Graduate Studies in Biomedical Technology and Medical Physics
University of Patras 2020

Physiology and Pathophysiology for Engineers and Physisists

part 3 - muscles

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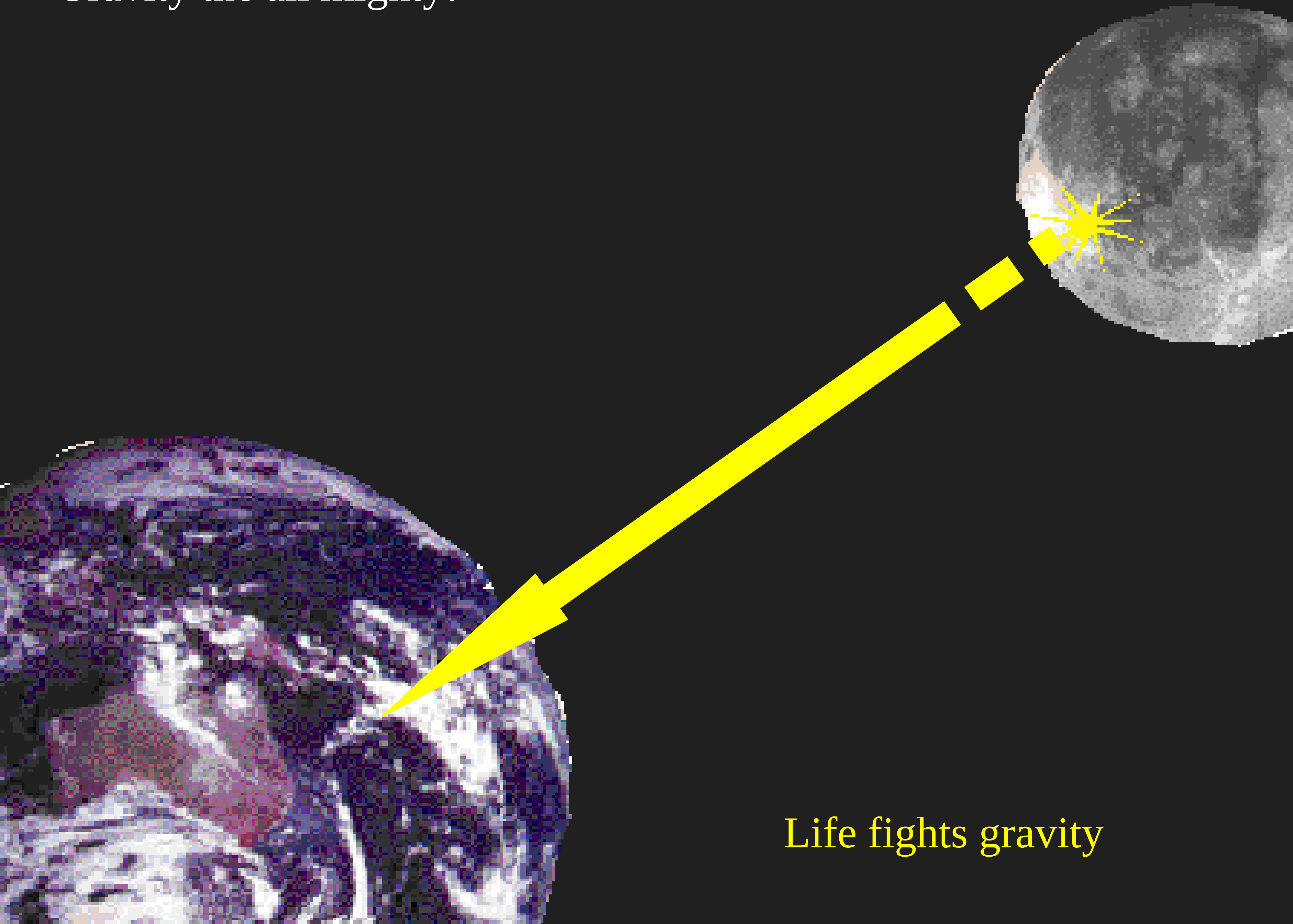
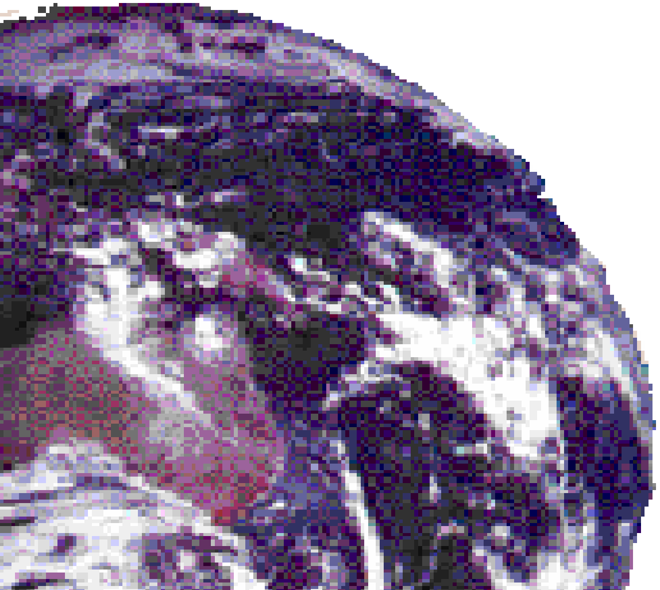
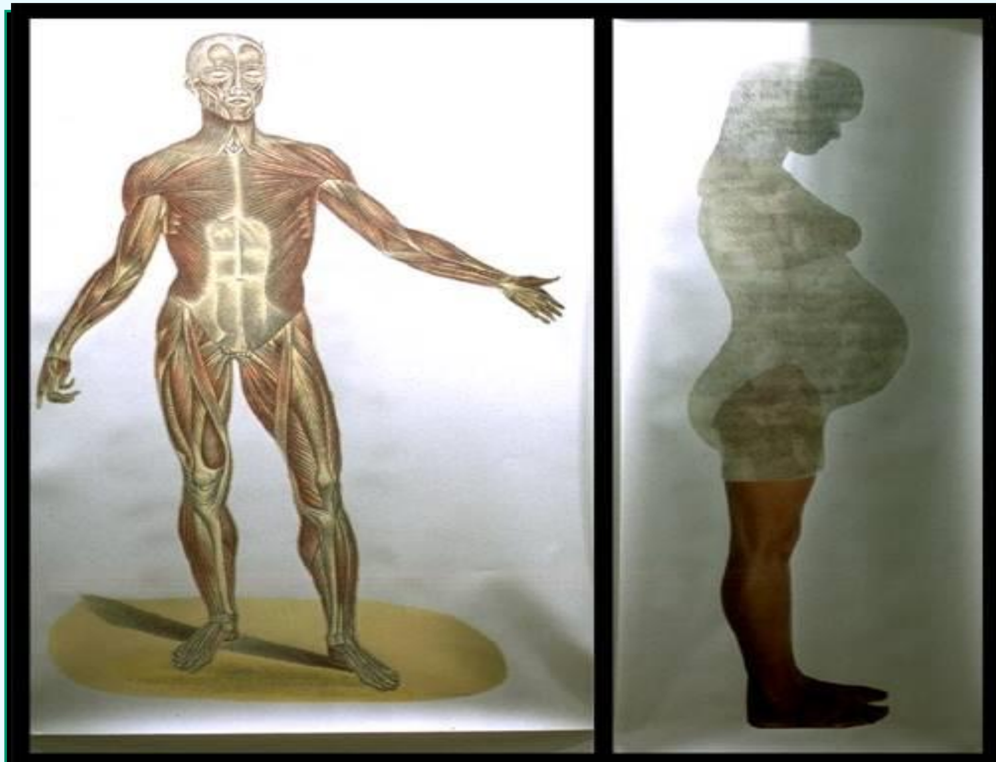
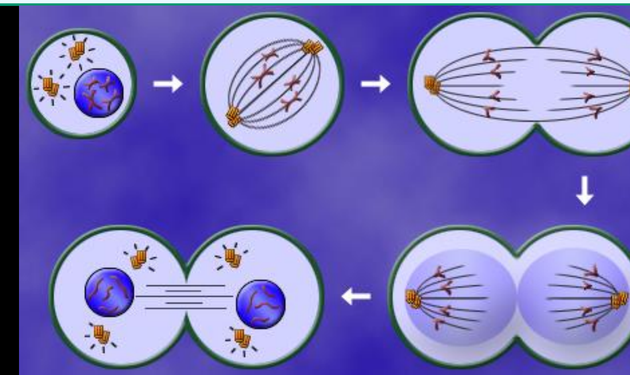
Gravity the all mighty!

