling of cross bridges.
- The **myosin heads contain ATP binding site** which **acts as an enzyme (ATPase)** that hydrolyze ATP to produce ADP + Pi + E.
- The energy liberated is consumed in **contraction which is an active process.**

Excitation-Contraction Coupling




1
α motor neuron
ACh
Action potential
2
End plate
Ca++
Sarcoplasmic reticulum
T tubule
3
Ca++
Sarcoplasmic reticulum
Ca++ released
Muscle fiber
Troponin
Tropomyosin
Actin
Myosin head
Z disk
Myosin thick filament
M line
4
5
1. α motor neuron releases ACh.
2. ACh binds to the postsynaptic receptor, initiating an action potential that spreads along the muscle cell membrane.
3. Action potential in T tubule alters conformation of the dihydropyridine (DHP) receptor, releasing Ca++ from the sarcoplasmic reticulum.
4. Ca++ binds to troponin, allowing actin-myosin binding.
5. Myosin heads pivot, shortening the sarcomere.


Muscle Relaxed
Sarcomere
A band
M line
z disk
I band
H zone
Muscle Contracted
Sarcomere
A band
M line
z disk
I band
H zone



Myofibril or fibril (complex organelle composed of bundles of myofilaments)

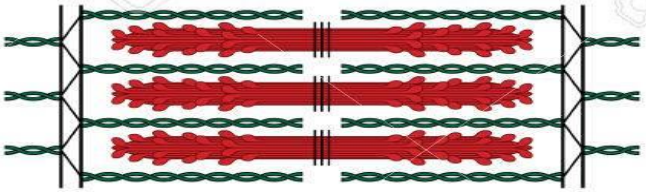
Sarcomere (contractile unit of a myofibril)

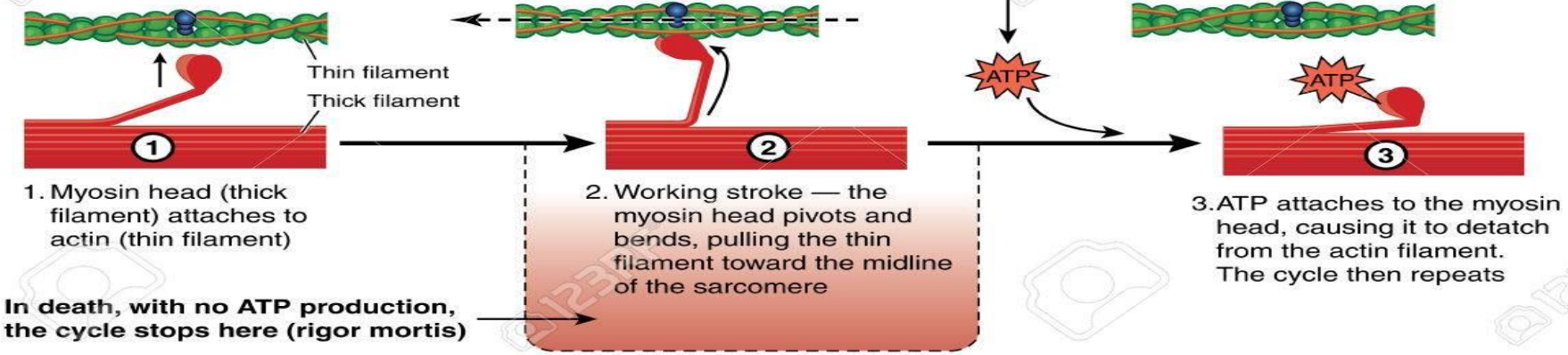
Sarcomere
(relaxed muscle)

Thin (actin) filament

Thick (myosin) filament

Sarcomere
(contracted muscle)





