Contraction of Skeletal Muscle

Textbook of medical physiology Guyton & Hall (13th edition)

UNIT II CHAPTER 6

Dr. Mohammed Alotaibi

Objectives of the lecture

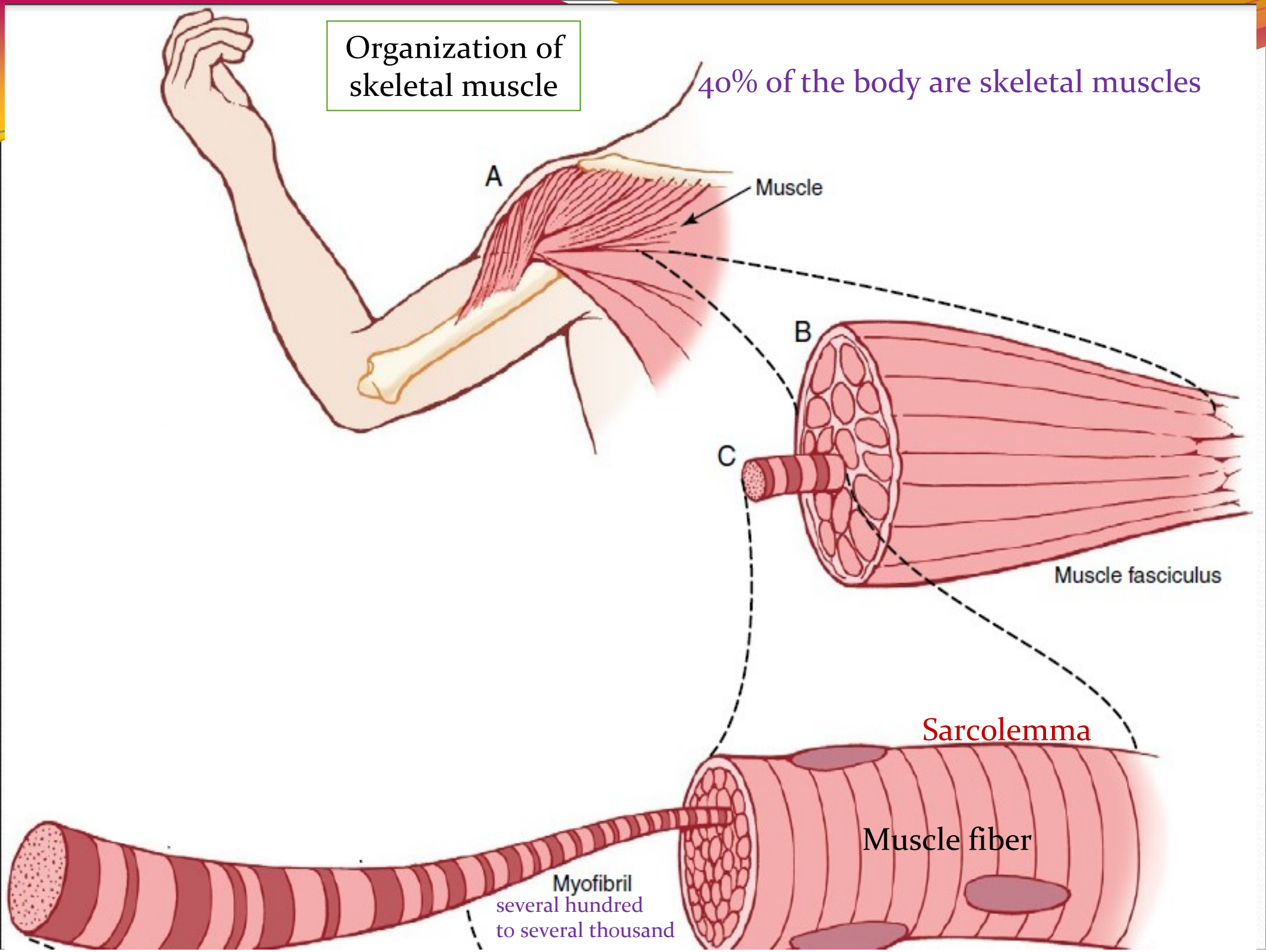
At the end of the lecture the student should be able to:

Know and describe the followings:

- The physiologic anatomy of the skeletal muscle.
- The general mechanism of skeletal muscle contraction.
- The molecular mechanism of skeletal muscle contraction & relaxation.
- Sliding filament mechanism.

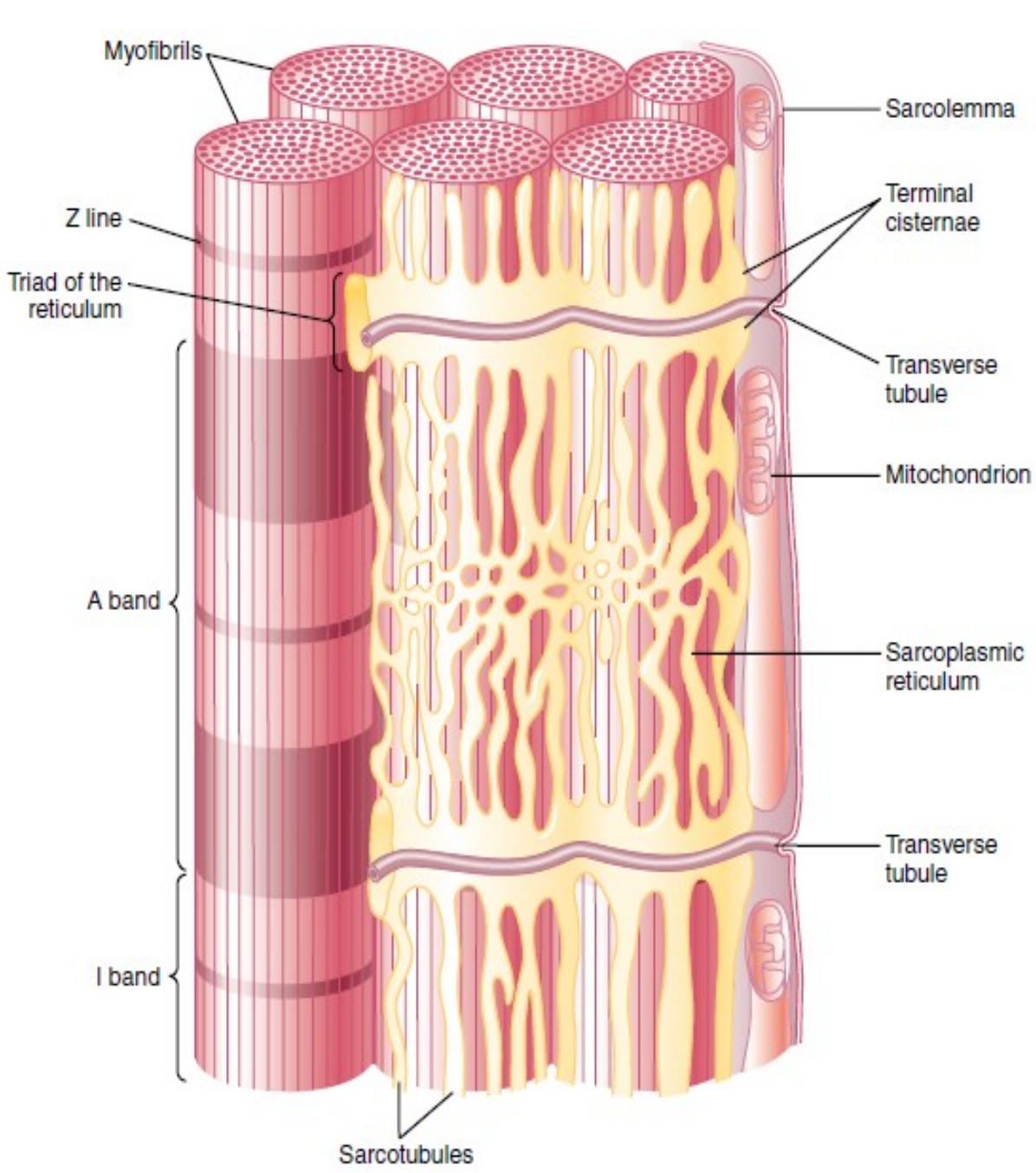
Organization of skeletal muscle

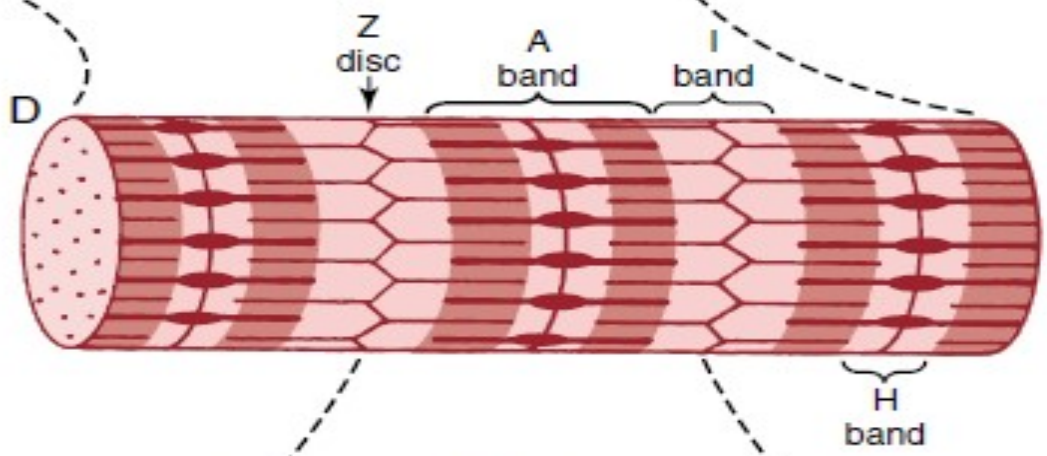
40% of the body are skeletal muscles



Physiological Anatomy of Skeletal Muscle

- **Sarcolemma** (plasma membrane) is a thin membrane enclosing a muscle fiber.
- Myofibrils are composed of **actin** and **myosin.**
- **Sarcoplasm** is the ICF between myofibrils.
- **Sarcoplamic reticulum** is a specialized endoplasmic

