MSS MODULE
PHYSIOLOGY (LECTURE 1)
PHYSIOLOGY OF MUSCLE I

BY

DR. FATMA FARRAG ALI

ASSOCIATE PROFESSOR OF MEDICAL PHYSIOLOGY

FACULTY OF MEDICINE-MUTAH UNIVERSITY

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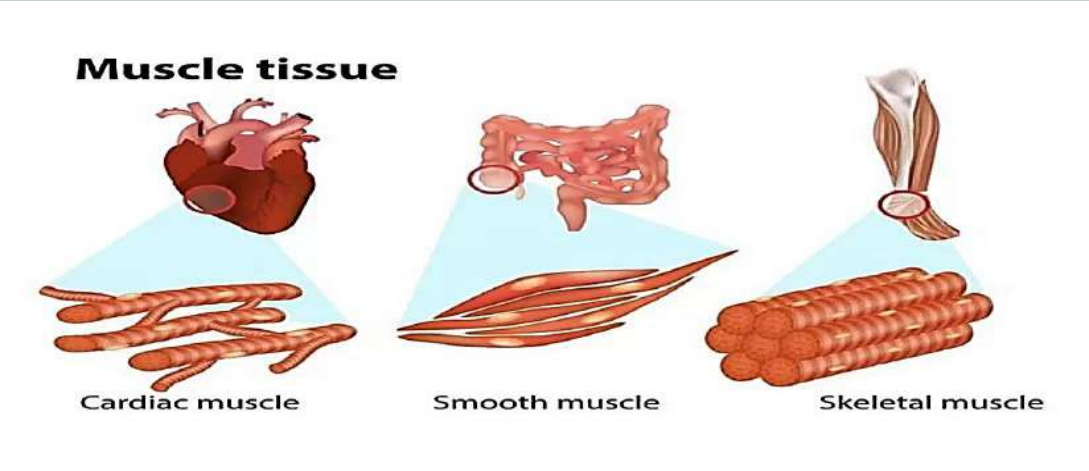

Muscle Tissue

- Muscle cells, like neurons, can be excited (excitable tissue) to produce an action potential that is transmitted along their cell membranes.
- Unlike neurons, they respond to stimuli by activating a contractile mechanism.
- The contractile proteins **myosin** and **actin** are abundant in muscle, where they are the primary structural components that bring about contraction.
- Muscle is generally divided into three types: skeletal, cardiac, and smooth muscles.

- **Skeletal muscle:**

✓ It makes up the great mass of the somatic musculature.
✓ It has well-developed cross-striations (striated muscle).
✓ It lacks anatomic and functional connections between individual muscle fibers.
✓ Contraction is initiated by action potentials in **somatic motor neurons** of the nervous system and is usually under voluntary control.

- **Cardiac muscle:**

✓ It is the muscle of the heart. Its contraction generates the pressure that propels blood through the circulatory system.
✓ It also has cross-striations (striated muscle) as skeletal muscle.
✓ It is functionally syncytial (gap junctions).
✓ Although it can be modulated via the **autonomic nervous system**, it can contract rhythmically in the absence of external innervation owing to the presence in the myocardium of **pacemaker cells** that discharge spontaneously.

- **Smooth muscle:**
  - Lacks cross-striations (non-striated).
  - It can be subdivided into two broad types: unitary (or single-unit) smooth muscle and multiunit smooth muscle.
  - In contrast to skeletal muscle, smooth muscle contraction is not normally under voluntary control. It occurs autonomously in some cases **(pacemaker cells)**, but frequently it occurs in response to signals from the autonomic nervous system, hormones, autocrine or paracrine signals, and other local chemical factors.
  - The type found in most **hollow viscera is functionally syncytial; single-unit** (gap junctions) and contains **pacemakers** that discharge irregularly.
  - Multiunit smooth muscle is organized into motor units similar to those in skeletal muscle. Cells are electrically isolated from each other (there are no gap junctions), allowing for fine motor control. It is found in a few specific regions such as the eye and the piloerector muscles in the skin.

Single-Unit vs Multi-Unit Smooth Muscle

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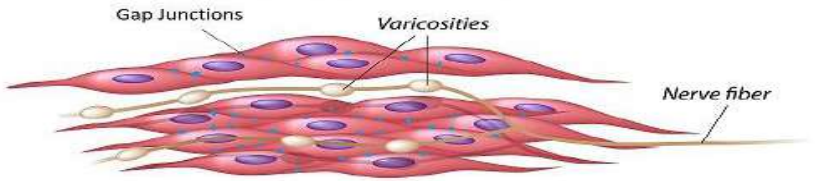
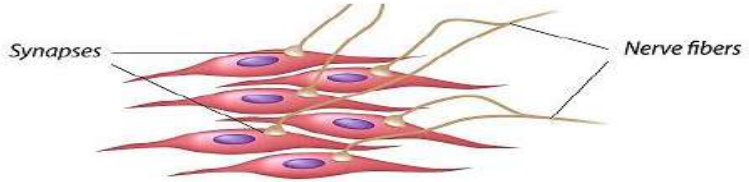
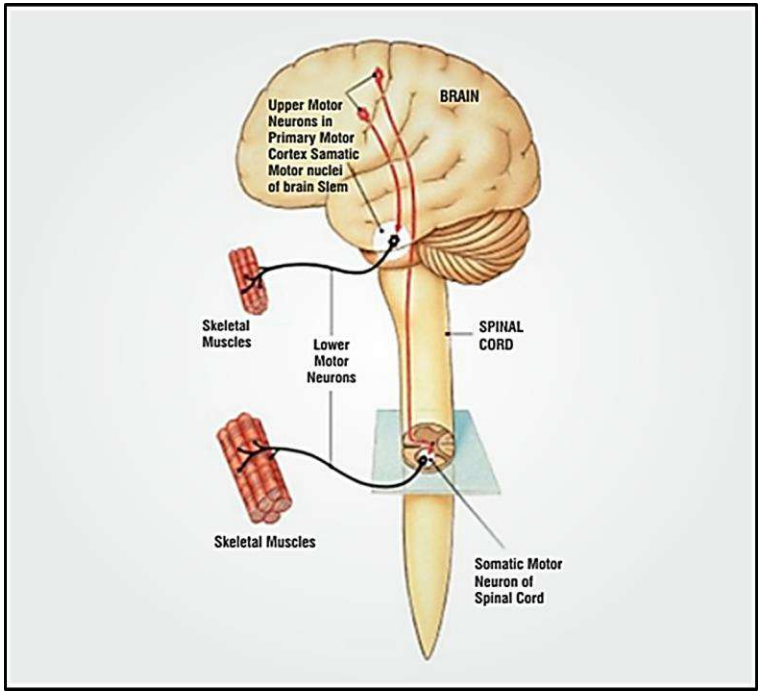
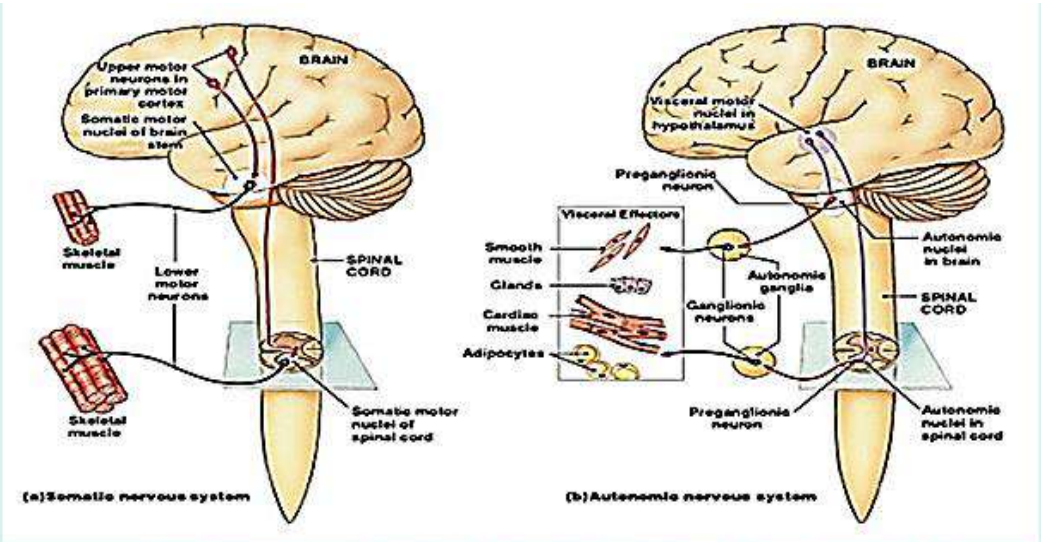