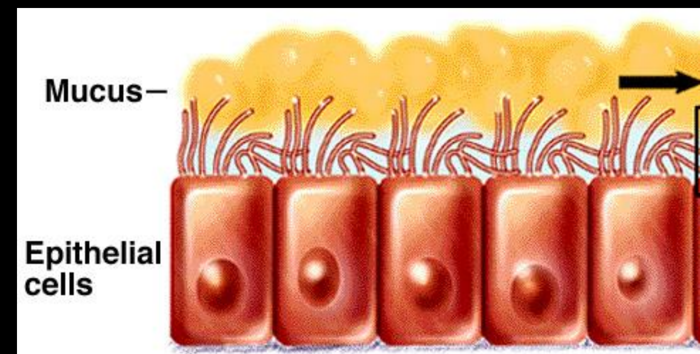


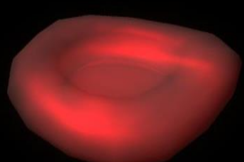
Look !
I can fight gravity.
I have muscles!

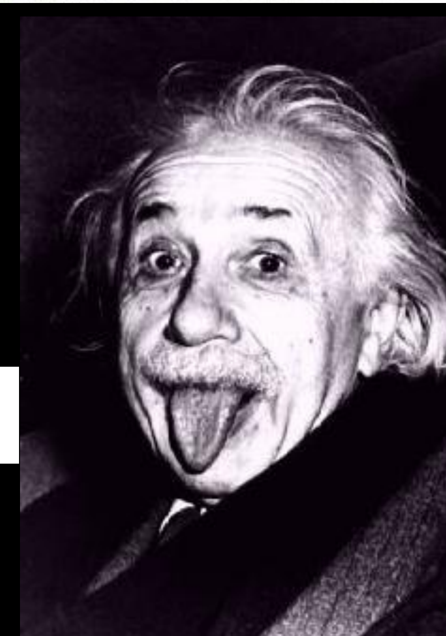












MOVEMENT is a whole body homeostatic mechanism

In all movements there is a common molecular mechanism : **sliding filaments actin/myosin**

MOTILITY

Examples of cell and organelle motility.

Cell division
Cytokinesis
Cell migration
Intracellular vesicular transport and
cytosis
Sperm motility
ovum transport
Axonal transport
Electromotility of outer hair cells and ciliary motility

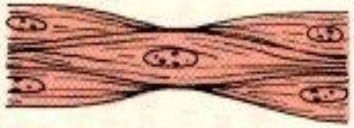
Types of Muscle Tissue

Skeletal - long cells called muscle fibers. Striated due to actin and myosin (proteins) ordinarily arranged in sarcomeres. Many nuclei, peripheral. Fibers tied together by connective tissue. **Voluntary**. Helps body and parts of body move.

Cardiac - found only in heart. Interconnected. Striated. One or two nuclei, central. **Involuntary**.

Smooth - walls of blood vessels, around hollow organs. Not striated. Single central nucleus. **Involuntary**.

A. Structure and function of 3 classes of muscle

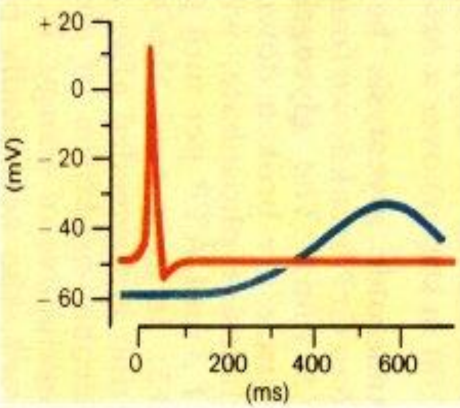


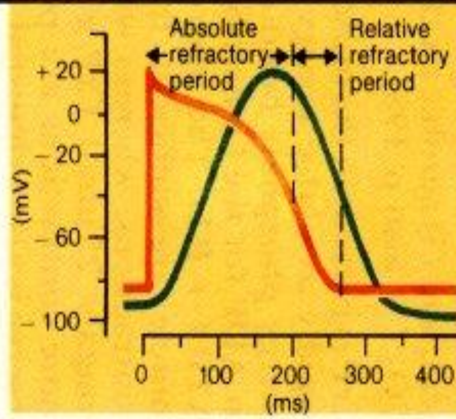
		Smooth muscle	Cardiac muscle	Skeletal muscle
Structure	Motor end-plate	None	None	Yes
	Fiber	Fusiform, short (max. 0.4 mm)	Branched	Cylindrical, long (max. 15 cm)
	Mitochondria	Few	Many	Few
	Nucleus/fiber	1:1	1:1	Several per fiber
	Sarcomere	None	Yes-max. length 2.6 µm	Yes-max. length 3.65 µm
	Syncytium	Yes (bridges)	Yes (functional)	No
	Sarcoplasmic reticulum	Poorly developed	Well developed	Extensively developed
	ATPase	Little	Average	Much
Function	Pacemaker	Yes (slow)	Yes (fast)	No (requires neural impulse)
	Response	Graded	All or none	Graded
	Tetanus	Yes	No	Yes
	Operating range	Variable length-tension curve	On rising portion of length-tension curve	On peak of length-tension curve