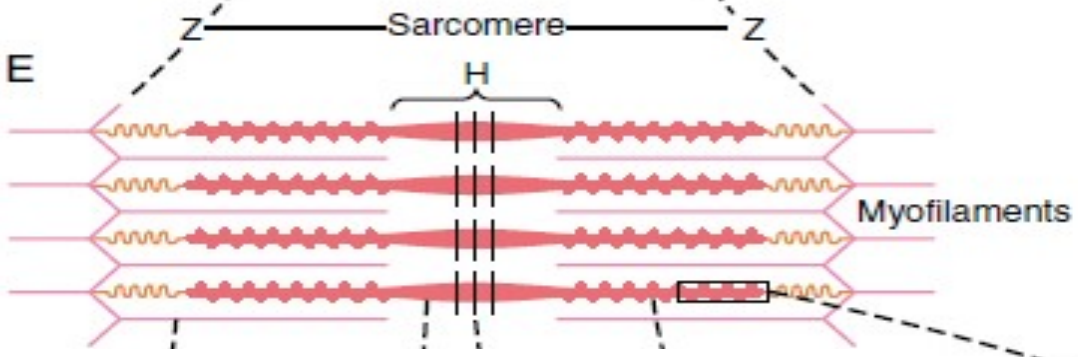




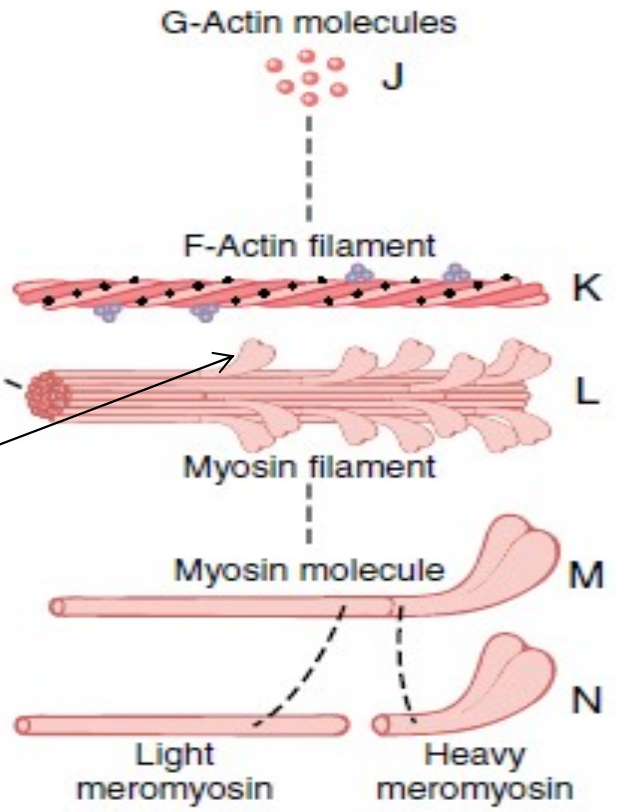
3000 Actin

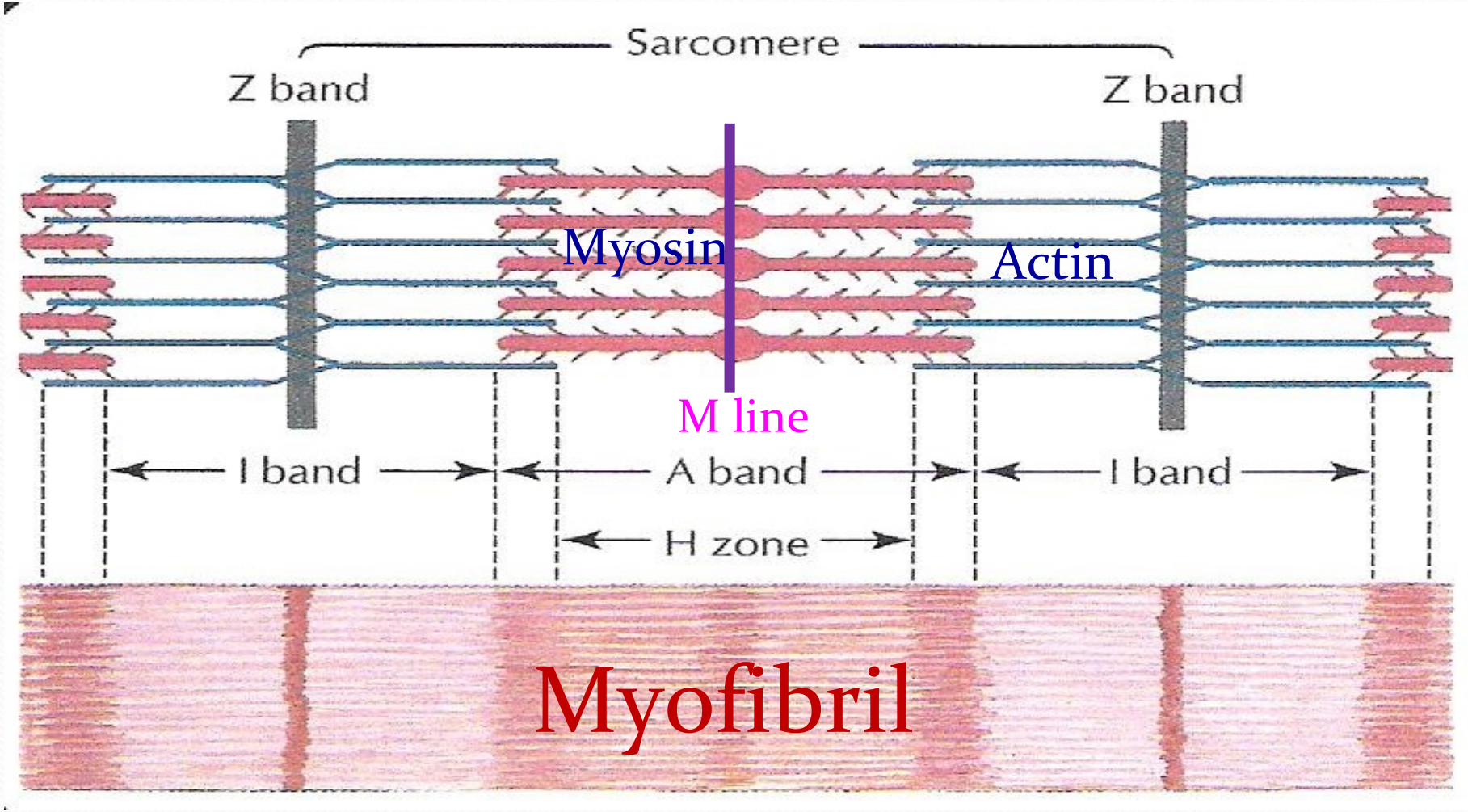
1500 Myosin

Responsible for the actual muscle contraction



Cross-bridges





The light and **dark** bands give skeletal and cardiac muscle their striated appearance.

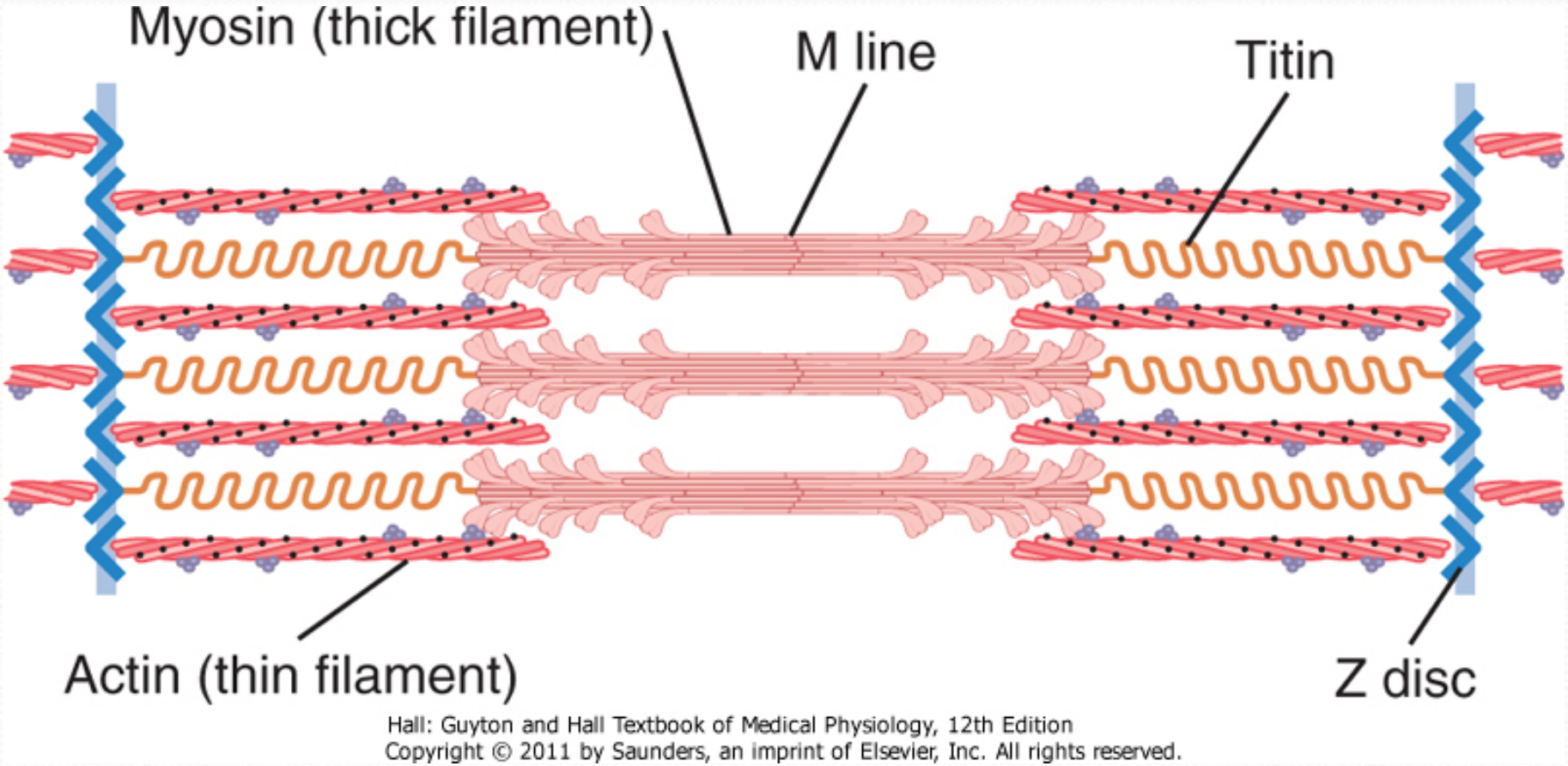


Fig. 6.3 Organization of proteins in a sarcomere

- **Titin** filaments keep the myosin and actin filaments in place.

General Mechanism of Skeletal Muscle Contraction

1. An action potential travels along a motor nerve to the motor end plate.
2. The nerve secretes acetylcholine (Ach).
3. The Ach binds to sarcolemma and opens gated channels.
4. Large amounts of Na^{+} enter the cell and initiates and AP.
5. AP travels along the sarcolemma the same as in a nerve cell.
6. AP causes depolarization and triggers release of Ca^{++} from the sarcoplasmic reticulum.
7. Ca^{++} initiates the contraction cycle.
8. After contraction, Ca^{++} ions are reabsorbed by the sarcoplasmic reticulum.

Molecular Mechanism of Muscle Contraction

Muscle Contraction Occurs by a Sliding Filament Mechanism

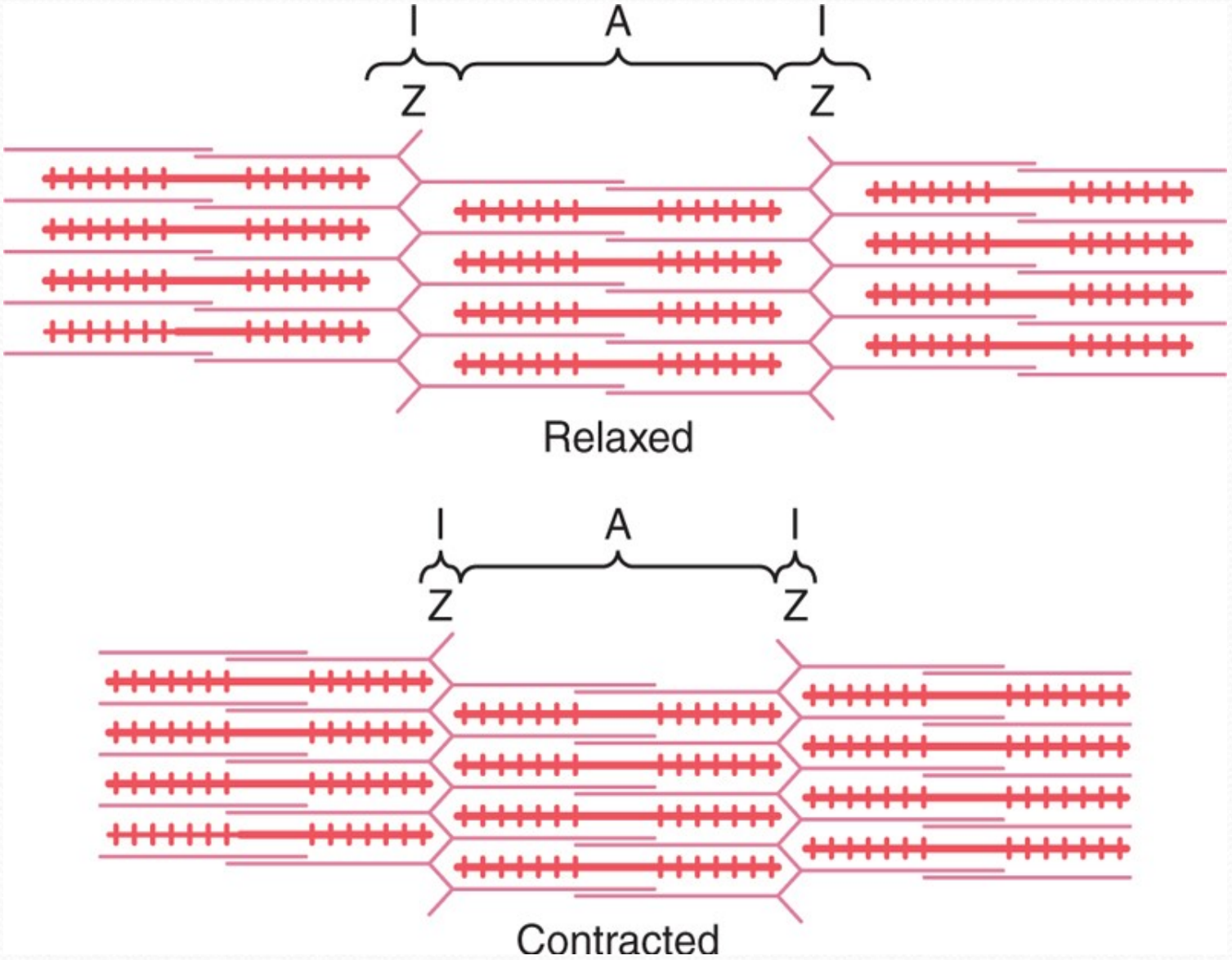


Figure 6-5. Relaxed and contracted states of a myofibril.

- **Molecular Characteristics of the Contractile Filaments**

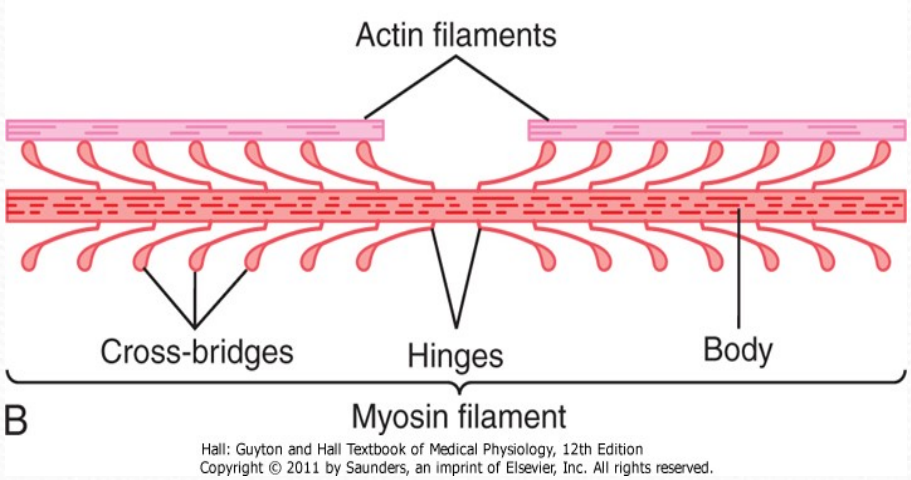
Myosin filaments are composed of multiple myosin molecules.