1. Myosin head (thick filament) attaches to actin (thin filament)

2. Working stroke — the myosin head pivots and bends, pulling the thin filament toward the midline of the sarcomere

3. ATP attaches to the myosin head, causing it to detatch from the actin filament. The cycle then repeats

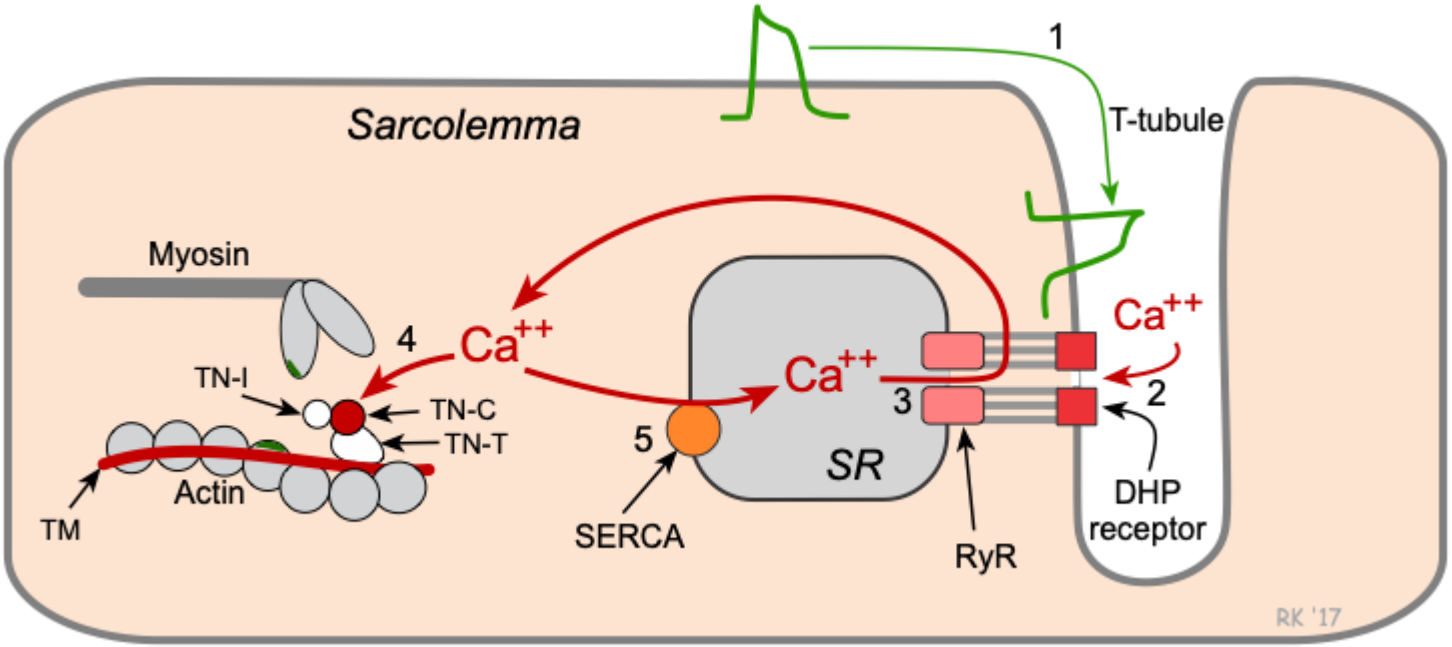
In death, with no ATP production, the cycle stops here (rigor mortis)

MECHANISM OF SKELETAL MUSCLE RELAXATION

- **Muscle contraction is terminated by removal of Ca^{2+} from troponin C.**
- The **SR** contain **Ca^{2+}-ATPase pumps (SERCA)** that pump calcium ions from the cytosol back into the lumen of the SR $\rightarrow \downarrow$ Ca^{2+} concentration in the sarcoplasm $\rightarrow$ release of Ca^{2+} from **troponin C.**
- ATP is required to provide the energy for the Ca^{2+} pumps.

N.B.

Both contraction & relaxation are active and need ATP




Thank
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