Single-Unit Smooth Muscle



Multi-Unit Smooth Muscle





Organization Similarities of SNS and ANS

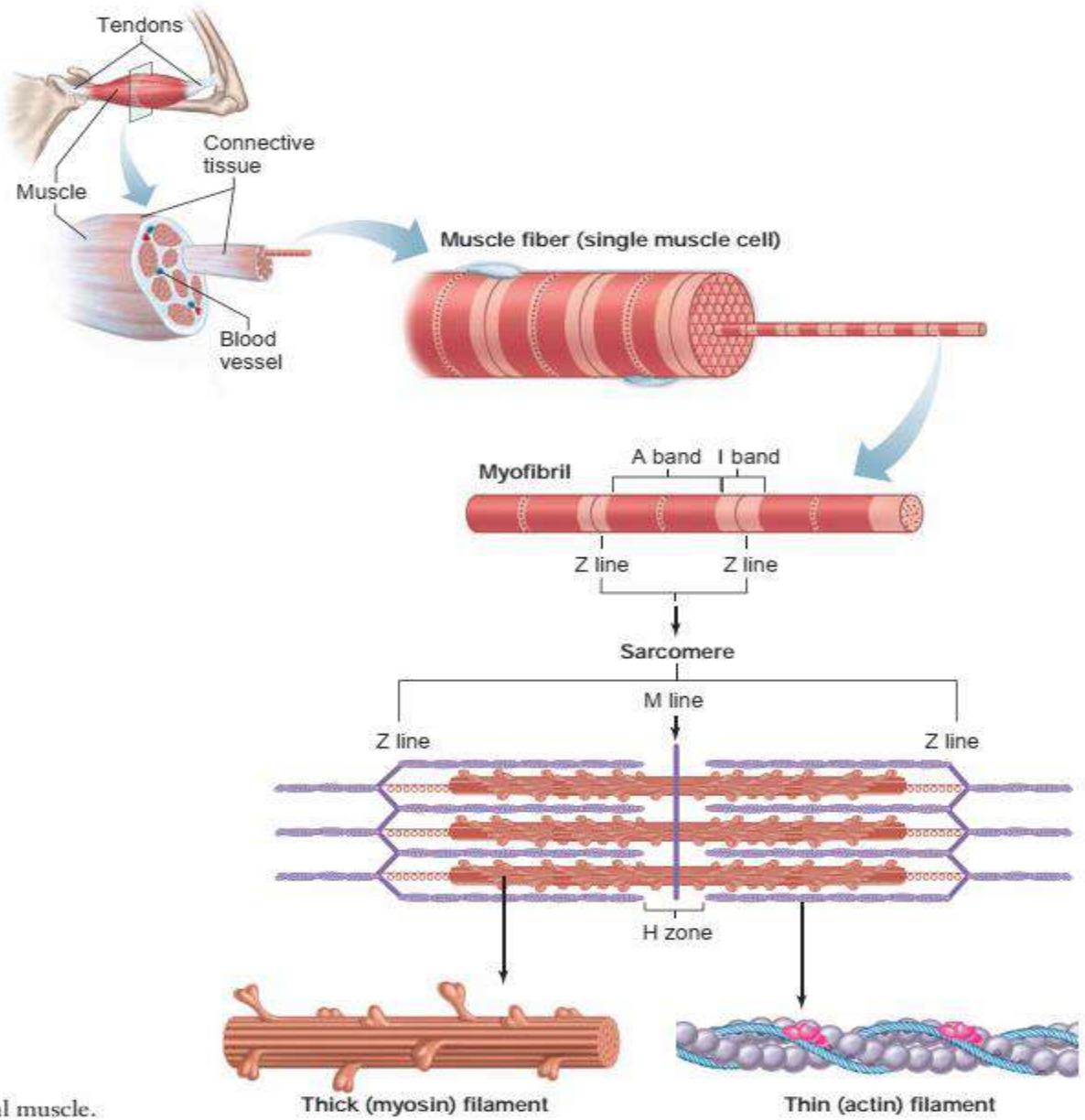
STRUCTURE OF SKELETAL MUSCLE

- Skeletal muscles are attached to bones of the skeleton at two sites (origin &insertion) by tendons.
- They are voluntary and controlled by **somatic motor nerves**.
- Skeletal muscle is formed of parallel individual muscle fibers completely separated from each other.
- Skeletal muscle → muscle fascicle → muscle fiber (cell) → myofibrils → filaments of contractile proteins; myofilaments (thick myosin and thin actin)
- Most of the cytoplasm of a fiber is filled with myofibrils.

The Myofibril

- Each myofibril shows alternating dark (A) and light (I) bands.
- In the **middle** of the **I band**, there is a **Z line**,
- In the **middle** of the **A band** there is a **light (H) band** in the **middle** of which **(M) line** is seen.
- 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**).

1. SKELETAL MUSCLE



skeletal muscle.

