BCH 450
Biochemistry of Specialized Tissues

V. Muscle Tissues

Nomenclature

- **Sarcolemma = plasma membrane**
- **Sarcoplasmic reticulum = endoplasmic reticulum**
- **Muscle fiber = cell**
- **Myofibril = subcellular fibers**
- **Sarcomere = functional unit of myofibril**

Overview of Muscle tissue

There are three types of muscle tissue:

- Skeletal muscle
- Cardiac muscle
- Smooth muscle

These muscle tissues differ in the:

- Structure of their cells
- Their body location
- Their function
- Means by which they are activated to contract

- **Skeletal Muscles:**

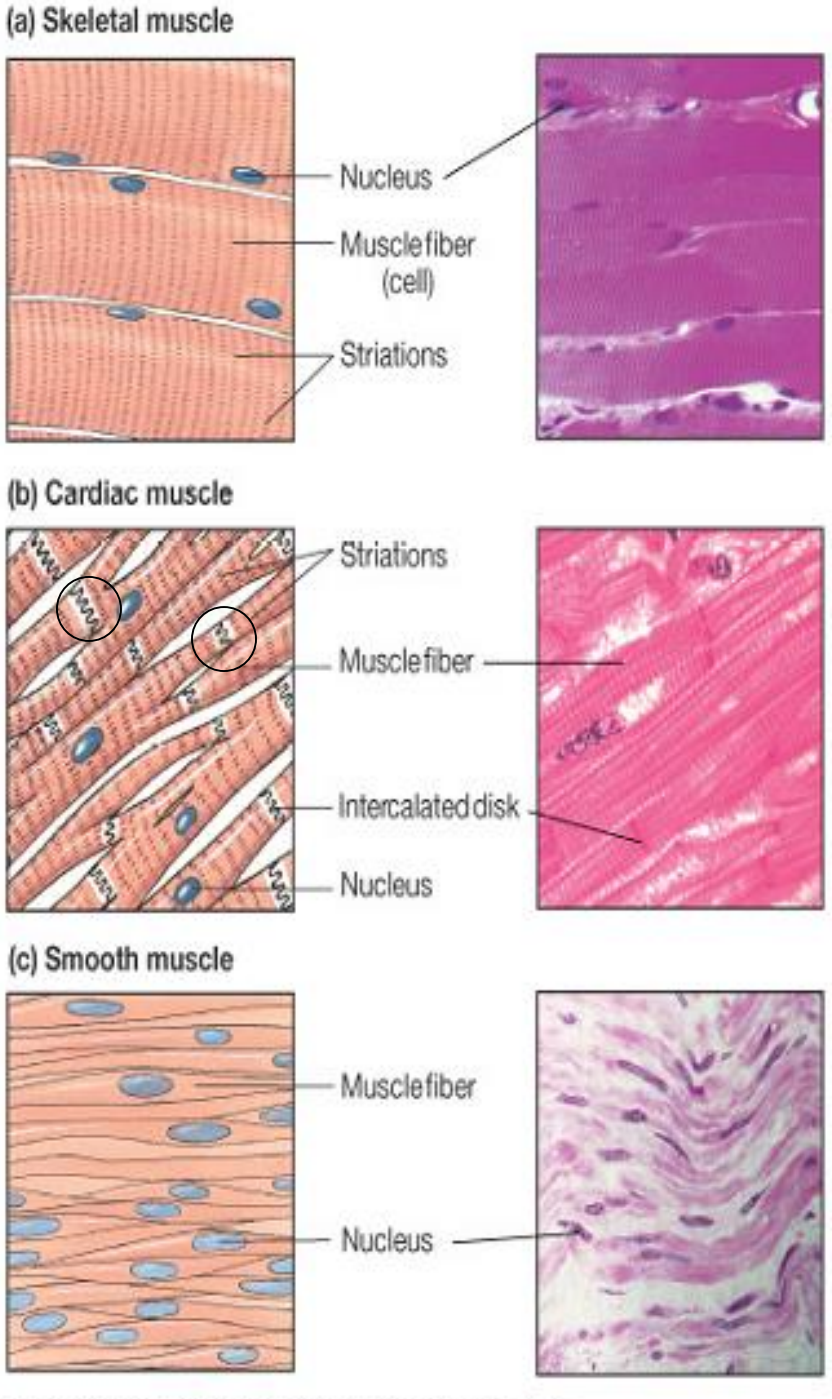
  Long multinucleated cells that respond only to motor-nerve signals, which cause Ca^{+2} release from sarcoplasmic reticulum and activation of actin-myosin interaction.

- **Cardiac Muscles:**

  Shorter mononucleated cells linked to each other by *intercalated disks* that contain many gap junctions. Capable of independent, spontaneous contraction, with electrical depolarization transmitted from cell to cell through gap junctions.

- **Smooth Muscles:**

  Spindle-shaped mononucleated cells. Contraction influenced by hormones and autonomic nerves. Contraction governed through myosin light chain kinase.



- **Skeletal muscle:** usually generates force on tendons and bones *(Work=Force x Distance)*. Motor-nerve action potentials trigger contraction of muscle cells; signal not transmitted between muscle cells. Isotonic (constant force) and isometric (constant length) contractions. Strength and rate of contraction regulated by number of muscle cells stimulated and by rate of neural stimuli.

- **Cardiac muscle:** regular contraction (systole) and relaxation (diastole), involving self-generated action potential of long duration, transmitted from cell to cell through gap junctions, but most contract after receiving electrical signal from neighboring cell. Generates pressure to move volume of liquid — *Work = Pressure x Volume*. Strength and rate of contraction regulated by hormones and autonomic nerves.

- **Smooth muscle:** generally surround hollow organs (*Work = Pressure x Volume*). Mechanisms of stimulation and contraction variable, but all regulated through myosin light chain (by *myosin light chain kinase*).

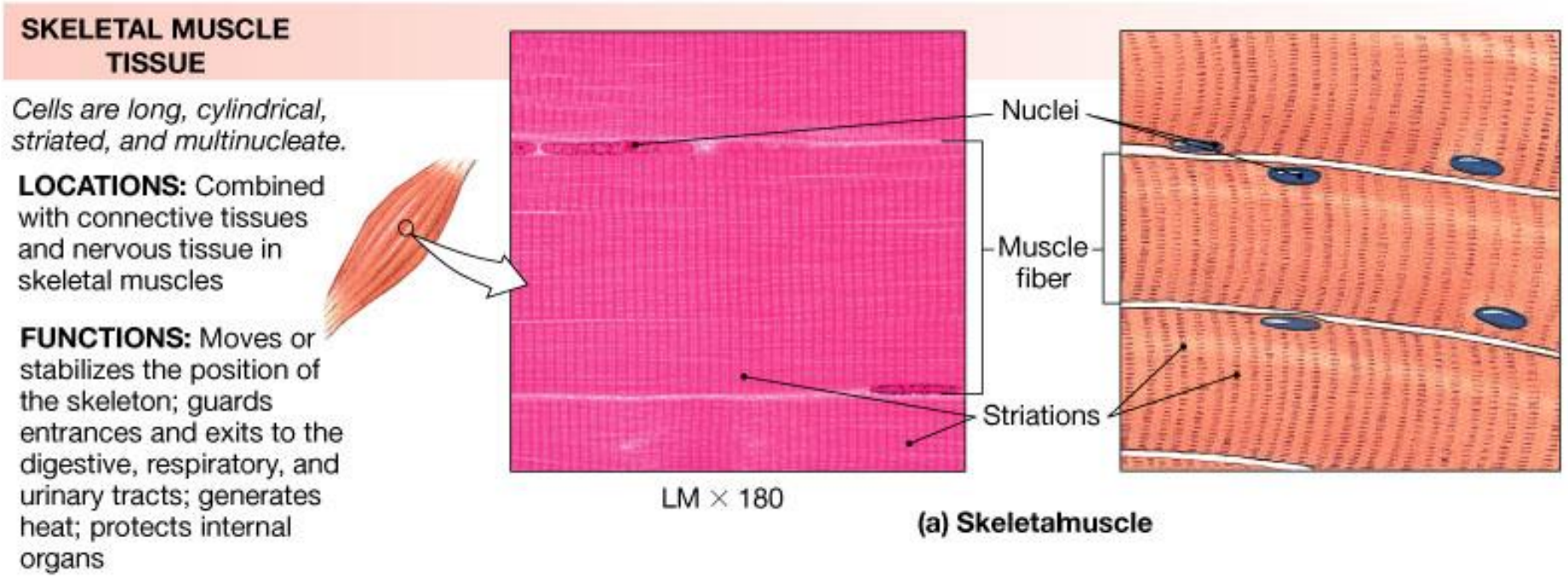
Overview of Muscle tissue

All skeletal and smooth muscle cells are elongated and are referred to as muscle fibers

- Muscle contraction depends on two types of myofilaments:
  - –Actin
  - –Myosin

Muscle Tissue
Skeletal Muscle Tissue

Attached to skeletal system
It has obvious striations
It is voluntary muscle under conscious control

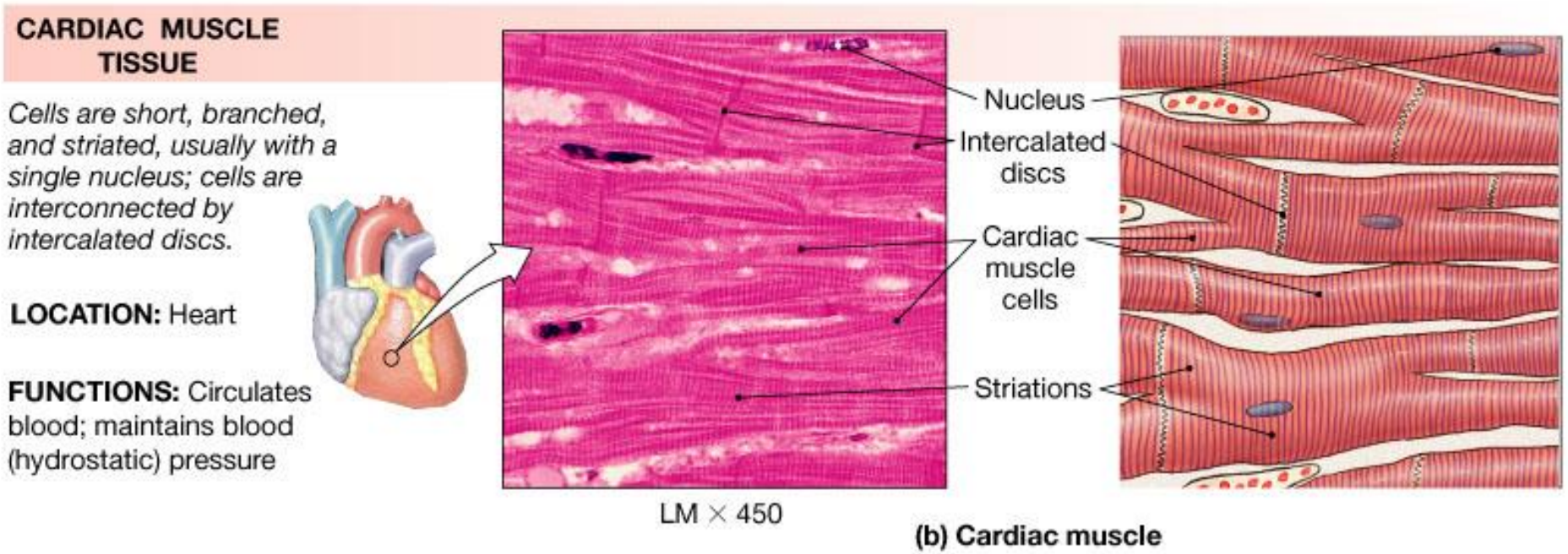


Muscle Tissue
Cardiac Muscles

It exists only in heart. It is striated but involuntary

Cardiac fibers are short, fat, branched and interconnected

They are interlocked by intercalated discs and function as a single unit

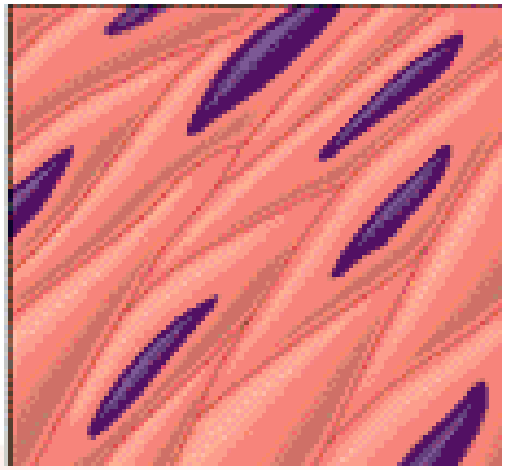


Muscle Tissue
Smooth muscles

It is found in the walls of hollow organs such as stomach, bladder and intestines

It has no striations

It is not subject to voluntary control

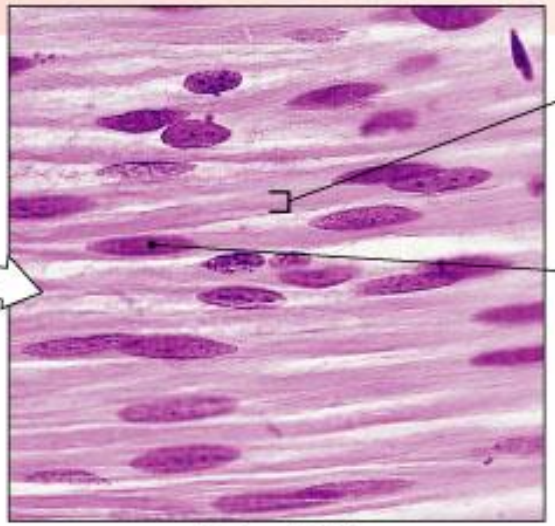


SMOOTH MUSCLE TISSUE

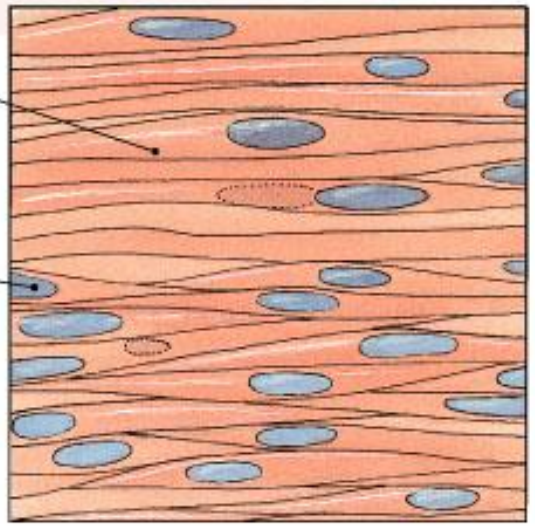
Cells are short, spindle-shaped, and nonstriated, with a single, central nucleus

LOCATIONS: Encircles blood vessels; found in the walls of digestive, respiratory, urinary, and reproductive organs

FUNCTIONS: Moves food, urine, and reproductive tract secretions; controls diameter of respiratory passageways; regulates diameter of blood vessels



LM × 235



(c) Smooth muscle

Differences in contractions

- Skeletal muscle can contract rapidly but tire easily and must be rested and the contractions vary in force depending on use.

- Cardiac muscle contracts at a steady rate but can accelerate to cope with demand.

- Smooth muscles contracts in steady, sustained contractions and continues on tirelessly.

Muscle functions

- Muscles performs four important functions in the body:

  -Producing movement

  -Maintaining posture

  -Stabilizing joints

  -Generating heat

Muscle functions
1- Producing movement

- Movement results from skeletal muscle contraction
- Skeletal muscle are responsible for all locomotion and manipulation
- Allows you to interact or react with your external environment

Muscle functions
2- Maintaining Posture

- Skeletal muscles are utilized constantly to maintain sitting, standing, and moving postures.

- Postural muscle develop to compensate for the never ending pull of gravity

  -Our developmental milestones as an infant are our initial victories over gravity.

  -Curves of the spinal column are shaped by the interplay of skeletal muscle and gravity

Muscle functions
3- Stabilizing Joints

- Skeletal muscle provide the dynamic stability of joints
- Many joints are poorly reinforced by ligaments and connective tissue
- Many joints have noncomplementary surface which do not contribute to stability.