Each Myosin molecule has:

(1) Head

(2) Tail

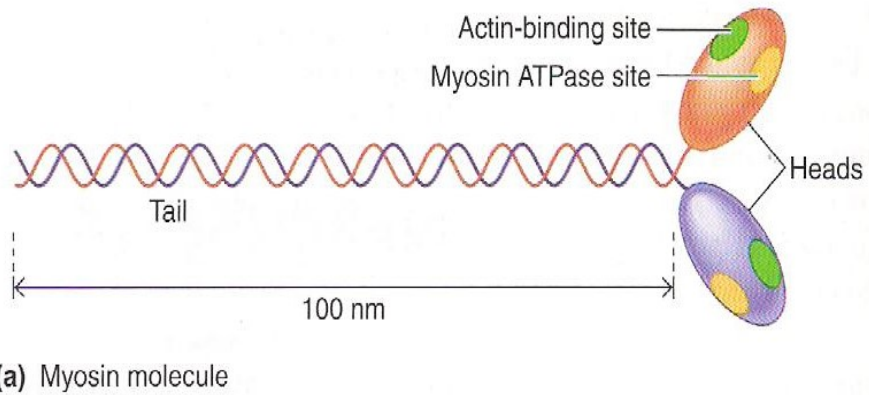
(3) Hinge (joint)



Each myosin head contains:

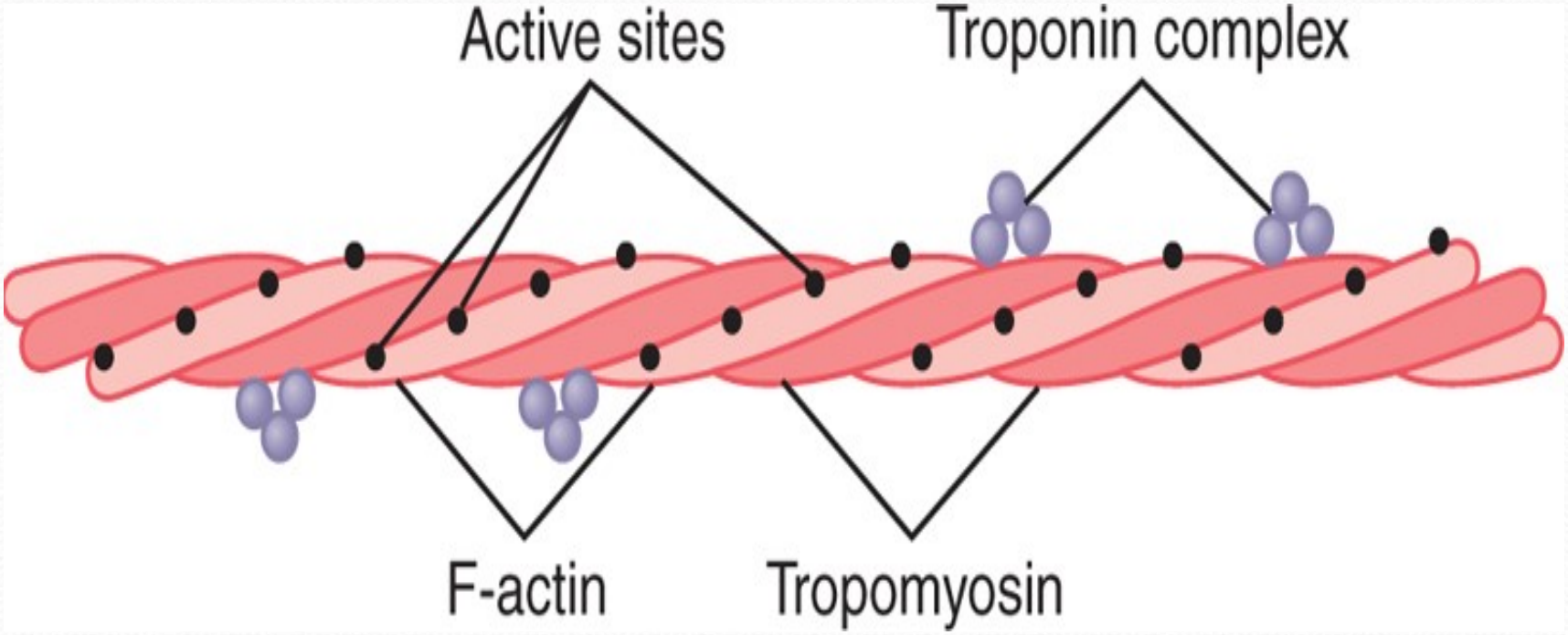
(1) Actin binding site

(2) Myosin ATPase site



- **Molecular Characteristics of the Contractile Filaments**

Actin filaments are composed of actin, tropomyosin and troponin



Double-Stranded:
backbone of the actin filament

Fig. 6.7 Actin filament

Molecular Mechanism

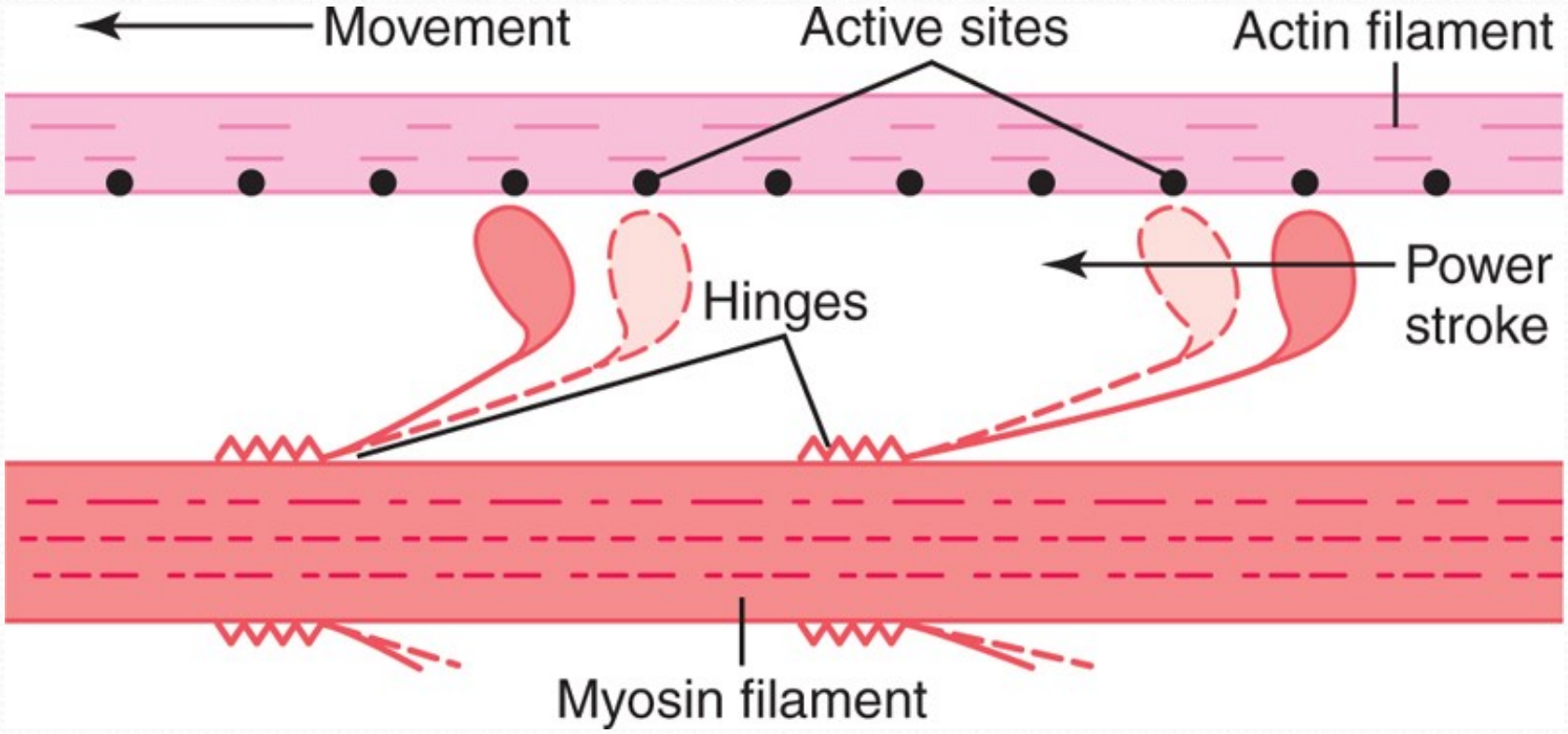
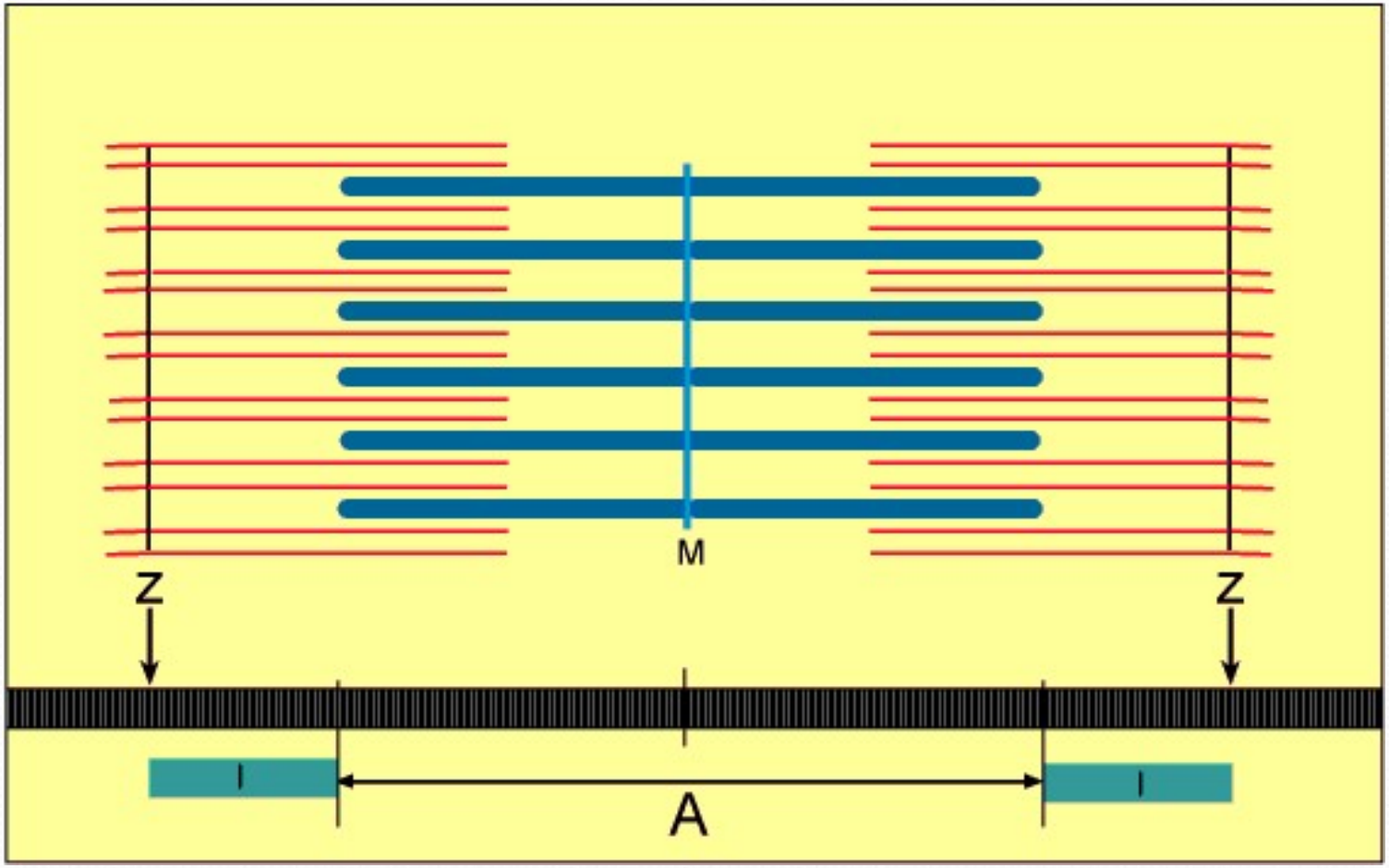


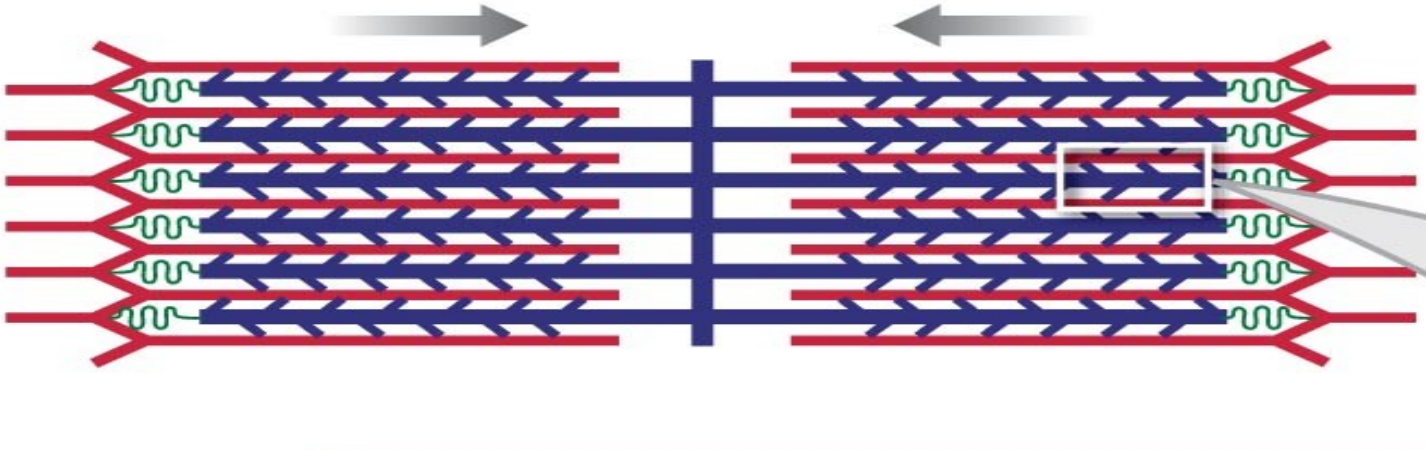
Fig. 6.8 "Walk-along" mechanism for muscle contraction.
The heads of the cross-bridges bend back and forth and step by step walk along the actin filament, pulling the ends of two successive actin filaments toward the center of the myosin filament.