The molecular structure of thick and thin filaments (Myofilaments)

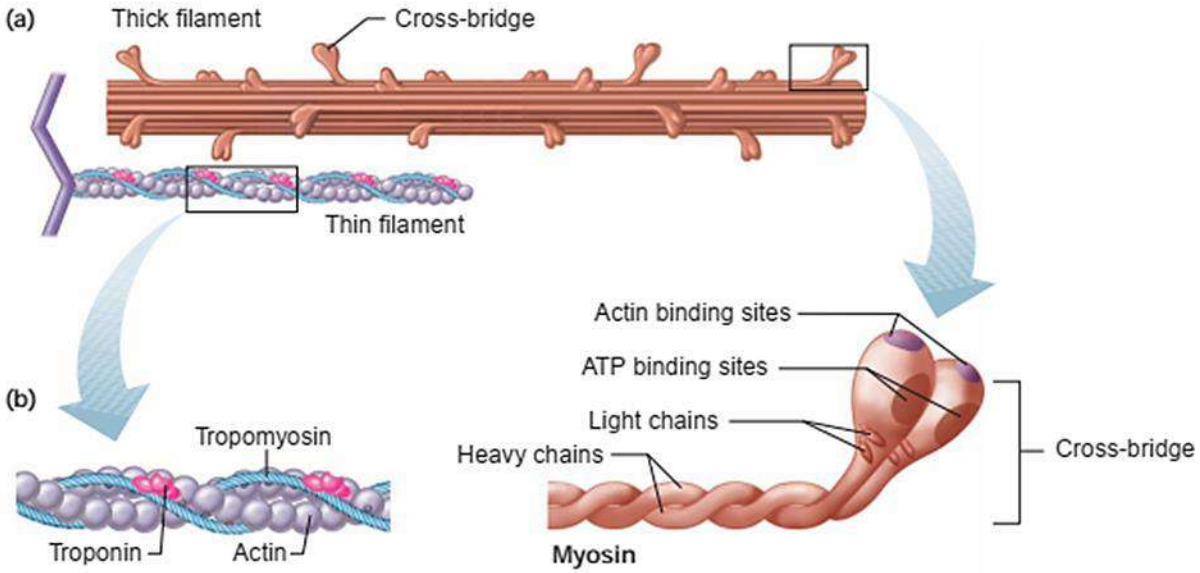
The thick filaments:

- ✓ Are composed of the **protein myosin**.
- ✓ Each myosin molecule consists of **two globular heads** (containing heavy and light chains) and **a long tail** formed by the two intertwined heavy chains.
- ✓ The tail of each myosin molecule lies along the axis of the thick filament.
- ✓ 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)** and 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.

The thin filaments:

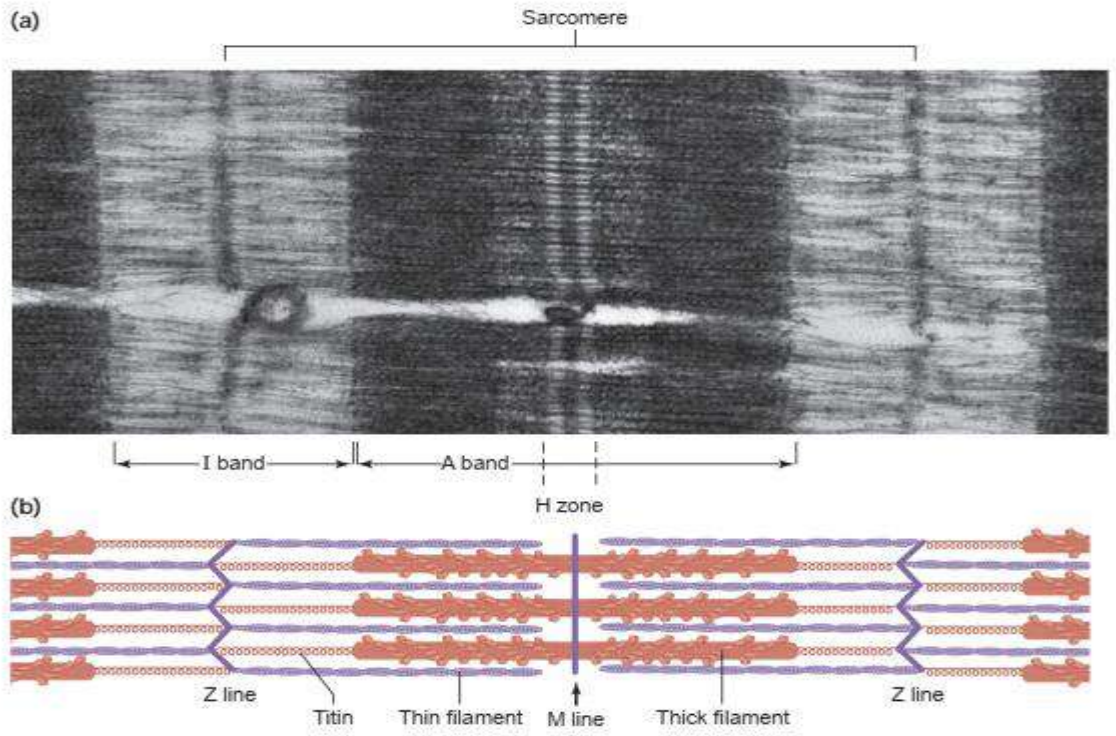
The thin filaments (which are about half the diameter of the thick filaments) are principally composed of:

- **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)**.

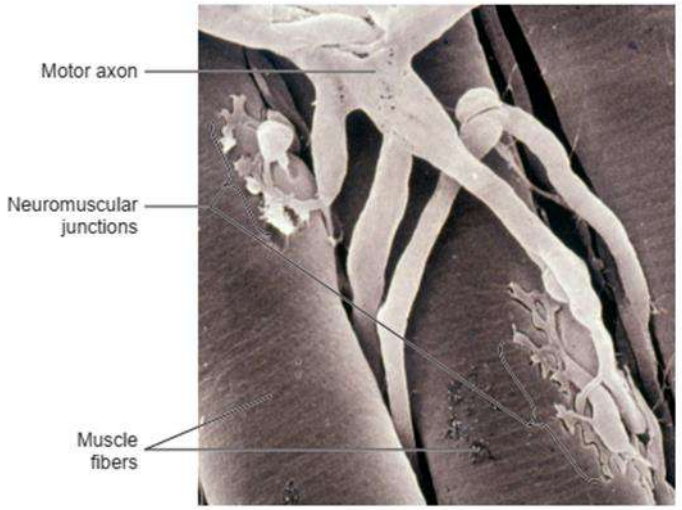


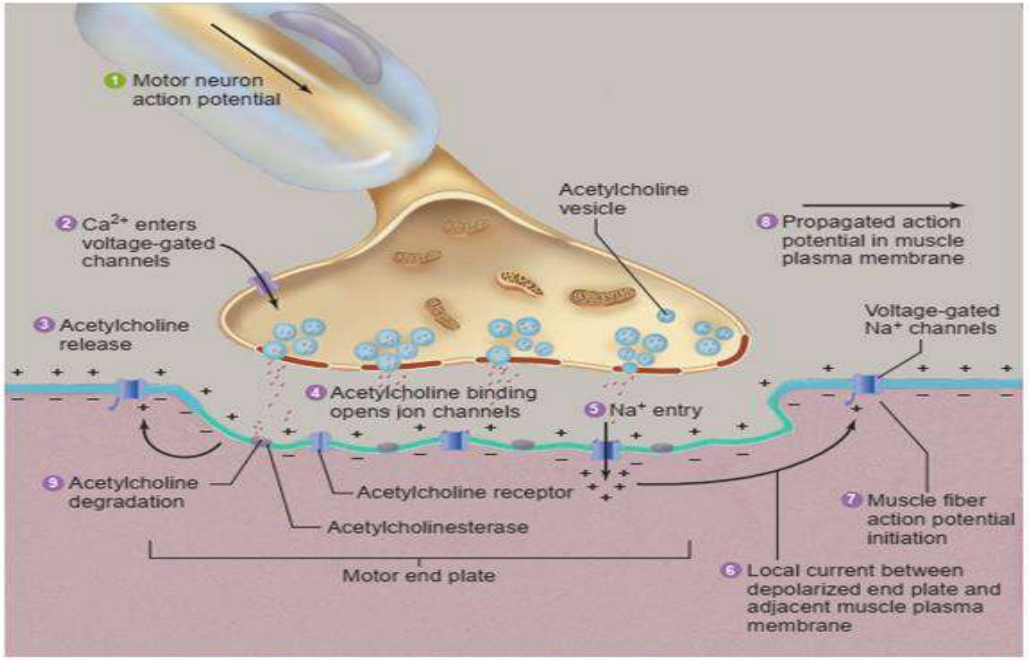
Sarcomere:

- It is the **functional unit** of skeletal muscle.
- It is the site where actual contraction occurs. It is the **contractile unit** of the skeletal muscle fiber.
- The two primary filaments (thick myosin and thin actin) are present in sarcomere.
- It is the area between two adjacent (successive) Z lines.



The NMJ and neuromuscular transmission





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**.

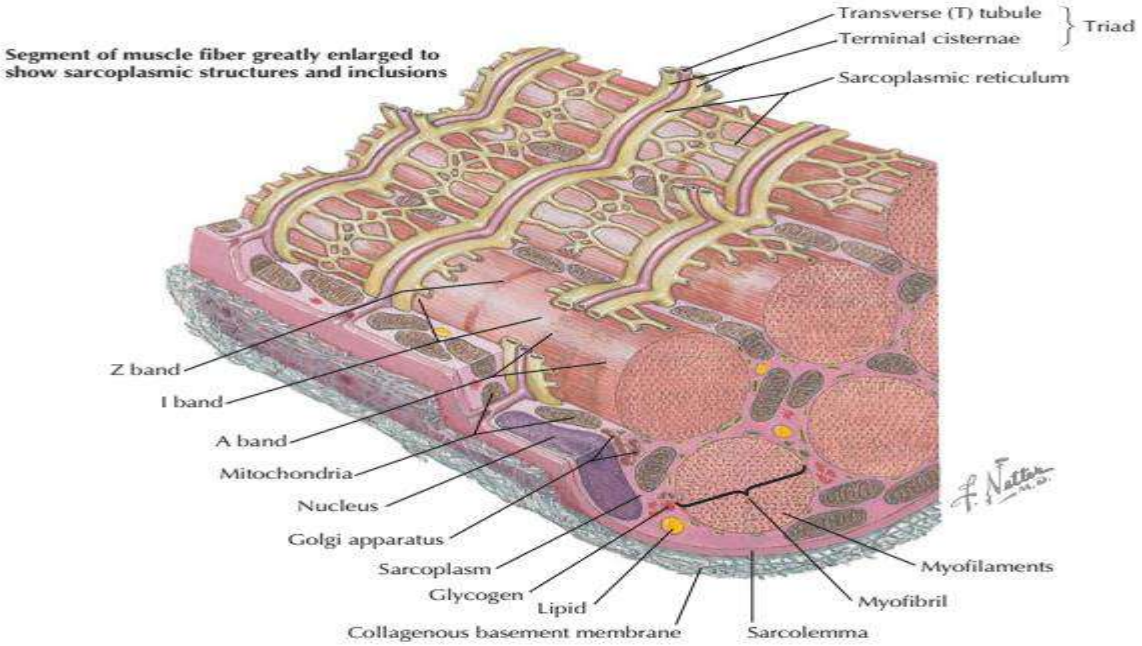
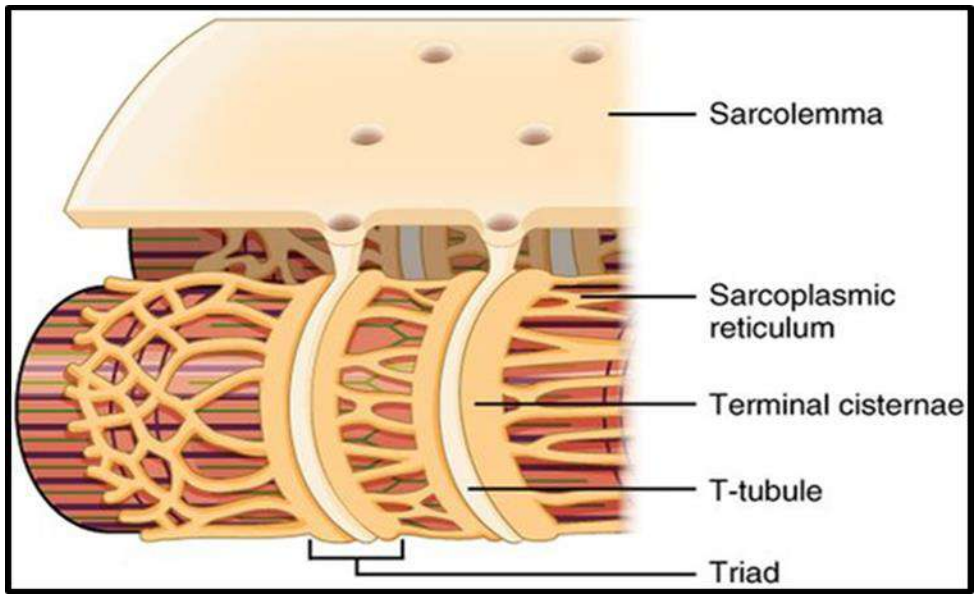


Figure 3.12 **Sarcoplasmic Reticulum** The sarcoplasmic reticulum is a complex network surrounding the myofibrils and storing high concentrations of Ca^{2+}, sequestered from the sarcoplasm. The membrane of the sarcoplasmic reticulum contains Ca^{2+}-ATPase, which is essential for this sequestration. 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+}.



Excitation–Contraction Coupling (ECC)

- In **a resting muscle fiber**, **tropomyosin** molecules **cover** the **myosin-binding site on actin**, thereby **preventing the cross-bridges from making contact with actin**.
- **Each tropomyosin molecule is held in this blocking position by** the smaller globular protein, **troponin**.
- **Troponin, which interacts with both actin and tropomyosin, is composed of three subunits: I (inhibitory), T (tropomyosin -binding) and C (Ca^{2+} - binding).**
- Thus, **troponin and tropomyosin cooperatively block the interaction of cross-bridges with the thin filament**.