Muscle functions
4- Generating Heat

- Muscles generate heat as they contract
- The heat generated is vitally important to maintain normal body temperature
- Skeletal muscle generates most of the heat because it represents 40% of body mass
- Excess heat must be released to maintain body temperature

Functional Characteristics of Muscles

- Excitability or irritability
  - -It has the ability to respond to a stimulus
- -Contractility
  - -It has the ability to shorten forcibly
- -Extensibility
  - - Muscle fibers can be stretched
- -Elasticity
  - -Resume its normal length after being shortened or elongated
  - ***-i.e. It can contract, stretch (extensible), shortened (elastic) and respond to stimuli***

Anatomy of Skeletal Muscle

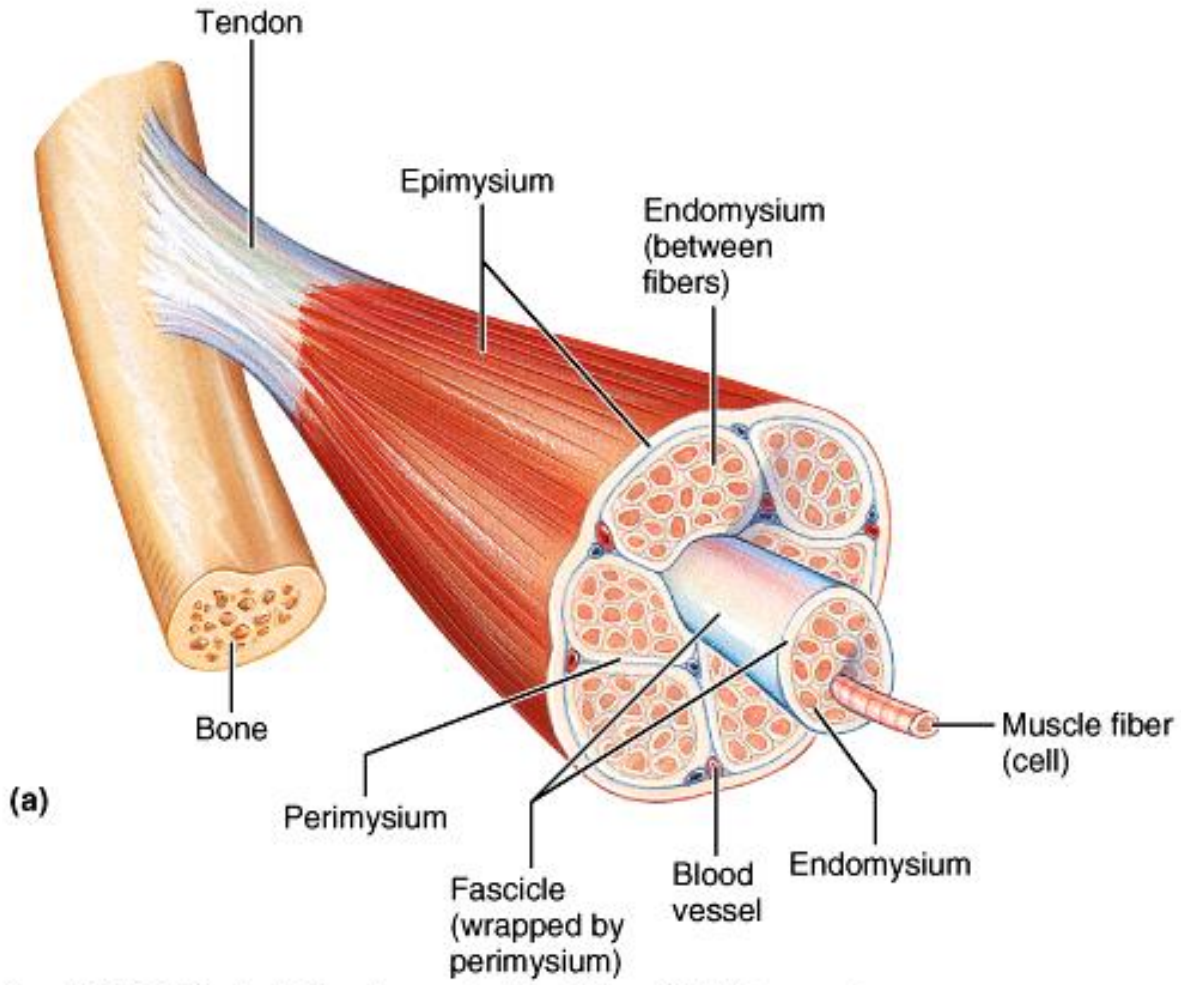
- Each skeletal muscle is a discrete organ with thousands of fibers
- Muscle Tissue contains:

  a- muscle fibers

  b- connective tissue

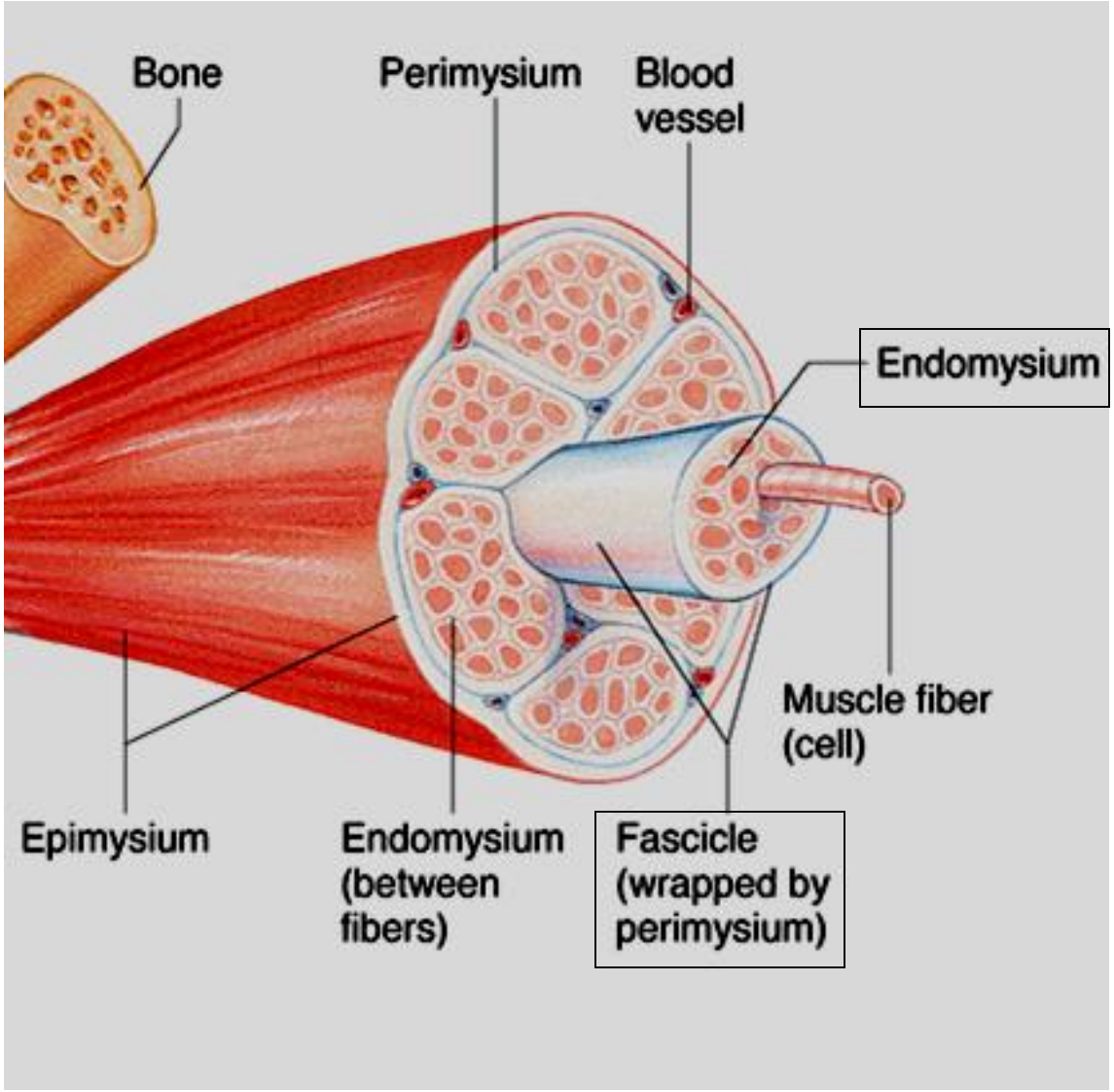
  c- nerve fibers

  d-blood vessels



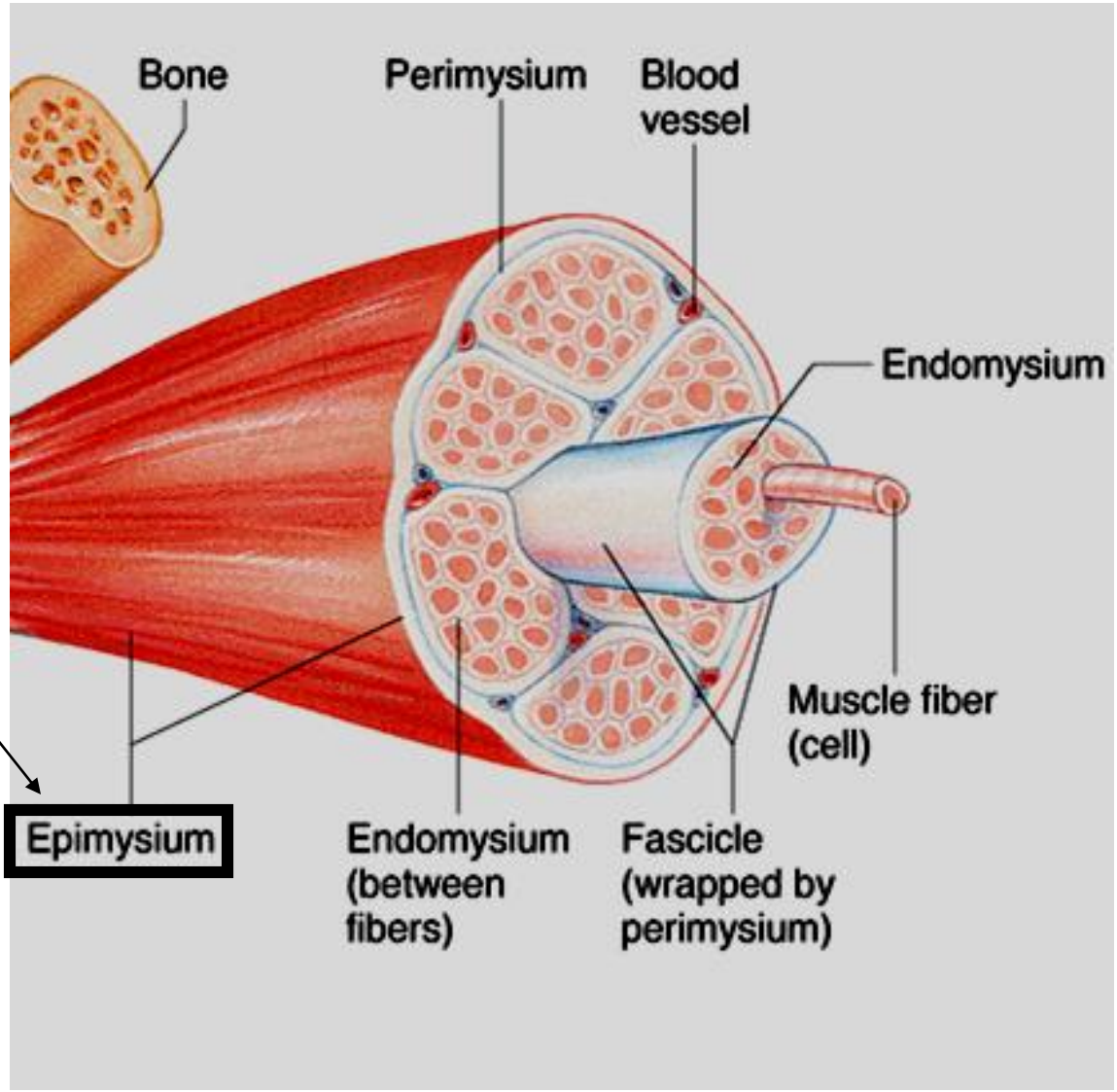
Connective Tissue Wrappings

- Each muscle fiber is wrapped by fine sheath of areolar connective called endomysium
- Several fibers are gathered side by side into bundles called fascicles
- Each fascicle is bound by collagen a fiber layer called the perimysium



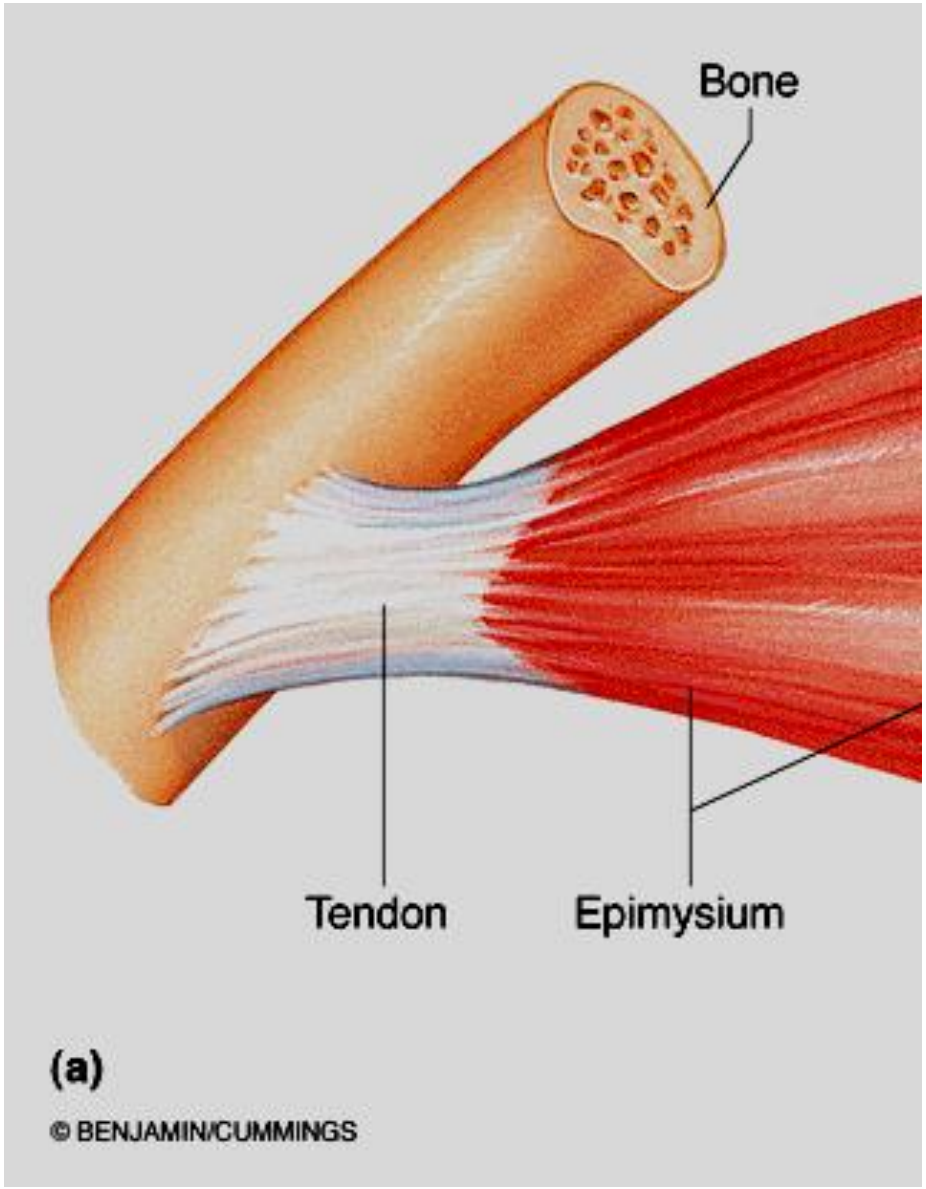
Connective Tissue Wrappings

- Fascicles are bound by a dense fibrous connective tissue layer called the epimysium
- The epimysium surrounds the entire muscle
- External to the epimysium is the deep fascia that binds muscles into functional groups



Connective Tissue Wrappings

- All the connective tissue layers are connected with one another as well as to the tendons that join muscles to bone
- When muscle fibers contract they pull these connective tissue sheaths which in turn transmit the force to the bone to be moved
- Connective tissues supports each cell