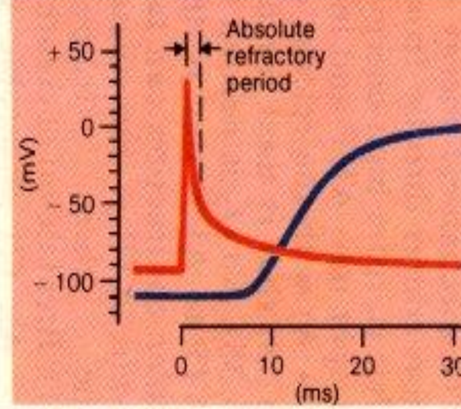
Response

Potential

Mechanical tension







Functions of Skeletal Muscles

Guard entrances and exits - guard openings to digestive and urinary tracts and provide voluntary control over swallowing, defecating, and urination.

Support soft tissues - abdominal wall and floor of the pelvic cavity composed of layers of muscles that support the weight of visceral organs and shield internal tissues from injury.

Muscular System: Includes all of the skeletal muscles that can be controlled voluntarily.

Skeletal muscle - attached to one bone at one end and, across a joint or several joints, to another bone at its other end.

Have more than 600 skeletal muscles.

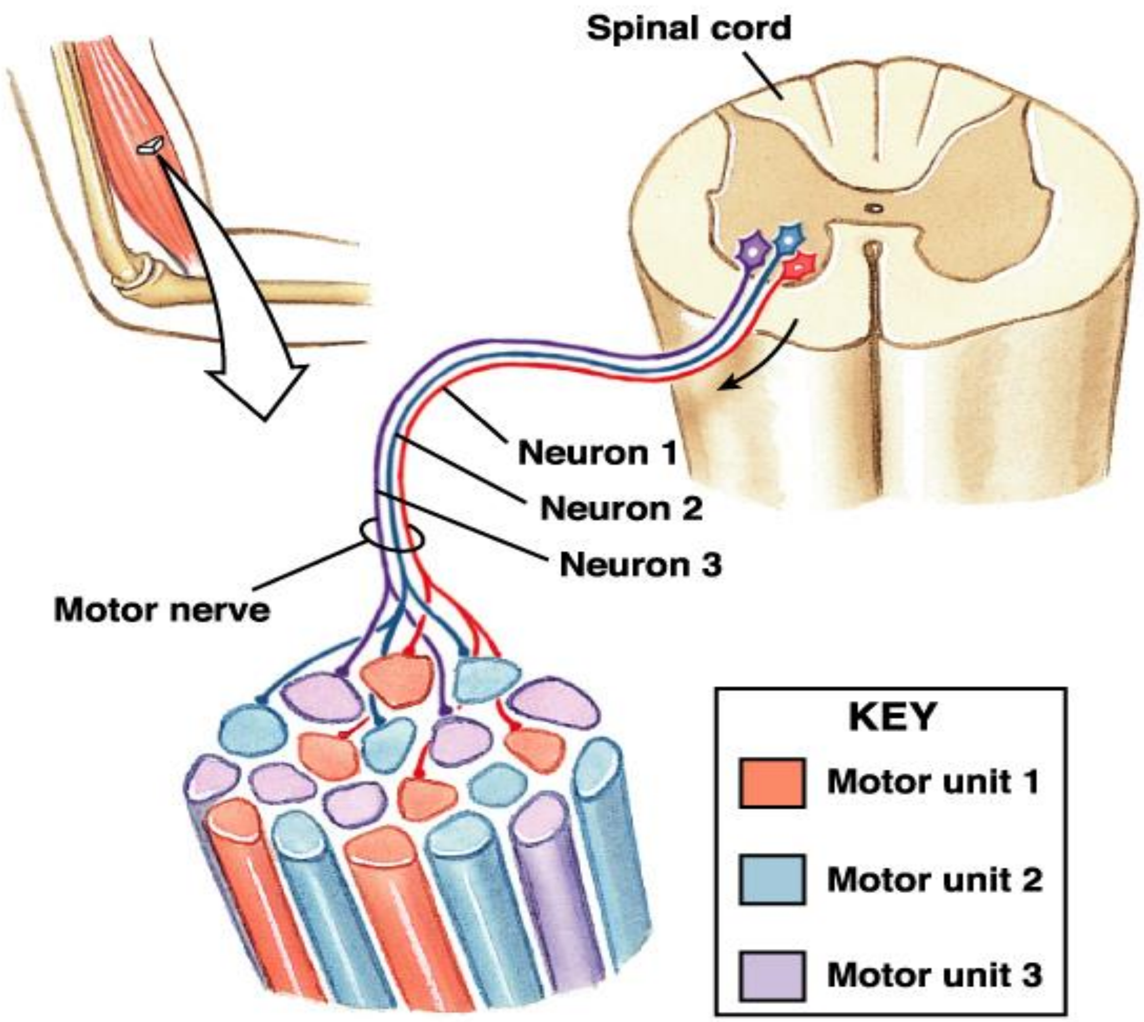
Muscle based on Latin *musculus* which means “little mouse.”

Striated muscle - fibers (cells) composed of alternating light and dark stripes (striations).

Voluntary muscle - contracts when we want it to.