Sliding Filament Mechanism



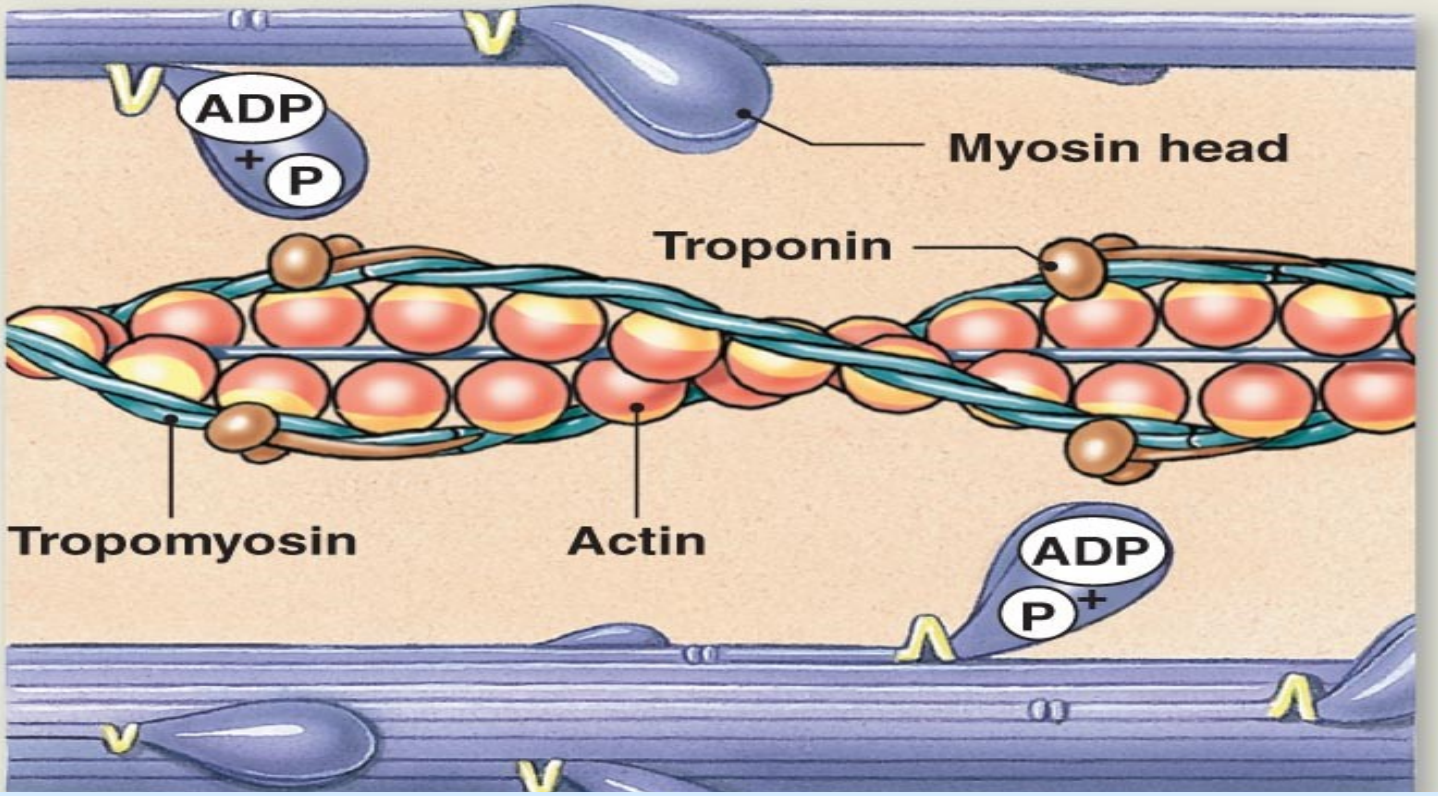
But what causes the actin filaments to slide inward among the myosin filaments?

Forces generated by interaction of the cross-bridges from the myosin filaments with the actin filaments



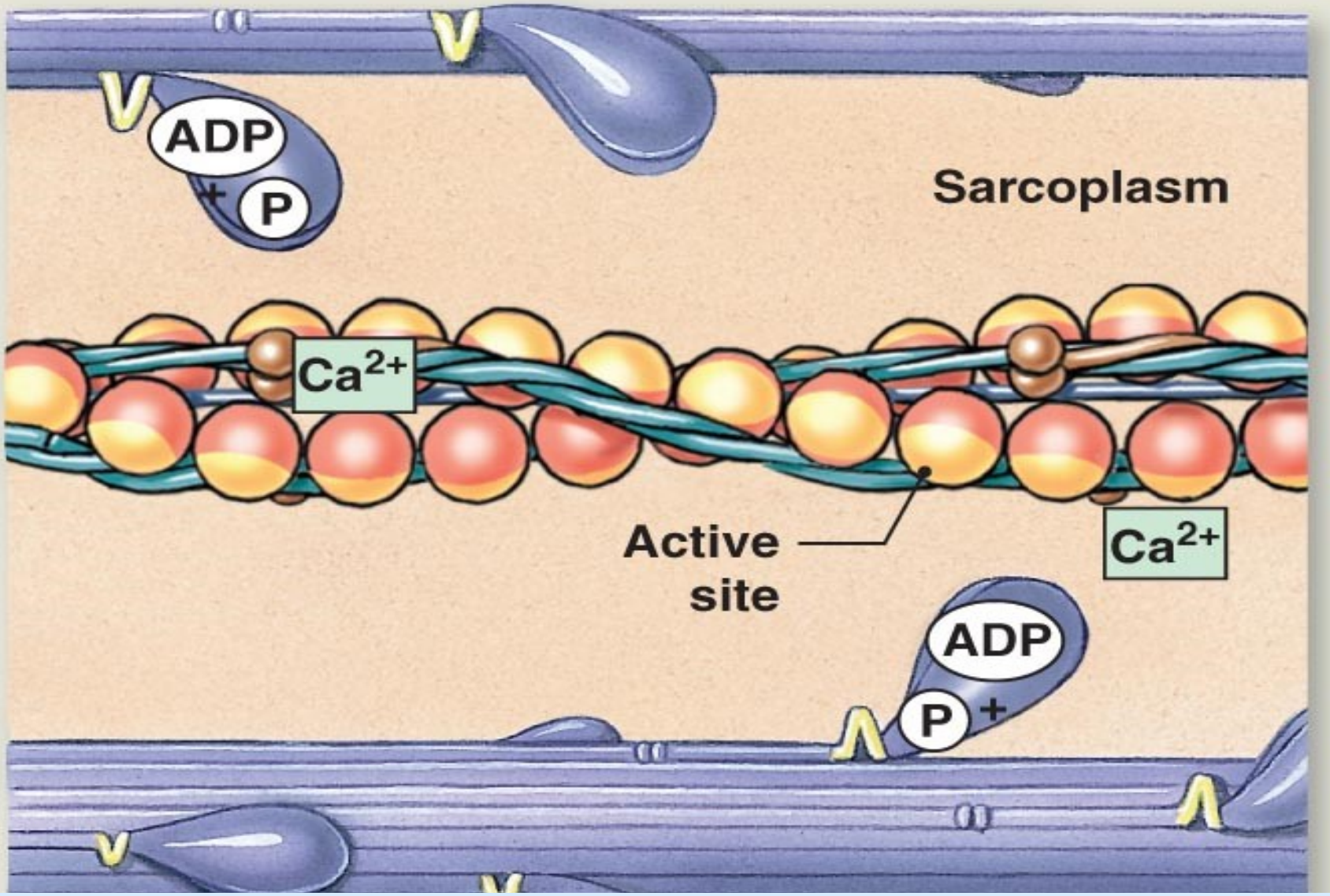
Forces are inactive

RESTING SARCOMERE



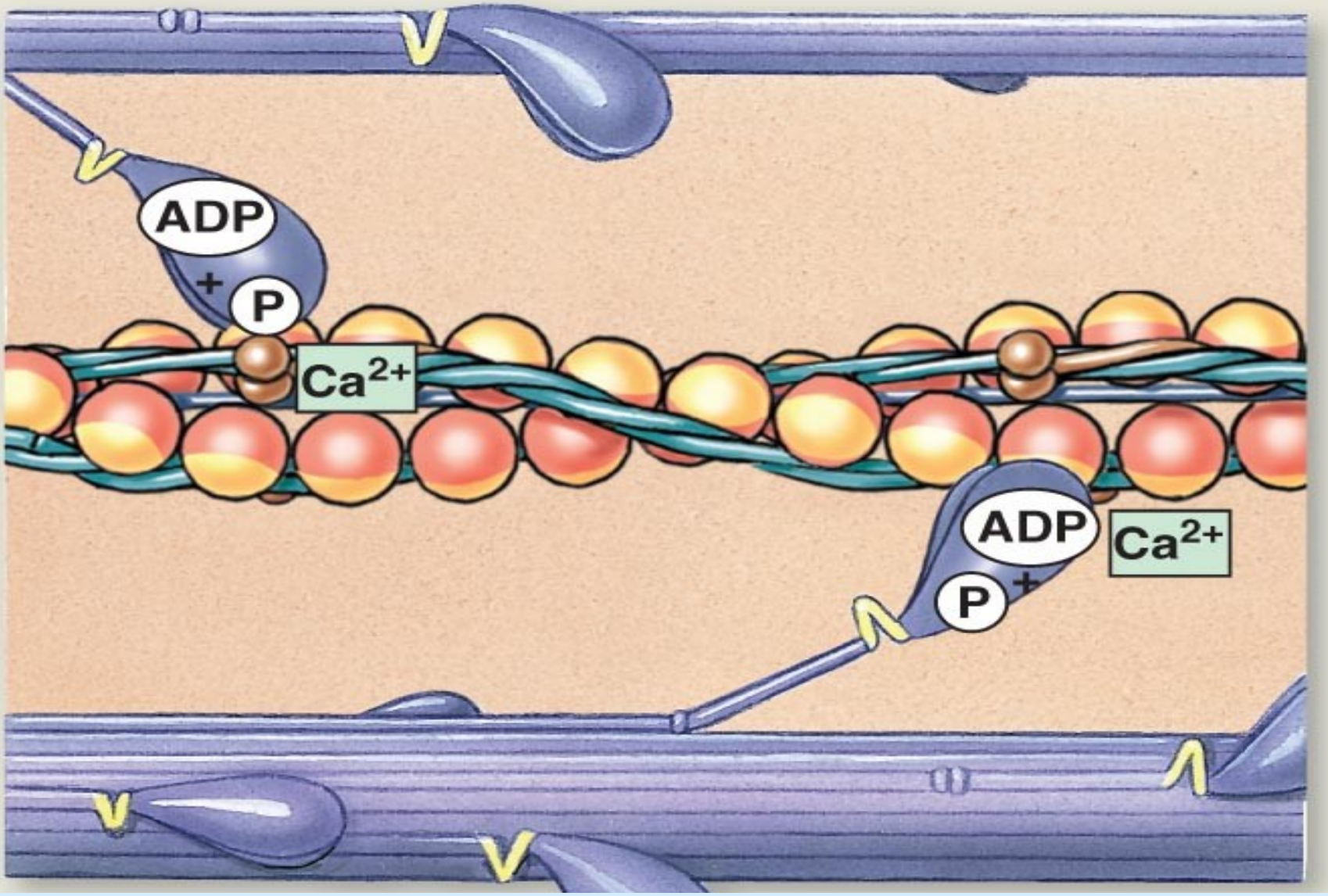
The heads of the cross bridges bind with ATP. **The ATPase activity** of the myosin head immediately cleaves the ATP but leaves the cleavage products, ADP plus phosphate ion, bound to the head.