Nerve and Blood Supply

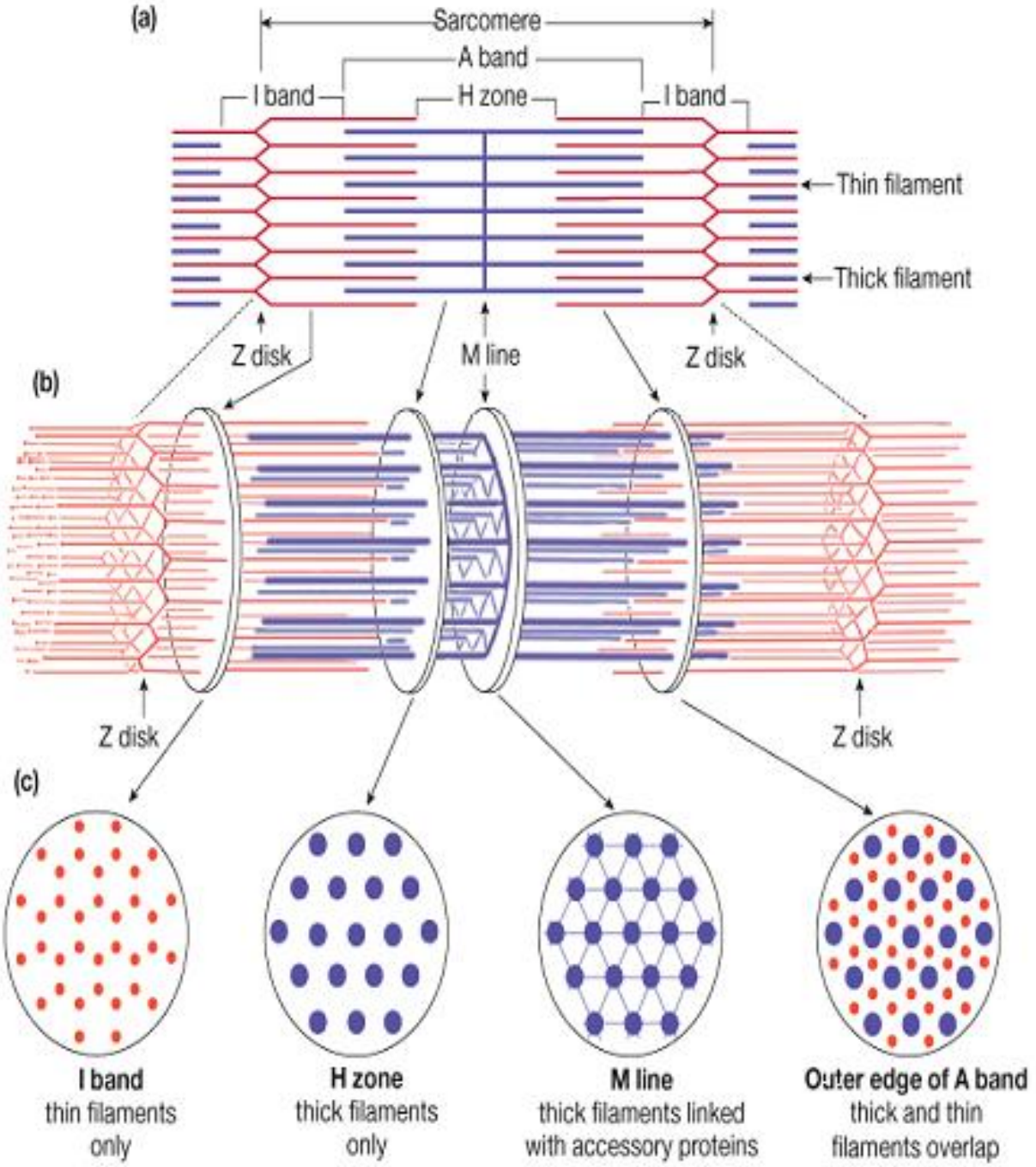
- Normal activity of skeletal muscle is totally dependent on its nerve and blood supply
- Each skeletal muscle fiber is controlled by a nerve ending (neuromuscular junction)
- Contracting muscle fibers use huge amounts of energy which requires a continuous supply of oxygen and nutrients transmitted by blood
- In general, each muscle is served by an artery and one or more veins

Myofibrils: Site of Contraction

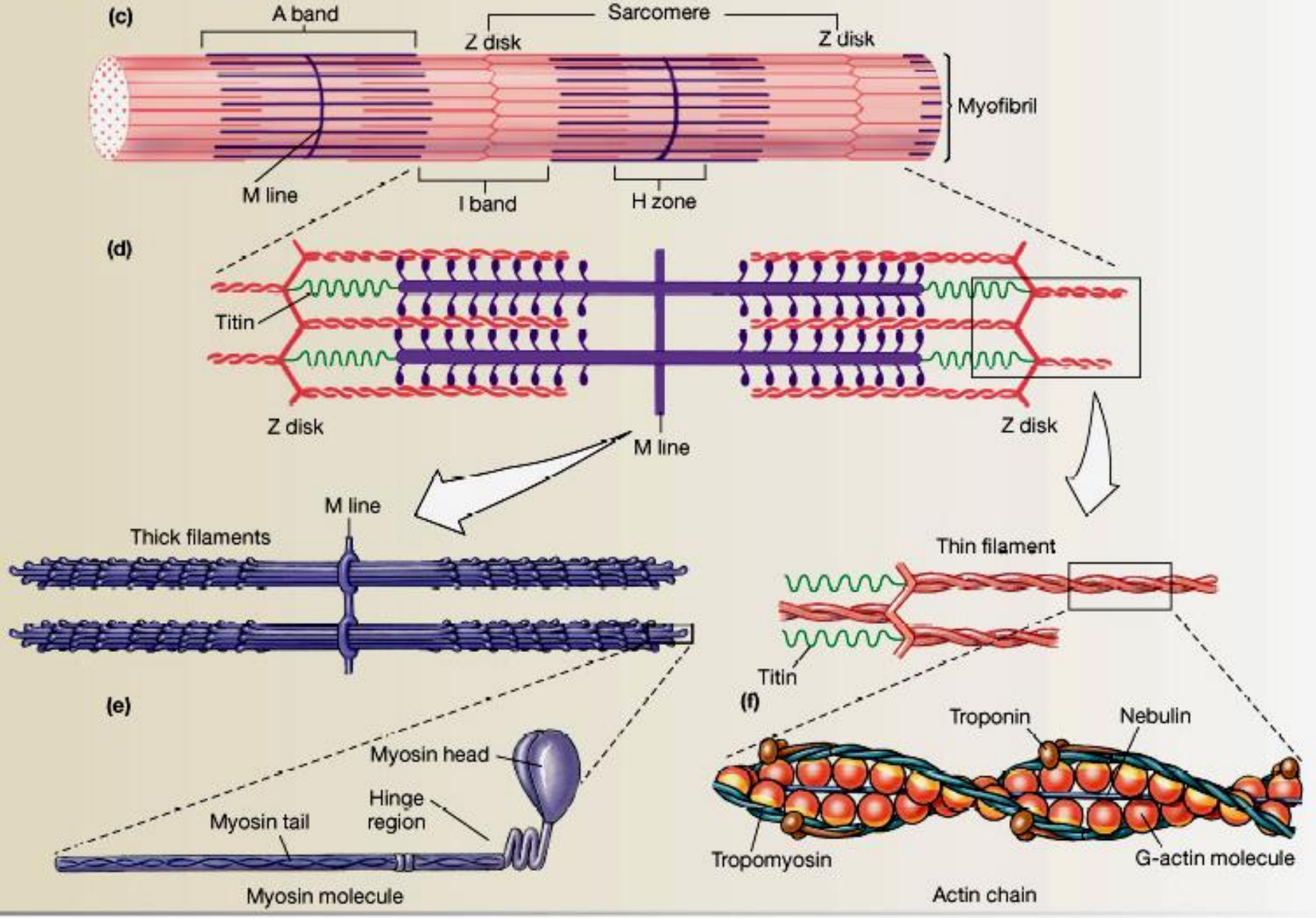
- **Actin – "thin fibers"**
- **Tropomyosin**
- **Troponin**
- **Myosin – "thick fibers"**
- **Tinin – “elastic fibers”**
- **Nebulin – “non-elastic fiber”**

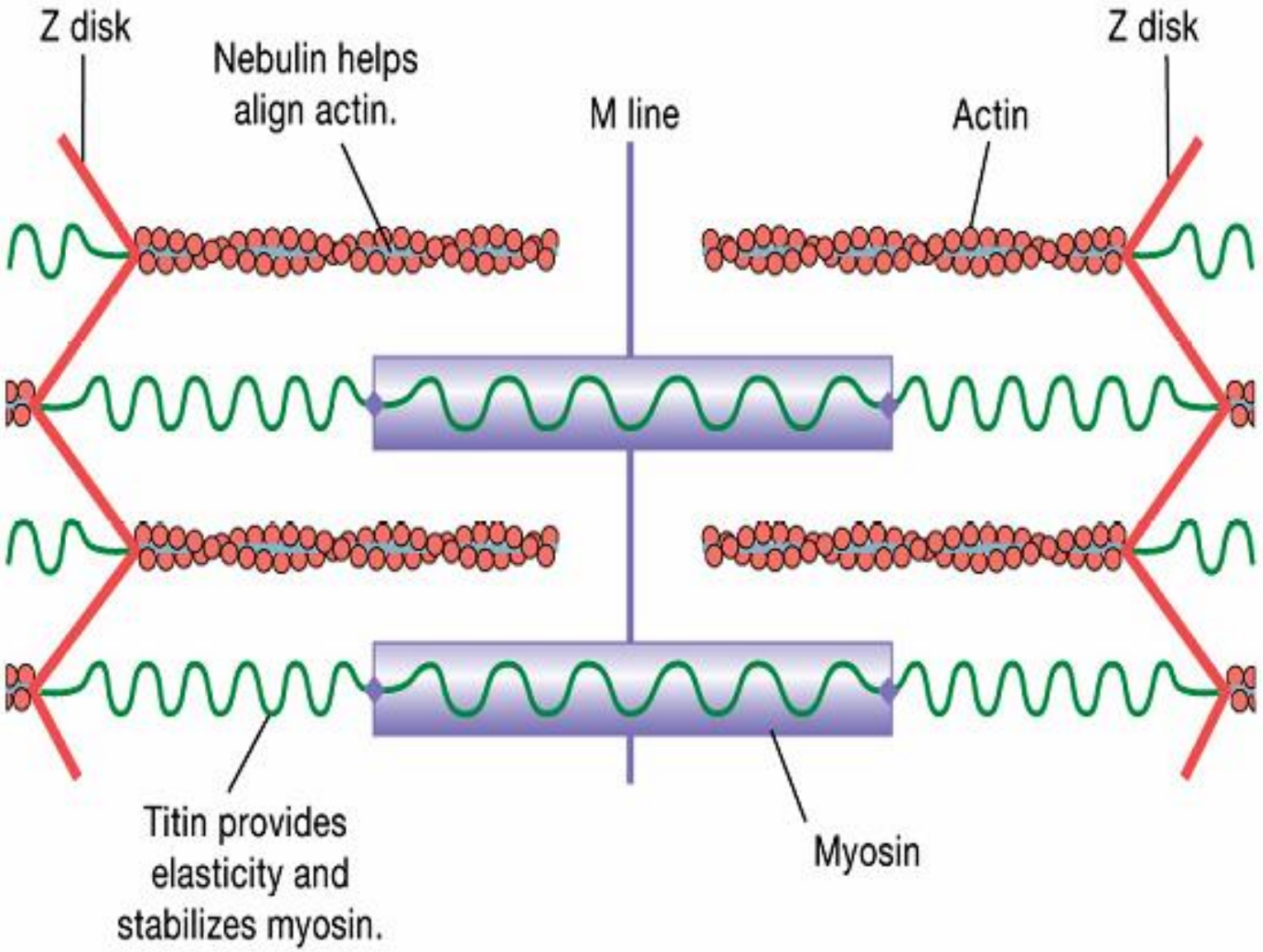
Muscle Zones

- Actin filaments slide over myosin filaments
- Z lines pulled towards center
- I band shortens
- A band length doesn't change
- Neither filament changes in length
- H zone disappears

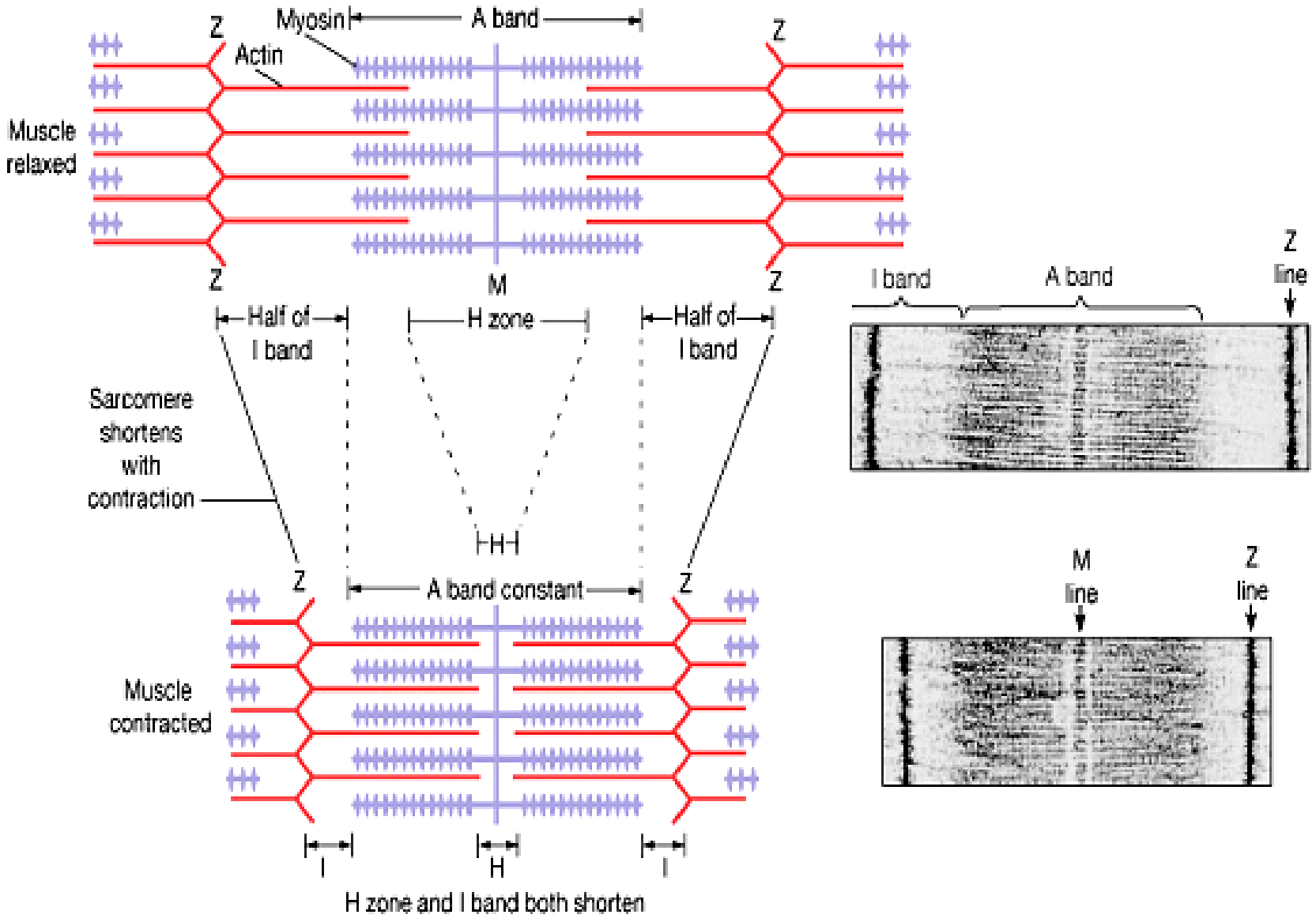


ULTRASTRUCTURE OF MUSCLE FIBER





Sliding Filament Theory of Muscle Contraction



Attachments

- **Most muscles span joints and have at least two attachments (an origin and an insertion)**
  - **Origin**
    - Attachment of a muscle that remains relatively fixed during muscular contraction
    - Generally a more proximal or axial location
  - **Insertion**
    - Attachment of a muscle that moves during muscular contraction
    - Generally a more distal or appendicular attachment

Contraction of Skeletal Muscle

- The principles of contraction of a muscle cell can be generalized to the entire muscle
- The force exerted is called tension, the resistance to the force is called the load
- A contracting muscle does not always shorten (isometric or isotonic)
- Skeletal muscle can contract with varying force for different periods of time which enhances its efficiency

