Contraction of Skeletal Muscle and Neuromuscular Transmission

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

UNIT II CHAPTER 6 & 7

Pages 75-95

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Objectives of the lecture

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

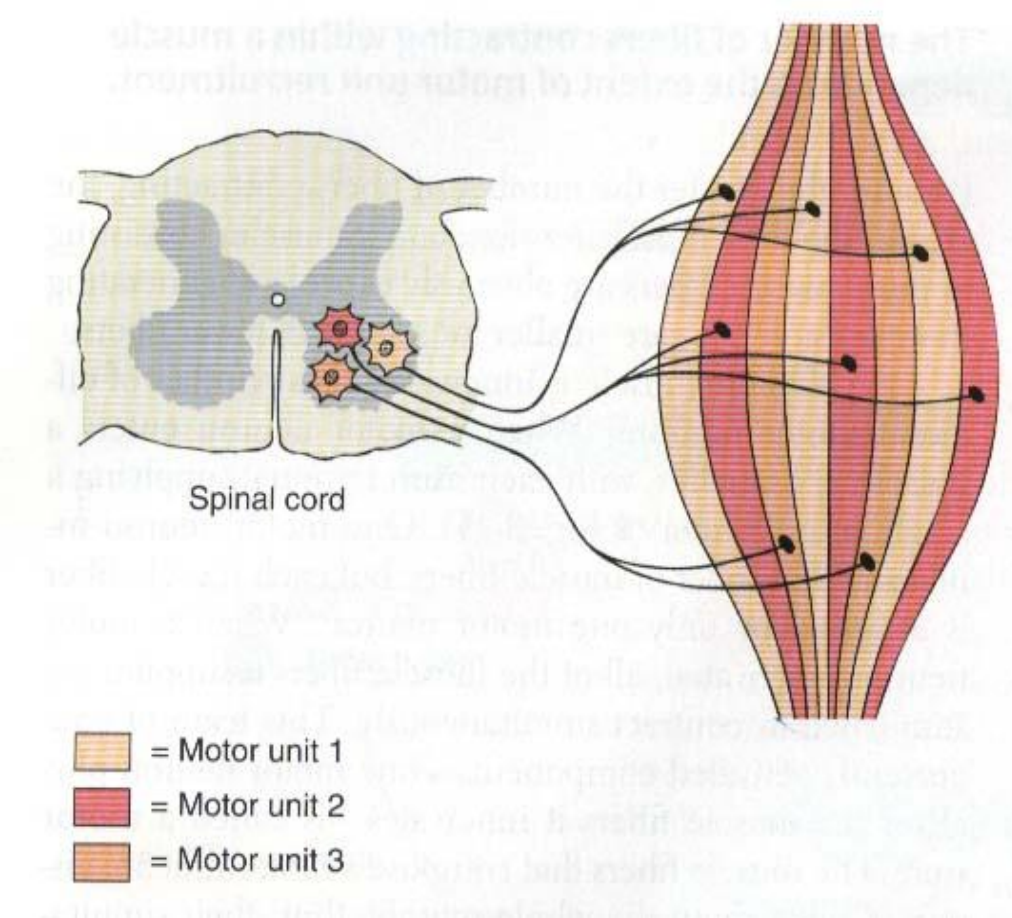
Know and describe the followings:

- The physiologic anatomy of the skeletal muscle and NM junction.
- The general mechanism of skeletal muscle contraction.
- Motor End Plate potential and how action potential and excitation-contraction coupling are generated in skeletal muscle.
- The molecular mechanism of skeletal muscle contraction & relaxation.
- Sliding filament mechanism.
- Drugs/ diseases affecting the neuromuscular transmission.

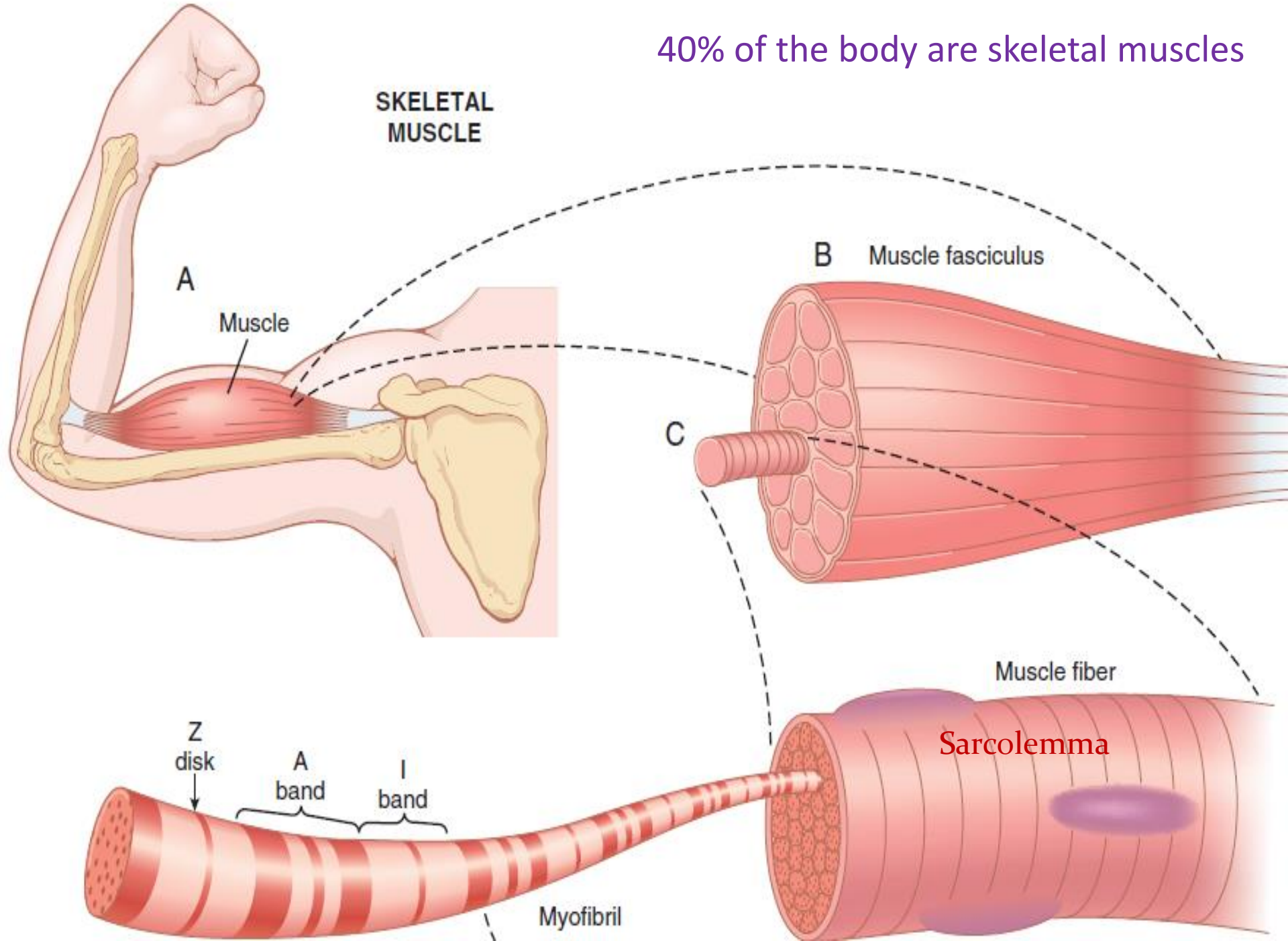
Motor Unit

What is a Motor Unit?

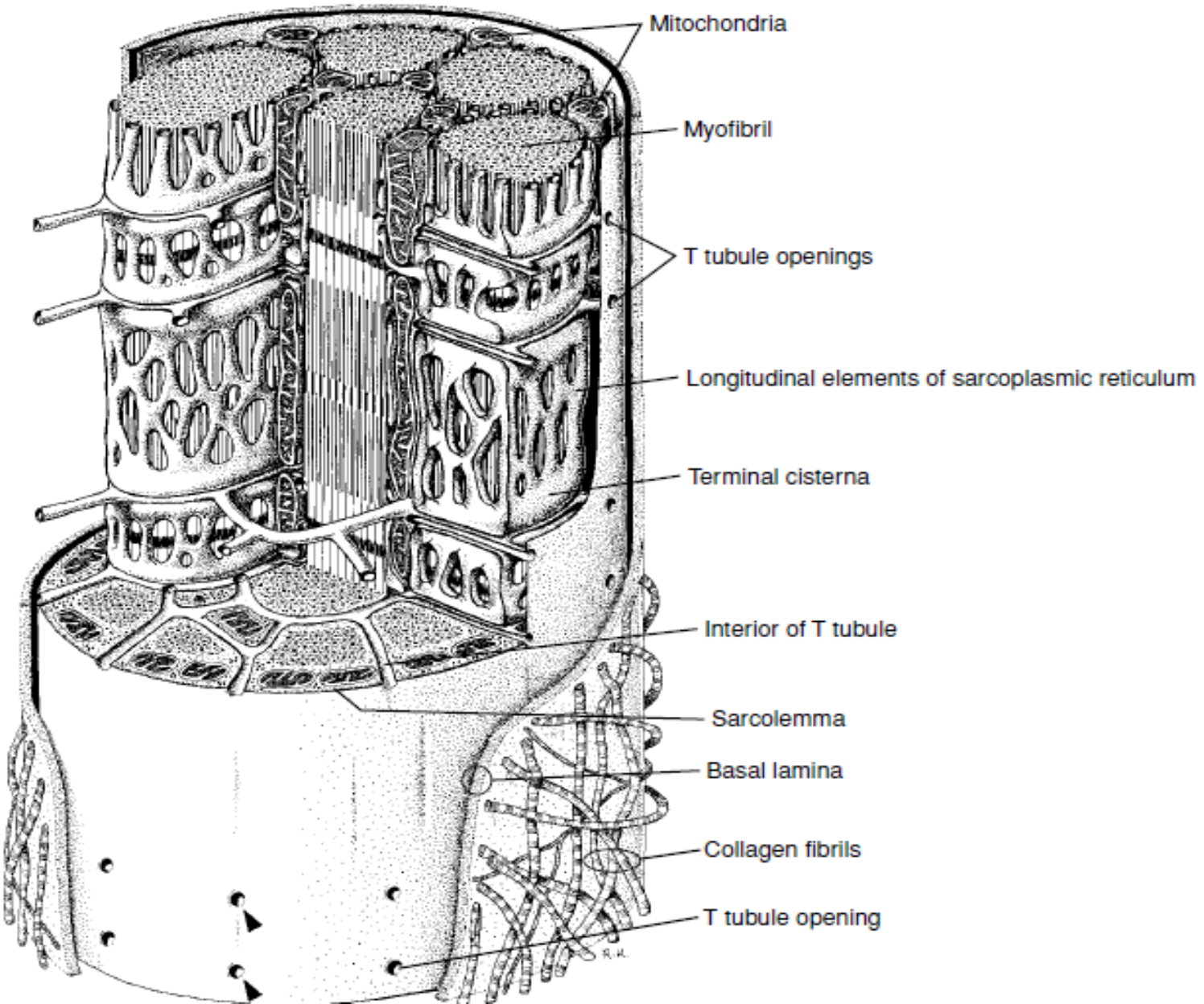
It is the *Motor Neuron* (Anterior Horn Cell , Axon) and *all the muscle fibers* it innervates.