STEP 1 ACTIVE-SITE EXPOSURE



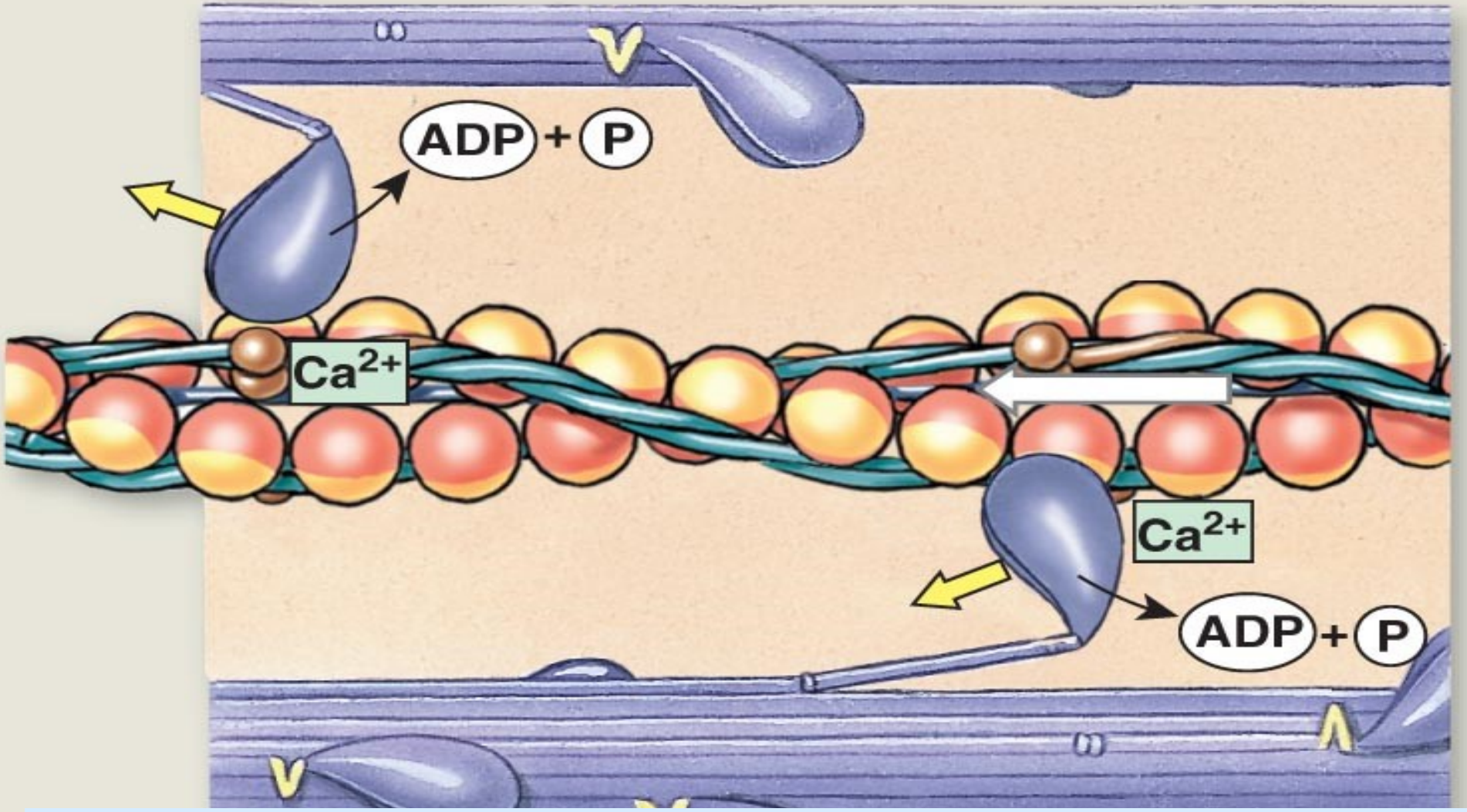
When the troponin-tropomyosin complex binds with **calcium** ions, active sites on the actin filament are uncovered and the myosin heads then bind with these sites.

STEP 2 CROSS-BRIDGE FORMATION



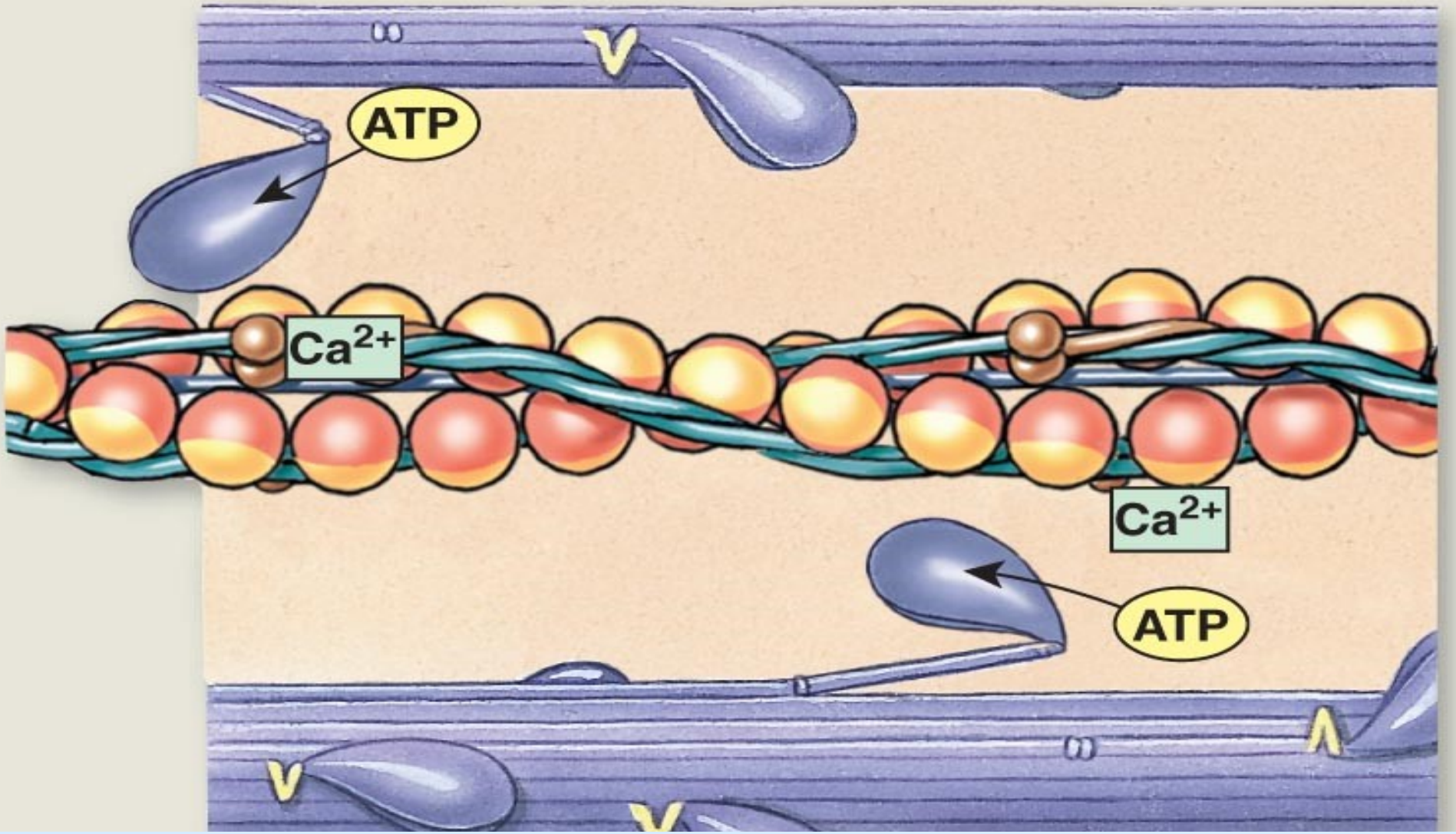
With the active sites on the actin exposed, the myosin heads bind to the actin, forming ***cross-bridges.***

STEP 3 PIVOTING OF MYOSIN HEAD



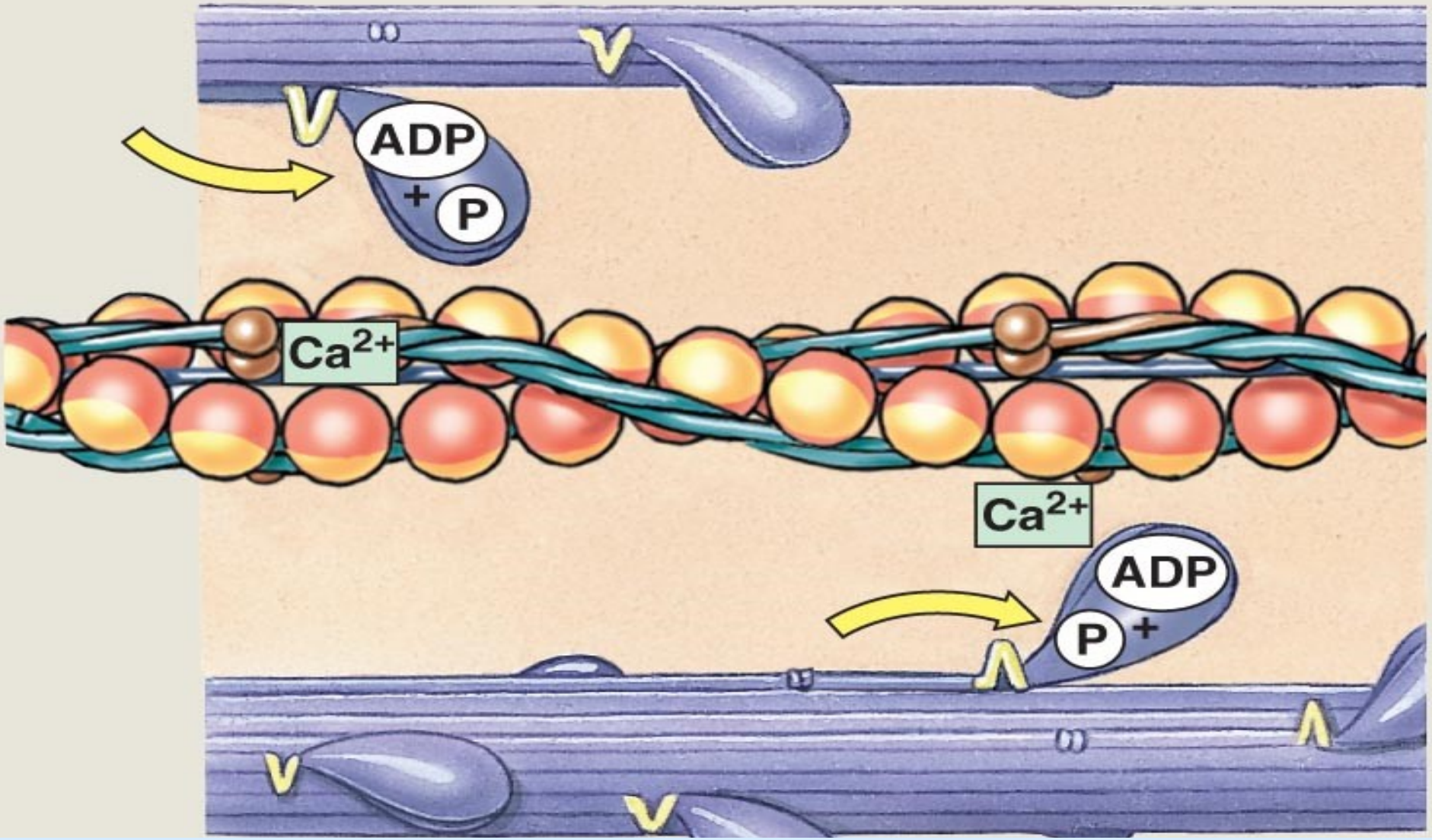
Binding the head of the cross-bridge with the active site causes a conformational change in the head, prompting the head to tilt toward the arm of the cross-bridge and providing the ***power stroke*** *for pulling the actin filament.*