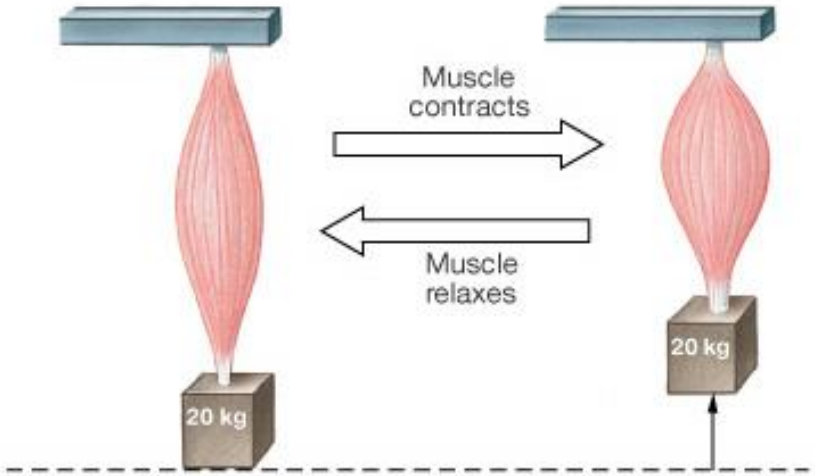
Types of Muscle contraction

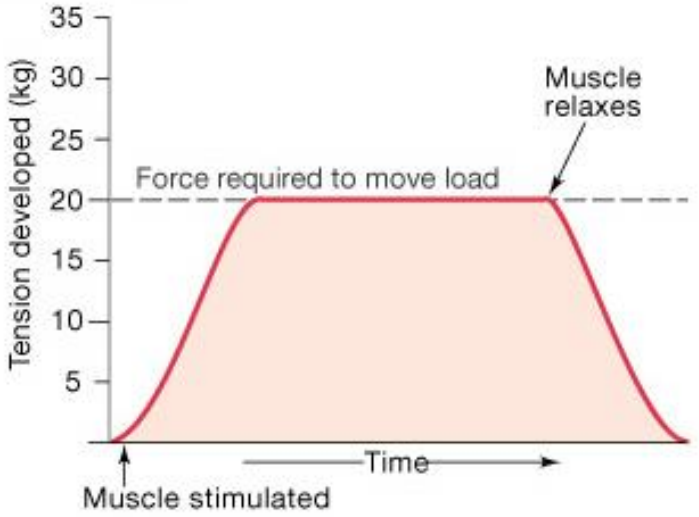
- **Isometric (mechanic)**
- Muscle exerts force without changing length.
  - eg. pulling against immovable object.
  - Postural muscles.

- **Isotonic (dynamic)**
  - Concentric (Muscle shortens during force production)
  - Eccentric (Muscle increase in length)

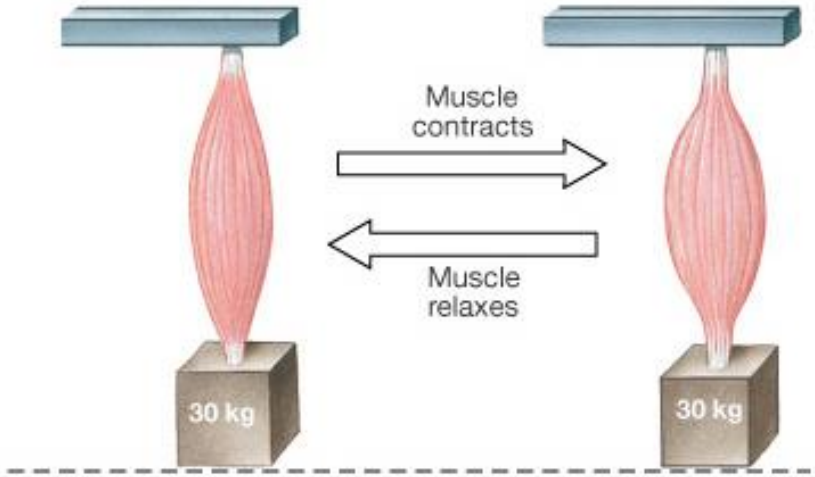
Mechanics of Body Movement: Joints

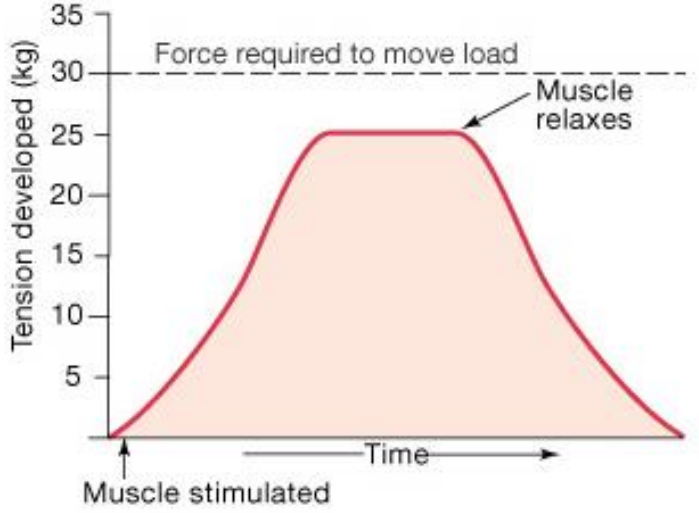
(a) Isotonic contraction: muscle contracts, shortens, and creates enough force to move the load.



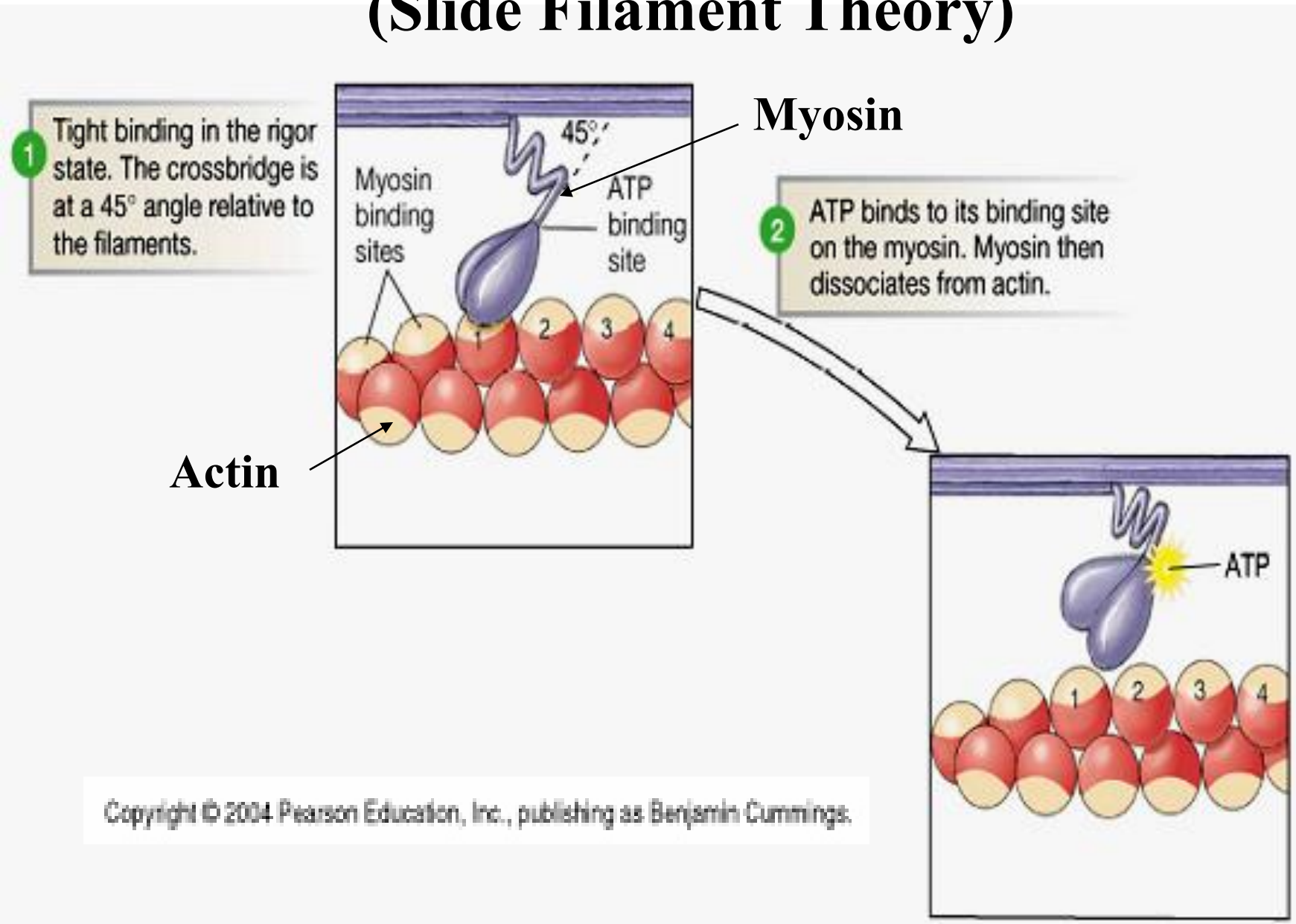


(b) Isometric contraction: muscle contracts but does not shorten. Force cannot move the load.

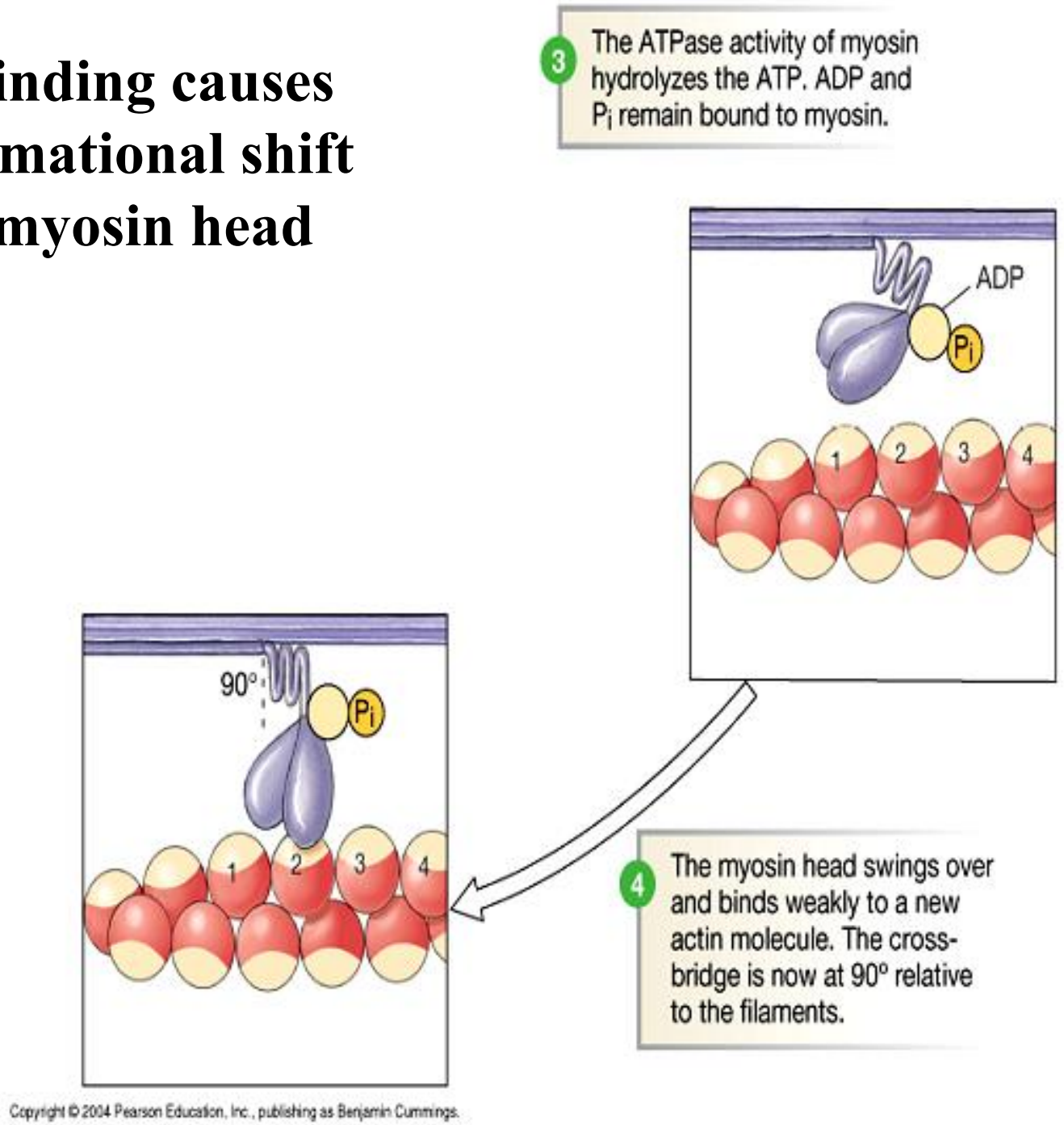




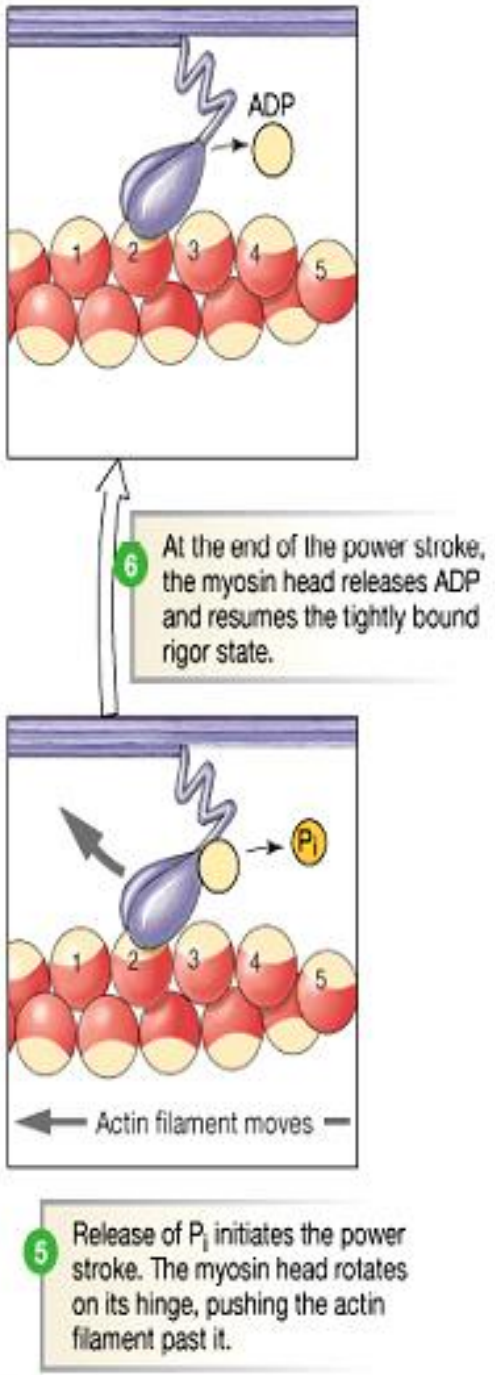
Mechanism of Cross-bridge Action (Slide Filament Theory)



ATP binding causes conformational shift in the myosin head



Binding of myosin to actin leads to release of Pi



Q: State the six steps of the Slide Filament Theory with more focus on the interaction between ATP, actin and myosin