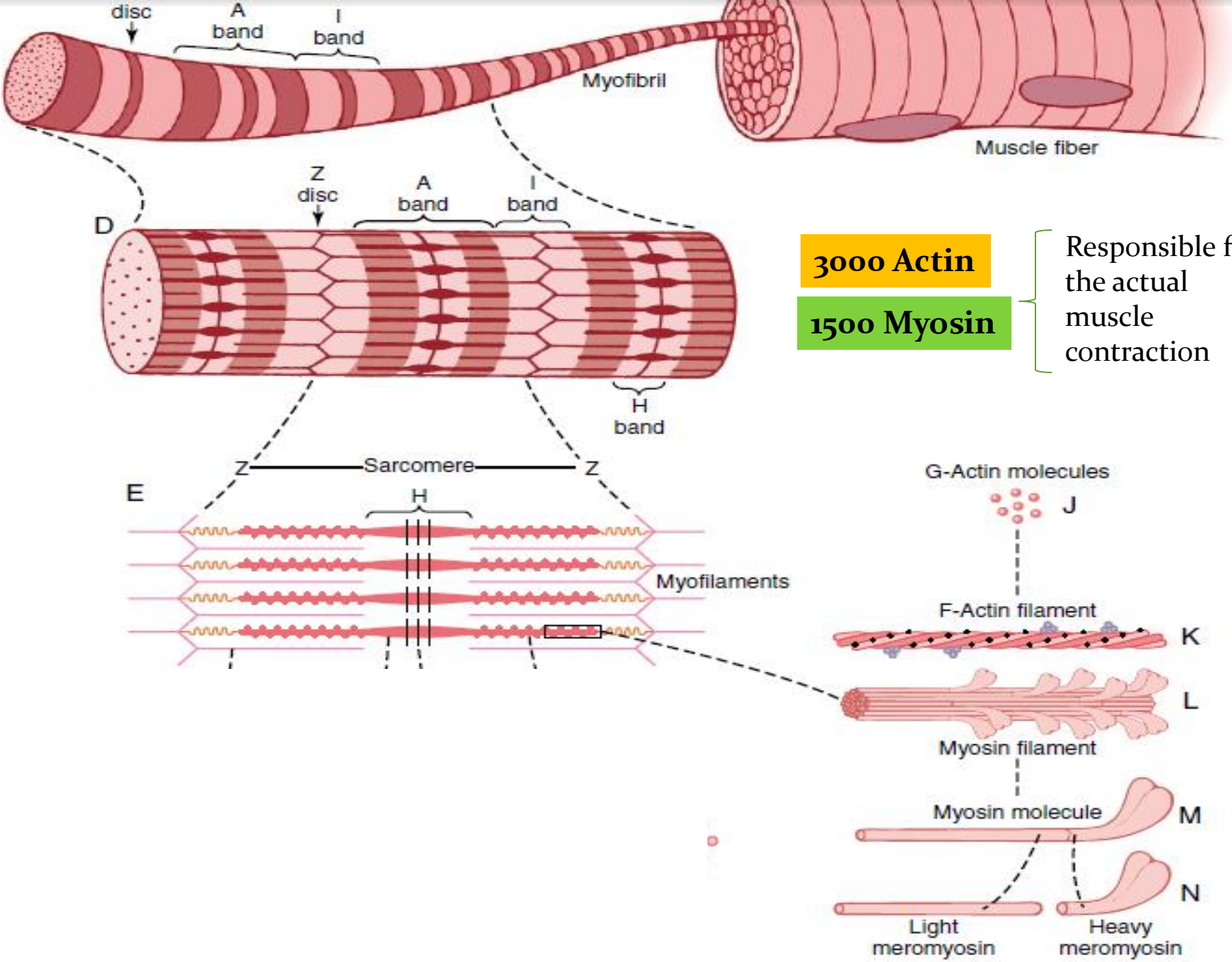


40% of the body are skeletal muscles



Physiological Anatomy of Skeletal Muscle fiber

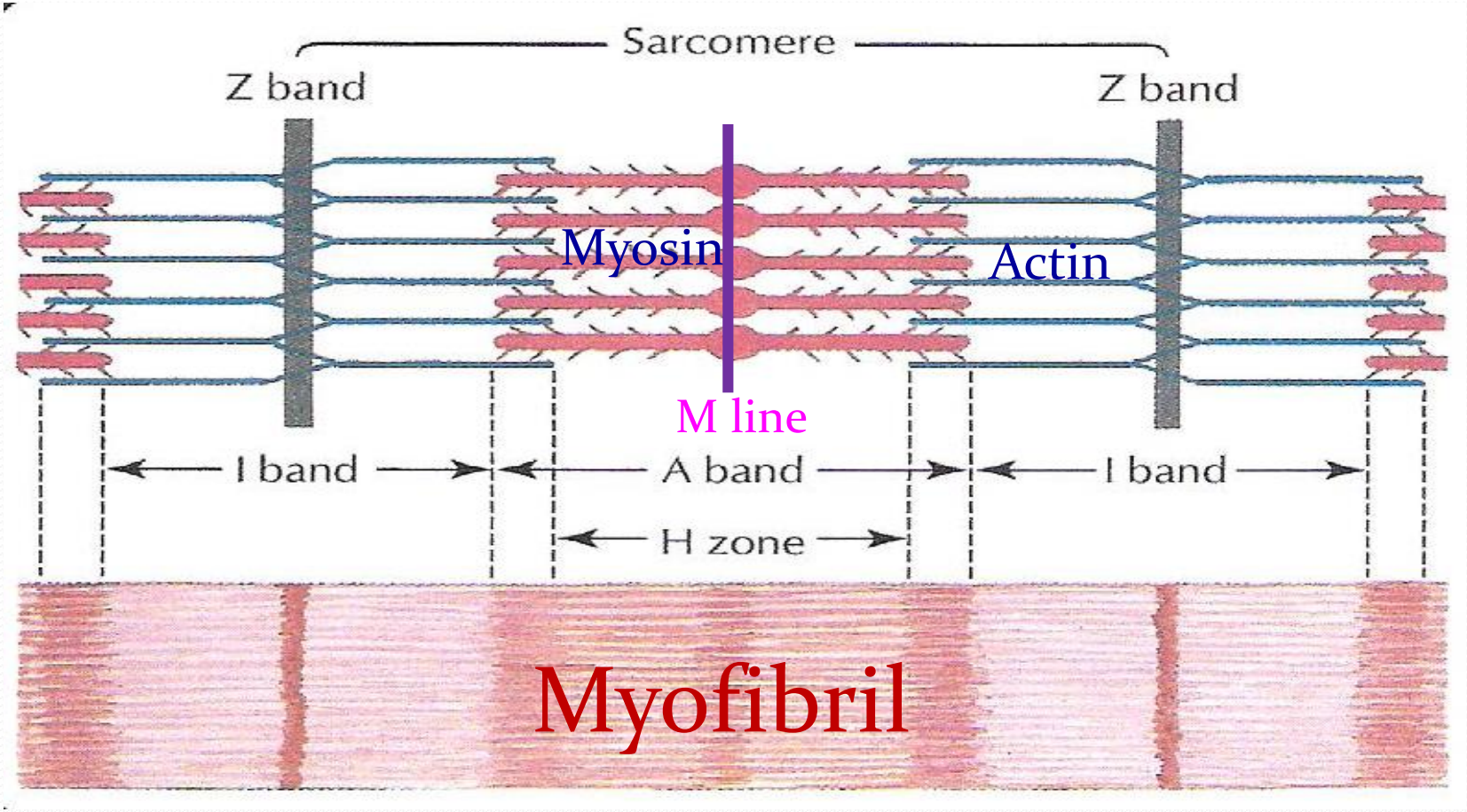




3000 Actin

1500 Myosin

Responsible for the actual muscle contraction



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

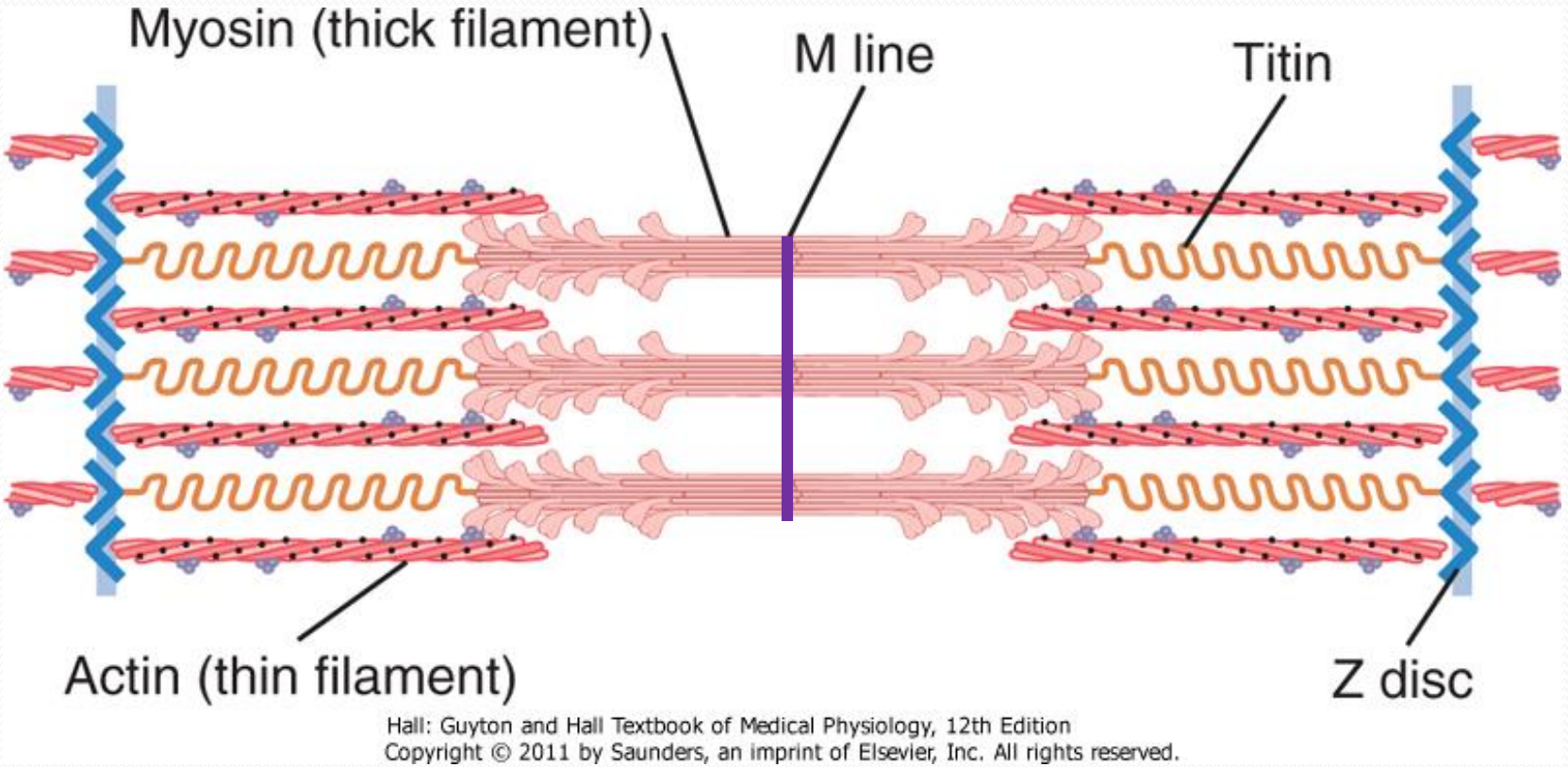
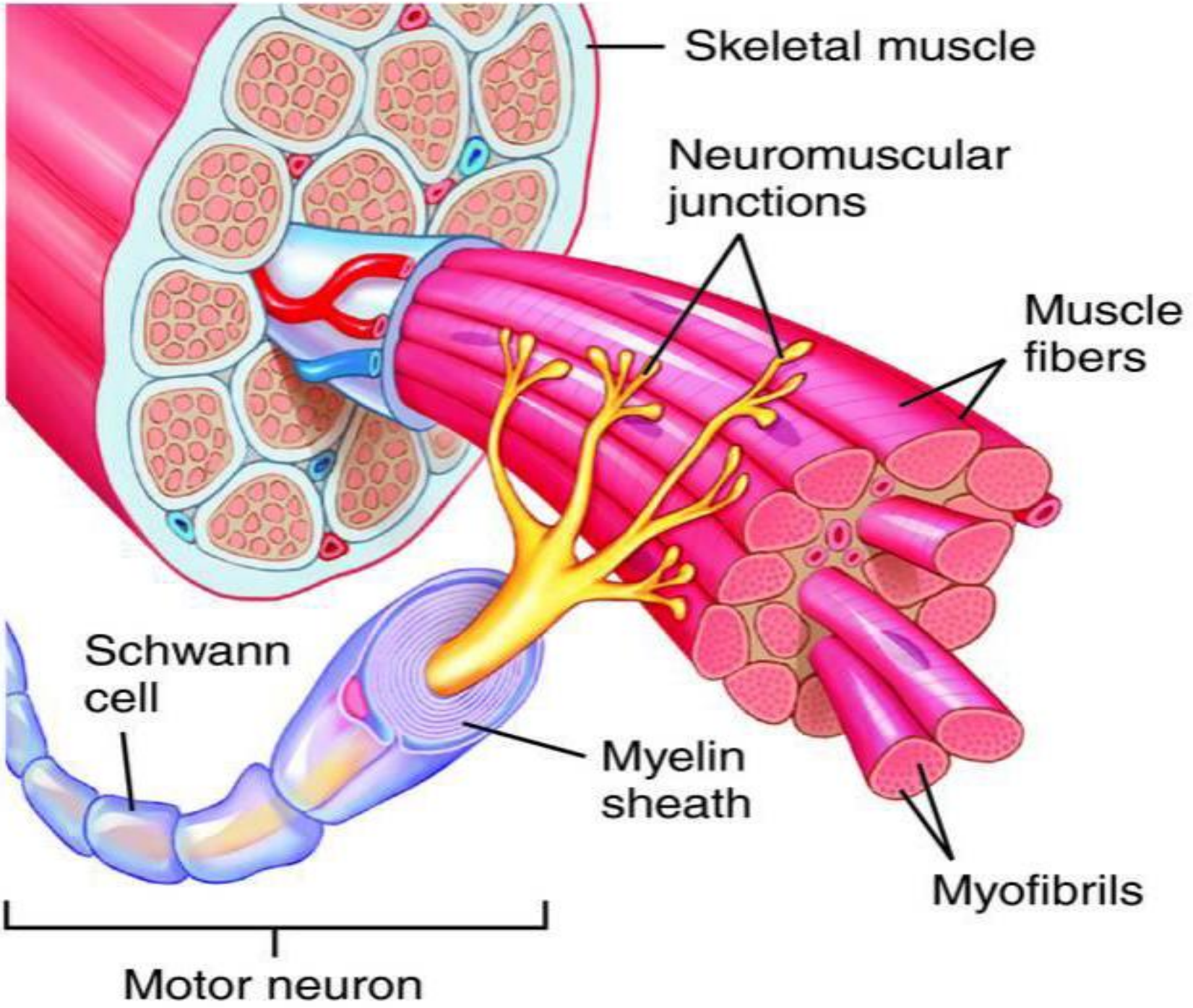