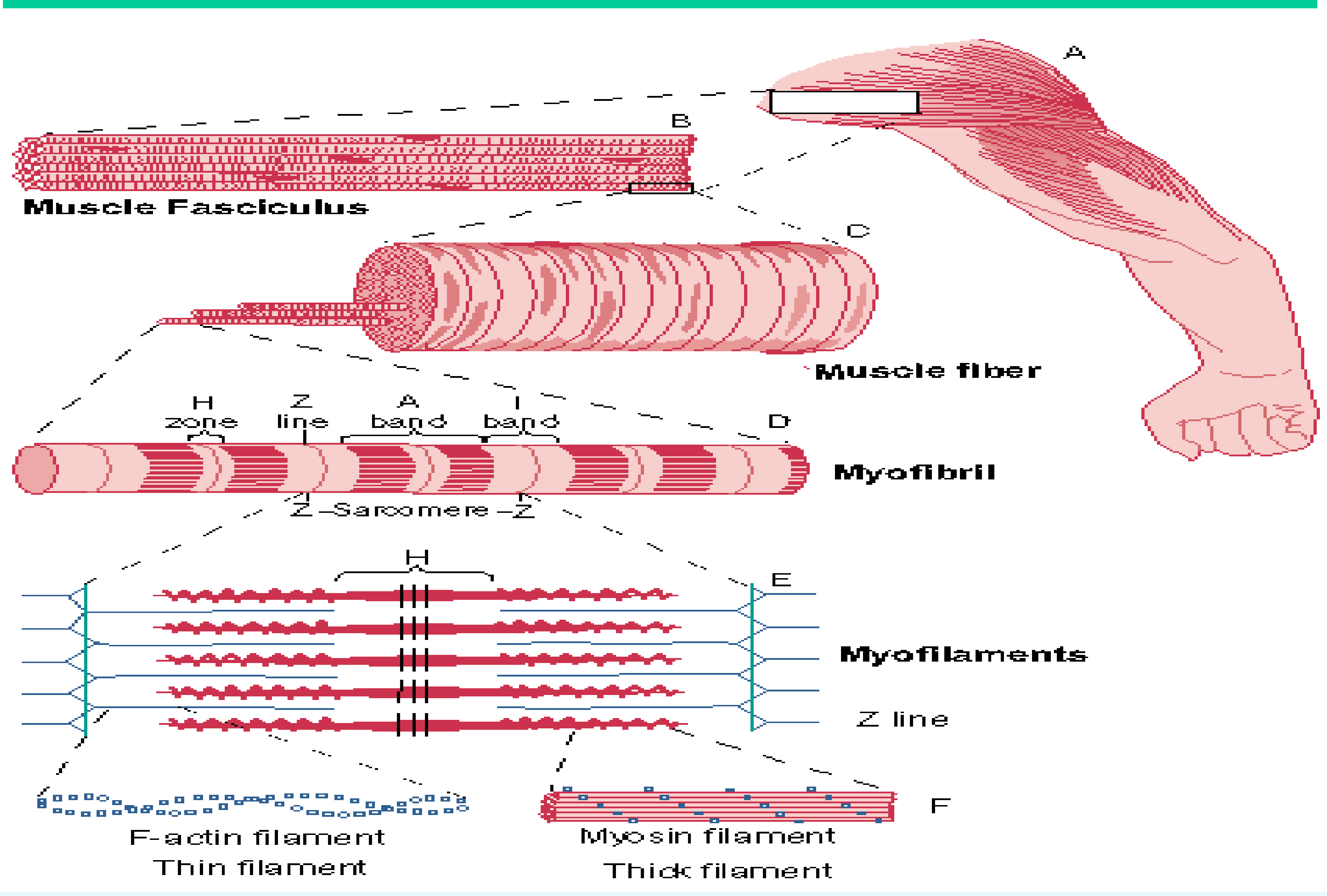
Motor Unit of Skeletal Muscle

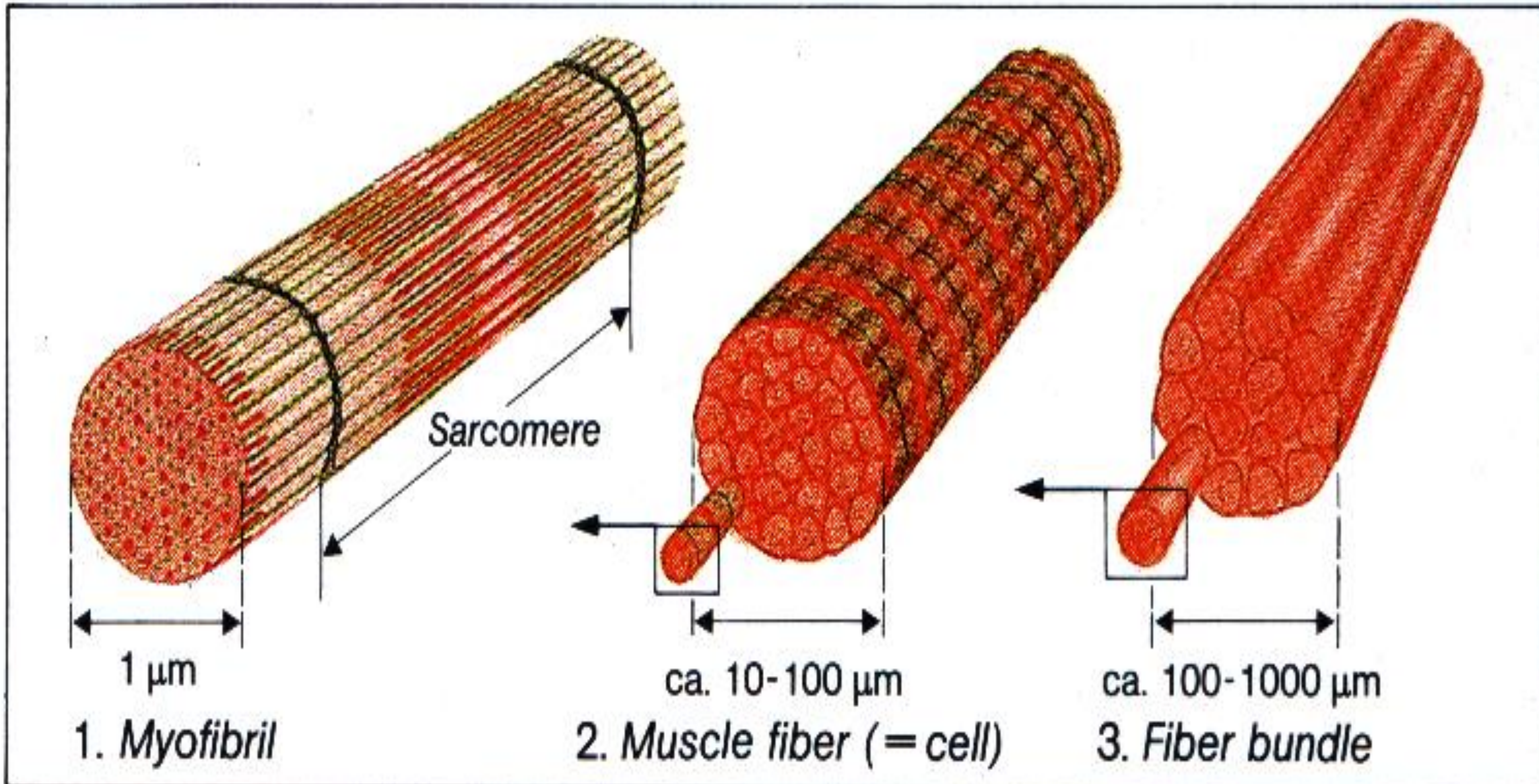
Motor unit =- motor neuron together with the muscle fibers it innervates.
In humans, a single motor unit causes the simultaneous contraction of 6-30 fibers (in some eye muscles) to over 1000 fibers (in powerful leg muscles).