STEP 4 CROSS-BRIDGE DETACHMENT

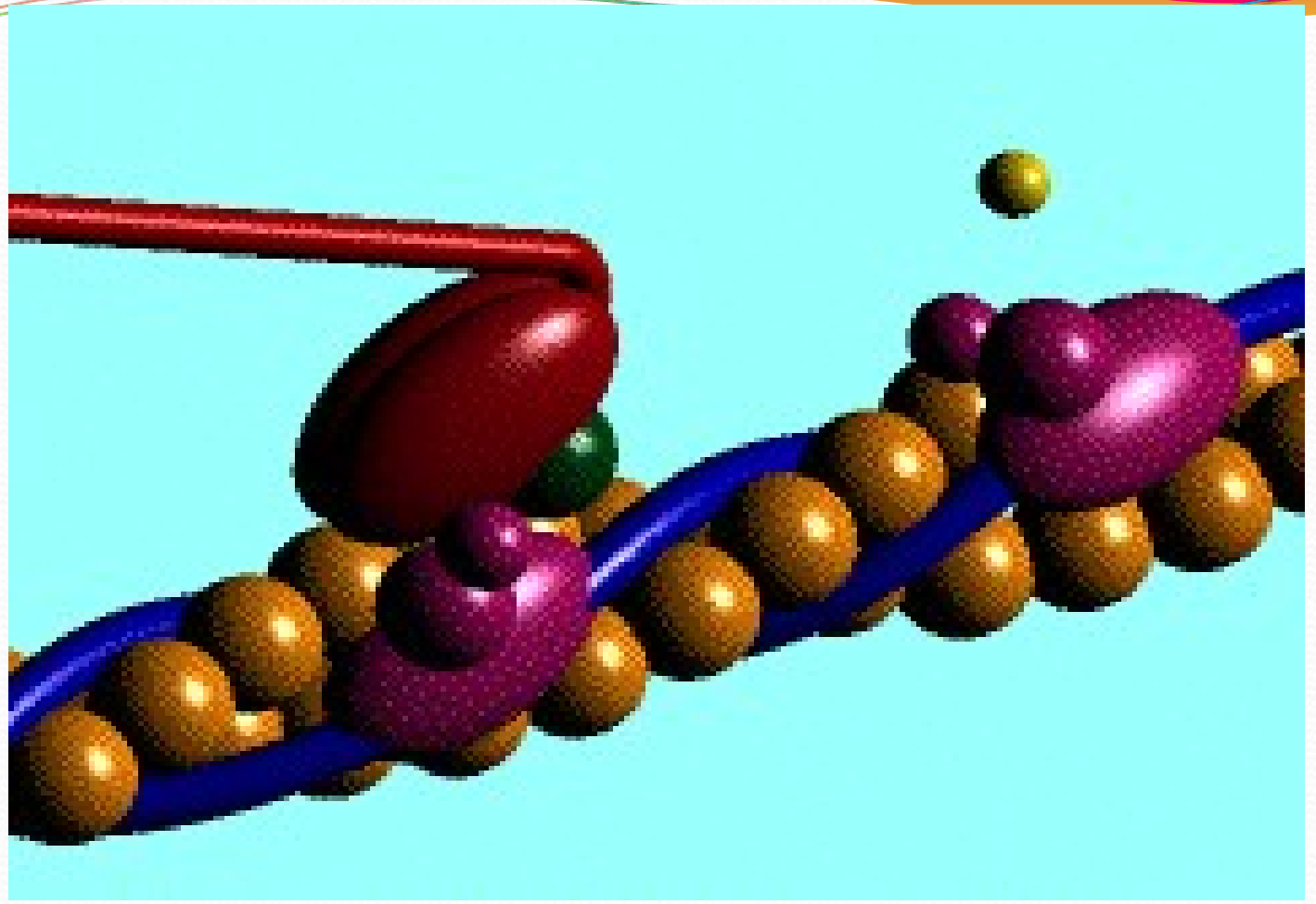


Once the head of the cross-bridge tilts, ADP and phosphate ion are released and new molecule of ATP binds. This binding of new ATP causes **detachment** of the head from the actin.

STEP 5 MYOSIN REACTIVATION



The new ATP is cleaved to begin the next cycle which **"cocks"** the head back to its perpendicular condition, ready to begin the new power stroke cycle.



What is Rigor Mortis ?

The *contracture* of skeletal muscles that begins several hours after death due to the loss of ATP.

Excitation of Skeletal Muscle: Neuromuscular Transmission and Excitation-Contraction Coupling

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UNIT II CHAPTER 7

Dr. Mohammed Alotaibi

Objectives of the lecture

At the end of the lecture the student should be able to:

Know and describe the followings:

- The physiologic anatomy of Neuromuscular Junction (NMJ).
- Motor end plate, synaptic trough/ gutter/ cleft.
-Motor End Plate potential and how action potential and excitation-contraction coupling are generated in skeletal muscle.
- Drugs/ diseases affecting the neuromuscular transmission.

Physiologic Anatomy of the Neuromuscular Junction

- Motor End Plate
- Synaptic trough/ gutter
- Presynaptic terminal
- Postsynaptic terminal
- Synaptic space/cleft
- Subneural cleft
- Acetylcholine (Ach)
- Synaptic vesicles
- Acetylcholinesterase

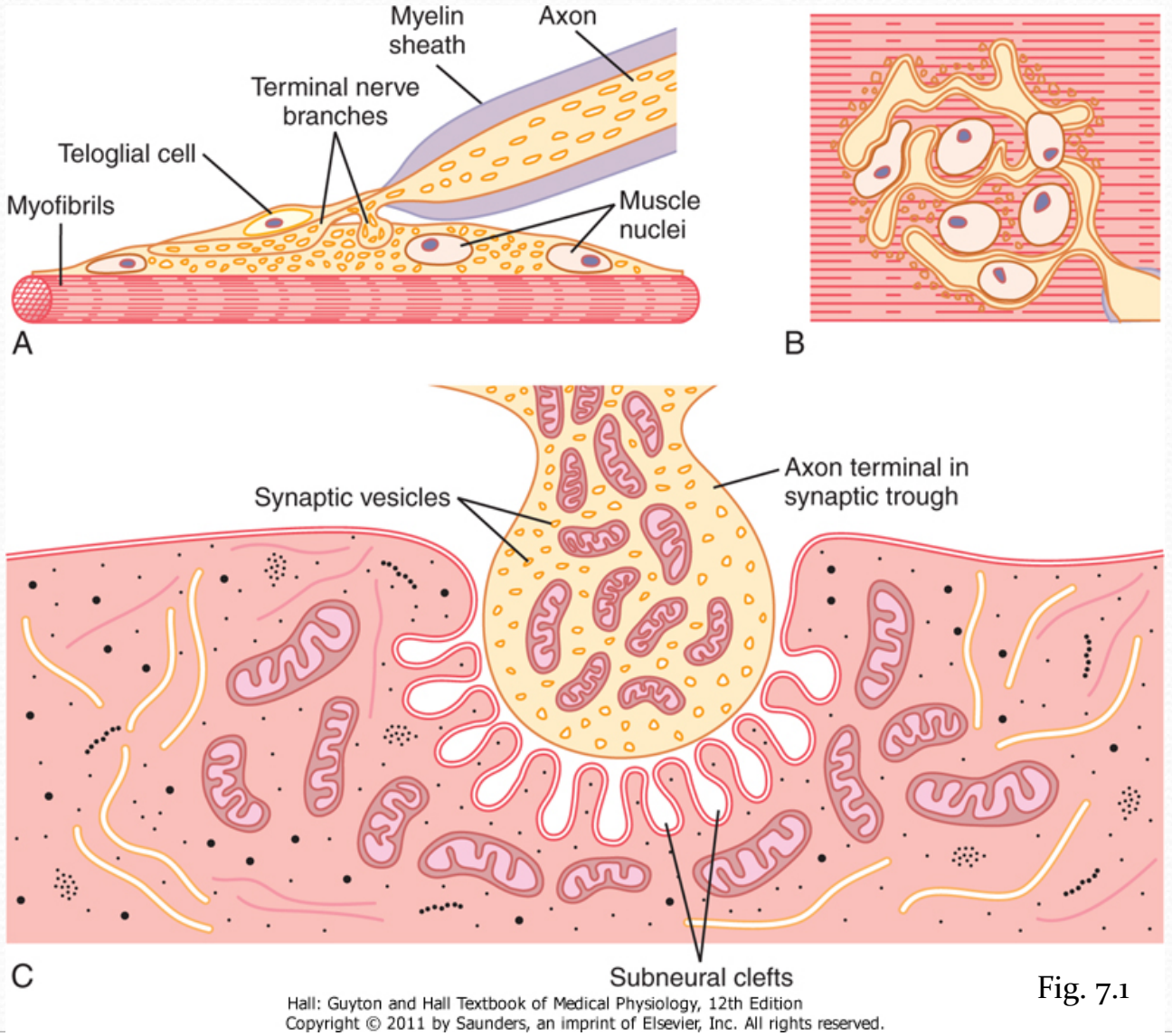


Fig. 7.1

Transmission of impulses from nerve endings to skeletal muscle fibers occurs via:

THE NEUROMUSCULAR JUNCTION (NMJ)

Secretion of Acetylcholine by the Nerve Terminals

- 125 vesicles of Ach are released.
- *Voltage-gated calcium channels.*
- Acetylcholine receptors (Ach-gated ion channels).
- *Voltage-gated Na+ channels.*

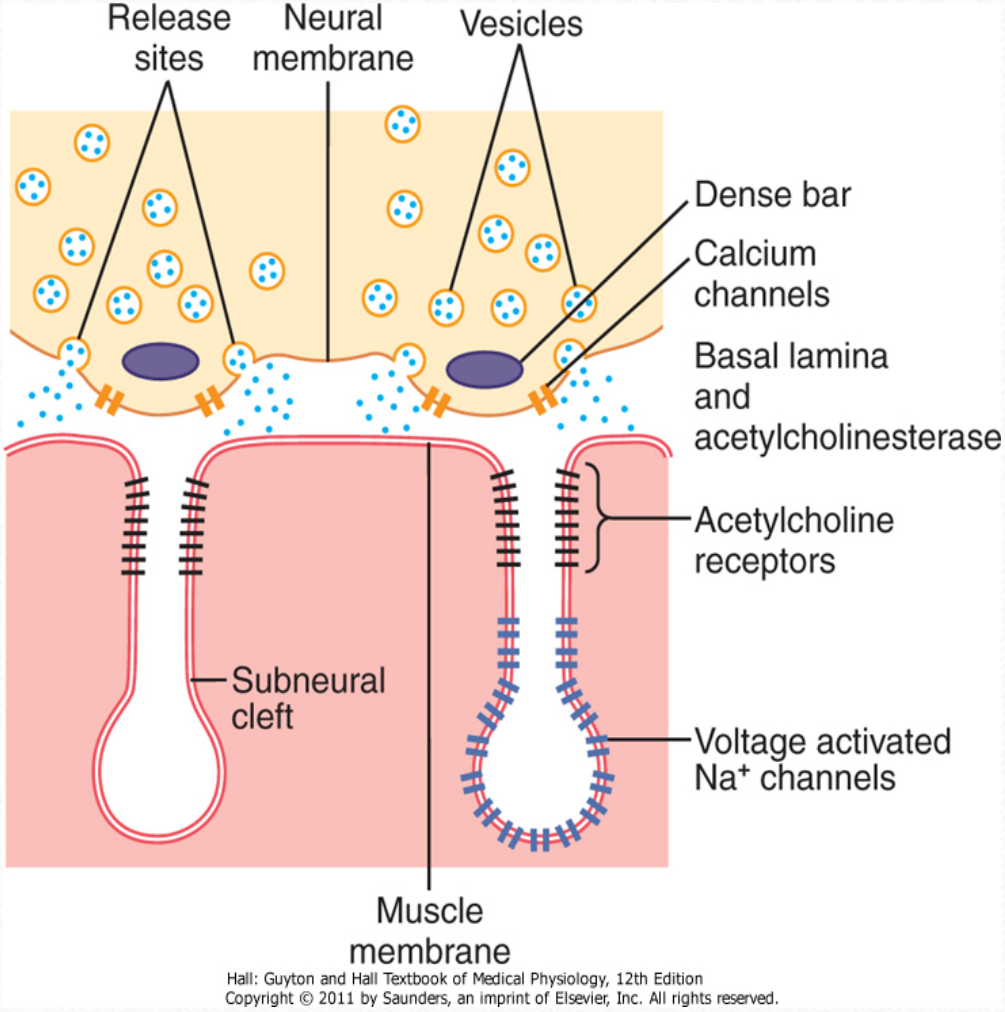


Fig. 7.2

Effect of Ach on the Postsynaptic Muscle Membrane

- Two molecules of Ach must attach to the receptor.
- Ach-channels open and allow Na^+, Ca^+, or K^+ ions to move through easily; but not negative ions such as Cl^-
- More Na+ ions will pass through which creates a local positive potential change inside the muscle fiber membrane, called the ***end plate potential (EPP).***
- EPP spreads along the muscle membrane