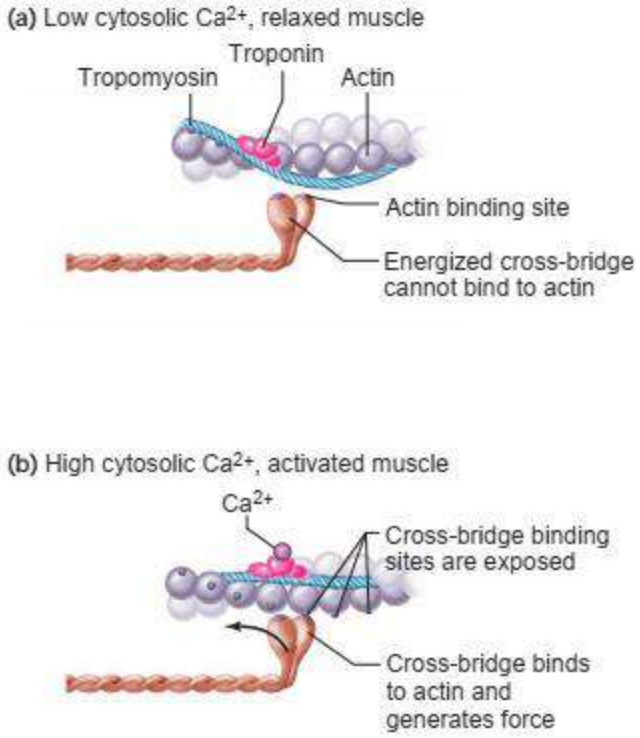


Figure 9.11 AP|R Activation of cross-bridge cycling by Ca^{21}. (a) Without calcium ions bound, troponin holds tropomyosin over cross-bridge binding sites on actin. (b) When Ca^{21} binds to troponin, tropomyosin is allowed to move away from cross-bridge binding sites on actin, and cross-bridges can bind to actin.

- As **depolarization is conducted into the T tubules**. **The T tubule membrane contains voltage-gated Ca^{2+} channels, also known as dihydropyridine receptors**.
- Although the dihydropyridine receptor is a voltage-gated Ca^{2+} channel, ion flux through this channel is not required for contraction of skeletal muscle. Rather, a **conformational change in the dihydropyridine receptor, caused by depolarization of the T-tubule**, is required.
- **These receptors are in close apposition to calcium channel proteins known as ryanodine receptors**, which are large proteins of the **SR** that extend into the gap between the terminal cisternae of the sarcoplasmic reticulum and the T-tubules.
- **Conformational change of the dihydropyridine receptors is believed to produce a subsequent conformational change in the ryanodine receptors, allowing stored Ca^{2+} to be released from the SR, initiating the contraction process.**
- **Ca^{2+} binds to troponin C, produces a change in the shape of troponin**, which relaxes its inhibitory grip and allows **tropomyosin to move away from the myosin-binding site on each actin molecule**.
- **Removing the blocking effect of tropomyosin allows myosin cross-bridges to bind actin and sliding of thin on thick filaments, producing movement**. The **sarcomere shorten (A band length doesn't change but the adjacent Z lines are brought closer together and I band and H zone are reduced)**.
- **The term excitation-contraction coupling refers to this linking of depolarization to Ca^{2+} release.**

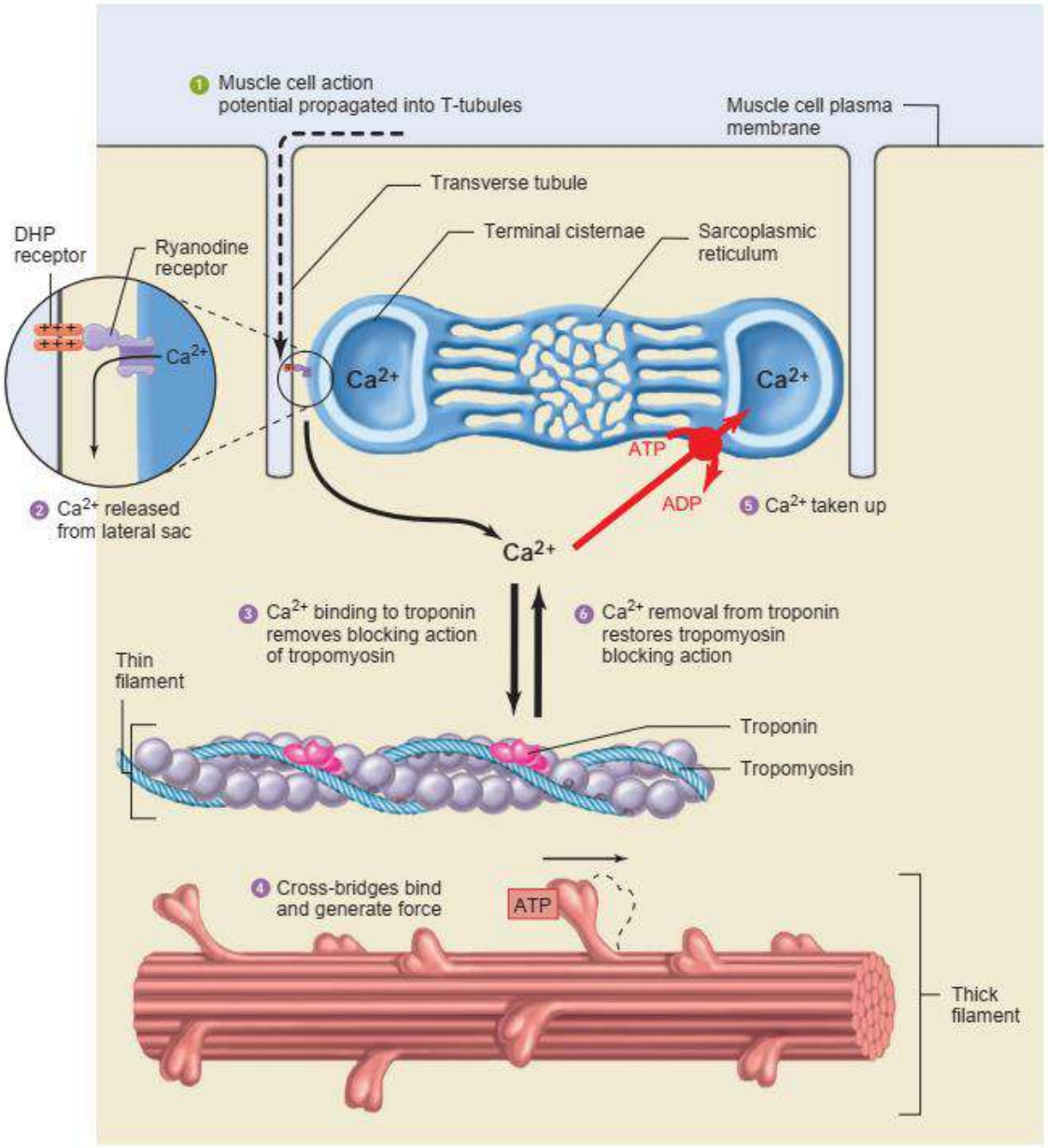


Figure 9.12 AP|R
Release and uptake of Ca^{21} by the sarcoplasmic reticulum during contraction and relaxation of a skeletal muscle fiber.

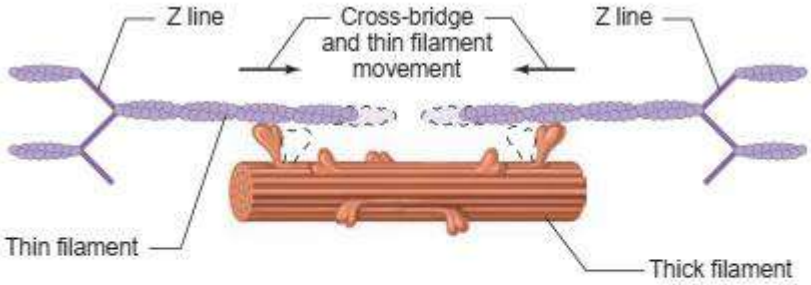


Figure 9.13 AP|R Cross-bridges in the thick filaments bind to actin in the thin filaments and undergo a conformational change that propels the thin filaments toward the center of a sarcomere. (Only a few of the approximately 200 cross-bridges in each thick filament are shown.)