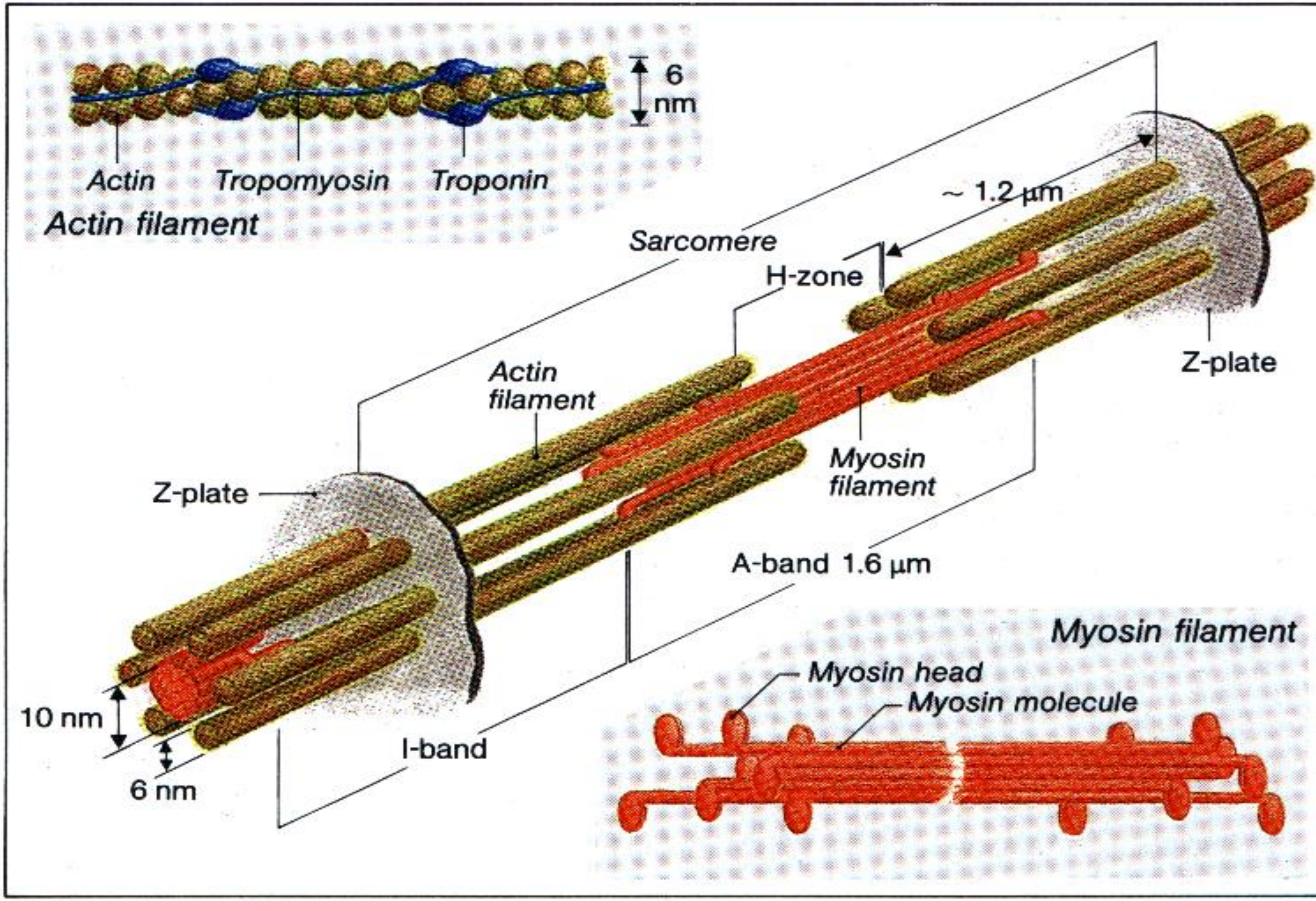
Contractile Apparatus of Striated Muscle