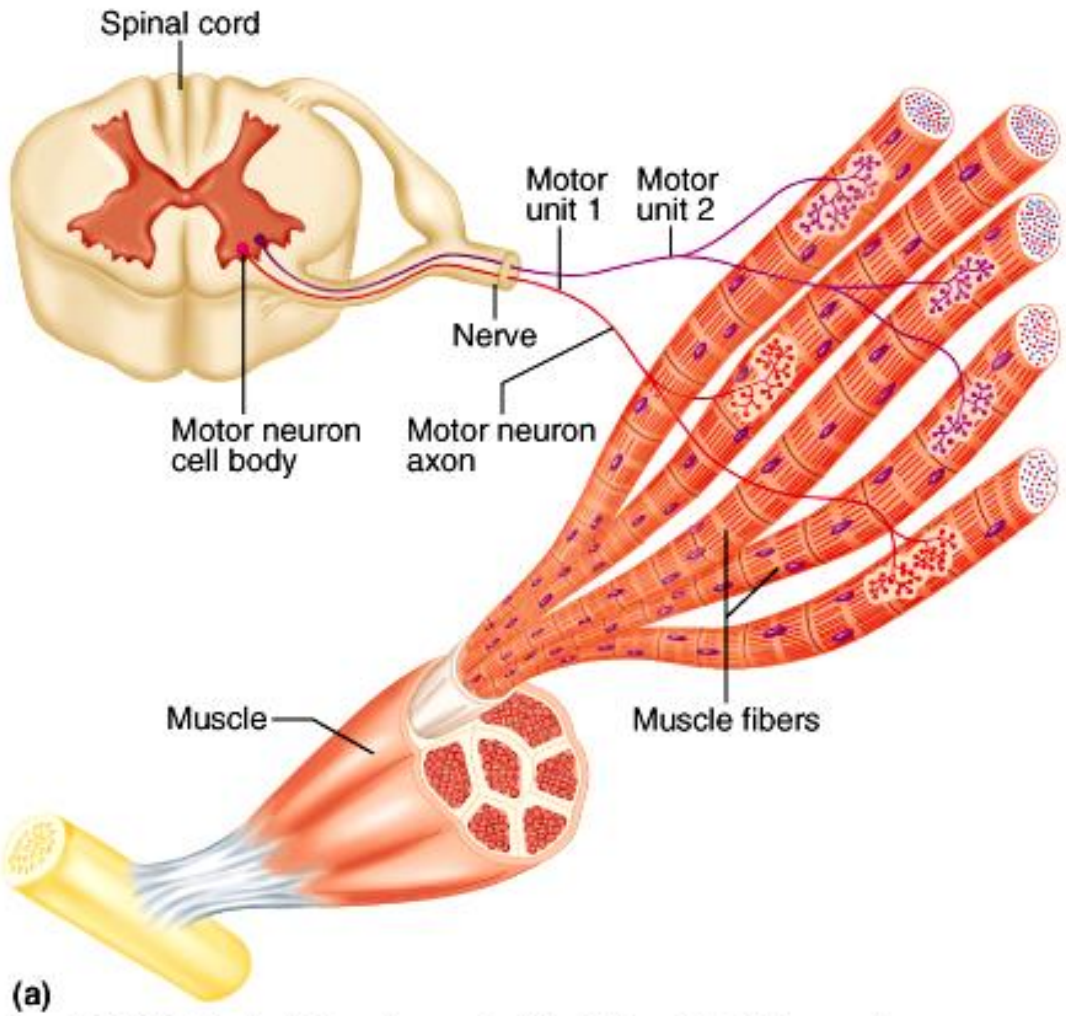
1. Tight binding in the rigor state, the cross-bridges is at 45° angel relative to the filament.
2. ATP binds to its site in myosin, then myosin dissociates from Actin
3. The ATPase activity hydrolyses ATP to ADP + Pi, which remain bound to myosin
4. The myosin head swings over and move to bind other actin molecule weakly at 90° angel relative to the filament
5. The release of Pi initiates the power stroke, the myosin head rotates over its hinge, pushing the actin filament past it
6. At the end of power stroke the ADP releases from myosin and myosin resumes the tightly bound rigor state.

The Motor Unit

- A Motor Unit is a neuron and all the muscle fibers it supplies
- Each muscle is served by at least one motor nerve which contains hundreds of motor neuron axons
- As a nerve enters a muscle it branches into a number of axonal terminals, each of which forms a neuromuscular junction with a single nerve fiber

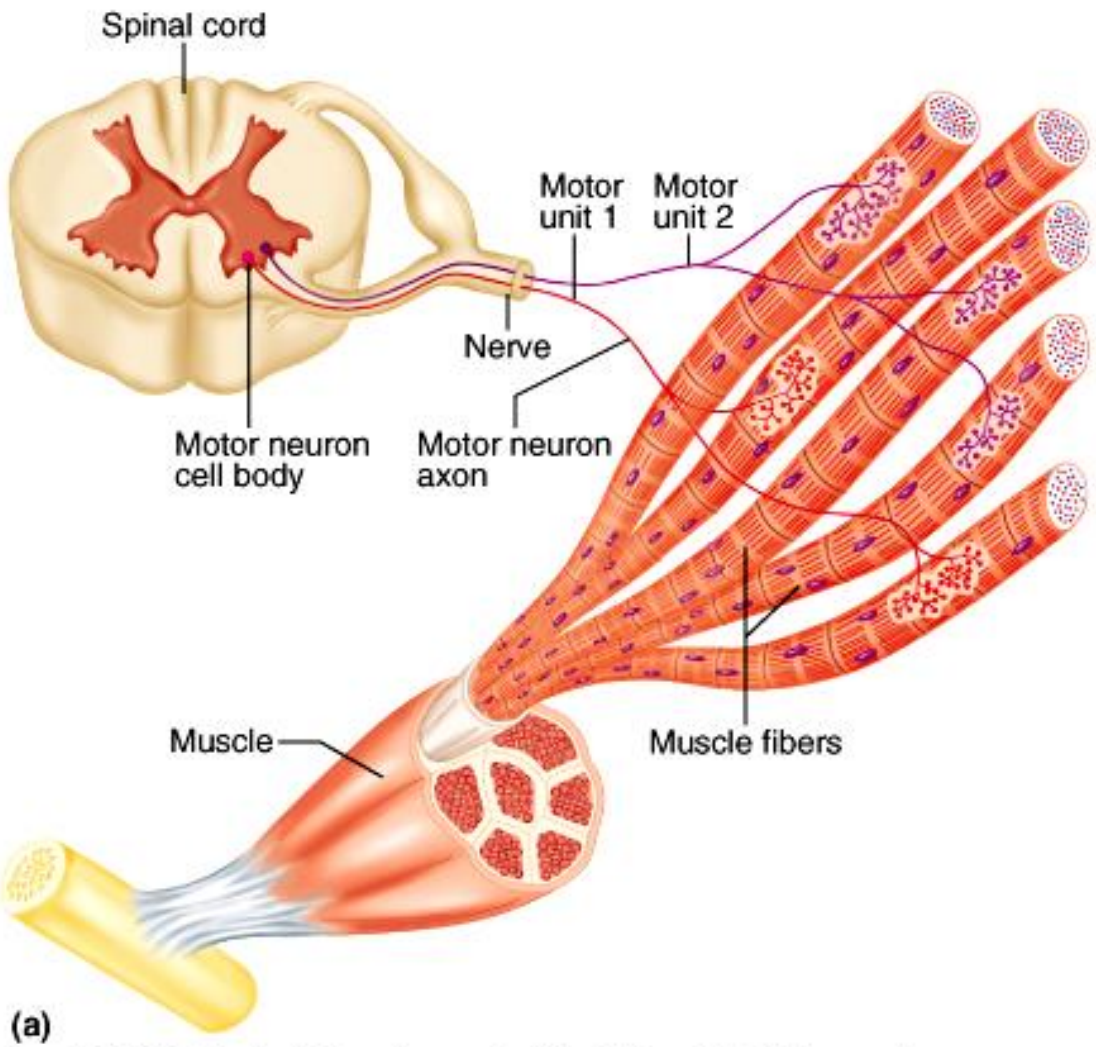
The Motor Unit

- When a motor neuron transmits an electrical impulse, all the muscle fibers that it innervates respond by contracting
- The average number of muscle fibers per unit is 150, but it ranges from 4 to several hundred



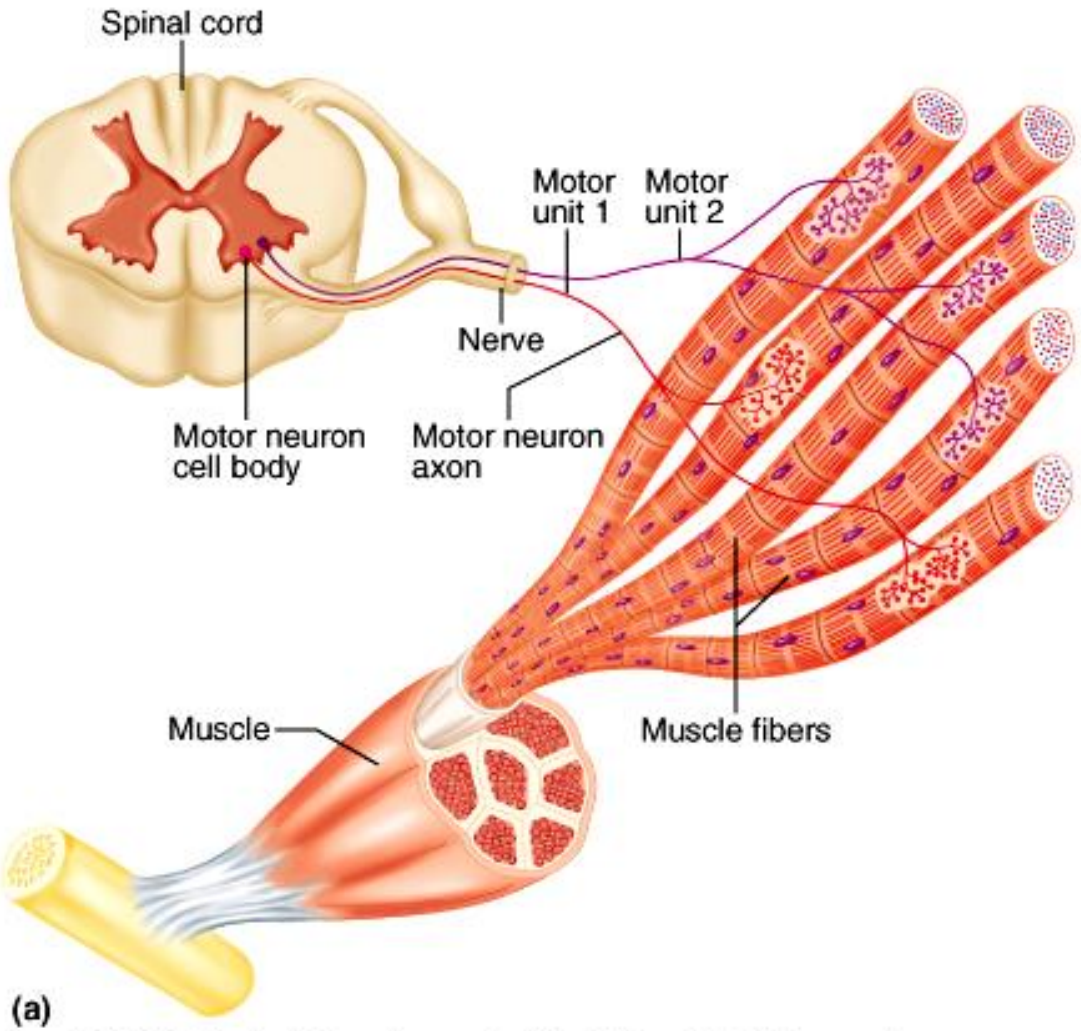
The Motor Unit

- Muscles that exert very fine control have small motor units (eyes, fingers)
- Large muscles of locomotion and weight bearing have large motor units and as a consequence have less precise control



The Motor Unit

- The muscle fibers in a unit are not clustered together but rather are spread throughout the entire muscle
- Stimulation of a single unit causes a weak contraction of the entire muscle
- This allows control of the intensity of the contraction



Skeletal Muscle Contraction: Mechanism

1- Somatic motor neuron releases Acetyl Choline (Ach) at neuromuscular junction.

2- Na^+ enters through ACh receptor-channel, leading to initiation of muscle action potential.

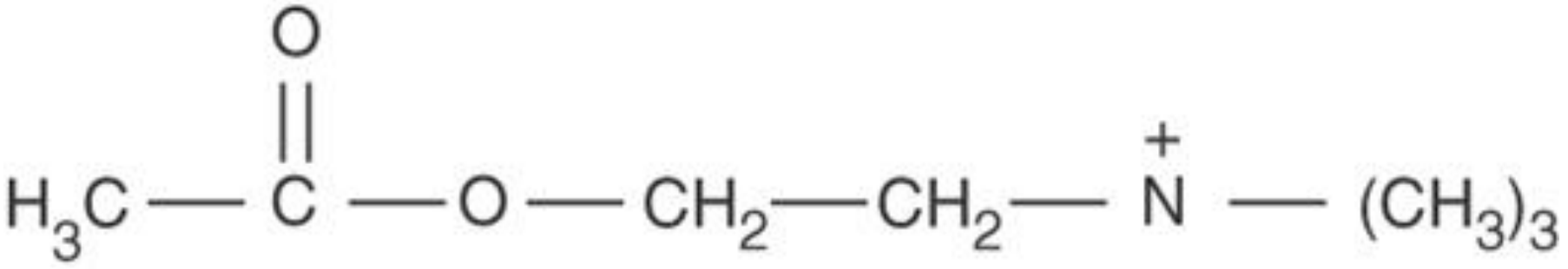
3-The action potential in t-tubules alters the conformation of dihydropyridine receptors (DHP receptors).

4- DHP receptors opens Ca^{2+} release channels in sarcoplasmic reticulum and Ca^{2+} enters cytoplasm.

5- Ca^{2+} binds to troponin, allowing strong actin-myosin binding

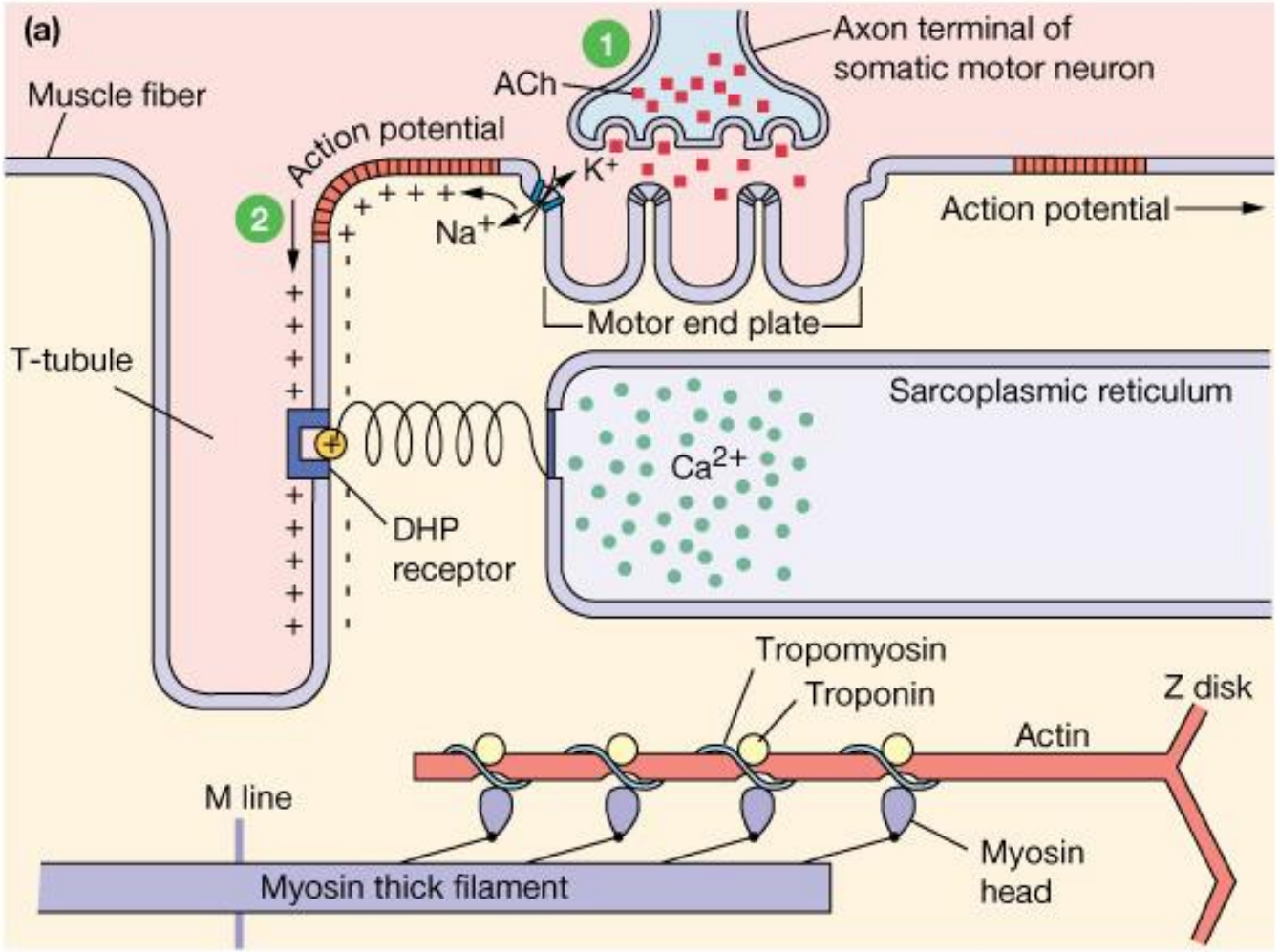
6- Myosin heads execute power stroke.