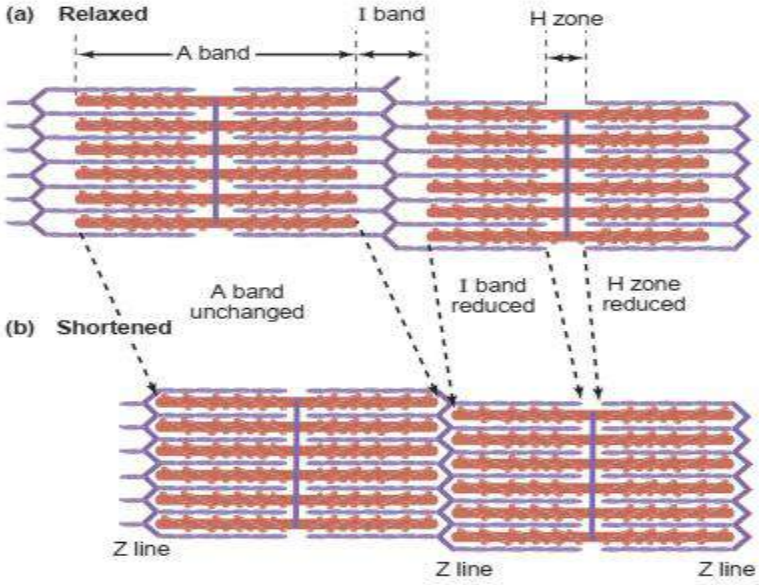


Figure 9.14 AP|R The sliding of thick filaments past overlapping thin filaments shortens the sarcomere with no change in thick or thin filament length. The I band and H zone are reduced.

Sliding- Filament Mechanism:

The sequence of events that occurs between the time a cross-bridge binds to a thin filament, moves, and then is set to repeat the process is known as a **cross-bridge cycle**.

Each cycle consists of four steps:

1. **Attachment of the energized cross-bridge to actin.**
2. **Movement of the bound cross-bridge (power stroke), producing tension in the thin filament.**
3. **Detachment of the cross-bridge from the thin filament.**
4. **Energizing the cross-bridge so it can again attach to a thin filament and repeat the cycle.**

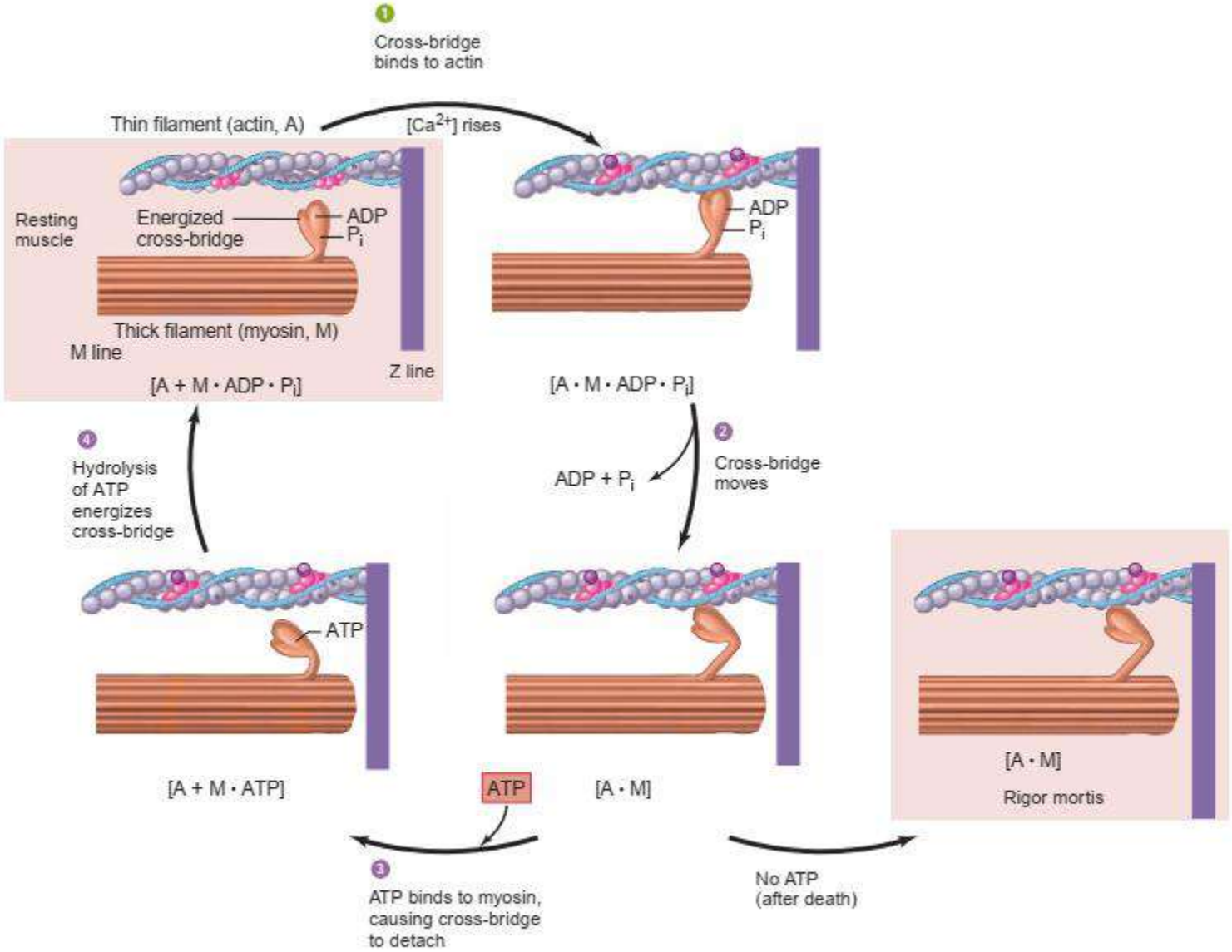


Figure 9.15 AP|R Chemical (shown in brackets) and mechanical representations of the four stages of a cross-bridge cycle. Cross-bridges remain in the resting state (pink box at left) when Ca^{21} remains low. In the rigor mortis state (pink box at right), cross-bridges remain rigidly bound when ATP is absent. In the chemical representation, A 5 actin, M 5 myosin, dots are between bound components, and plus signs are between detached components.

MECHANISM OF SKELETAL MUSCLE RELAXATION

- **A contraction is terminated by removal of Ca^{2+} from troponin C**, which is achieved by **lowering the Ca^{2+} concentration in the cytosol** back to its prerelease level.
- The membranes of the SR contain **Ca^{2+}-ATPases** that pump calcium ions from the cytosol back into the lumen of the SR.
- ATP is required to provide the energy for the Ca^{2+} pump.