Contractile Apparatus of Striated Muscle

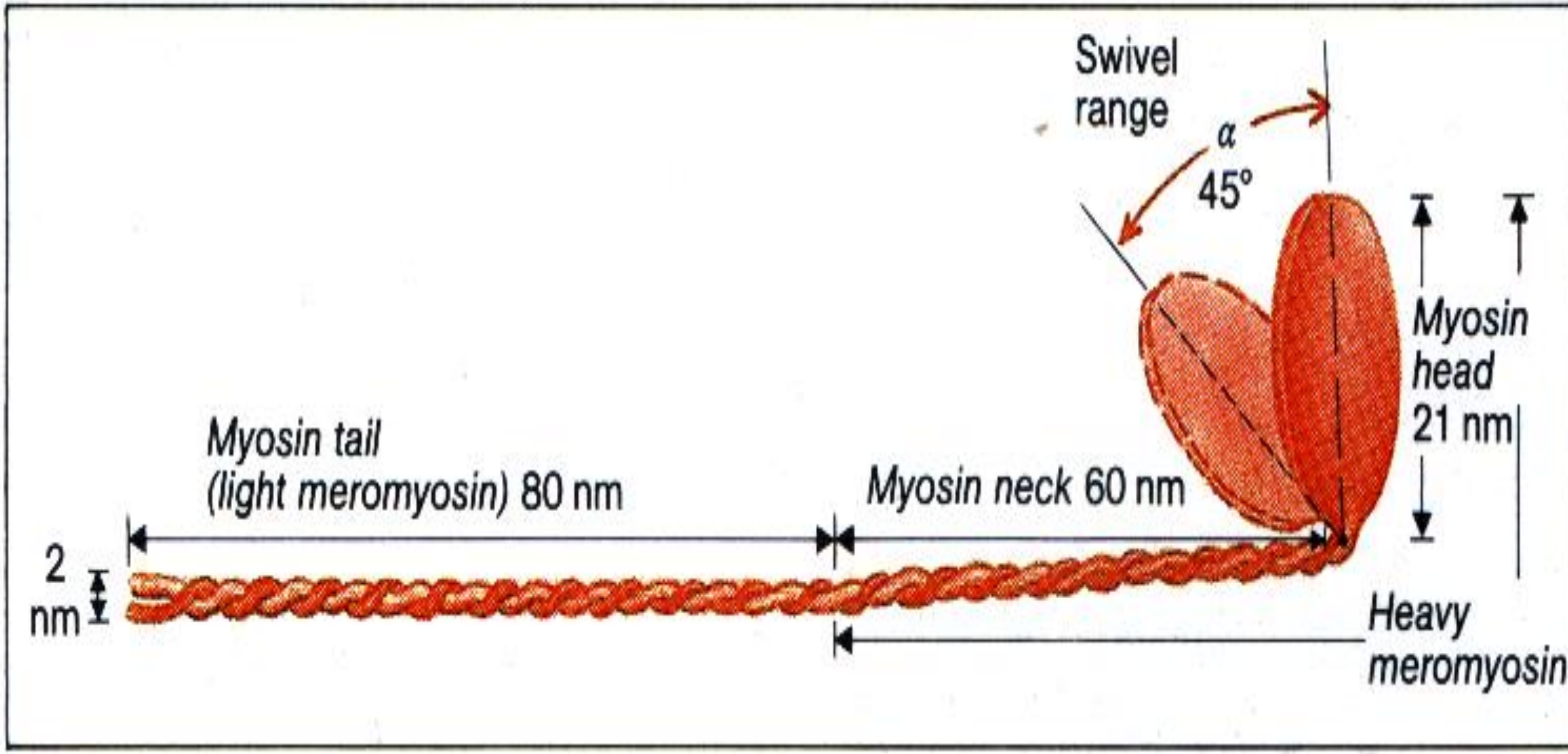




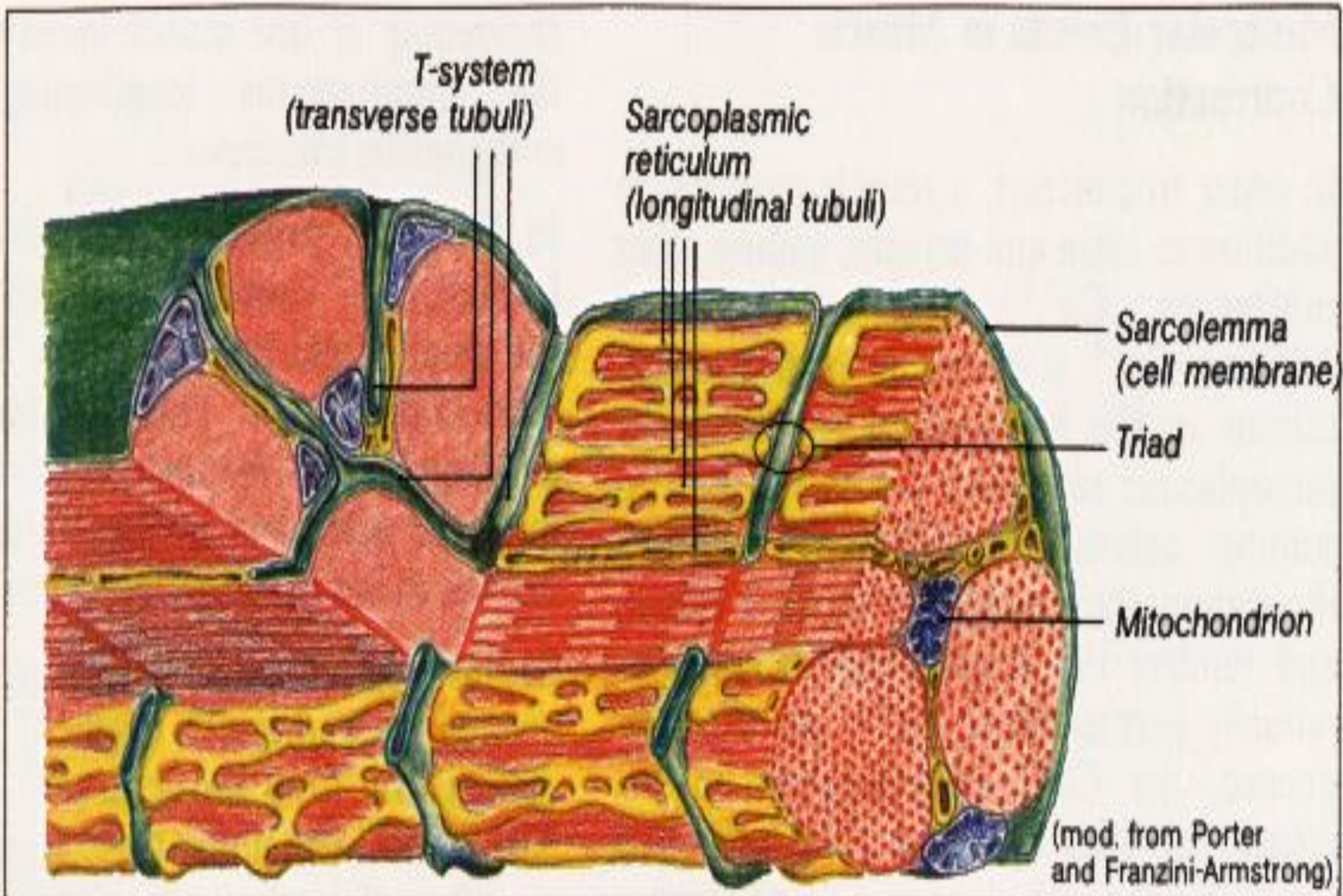
A. Fine structure of striated muscle



B. Structure of the sarcomere



C. Myosin molecule



A. Sarcotubular system of the muscle cell (= fiber)

Skeletal Muscle - Microscopic Anatomy

Composed of individual specialized cells called **muscle fibers**. Have long, cylindrical shape and numerous nuclei. Look more like fibers than like “typical” cells.