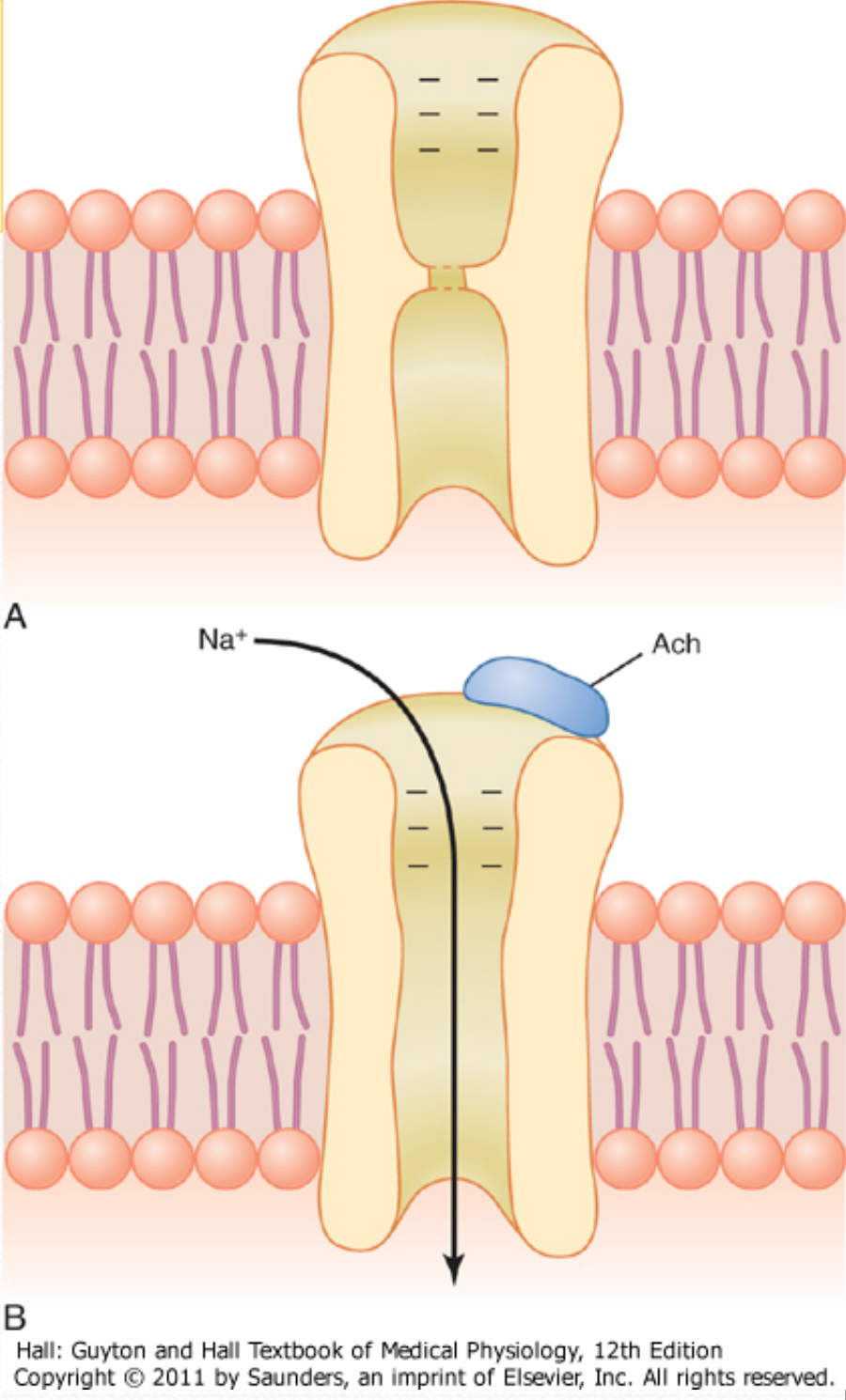
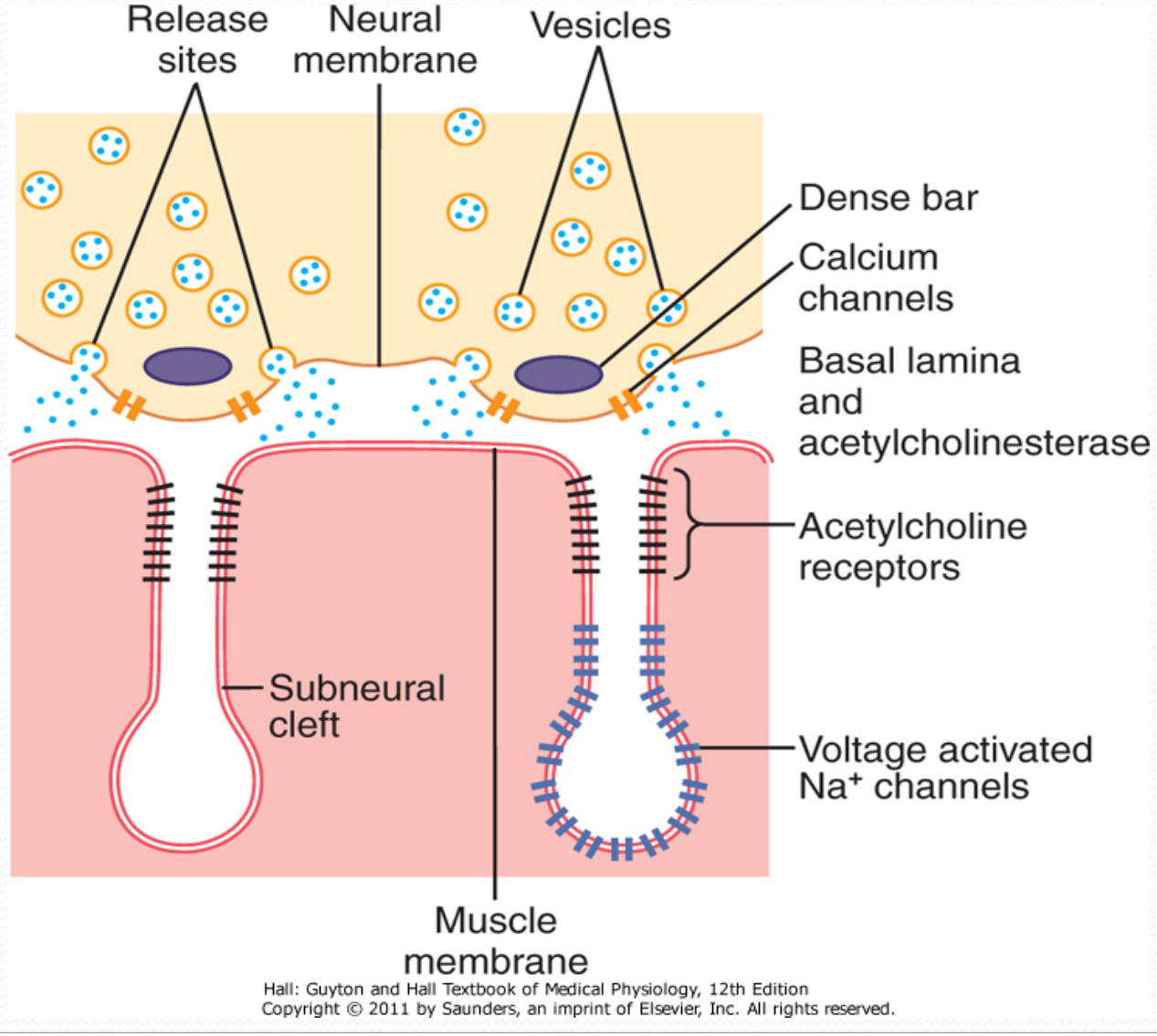


Fig. 7.3 Acetylcholine gated channels
A. Closed B. After AcH attaches

EPP opens Voltage gated Na+ Channels

- Sudden influx of Na^+ when Ach-gated channels open increases electrical potential in the positive direction as much as 50-75 mV and creates a local EPP. This will open voltage gated Na+ channels.



Spread of the AP via Transverse Tubules

Excitation-Contraction Coupling

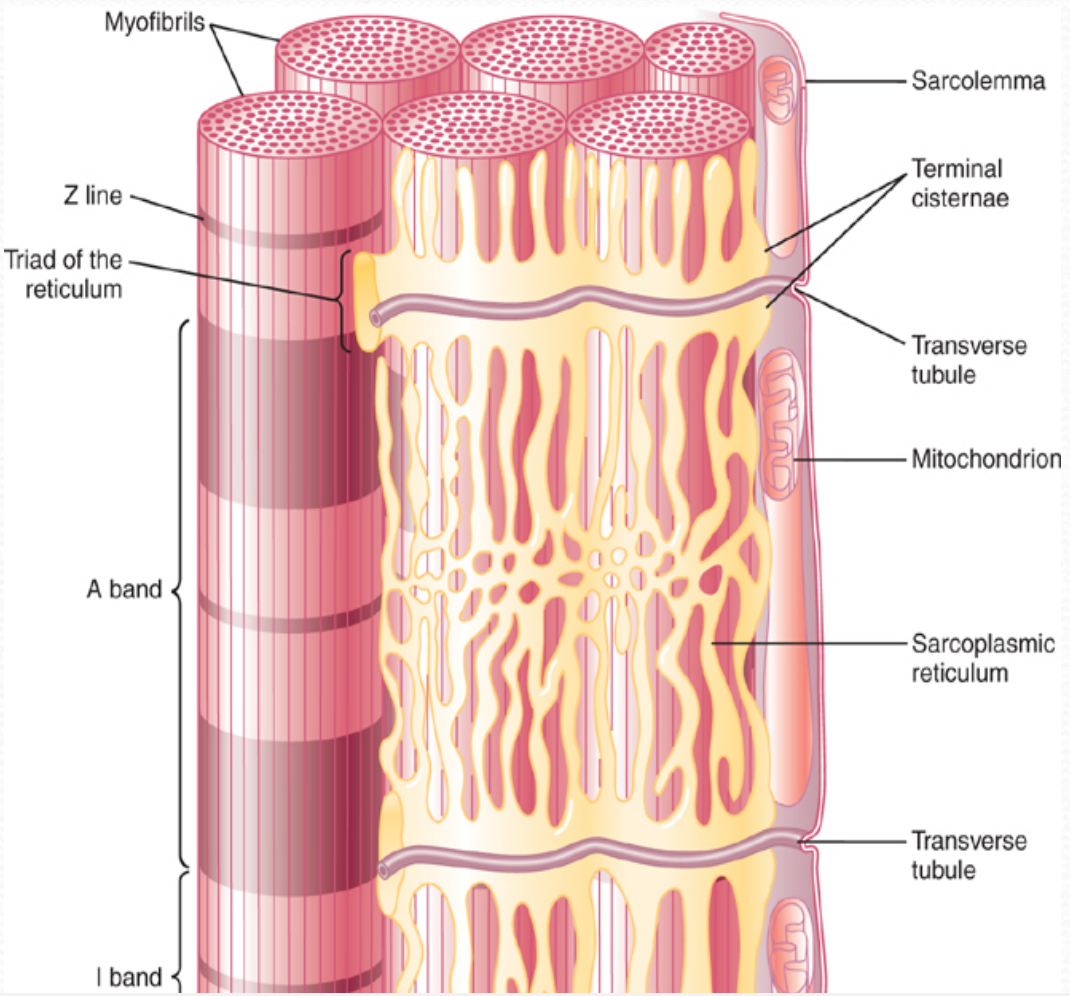
T-Tubule-Sarcoplasmic Reticulum System.

-T-tubules are small and run transverse to the myofibrils.

- The **sarcoplasmic reticulum** is composed of 2 parts:

(1) large chambers called terminal cisternae

(2) long longitudinal tubules



The T tubule action potentials cause Ca++ release inside the muscle fiber in the immediate vicinity of the myofibrils, and this Ca++ then cause contraction. This overall process is called *excitation-contraction coupling*.

Release of Calcium Ions by the Sarcoplasmic Reticulum

- As the AP reaches the T-tubule, the voltage change is sensed by dihydropyridine receptors (DHP) linked to calcium release channels (Ryanodine receptors) which triggers the release of Ca^{++} initiating contraction.

- **Calcium pump** removes calcium ions after contraction occurs.
- Calcium binds to *calsequestrin.*

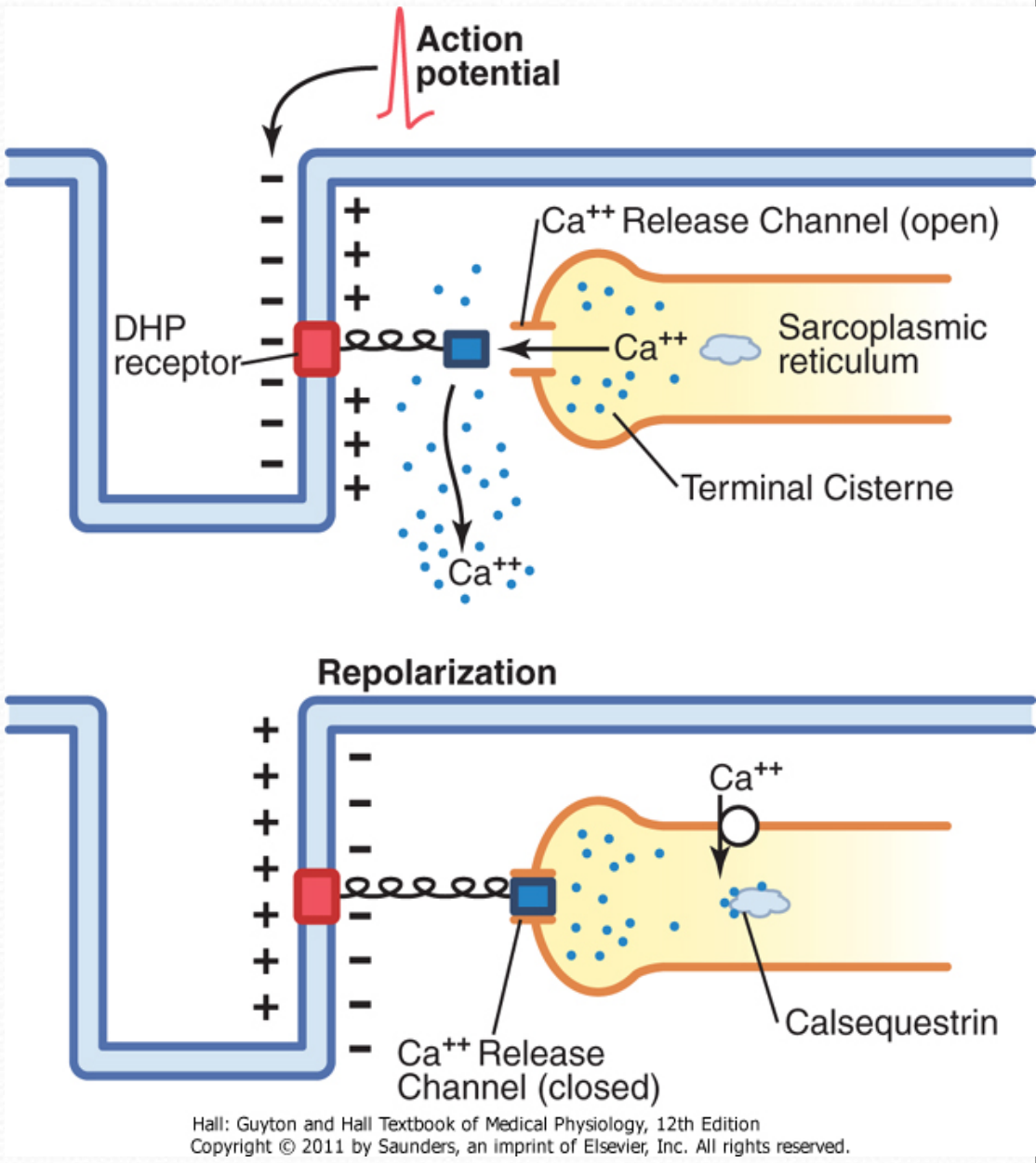


Fig. 7.6 Excitation-contraction coupling in skeletal muscle.