Fig. 6.3 Organization of proteins in a sarcomere

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

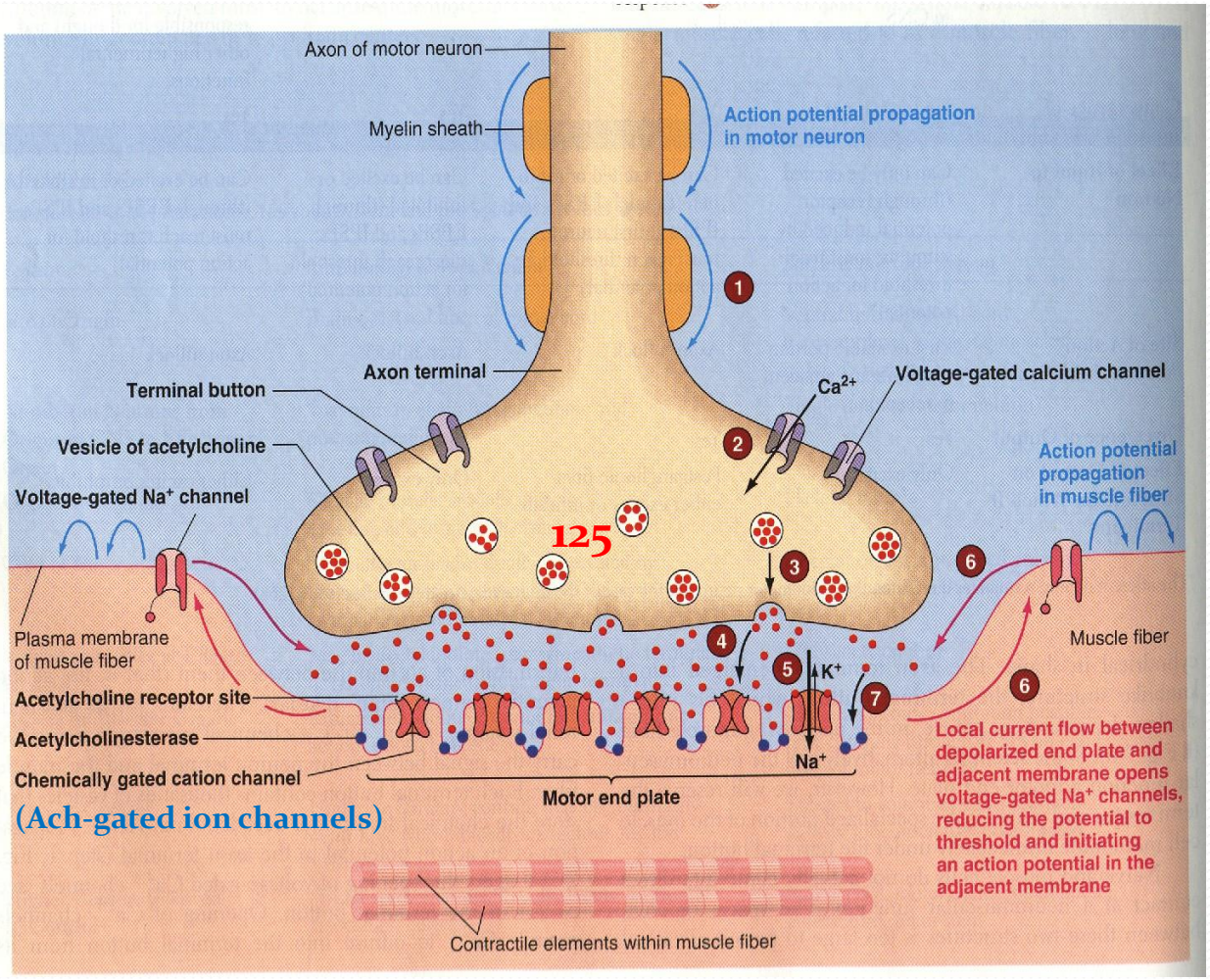

Skeletal muscle
Neuromuscular junctions
Muscle fibers
Schwann cell
Myelin sheath
Myofibrils
Motor neuron

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

THE NEUROMUSCULAR JUNCTION (NMJ)

Physiologic Anatomy of the Neuromuscular Junction

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



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 fiber membrane

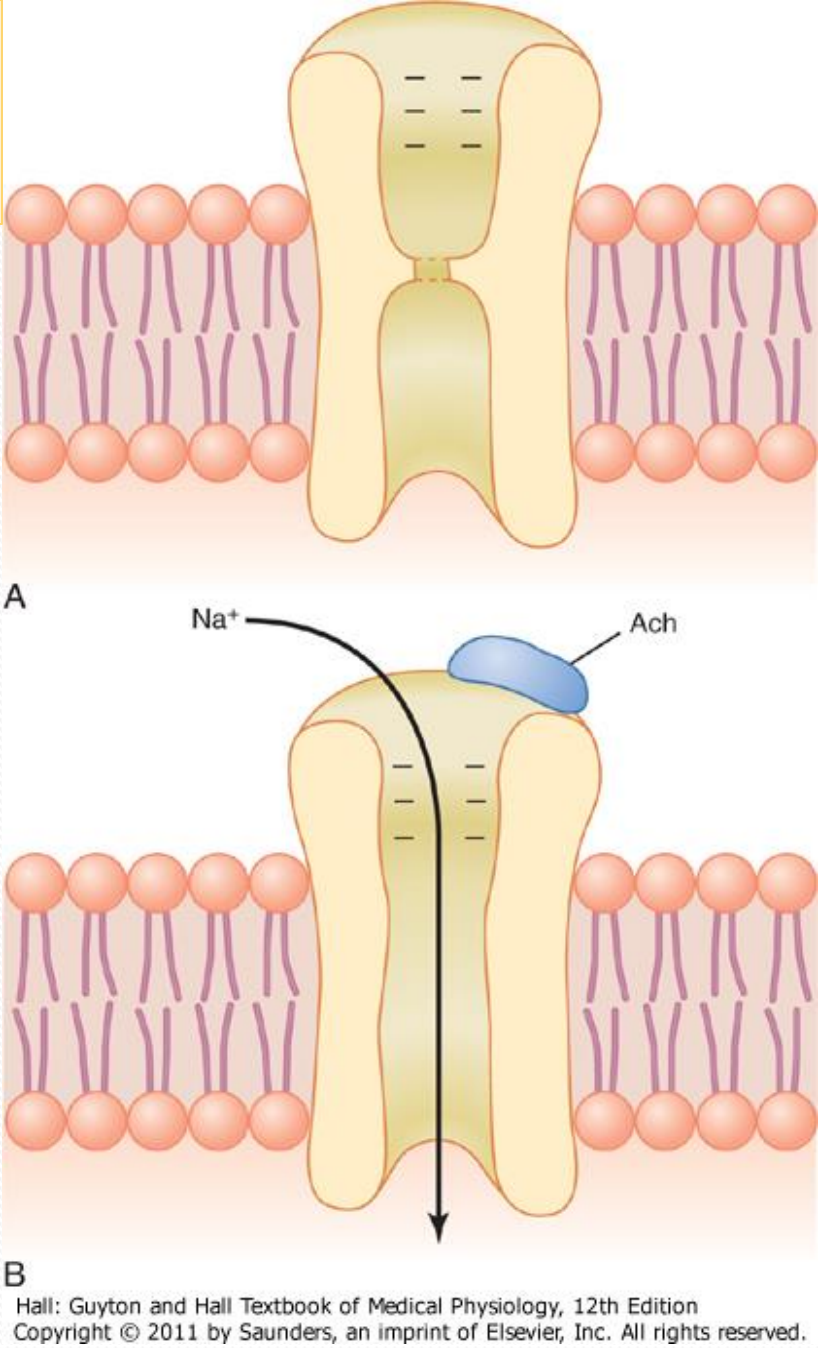
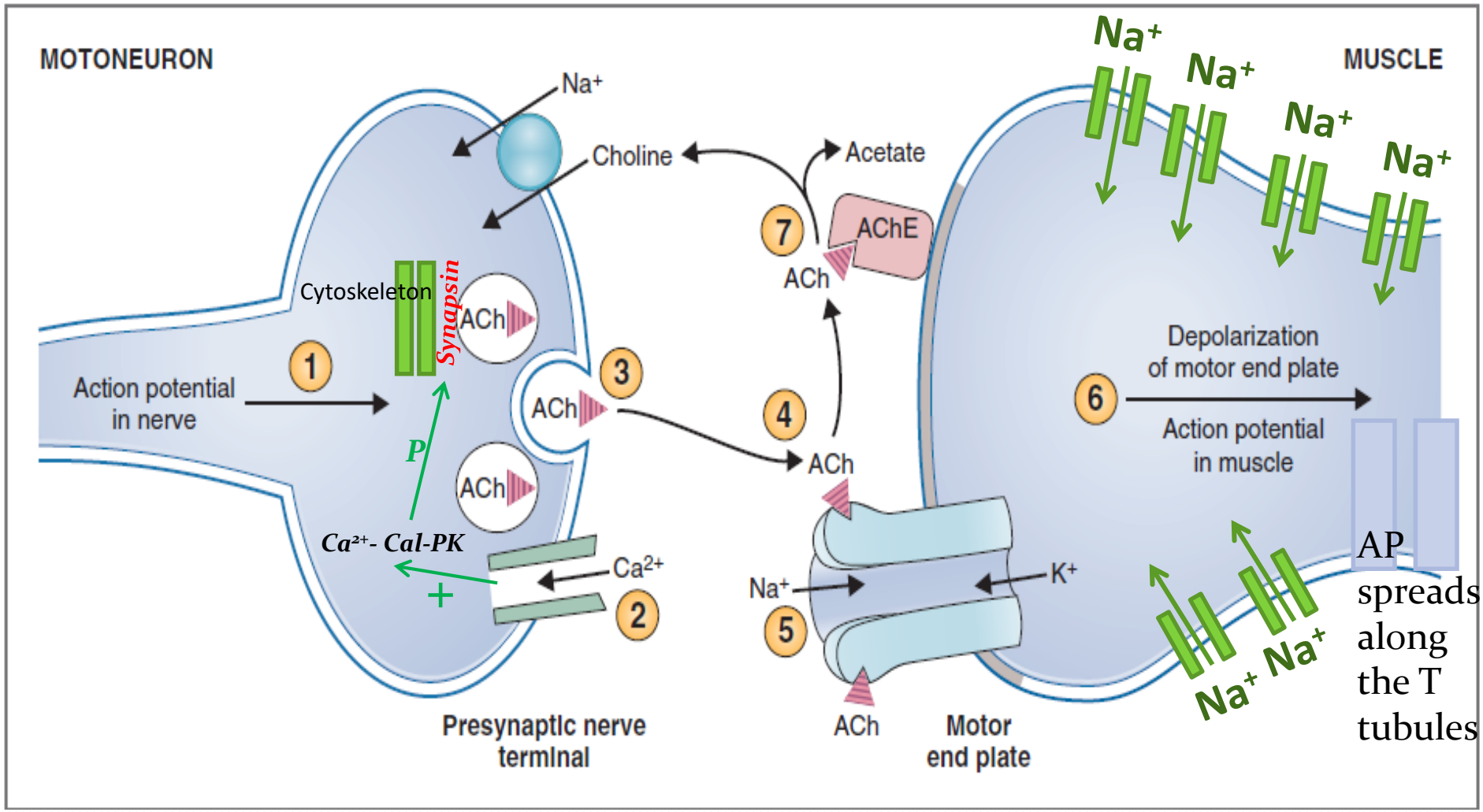