Muscle fibers - range in length from 0.1 cm (stapedius muscle in inner ear) to 30 cm (sartorius muscle of anterior thigh). Diameters range from 0.1mm to 1 mm.

Muscle fibers contain smaller fibers called **myofibrils**.

Myofibrils made up of thick and thin threads called **myofilaments**.

Thick myofilaments made up of fairly large protein, **myosin**.

Thin myofilaments made up of smaller protein, **actin**.

Sarcolemma - plasma membrane that encloses each skeletal muscle fiber. Fiber contains several nuclei that are located near the sarcolemma.

Sarcoplasm - specialized cytoplasm found in muscle fibers. Contains many mitochondria and a large number of myofibrils which run lengthwise and parallel to one another.

Sarcoplasmic reticulum (SR) - around each myofibril and running parallel to it. Network of tubes and sacs which contain calcium ions. Somewhat like smooth ER.

Transverse (T) tubules - run at right angles to SR. Tubular organelles that run across fiber to the outside. Sarcolemma lines T tubule.

What makes one muscle larger than another?

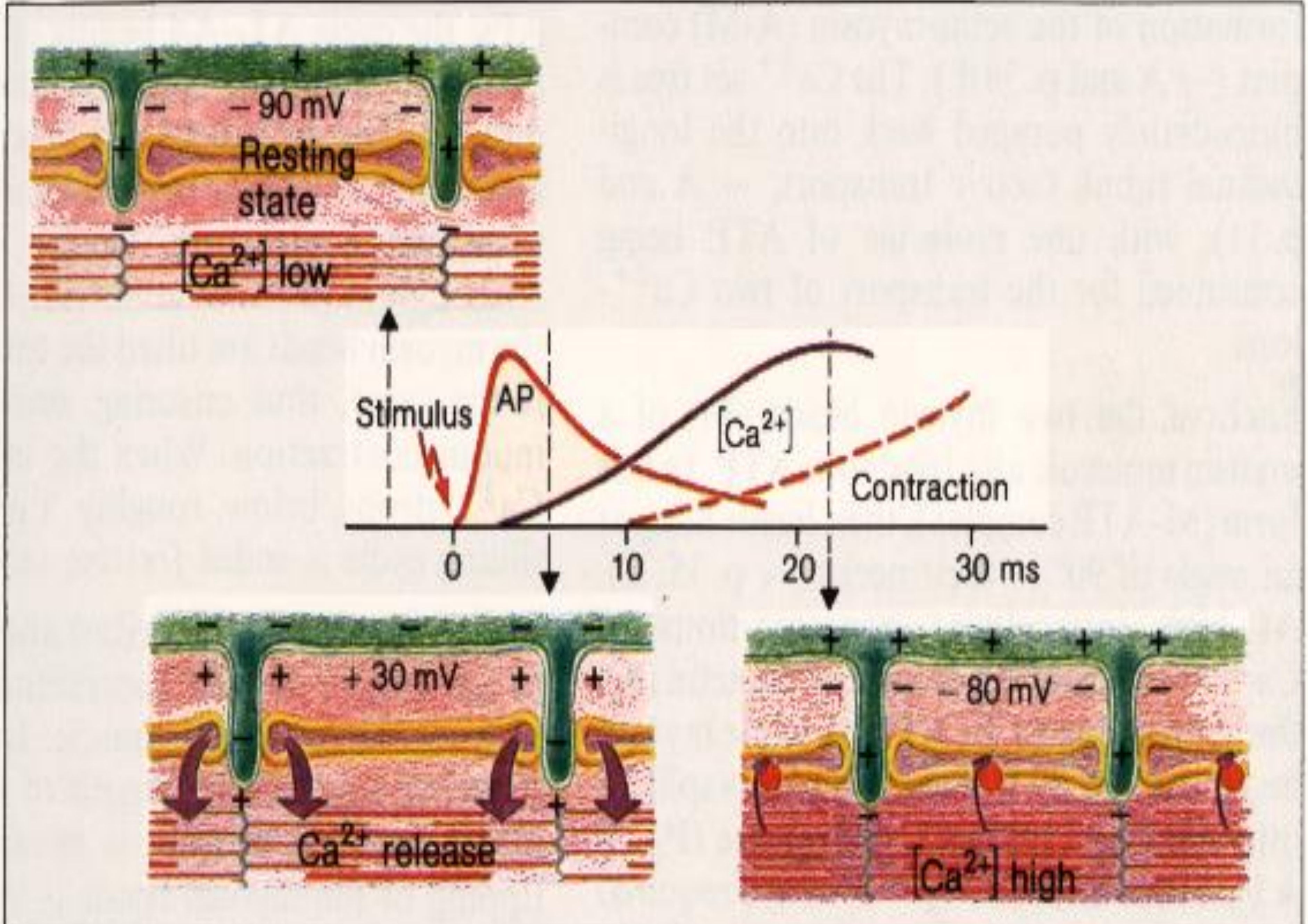
Generally, the larger muscle contains more bundles of fibers.
Largest muscles found where large, forceful movements are common, e.g. back and legs.
When a muscle is enlarged by exercise, the fibers increase in diameter, but the number of fibers remains the same.

Sarcomere = Fundamental unit of muscle contraction. Extends from one Z line to the next.