7- Actin filament slides toward center of sarcomere.



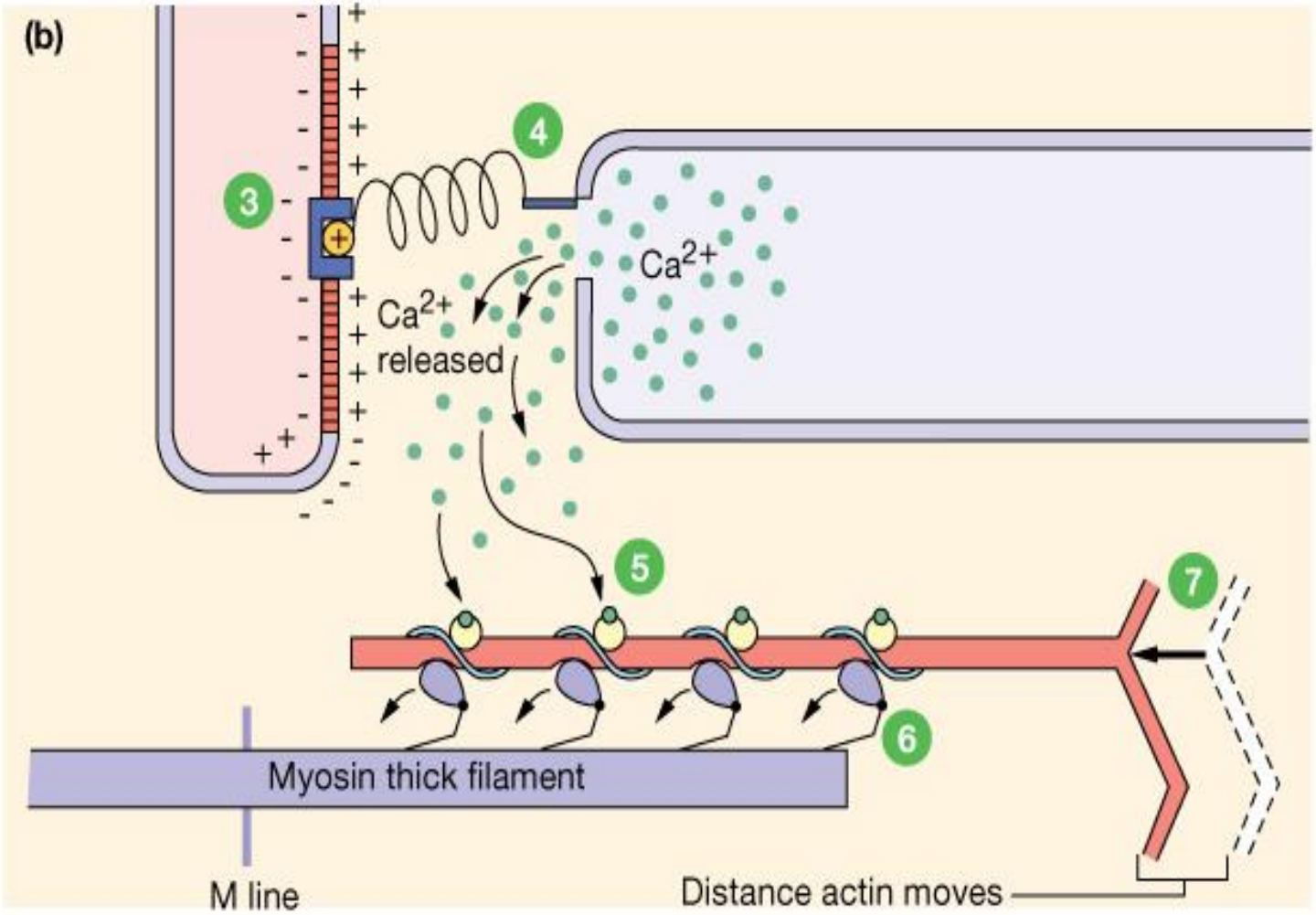
AcetylCholine (ACh)

Skeletal Muscle Contraction: Mechanism



1 Somatic motor neuron releases ACh at neuromuscular junction.

2 Net entry of Na^+ through ACh receptor-channel initiates a muscle action potential.



3 Action potential in t-tubule alters conformation of DHP receptor.

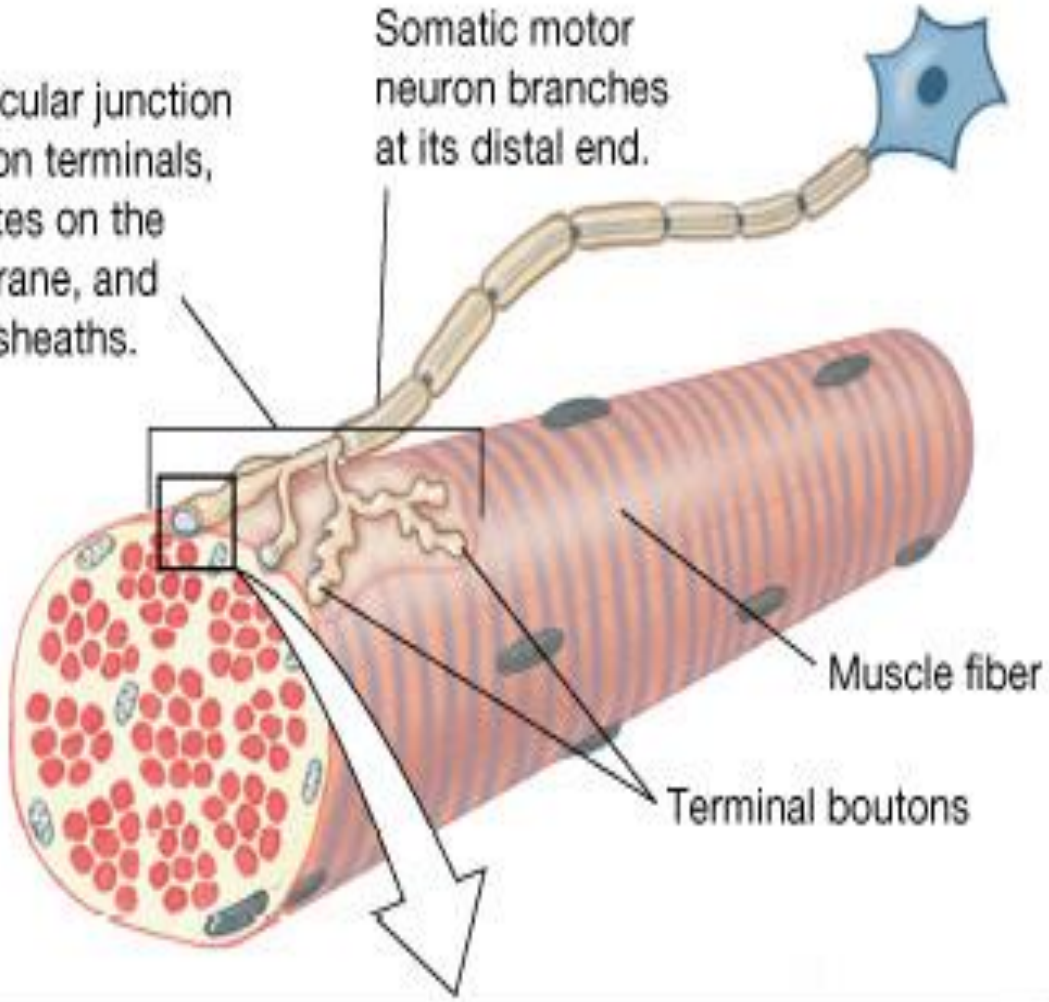
4 DHP receptor opens Ca^{2+} release channels in sarcoplasmic reticulum and Ca^{2+} enters cytoplasm.

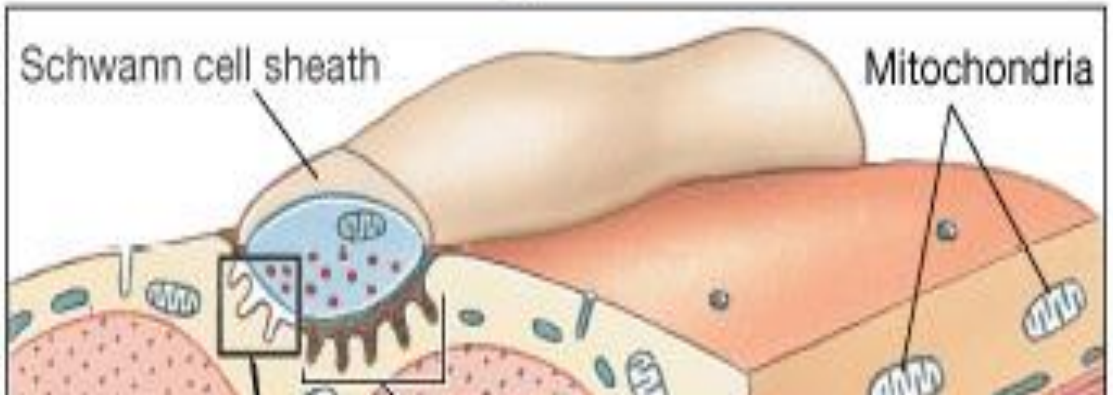
5 Ca^{2+} binds to troponin, allowing strong actin-myosin binding.

6 Myosin heads execute power stroke.

7 Actin filament slides toward center of sarcomere.

The neuromuscular junction consists of axon terminals, motor end plates on the muscle membrane, and Schwann cell sheaths.





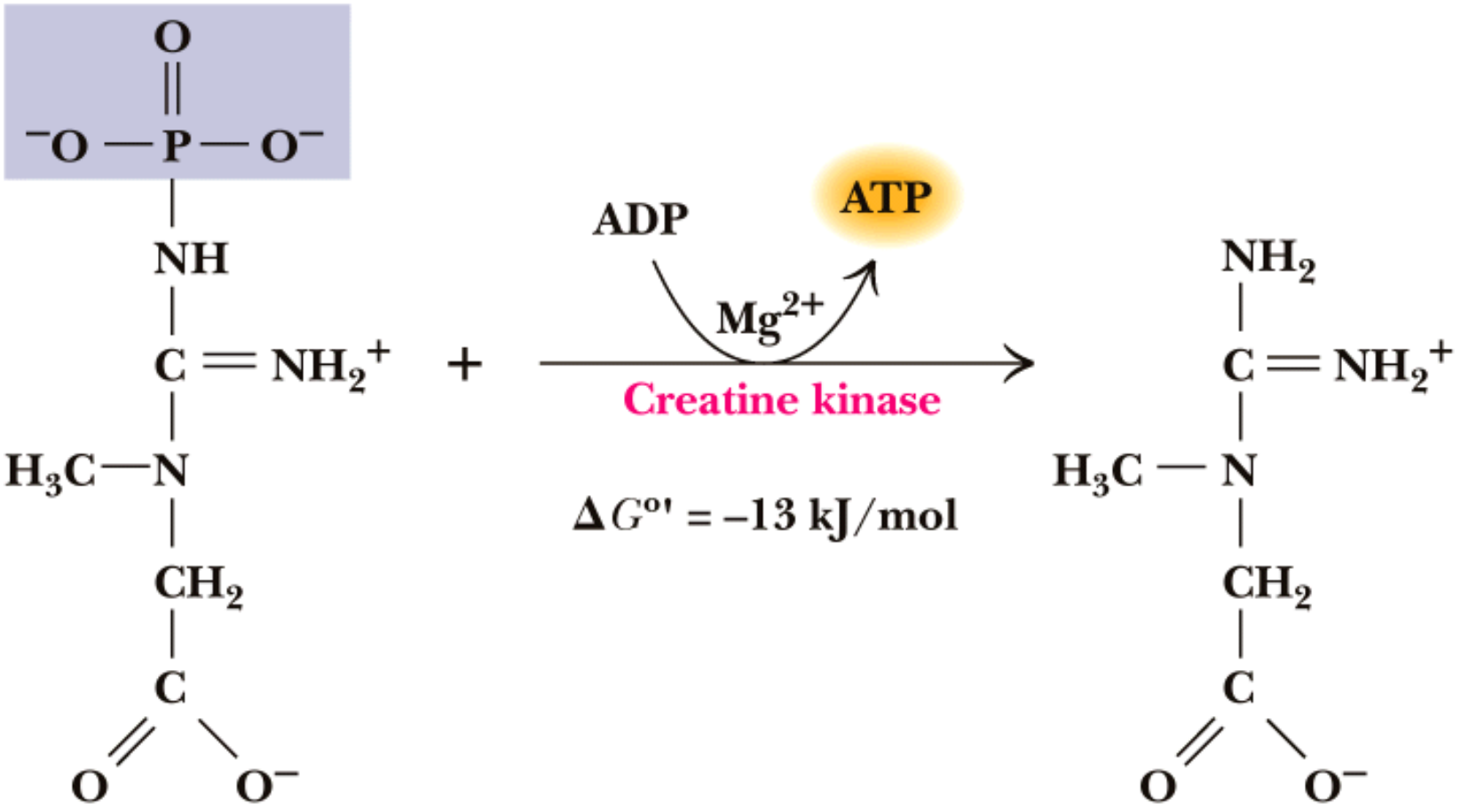
Energy for muscle activity

- **ATP is required for muscle contraction.**
  - **Myosin ATPase breaks down ATP as fiber contracts.**
- **Sources of ATP**
  - **-Phosphocreatine (PC)**
  - **-Glycolysis**
  - **-Oxidative phosphorylation**

Creatine Kinase in Muscle

- Muscles must be prepared for rapid provision of energy
- Creatine kinase and phosphocreatine act as a buffer system, providing additional ATP for contraction
- Glycogen provides additional energy, releasing glucose for glycolysis
- Glycolysis rapidly lowers pH, causing muscle fatigue

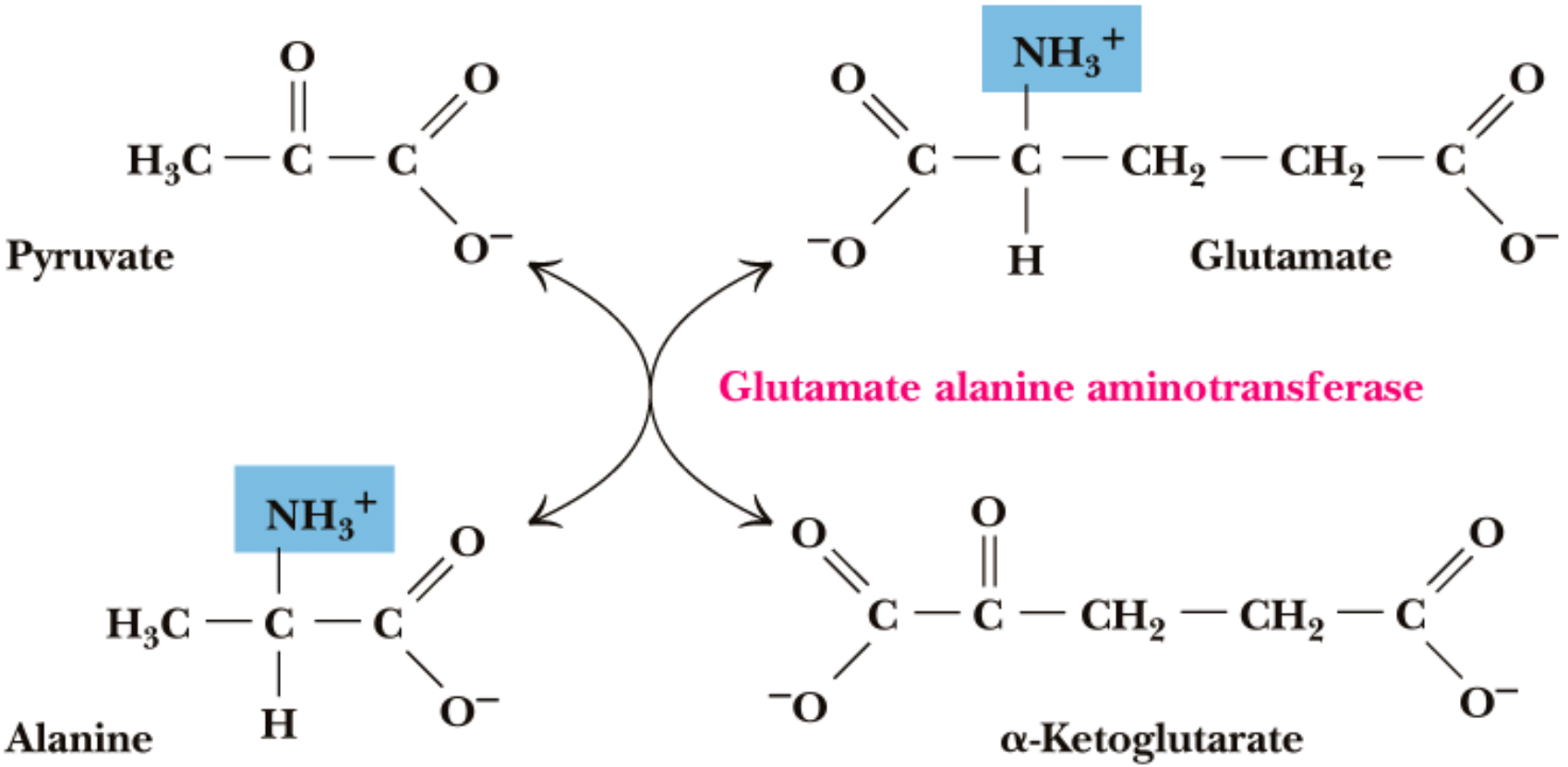
Garrett & Grisham: Biochemistry, 2/e
Figure 28.10