Fig. 7.3 Acetylcholine gated channels
A. Closed B. After Ach attaches



When Ach-gated channels open, sudden influx of Na^+ will increase electrical potential in the positive direction as much as 50-75 mV and creates a local ***EPP***. This will open **voltage gated Na+ channels**.

Release of Calcium Ions by the Sarcoplasmic Reticulum

- As the AP reaches the T-tubule, the voltage change is sensed by [***voltage-gated calcium channel*** 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.*

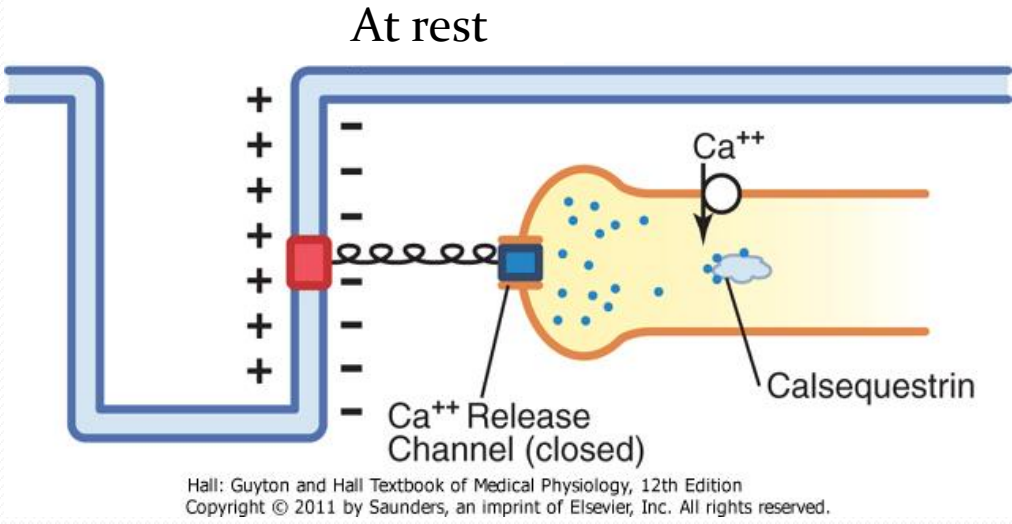
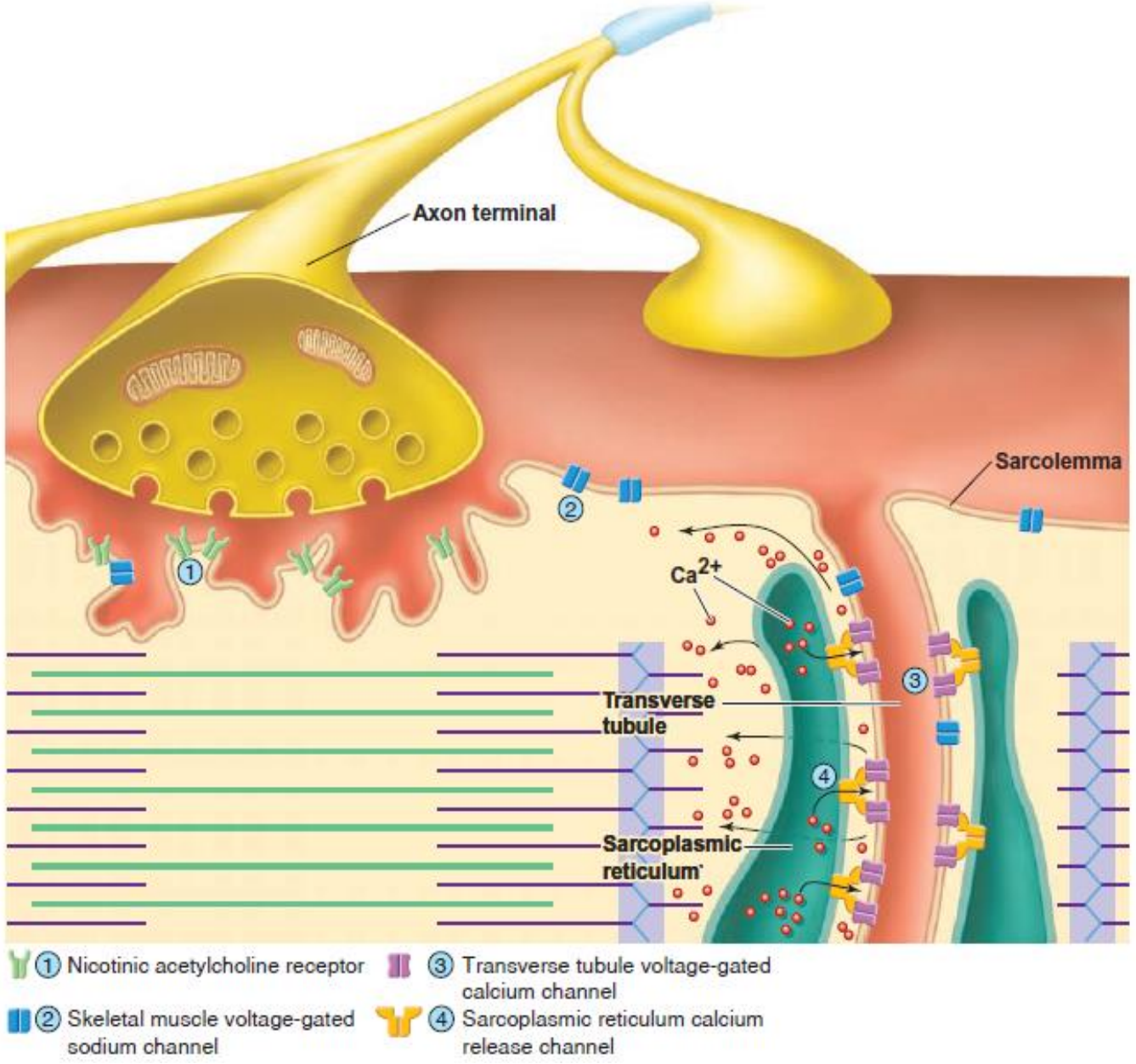


Fig. 7.6 Excitation-contraction coupling in skeletal muscle.

EXCITATION-CONTRACTION COUPLING

Excitation-contraction coupling in skeletal muscle. (1) ACh released by somatic motor neurons binds to nicotinic ACh receptors in the sarcolemma, causing a depolarization that stimulates (2) voltage-gated channels, producing action potentials. (3) The conduction of action potentials along the transverse tubules stimulates the opening of voltage-gated Ca^{2+} channels. (4) These channels in the transverse tubules are mechanically coupled to Ca^{2+} release channels in the sarcoplasmic reticulum, causing them to open. Ca^{2+} then diffuses out of the sarcoplasmic reticulum, so that it can bind to troponin and stimulate muscle contraction.