Structural Proteins of Skeletal Muscle

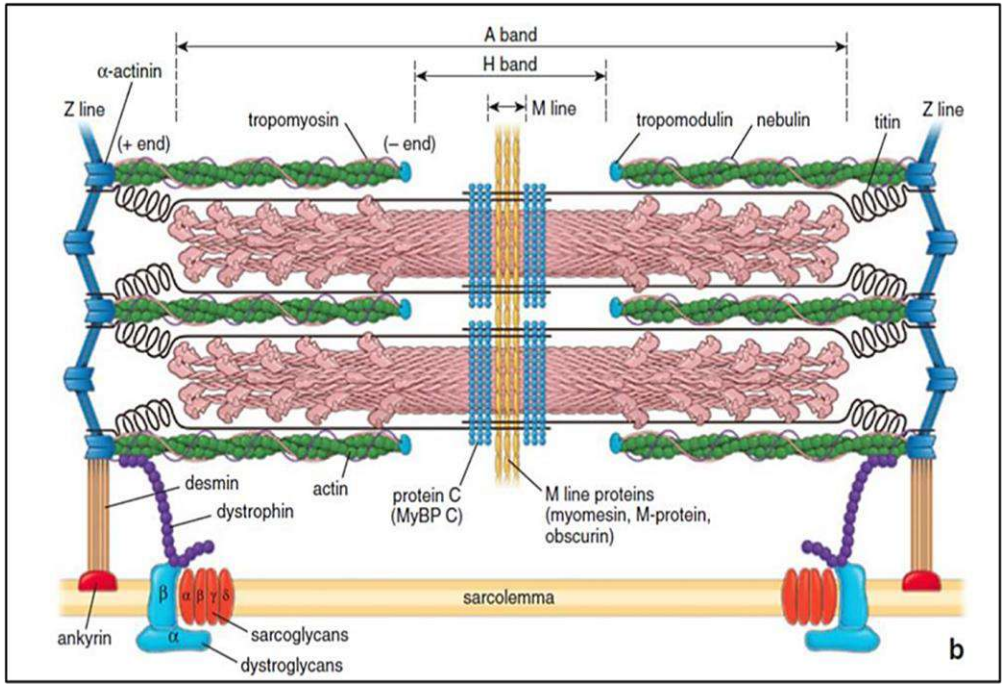
DYSTROPHIN–GLYCOPROTEIN COMPLEX

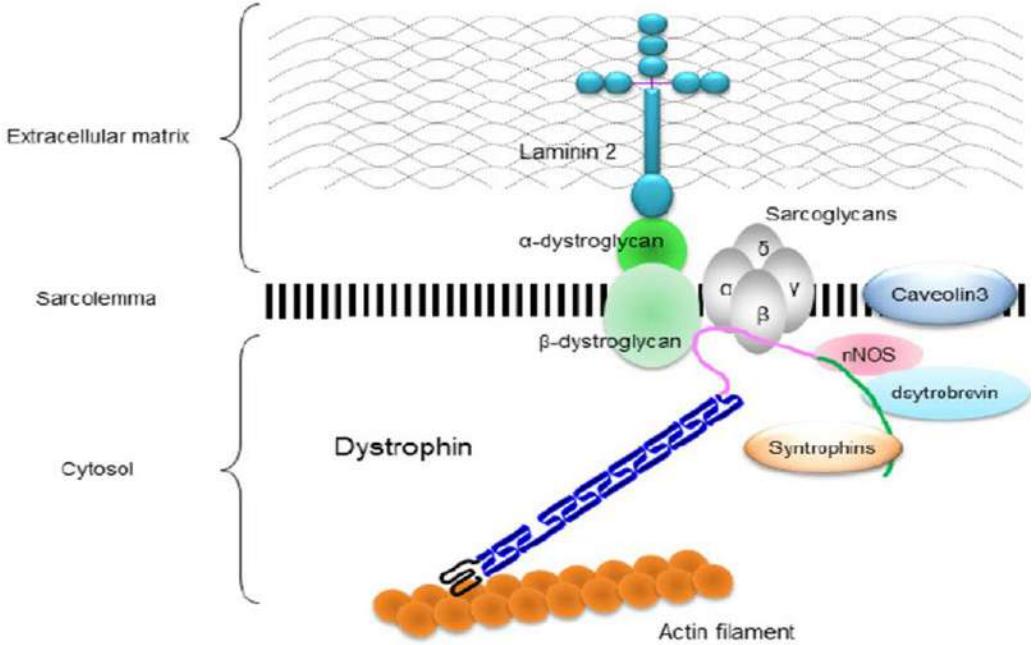
- The **dystrophin** protein forms a rod that connects the thin actin filaments to the transmembrane protein β-**dystroglycan** in the sarcolemma by smaller proteins in the cytoplasm, **syntrophins.**
- β-dystroglycan is connected to laminin 2 in the extracellular matrix by α-**dystroglycan**.
- The dystroglycans are in turn associated with a complex of four transmembrane glycoproteins: α-, β-, γ-, and δ-**sarcoglycans.**
- This **dystrophin–glycoprotein complex** adds strength to the muscle by providing a scaffolding for the fibrils and connecting them to the extracellular environment. Disruption of this tightly structure can lead to several different pathologies, or **muscular dystrophies**.

Titin

A structural protein that:

- Provides an elastic connection between the opposing ends of actin and myosin filaments (**connects Z line to M line**).
- Stabilizes the thick filament.
- Maintains the alignment of thick filaments in the middle of each sarcomere.


A band
H band
M line
α-actinin
Z line
(+ end)
tropomyosin
(– end)
tropomodulin
nebulin
titin
Z line
desmin
dystrophin
actin
protein C
(MyBP C)
M line proteins
(myomesin, M-protein,
obscurin)
sarcolemma
ankyrin
sarcoglycans
dystroglycans
b


Extracellular matrix
Laminin 2
Sarcoglycans
α-dystroglycan
Sarcolemma
Caveolin3
β-dystroglycan
nNOS
dsytrobrevin
Cytosol
Dystrophin
Syntrophins
Actin filament

Types of Skeletal Muscle Fibers

Three principal types of skeletal muscle fibers can be distinguished:

1. Slow-oxidative fibers (type I).

2. Fast-oxidative-glycolytic fibers (type IIA).

3. Fast-glycolytic fibers (type IIB).

	Type I	Type IIB
Other names	Slow – Oxidative (SO)	Fast – Glycolytic (FG)
Myosin ATPase activity	Slow	Fast
Contraction Velocity	Slow	Fast
Sarcoplasmic Reticulum	Less extensive	More extensive for rapid release of calcium ions to initiate contraction.
Color	Red	Pale (white)
Myoglobin content	High	Low
Primary source of ATP Production	Oxidative Phosphorylation	Glycolysis
Glycolytic Capacity	Low	High
Glycogen content	Low	High
Examples	Muscles of the back and leg	Extraocular and hand muscles
Rate of Fatigue	Slow (Resistant to fatigue)	Fast (Fatigue rapidly)
Fiber diameter	Small	Large