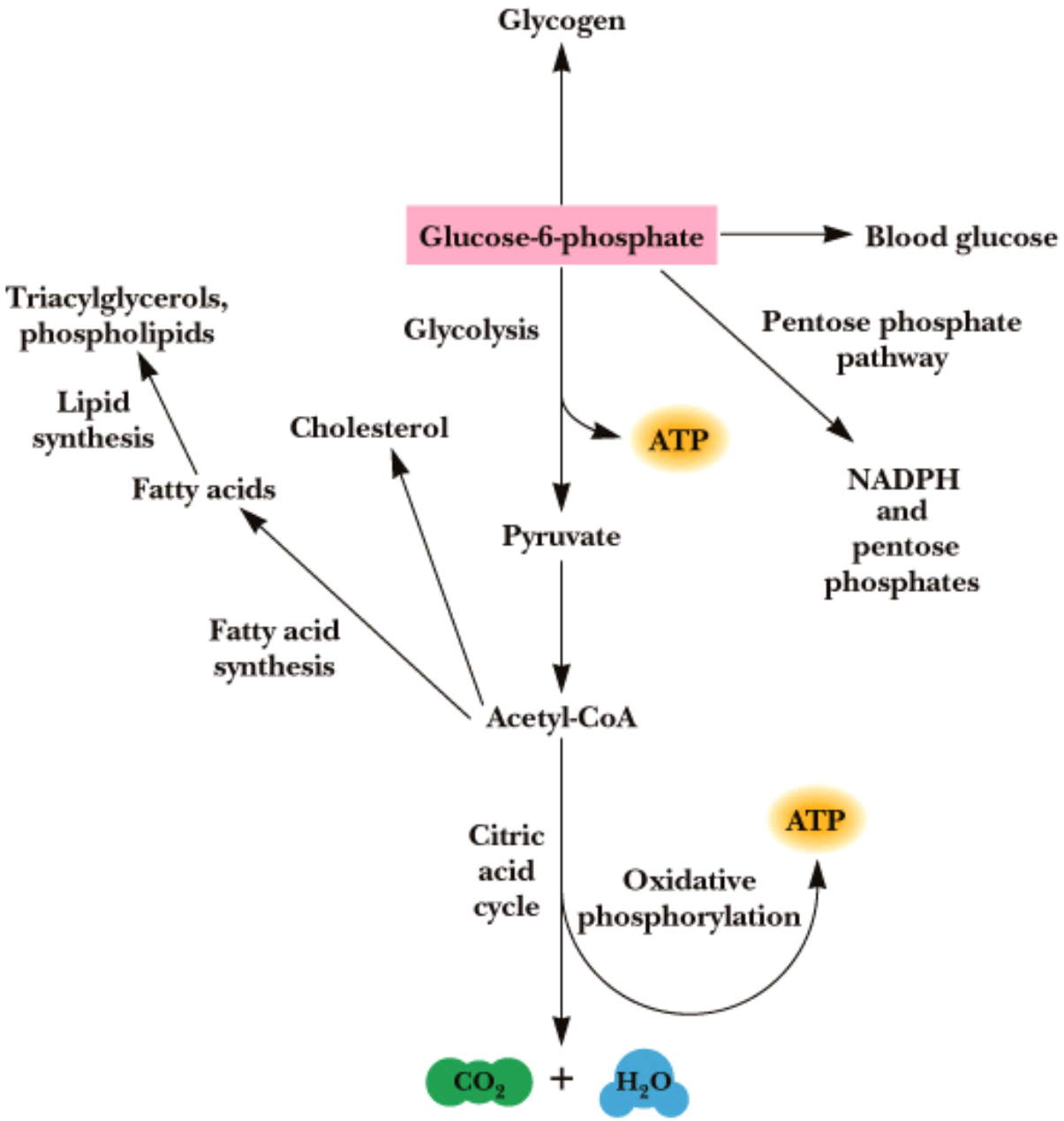


Muscle Protein Degradation

- During fasting or high activity, amino acids degrade to pyruvate, which can be transaminated to alanine
- Alanine circulates to liver, where it is converted back to pyruvate - food for gluconeogenesis
- This is a fuel of last resort for the fasting or exhausted organism

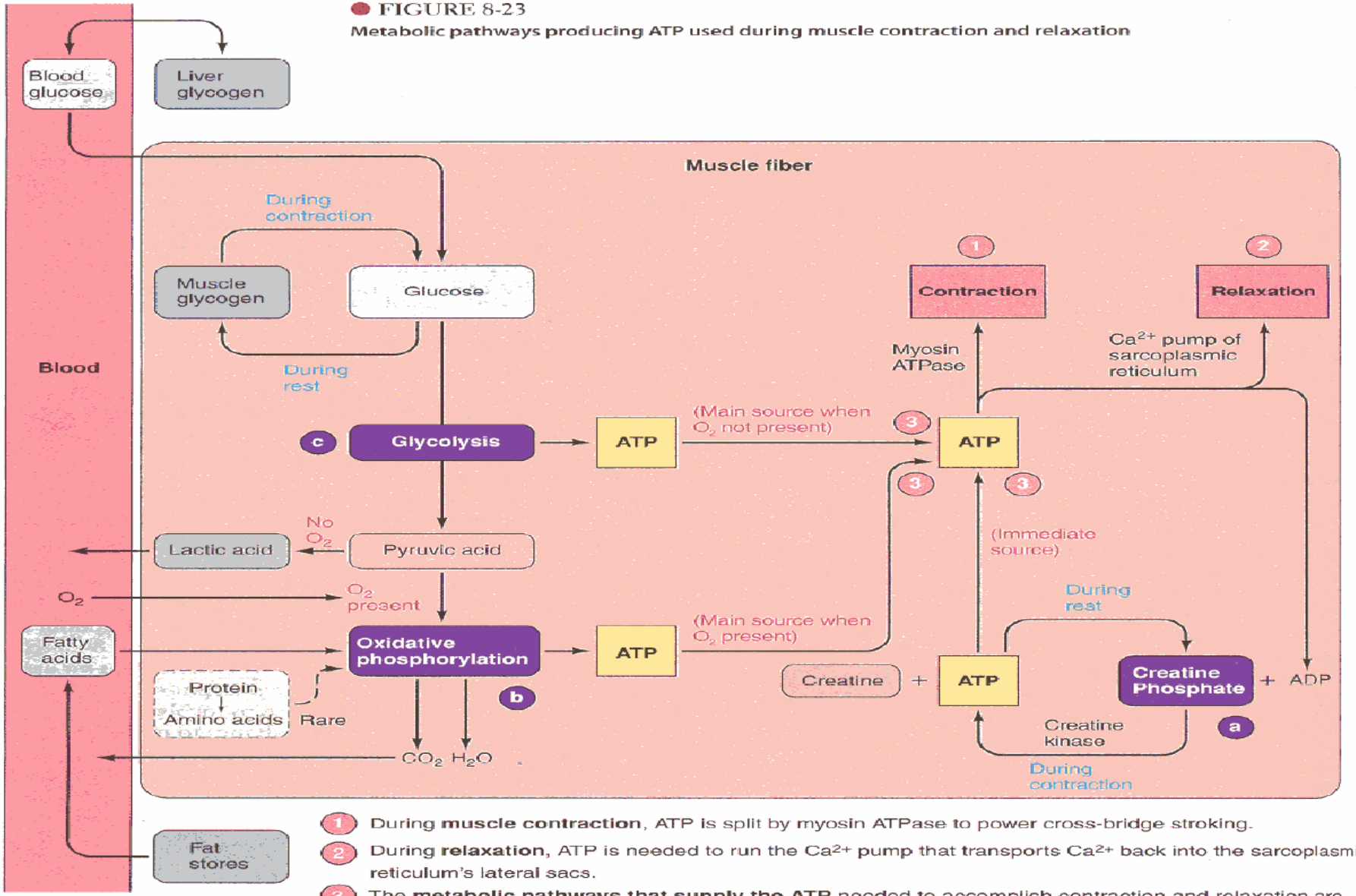
Garrett & Grisham: Biochemistry, 2/e
Figure 28.11




Glycogen
Glucose-6-phosphate
Blood glucose
Triacylglycerols, phospholipids
Glycolysis
Pentose phosphate pathway
Lipid synthesis
Cholesterol
ATP
Fatty acids
NADPH and pentose phosphates
Pyruvate
Fatty acid synthesis
Acetyl-CoA
ATP
Citric acid cycle
Oxidative phosphorylation
CO_2
+
H_2O

● FIGURE 8-23

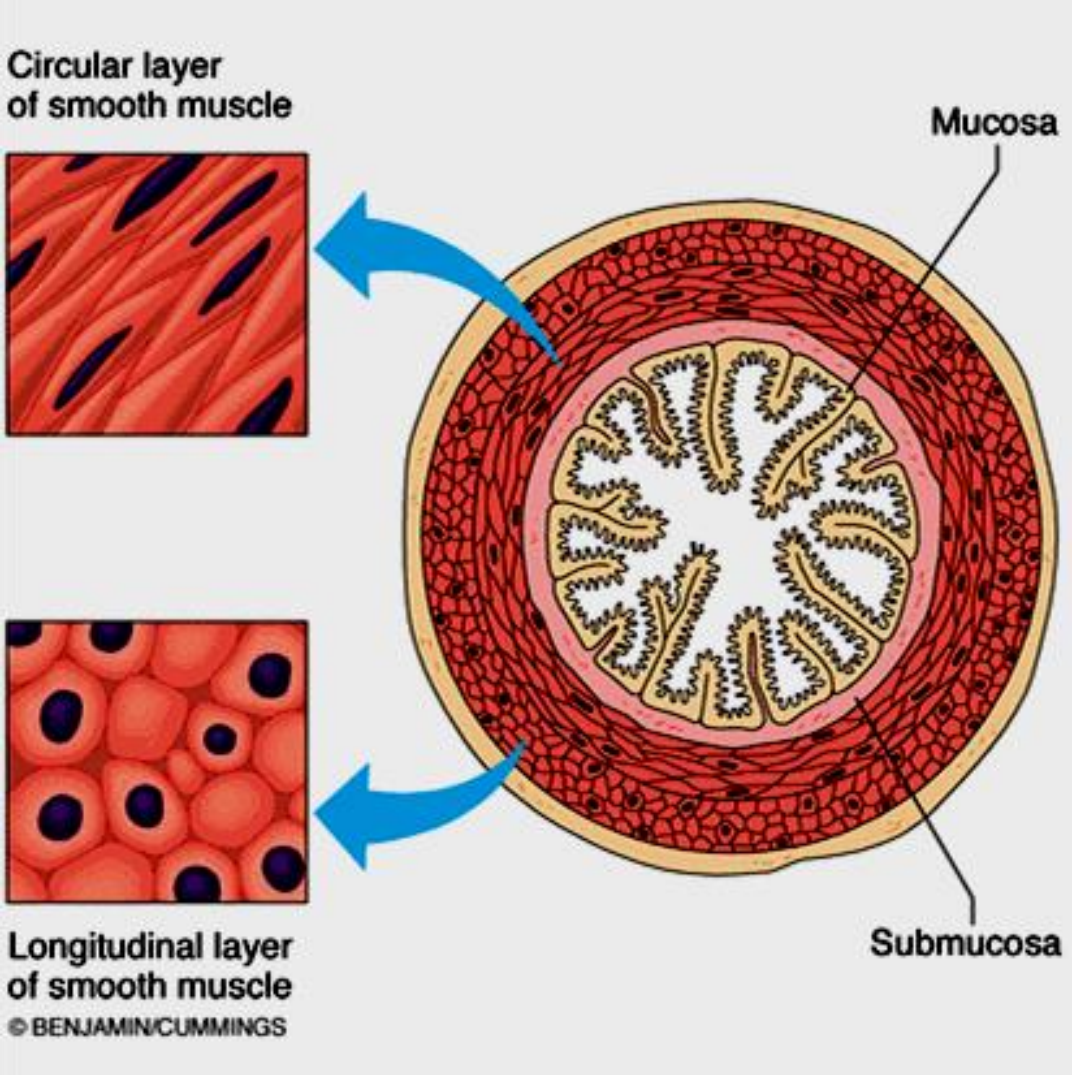
Metabolic pathways producing ATP used during muscle contraction and relaxation



1. During **muscle contraction**, ATP is split by myosin ATPase to power cross-bridge stroking.
2. During **relaxation**, ATP is needed to run the Ca^{2+} pump that transports Ca^{2+} back into the sarcoplasmic reticulum's lateral sacs.
3. The **metabolic pathways that supply the ATP** needed to accomplish contraction and relaxation are
   - a. transfer of a high-energy phosphate from **creatine phosphate** to ADP (immediate source);
   - b. **oxidative phosphorylation** (the main source when O_2 is present), fueled by glucose derived from muscle glycogen stores or by glucose and fatty acids delivered by the blood; and
   - c. **glycolysis** (the main source when O_2 is not present). The end product of glycolysis, pyruvic acid, is converted into lactic acid when the lack of O_2 prevents pyruvic acid from being further processed by the oxidative phosphorylation pathway.

Smooth Muscles

- Smooth muscle lacks the courser connective tissue seen in skeletal muscle
- Small amounts of endomysium is found between smooth muscle fibers



Regulation of Contraction

- **Calcium mediates the interaction of myosin with actin.**
- **Actin activates the myosin ATPase (200 x)**

- **3 major states of muscles:**
  - **Relaxed (low calcium)**
  - **Contracting (high calcium + ATP)**
  - **Rigor (high calcium, no ATP)**

In resting muscle (0.1 mM Ca^{2+}) the high affinity sites of TnC are occupied and the low affinity sites empty

Upon calcium release from the sarcoplasmic reticulum (SR; a rise to about 10 mM), the low affinity sites are titrated with calcium, inducing a global conformational change within TnC.