Muscle Action Potential (AP)

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

Molecular Mechanism of Muscle Contraction

Muscle Contraction Occurs by a Sliding Filament Mechanism

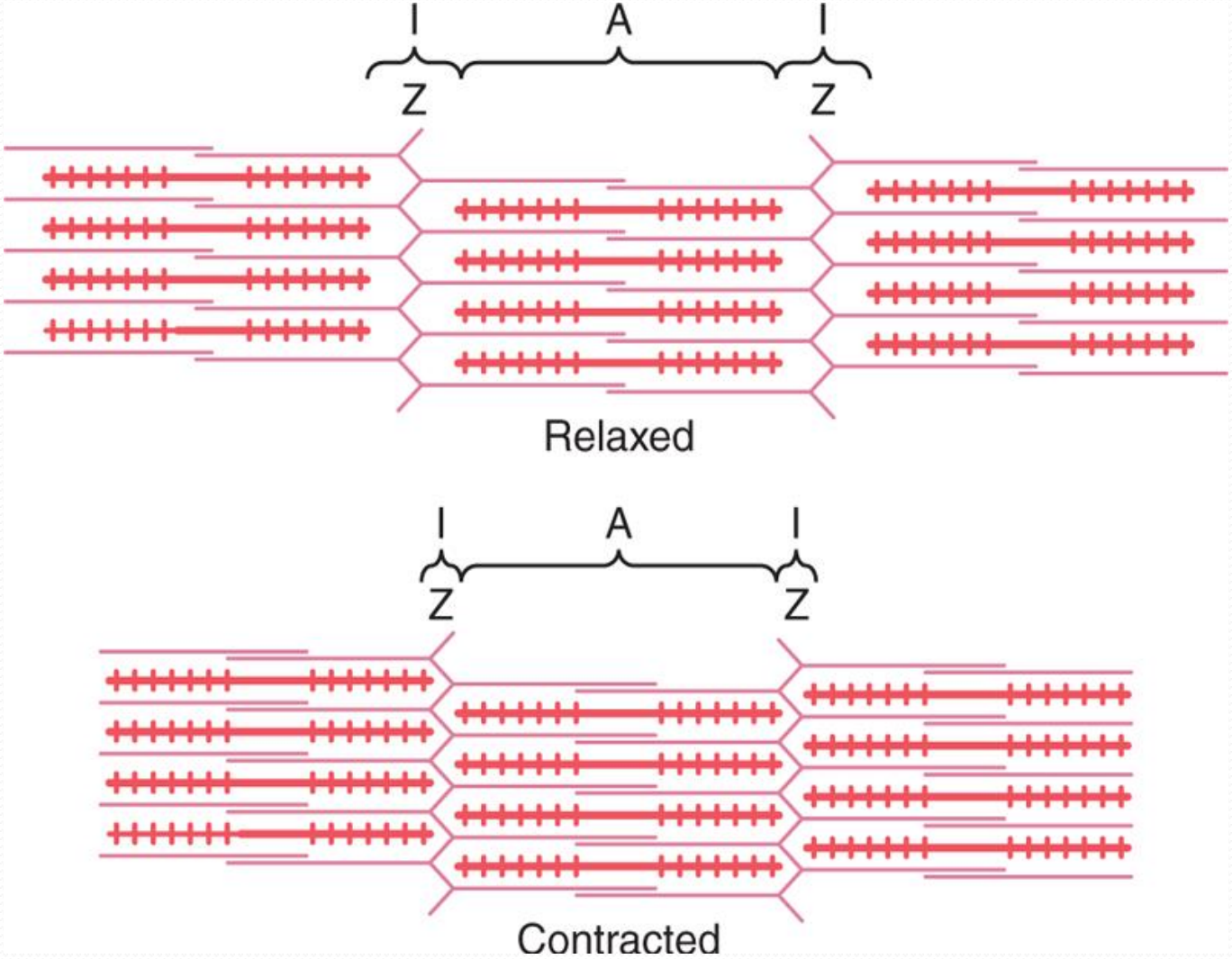


Figure 6-5. Relaxed and contracted states of a myofibril.

- **Molecular Characteristics of the Contractile Filaments**

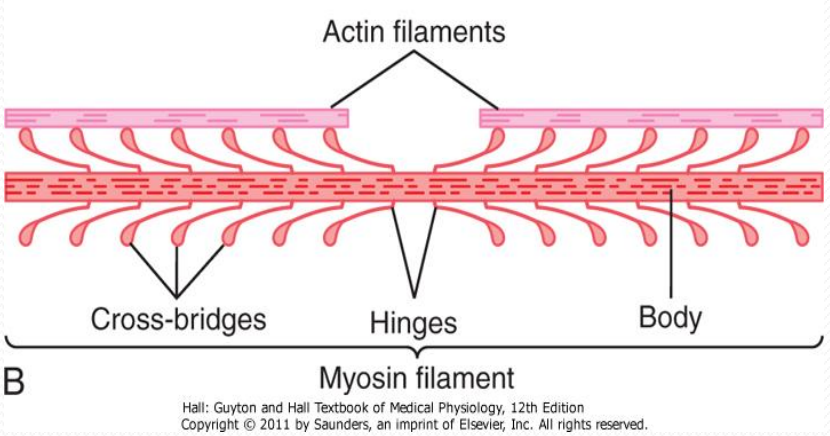
Myosin filaments are composed of multiple myosin molecules.

Each Myosin molecule has:

(1) Head

(2) Tail

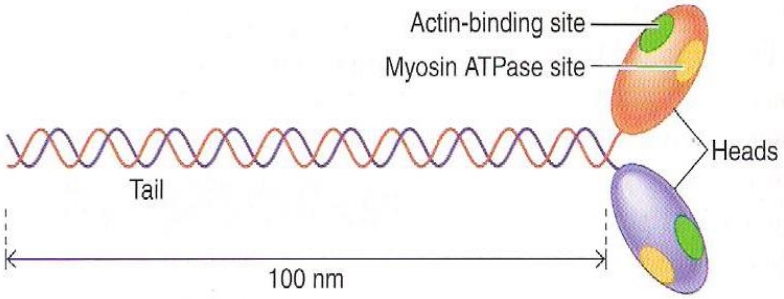
(3) Hinge (joint)



Each myosin head contains:

(1) Actin binding site

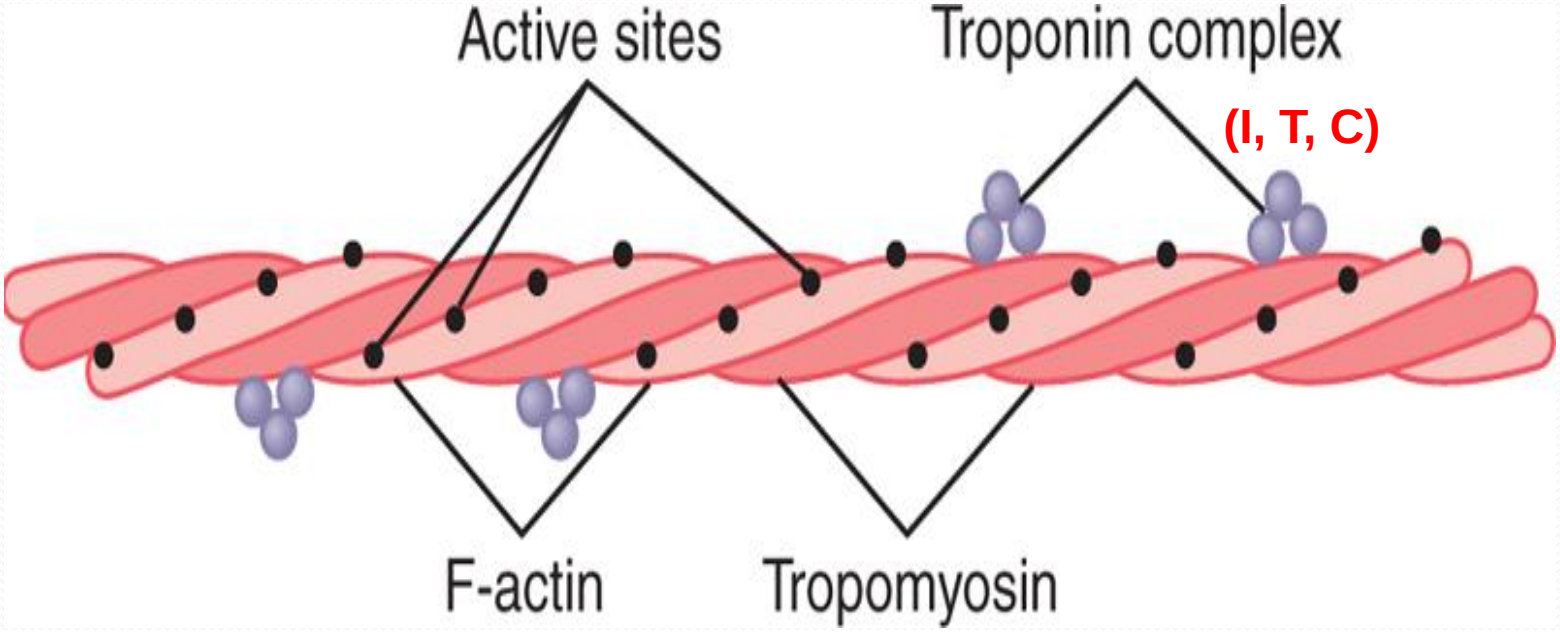
(2) Myosin ATPase site



(a) Myosin molecule

- **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

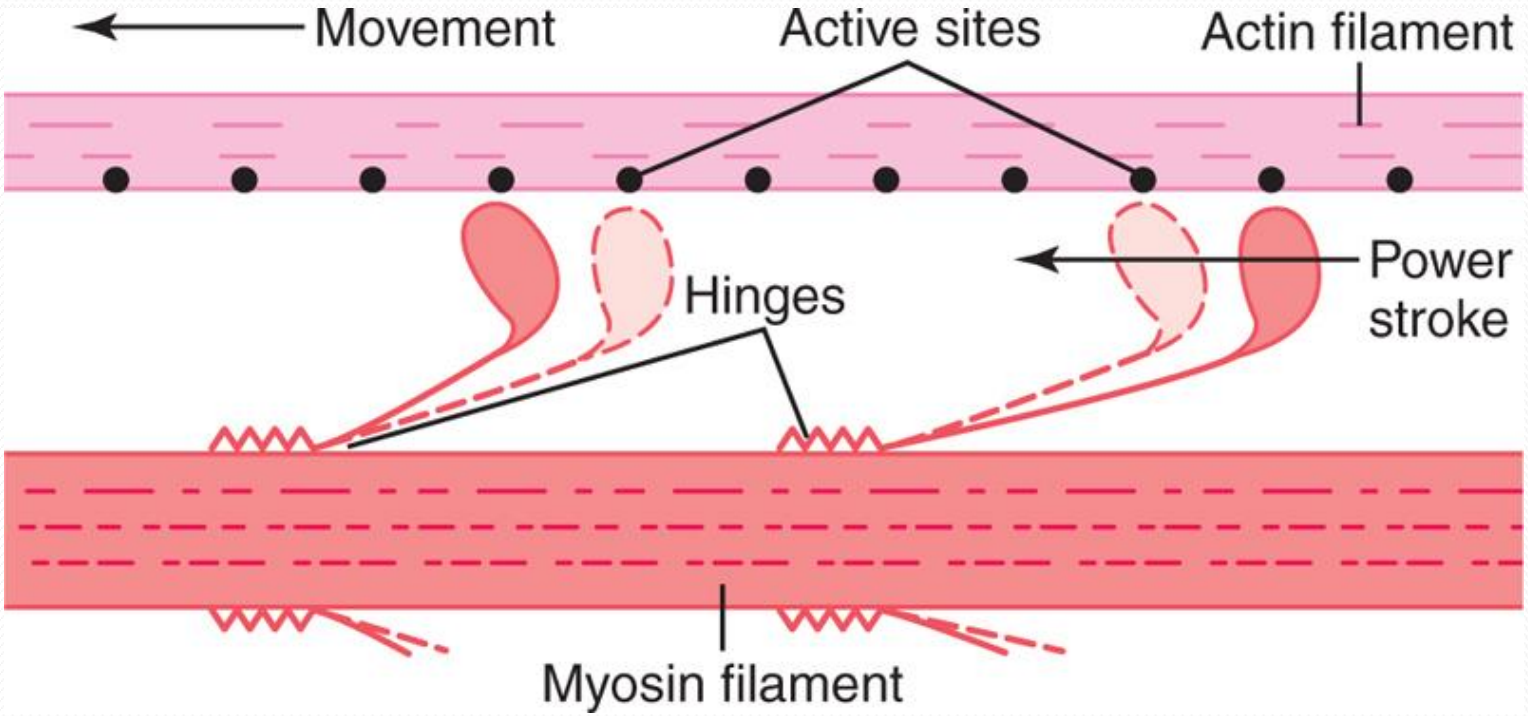
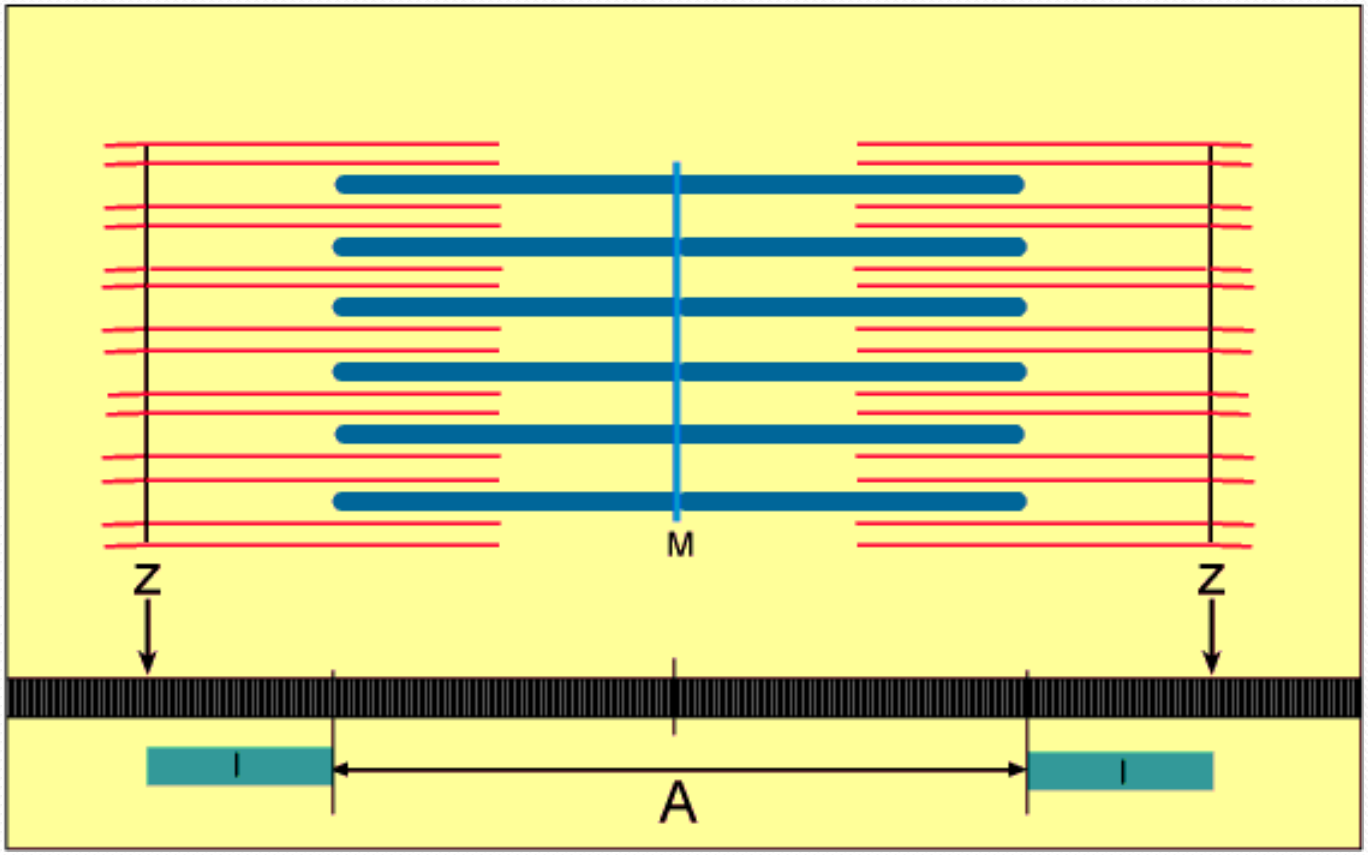


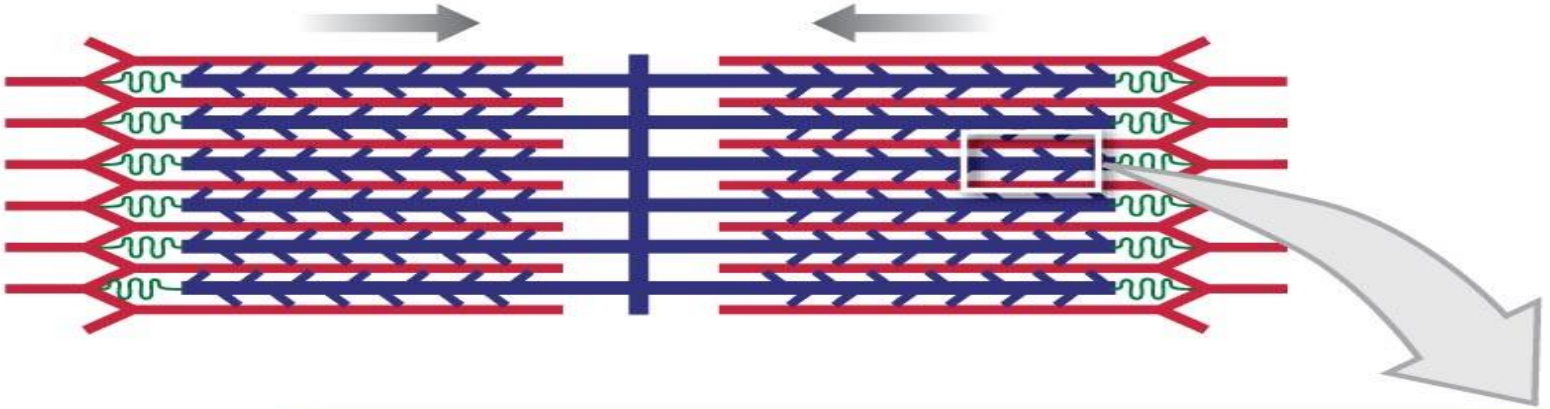
Fig. 6.8 "Walk-along" mechanism for muscle contraction.
The heads of the cross-bridges bend back and forth and step by step walk along the actin filament, pulling the ends of two successive actin filaments toward the center of the myosin filament.

Sliding Filament Mechanism

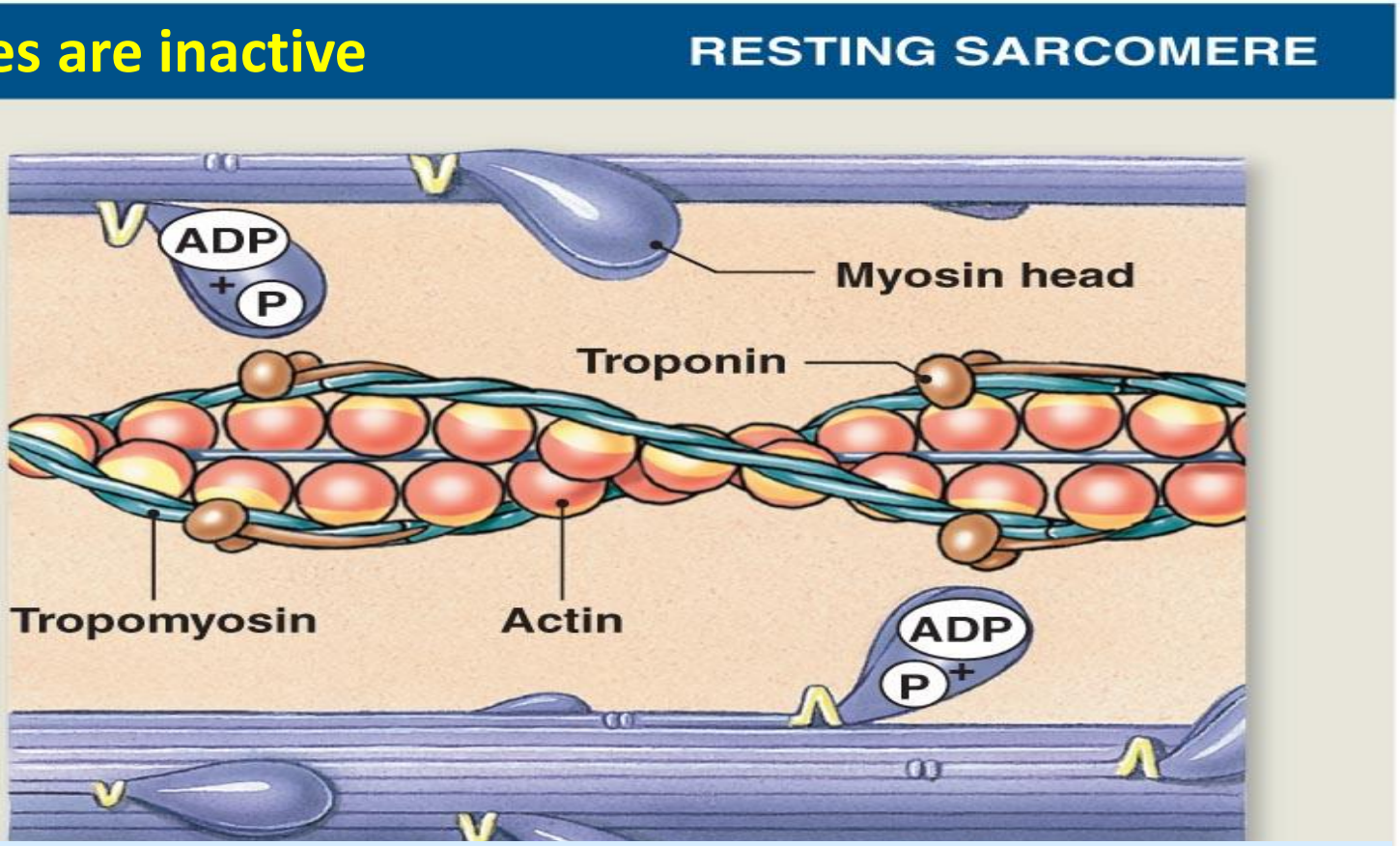


But what causes the actin filaments to slide inward among the myosin filaments?