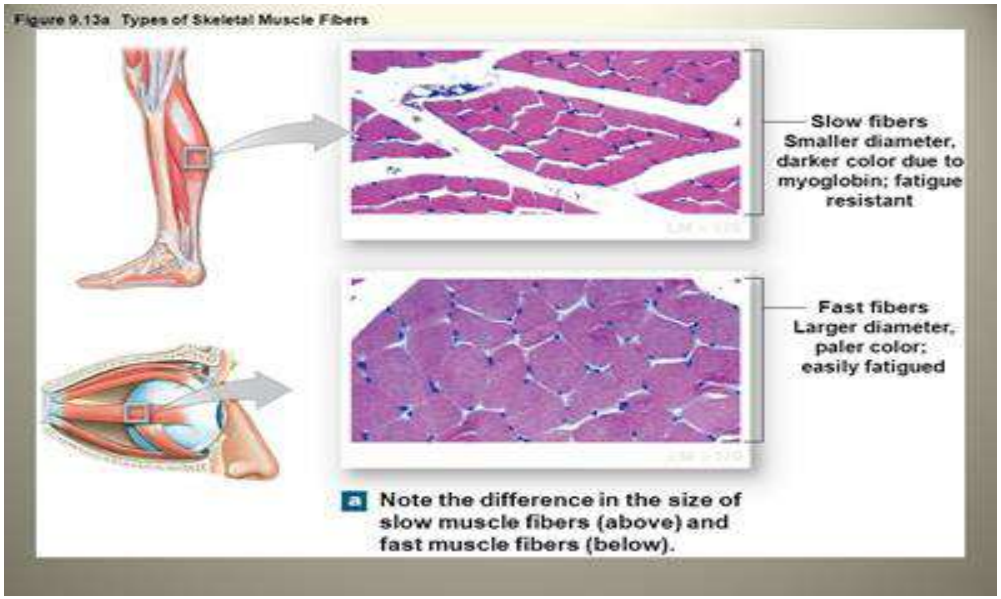
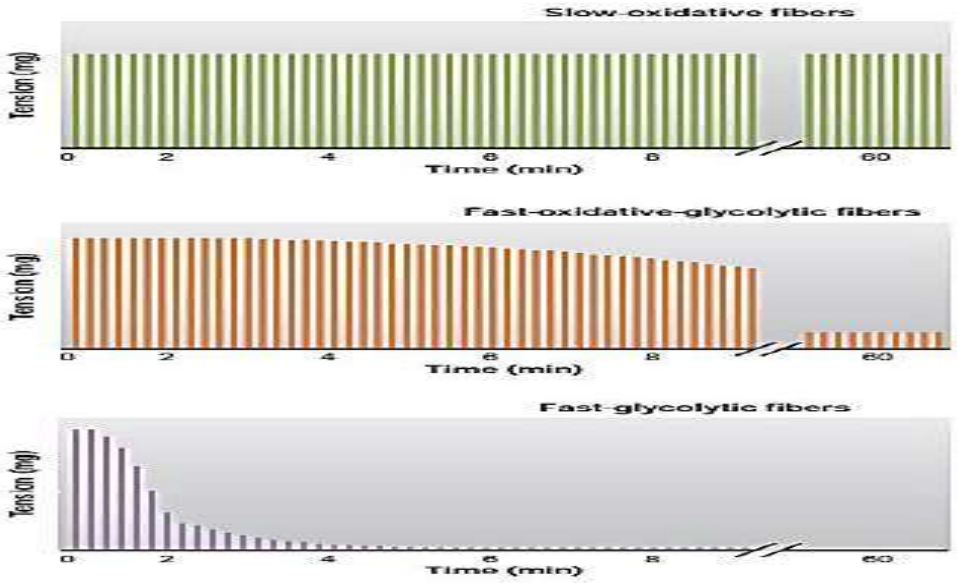


Figure 9.13a Types of Skeletal Muscle Fibers
Slow fibers
Smaller diameter, darker color due to myoglobin; fatigue resistant
Fast fibers
Larger diameter, paler color; easily fatigued
a Note the difference in the size of slow muscle fibers (above) and fast muscle fibers (below).


Slow-oxidative fibers
Tension (mg)
0
2
4
6
8
60
Time (min)
Fast-oxidative-glycolytic fibers
Tension (mg)
0
2
4
6
8
60
Time (min)
Fast-glycolytic fibers
Tension (mg)
0
2
4
6
8
60
Time (min)

MOTOR UNIT

The axons of motor neurons (or somatic efferent neurons) are myelinated and are the largest-diameter axons in the body.

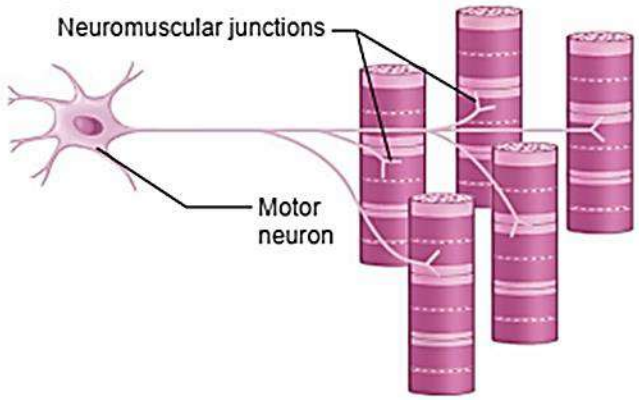
Upon reaching a muscle, the axon of a motor neuron divides into many branches, each branch forming a single junction with a muscle fiber (NMJ).

A single motor neuron innervates many muscle fibers.

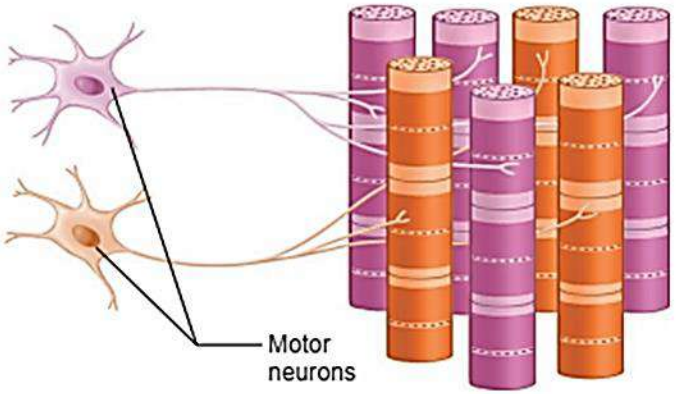
A motor unit :

- **Each single motor neuron and the muscle fibers it innervates constitute a motor unit.**
- **The number of muscle fibers in a motor unit varies.**
- **In muscles such as those of the hand and those concerned with motion of the eye (ie, muscles concerned with fine, graded, precise movement), each motor unit innervates very few (on the order of three to six) muscle fibers.**
- **On the other hand, values of 600 muscle fibers per motor unit can occur in human leg muscles.**
- **The group of muscle fibers that contribute to a motor unit can be intermixed within a muscle.**
- **Each spinal motor neuron innervates only one kind of muscle fiber, so that all the muscle fibers in a motor unit are of the same type.**

(a) Single motor unit



(b) Two motor units



Thank You