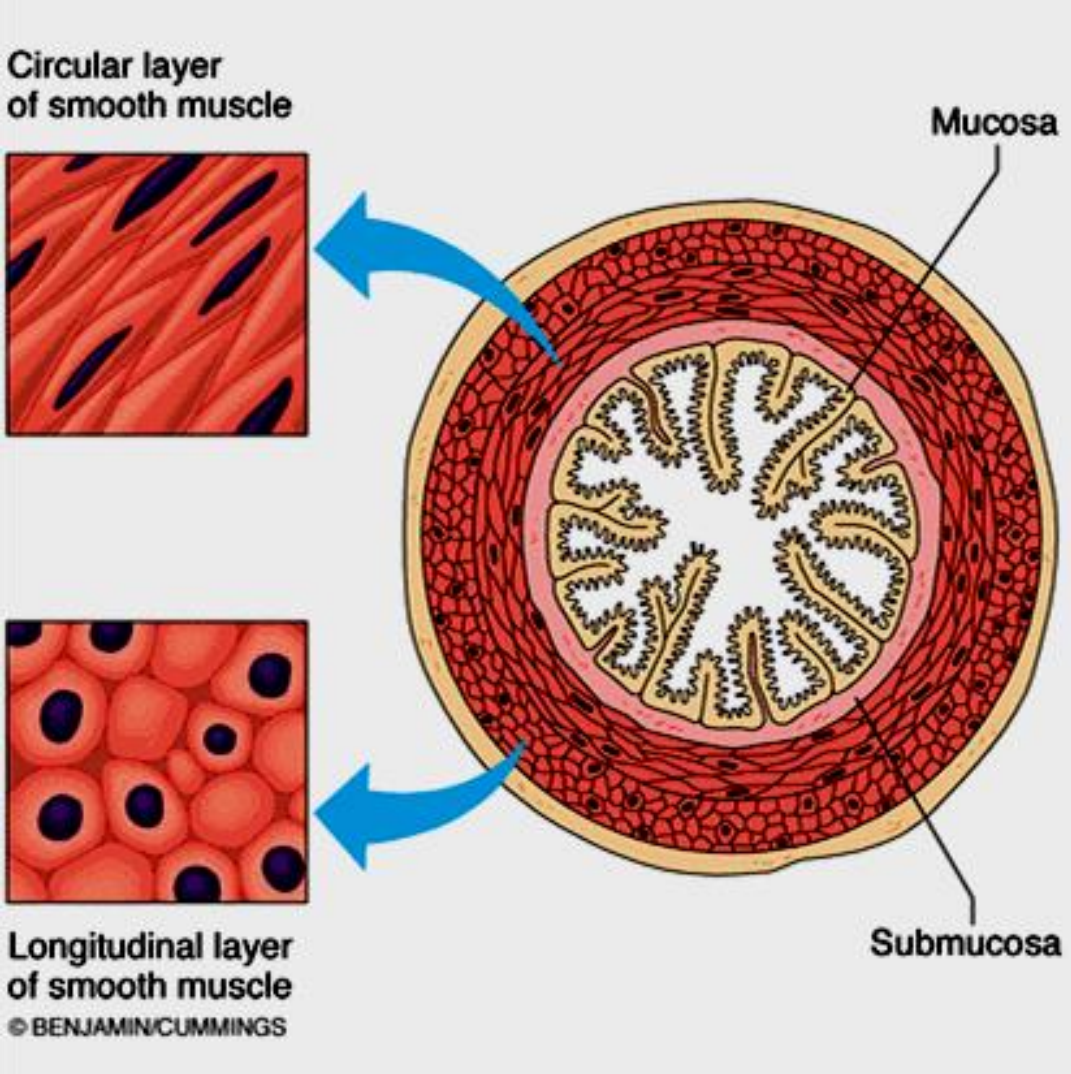
This conformational changes is transmitted to the TnT subunits, which in turn alters the position of tropomyosin, allowing for S1 binding.

Thus, Ca^{2+} controls muscle contraction by an allosteric mechanism, where the flow of information is:

Ca^{2+} → Troponin → Tropomyosin → actin → myosin

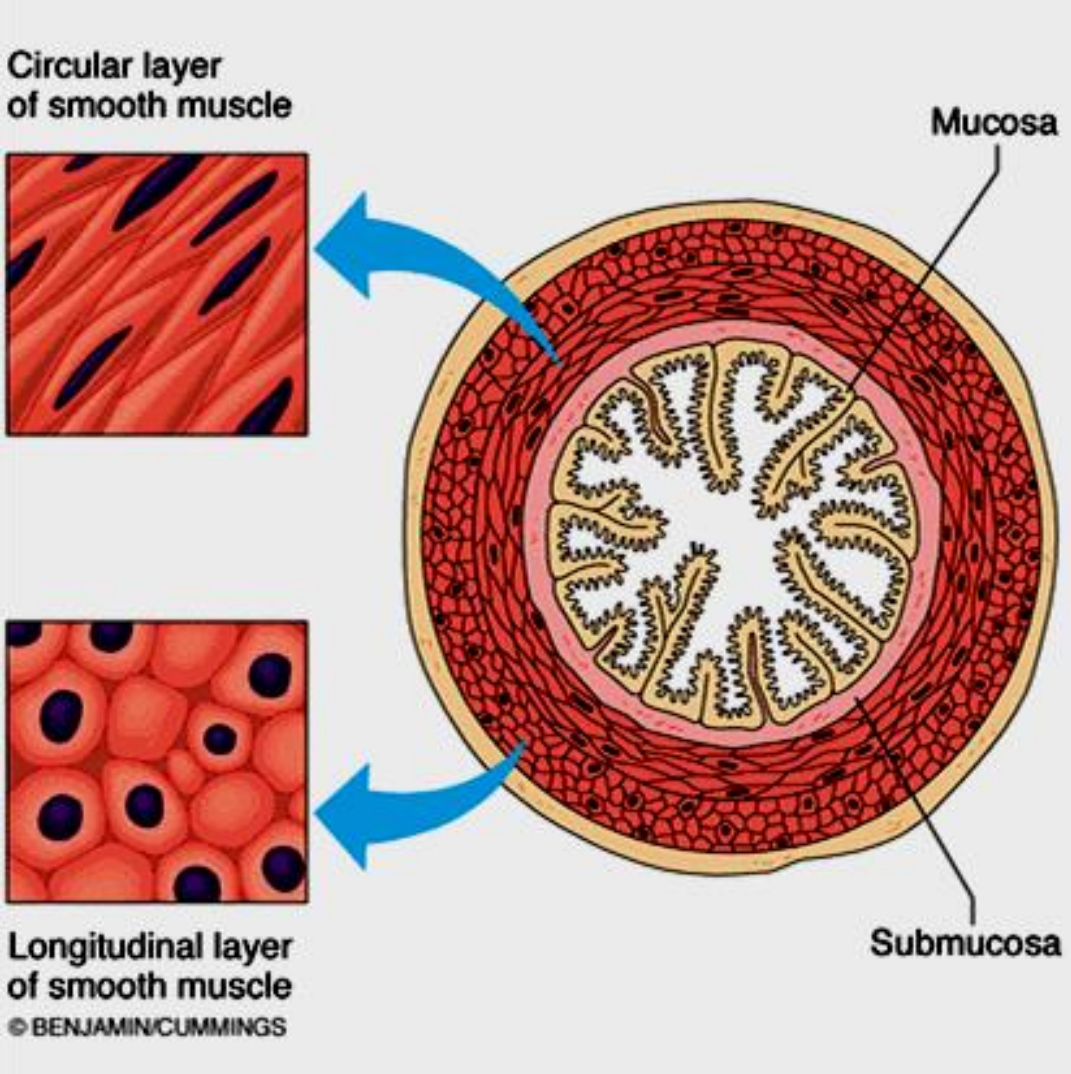
Smooth Muscles

- Smooth muscles are organized into sheets of closely apposed fibers
- These sheets occur in the walls of all but the smallest blood vessels and in the walls of hollow organs of the respiratory, urinary digestive and reproductive tracts



Smooth Muscles

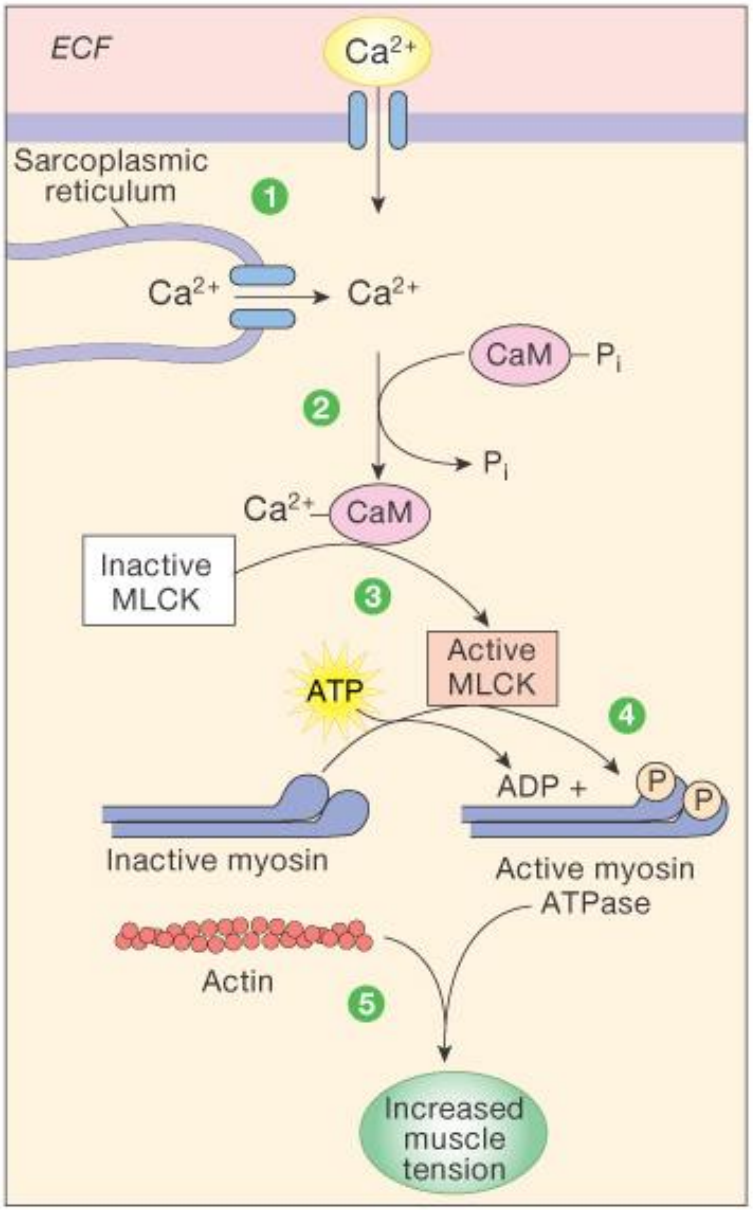
- In most cases two sheets of muscles are present with their fibers aligned at right angle to each other
- These forms the longitudinal (long axis) and circular (encircling) layer
- These two layers squeeze the contents of the organ



Smooth Muscle Contraction: Mechanism

1- Intracellular calcium concentrations increase when Ca^{2+} enters cell and is released from sarcoplasmic reticulum.
2- Ca^{2+} binds to calmodulin (CaM).
3- Ca^{2+}-calmodulin activates myosin light chain kinase (MLCK)
4- MLCK phosphorylates light chains in myosin heads and increases myosin ATPase activity.
5- Active myosin crossbridges slide along actin and create muscle tension

Smooth Muscle Contraction: Mechanism

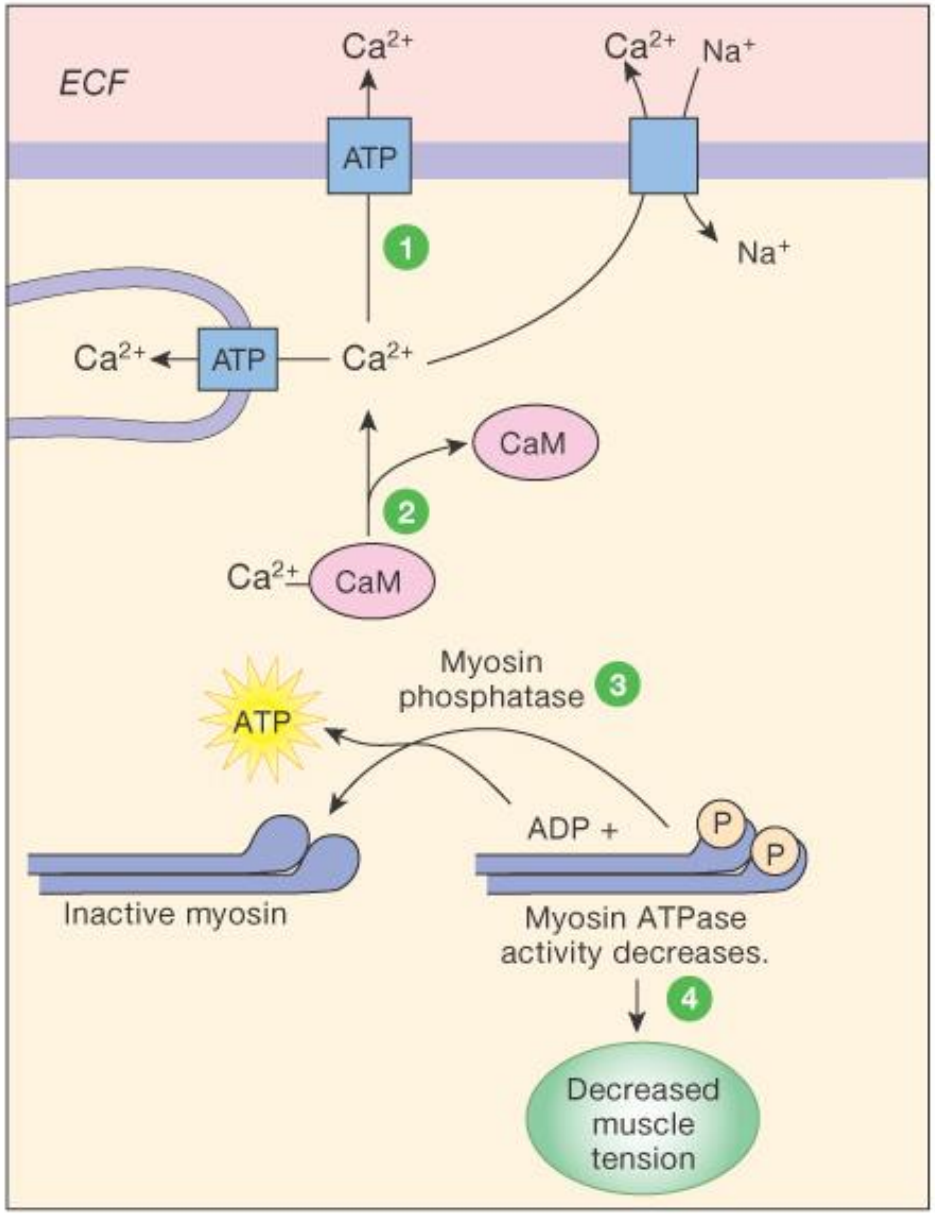


1. Intracellular Ca^{2+} concentrations increase when Ca^{2+} enters cell and is released from sarcoplasmic reticulum.
2. Ca^{2+} binds to calmodulin (CaM).
3. Ca^{2+}–calmodulin activates myosin light chain kinase (MLCK).
4. MLCK phosphorylates light chains in myosin heads and increases myosin ATPase activity.
5. Active myosin crossbridges slide along actin and create muscle tension.

Smooth Muscle Relaxation: Mechanism

1- Free Ca^{2+} in cytosol decreases when Ca^{2+} is pumped out of the cell or back into the sarcoplasmic reticulum.
2- Ca^{2+} unbinds from calmodulin (CaM).
3- Myosin phosphatase removes phosphate from myosin, which decreases myosin ATPase activity.
4- Less myosin ATPase results in decreased muscle tension.

Smooth Muscle Relaxation: Mechanism



1. Free Ca^{2+} in cytosol decreases when Ca^{2+} is pumped out of the cell or back into the sarcoplasmic reticulum.

2. Ca^{2+} unbinds from calmodulin (CaM).

3. Myosin phosphatase removes phosphate from myosin, which decreases myosin ATPase activity.

4. Less myosin ATPase results in decreased muscle tension.

Summary: Comparison of Three Muscle Types

Table 12-3: Comparison of Three Muscle Types

	SKELETAL	SMOOTH	CARDIAC
Appearance under light microscope	Striated	Smooth	Striated
Fiber arrangement	Sarcomeres	Longitudinal bundles	Sarcomeres
Fiber proteins	Actin, myosin; troponin and tropomyosin	Actin, myosin, tropomyosin	Actin, myosin; troponin and tropomyosin
Control	■ Voluntary ■ Ca^{2+} and troponin ■ Fibers independent	■ Involuntary ■ Ca^{2+} and calmodulin ■ Fibers electrically linked via gap junctions	■ Involuntary ■ Ca^{2+} and troponin ■ Fibers electrically linked via gap junctions
Nervous control	Somatic motor neuron	Autonomic neurons	Autonomic neurons
Hormonal influence	None	Multiple hormones	Epinephrine
Location	Attached to bones; a few sphincters close off hollow organs	Forms the walls of hollow organs and tubes; some sphincters	Heart muscle
Morphology	Multinucleate; large, cylindrical fibers	Uninucleate; small spindle-shaped fibers	Uninucleate; shorter branching fibers
Internal structure	T-tubule and sarcoplasmic reticulum	No t-tubules; sarcoplasmic reticulum reduced or absent	T-tubule and sarcoplasmic reticulum
Contraction speed	Fastest	Slowest	Intermediate
Contraction force of single fiber	All-or-none	Graded	Graded
Initiation of contraction	Requires input from motor neuron	Can be autorhythmic	Autorhythmic