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

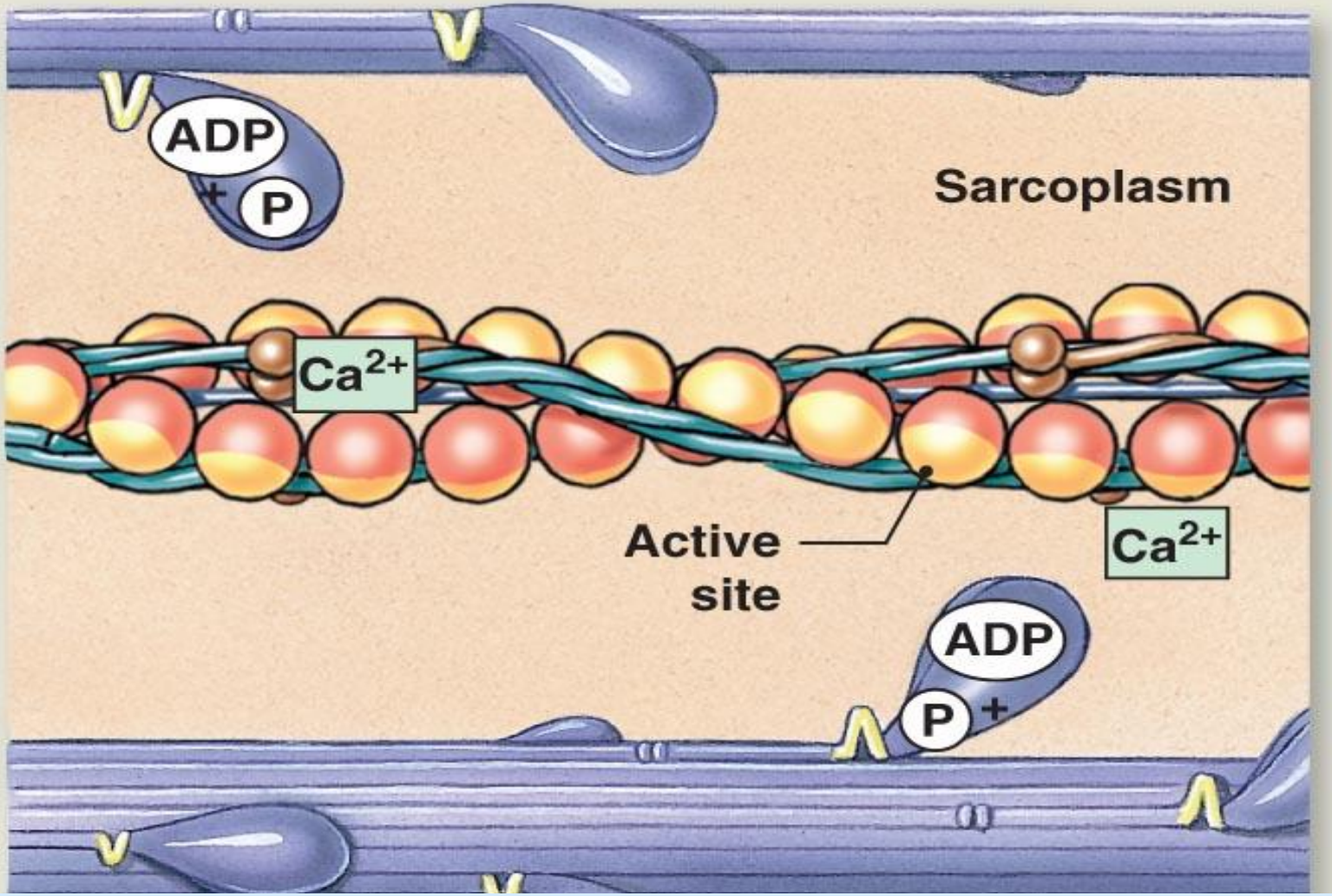


Forces are inactive



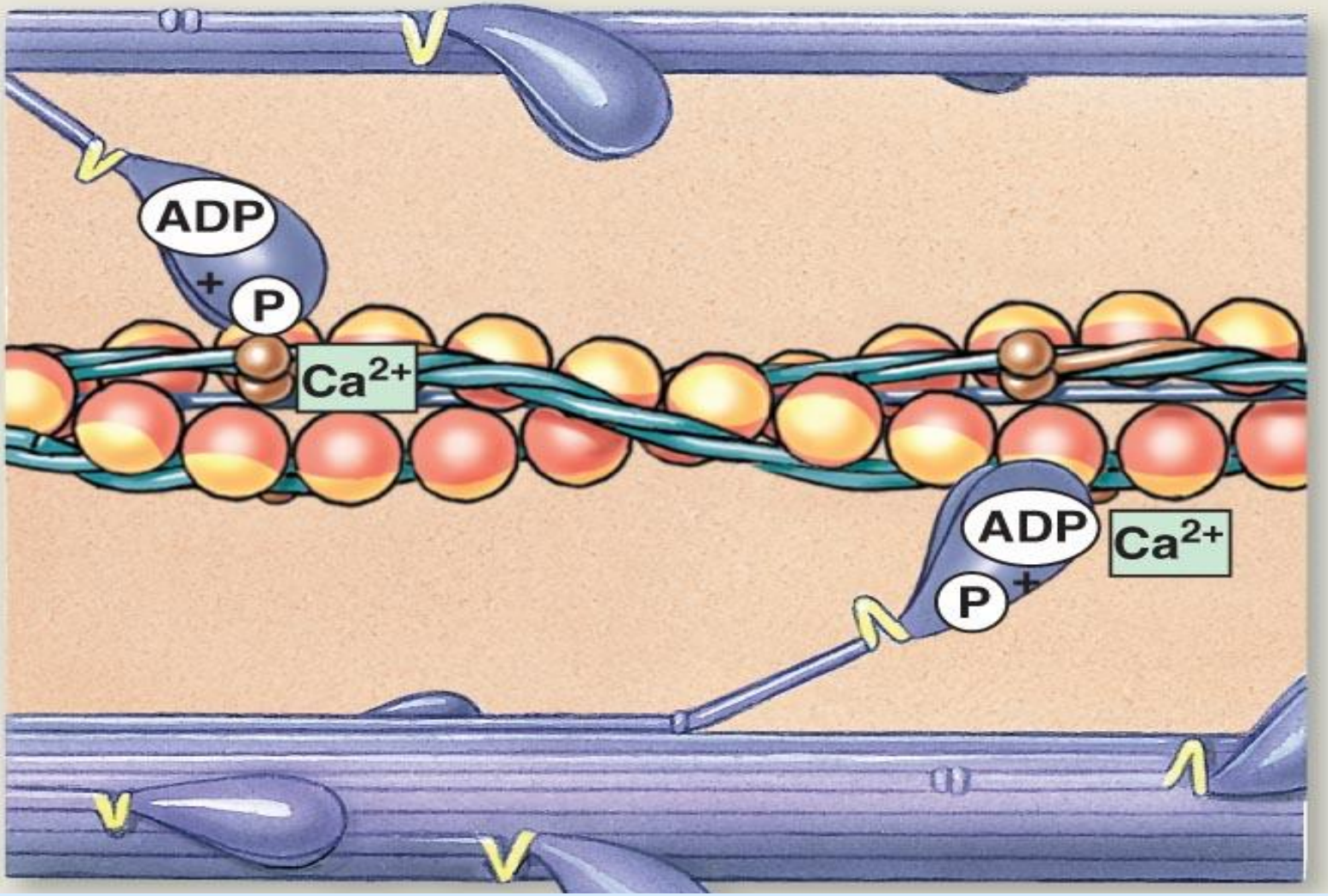
The heads of the cross bridges bind with ATP. **The ATPase activity** of the myosin head immediately cleaves the ATP but leaves the cleavage products, ADP plus phosphate ion, bound to the head.

STEP 1 ACTIVE-SITE EXPOSURE



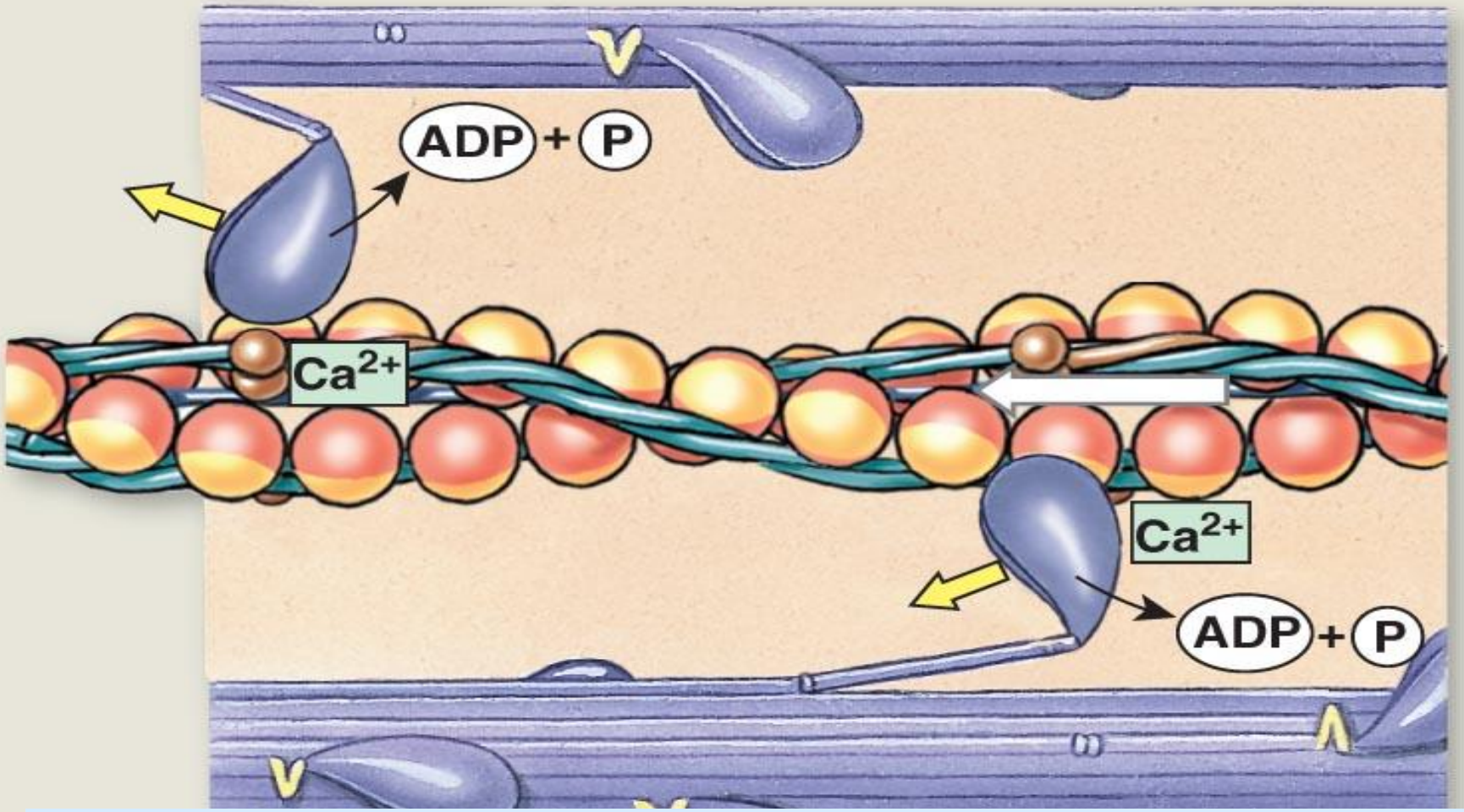
When the troponin-tropomyosin complex binds with **calcium** ions, active sites on the actin filament are uncovered and the myosin heads then bind with these sites.