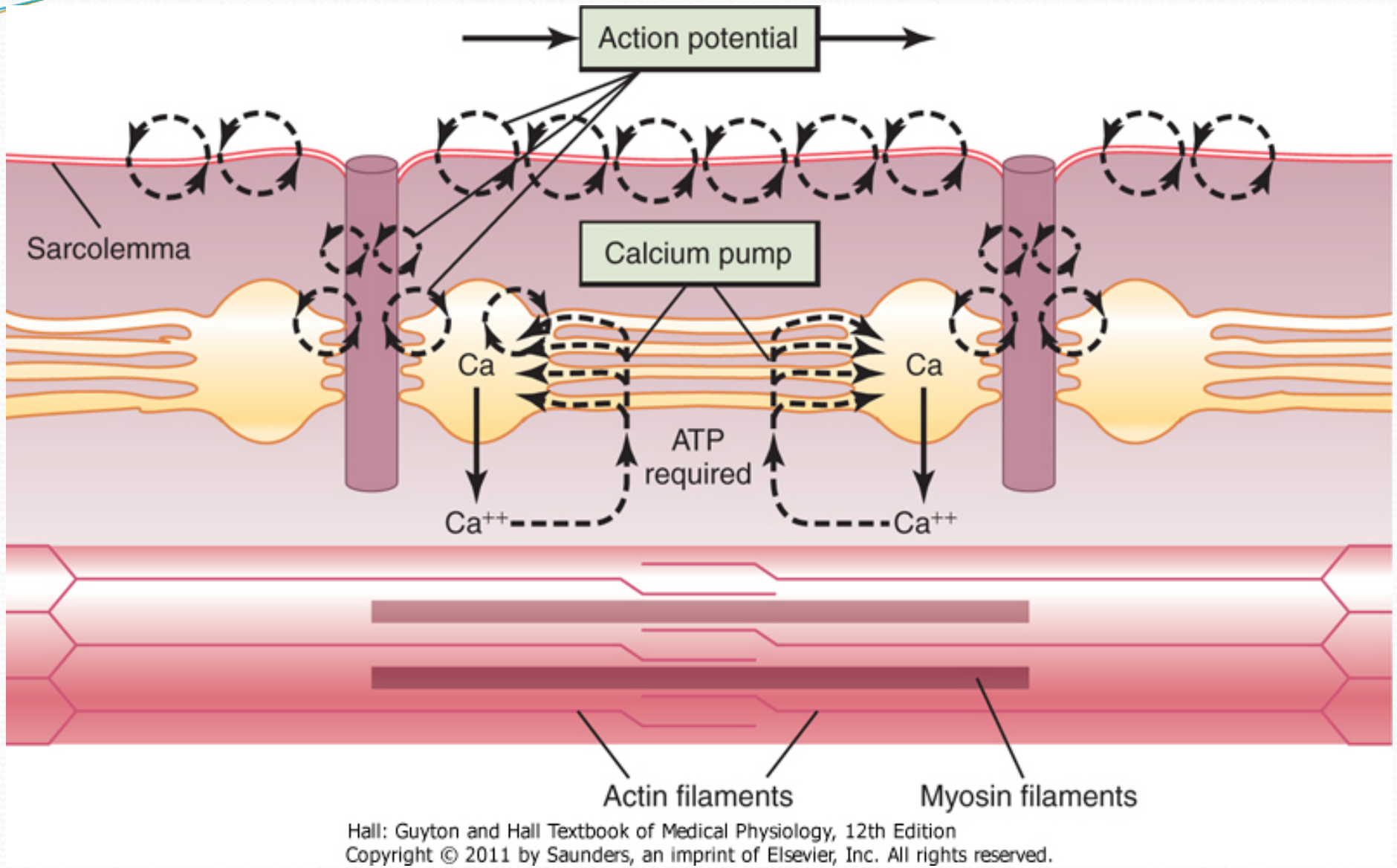


Fig. 7.7 Excitation-contraction coupling in the muscle showing (1) an AP that causes the release of Ca ions from the sarcoplasmic reticulum and then (2) re-uptake of the calcium ions by the calcium pump.

Destruction of the Released Acetylcholine

- Most of the Ach is destroyed by the enzyme **acetylcholinesterase** into acetate ion and choline**.**

[choline is reabsorbed actively into the neural terminal to be reused to form new acetylcholine]

- A small amount diffuses out of the synaptic space.

Safety factor for transmission at the neuromuscular junction

Fatigue of the Junction

- Each impulse that arrives at the junction causes about 3X as much EPP as required to stimulate the muscle fiber.

Therefore, the normal NMJ is said to have a ***high*** ***safety factor.***

- Overstimulation, however, diminishes the number of Ach vesicles.

This situation is called ***fatigue*** of the NMJ.

- Fatigue of the NMJ occurs rarely and only at exhausting levels of muscle activity.

Muscle Action Potential (AP)

	Skeletal Muscle	Large Nerves
Resting Membrane Potential	-80 to -90 mV	-80 to -90 mV
Duration of the Action Potential	1-5 milliseconds	0.2-1.0 milliseconds
Velocity of Conduction	3-5 m/sec	39-65 m/sec

Drugs That Enhance or Block Transmission at the Neuromuscular Junction

Drugs That Stimulate the Muscle Fiber by Ach-Like Action:

- ***Methacholine, Carbachol, and Nicotine.***

They act for minutes or hours—are not destructed by cholinesterase.

Drugs That Stimulate the NMJ by Inactivating Acetylcholinesterase:

- ***Neostigmine, Physostigmine*** [inactivate acetylcholinesterase for several hours]

- ***Diisopropyl fluorophosphate*** (nerve gas poison) [inactivates acetylcholinesterase for weeks -------can cause death because of respiratory muscle spasm]

Drugs That Enhance or Block Transmission at the Neuromuscular Junction

Drugs That Block Transmission at the NMJ

- **Curare & Curariform like-drugs.**

  Prevent passage of impulses from the nerve ending into the muscle by blocking the action of Ach on its receptors.

- **Botulinum Toxin.**

  Bacterial poison that decreases the quantity of Ach release by the nerve terminals.

EPP and Excitation of the Skeletal Muscle Fiber

Three separate EPP:

- End plate potentials A
- End plate potentials B
- End plate potentials C

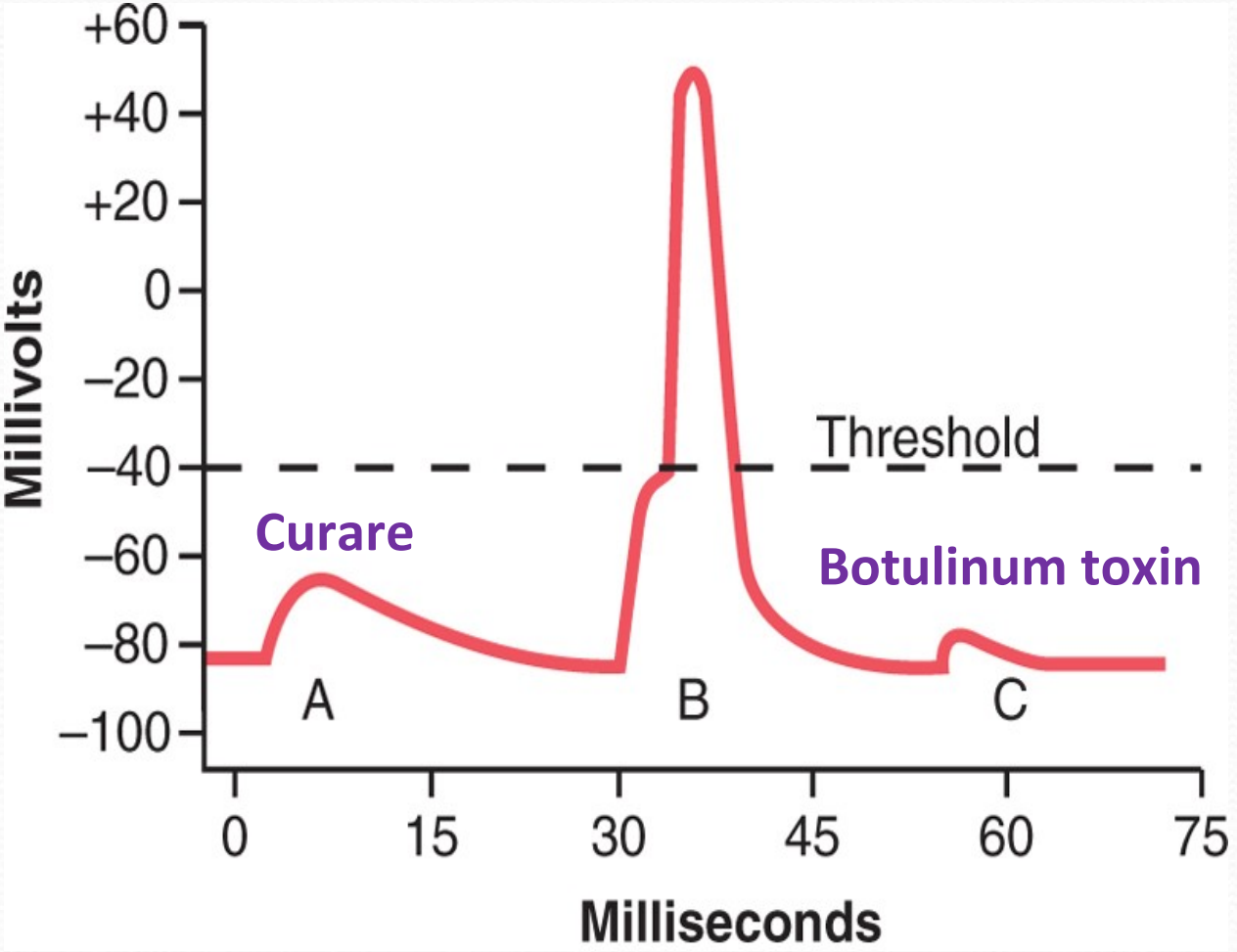
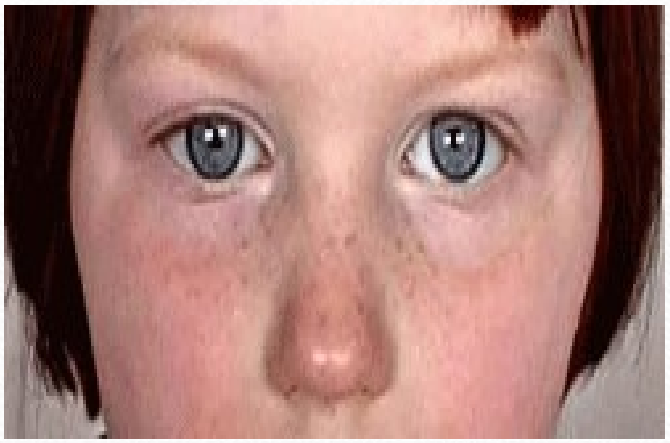


Fig. 7.4 End Plate Potentials in mV. A & C: weakened end potential in a muscle too weak to elicit an AP; B: Normal end plate potential eliciting an AP.

Myasthenia Gravis



- Disease of adult females affects eyelid, extra ocular bulbar and proximal limb muscles.

- Presents with ptosis, dysarthria, dysphagia, and proximal limb weakness in hands& feet.

Myasthenia Gravis

Autoimmune disorder [patients develop antibodies which block or destroy their own Ach receptors**].**

- Occurs in about 1 in every 20,000 persons.
- Causes muscle weakness because of the inability of the NMJ to transmit enough signals from the nerve fibers to the muscle fibers.
- The EPP that occur in the muscle fibers is mostly too weak to initiate opening of the voltage-gated sodium channels.
- Patient may die of respiratory failure.

Myasthenia Gravis

Treatment:

- Administration of anticholinesterase drugs such as Neostigmine which allows larger than normal amounts of Ach to accumulate in the synaptic space.
- **Corticosteroids** and **Immunosuppressant drugs** to inhibit the immune system, limiting antibody production.

- The End