STEP 2 CROSS-BRIDGE FORMATION



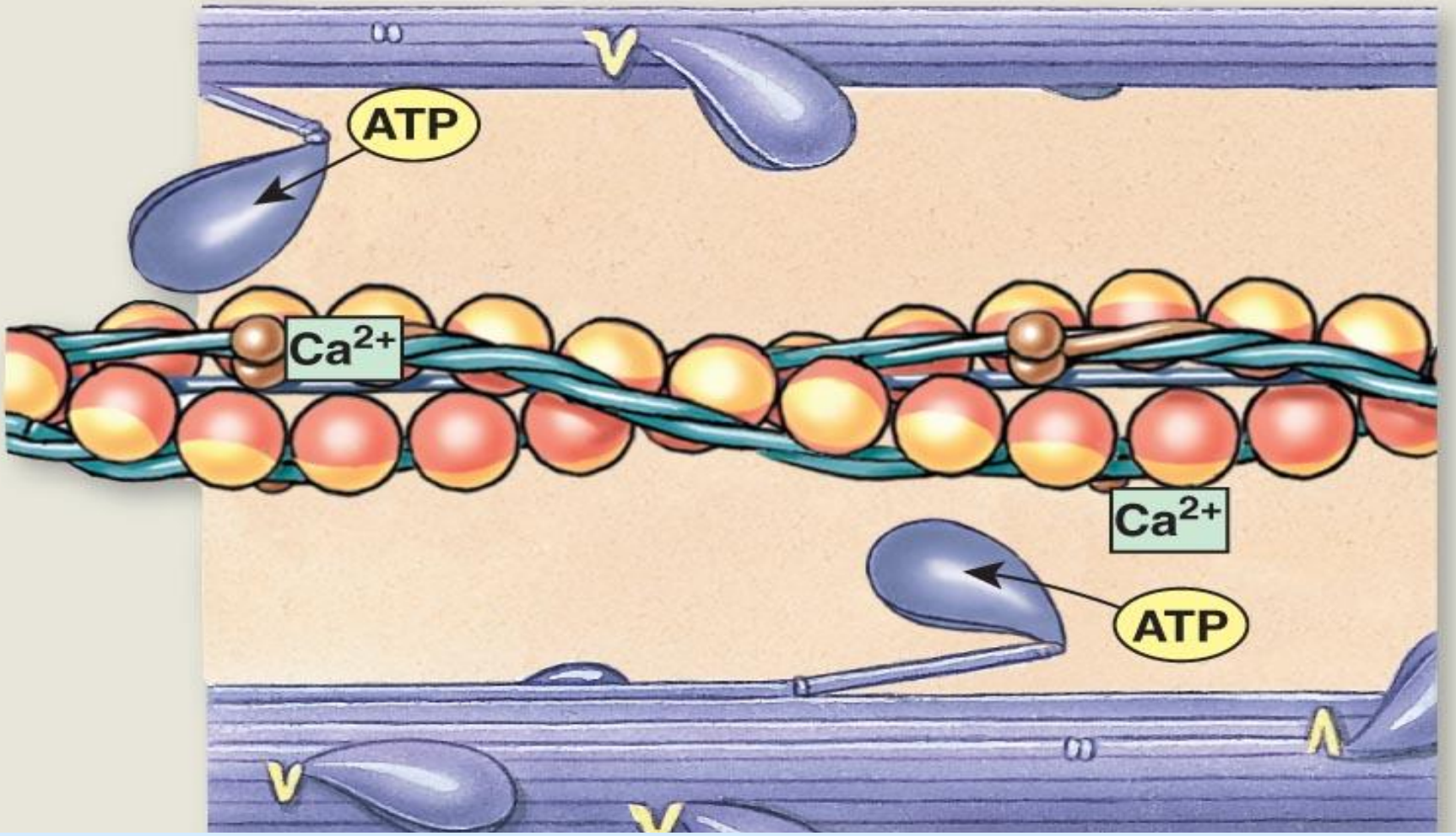
With the active sites on the actin exposed, the myosin heads bind to the actin, forming ***cross-bridges.***

STEP 3 PIVOTING OF MYOSIN HEAD



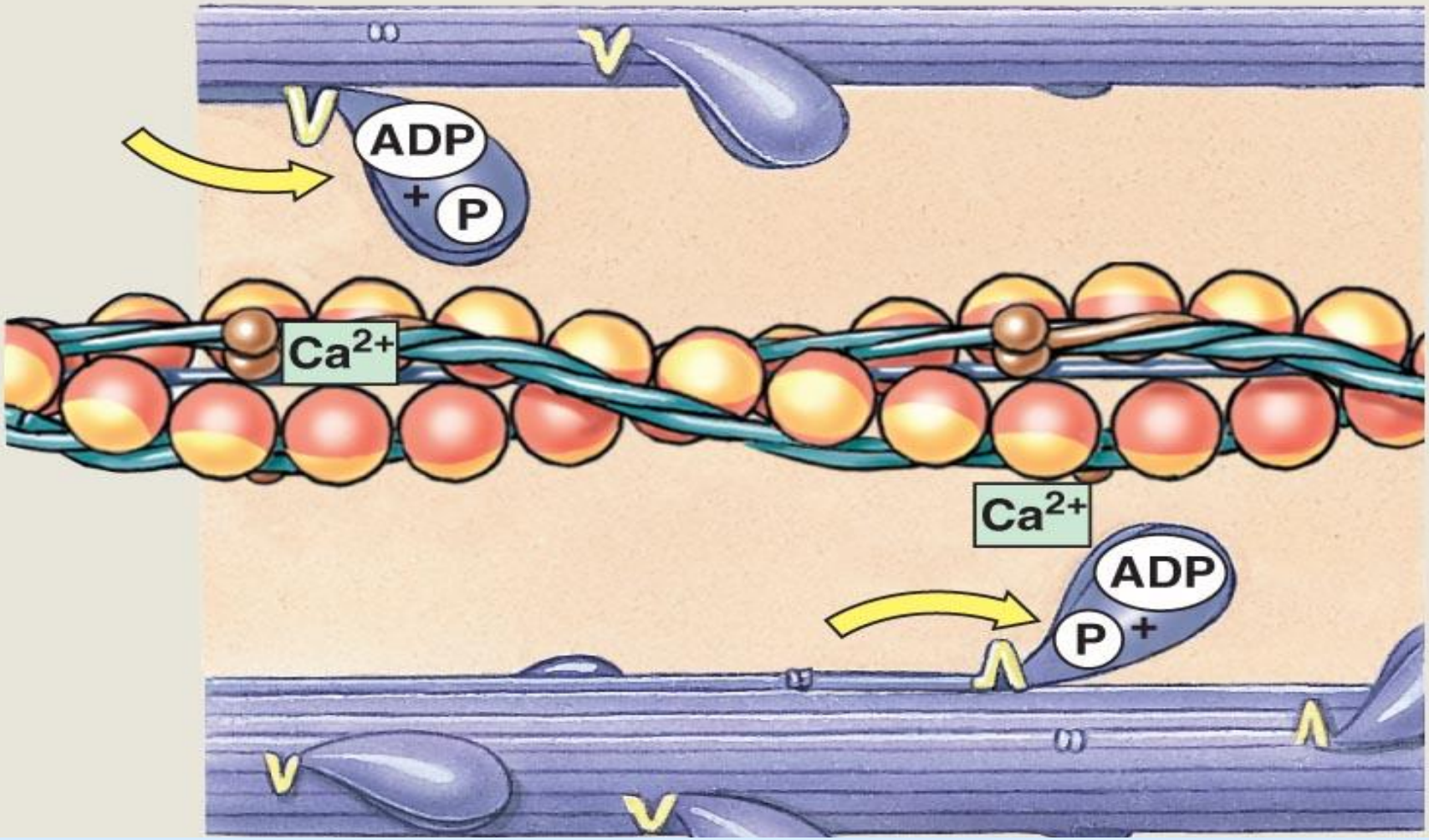
Binding the head of the cross-bridge with the active site causes a conformational change in the head, prompting the head to tilt toward the arm of the cross-bridge and providing the ***power stroke*** for pulling the actin filament.

STEP 4 CROSS-BRIDGE DETACHMENT

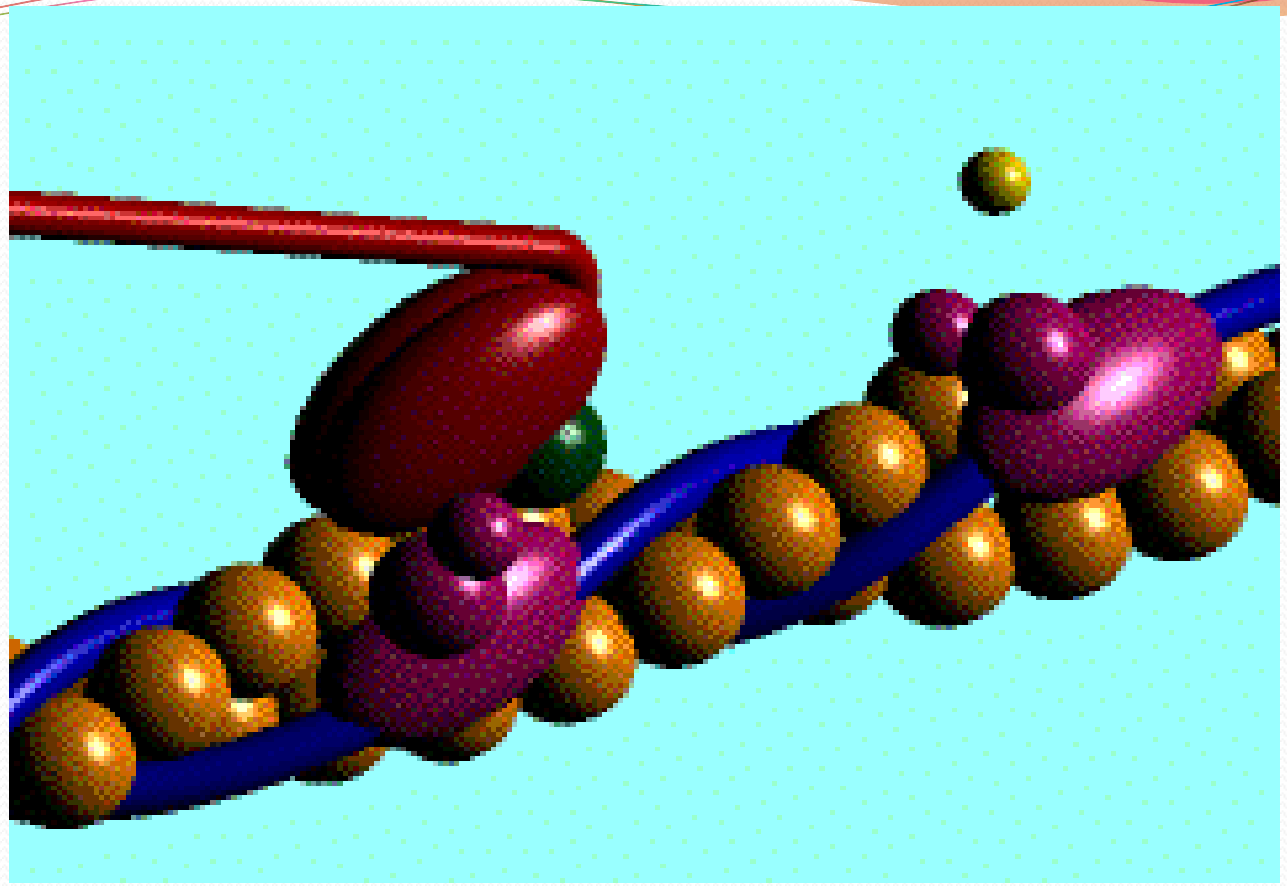


Once the head of the cross-bridge tilts, ADP and phosphate ion are released and new molecule of ATP binds. This binding of new ATP causes **detachment** of the head from the actin.

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.

Drugs That Enhance 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 Block Transmission at the Neuromuscular Junction

Drugs That Block Transmission at the NMJ

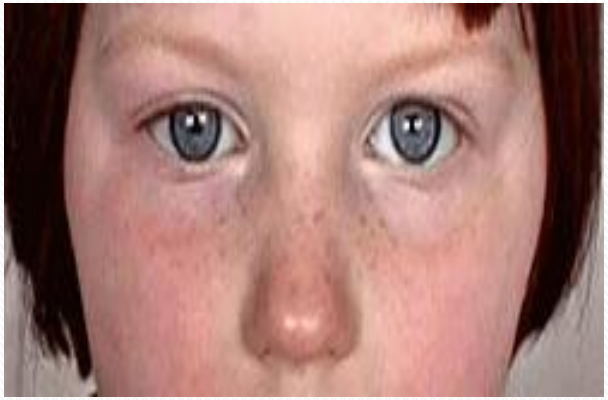
- **Curare & Curariform like-drugs.**

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

- **Botulinum Toxin.**

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

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