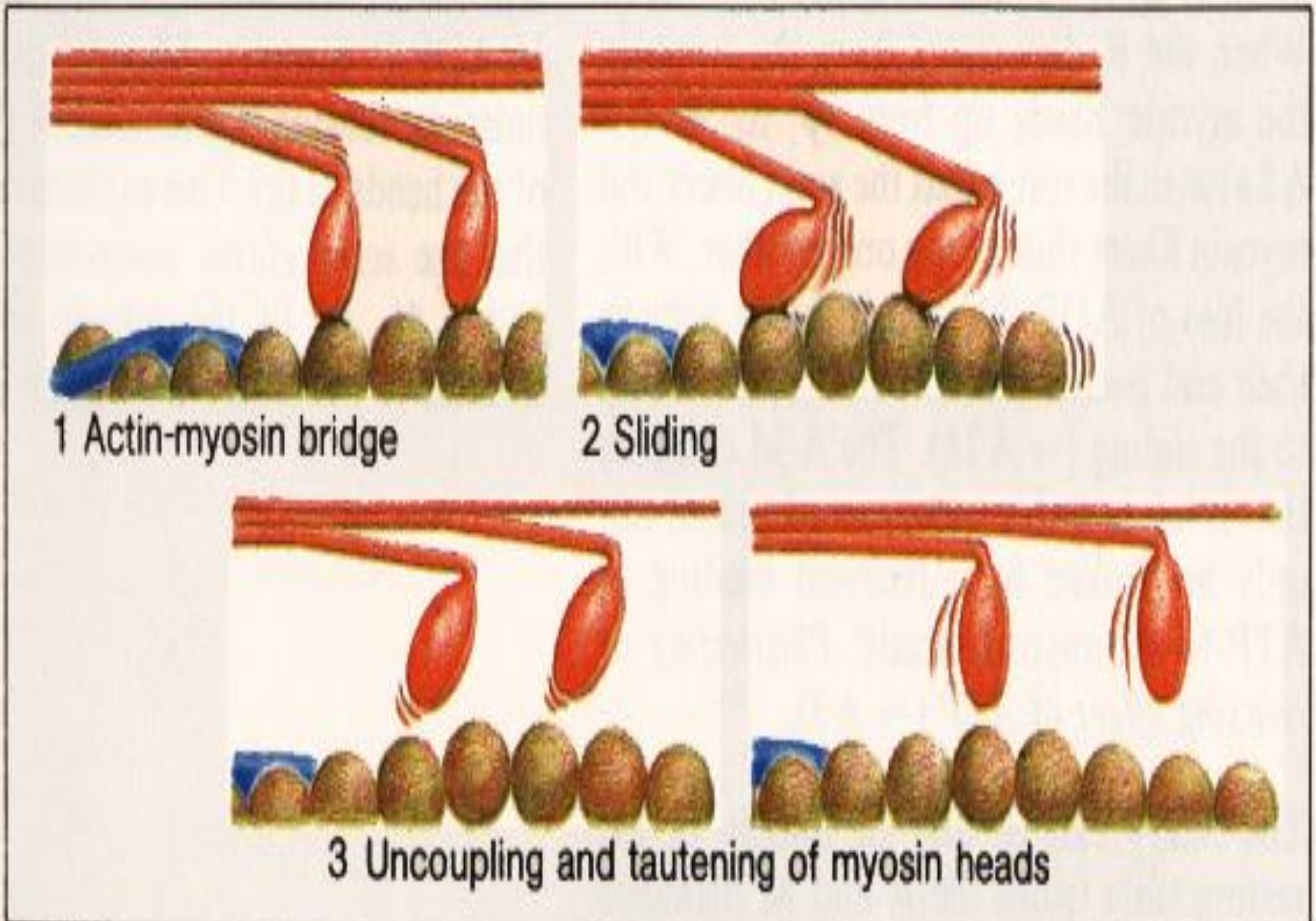
Muscle Contraction

- Under nervous control. Cannot contract without being stimulated.
- Contraction initiated by a chemical released from a nerve cell (neuron).

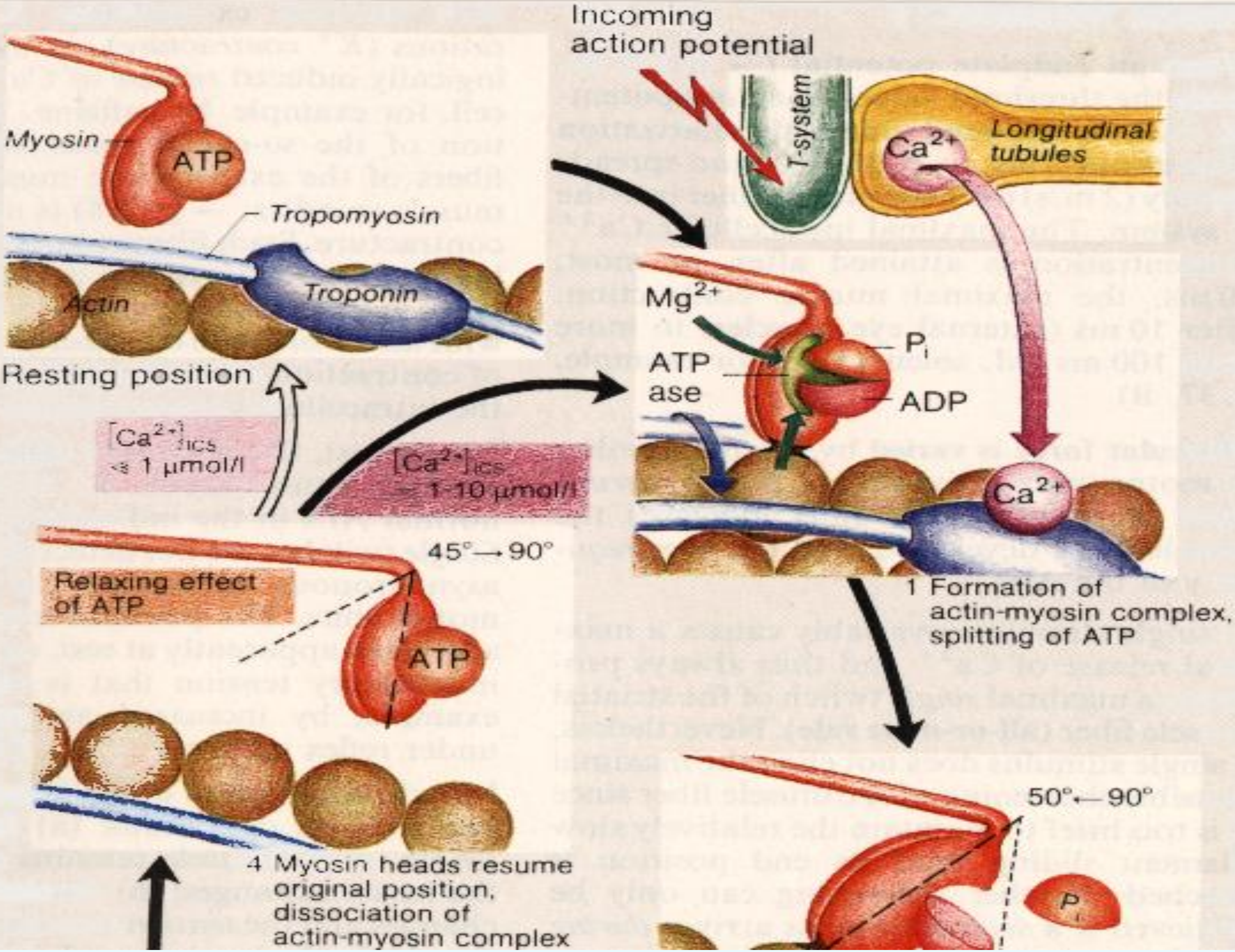
Contraction of Striated Muscle



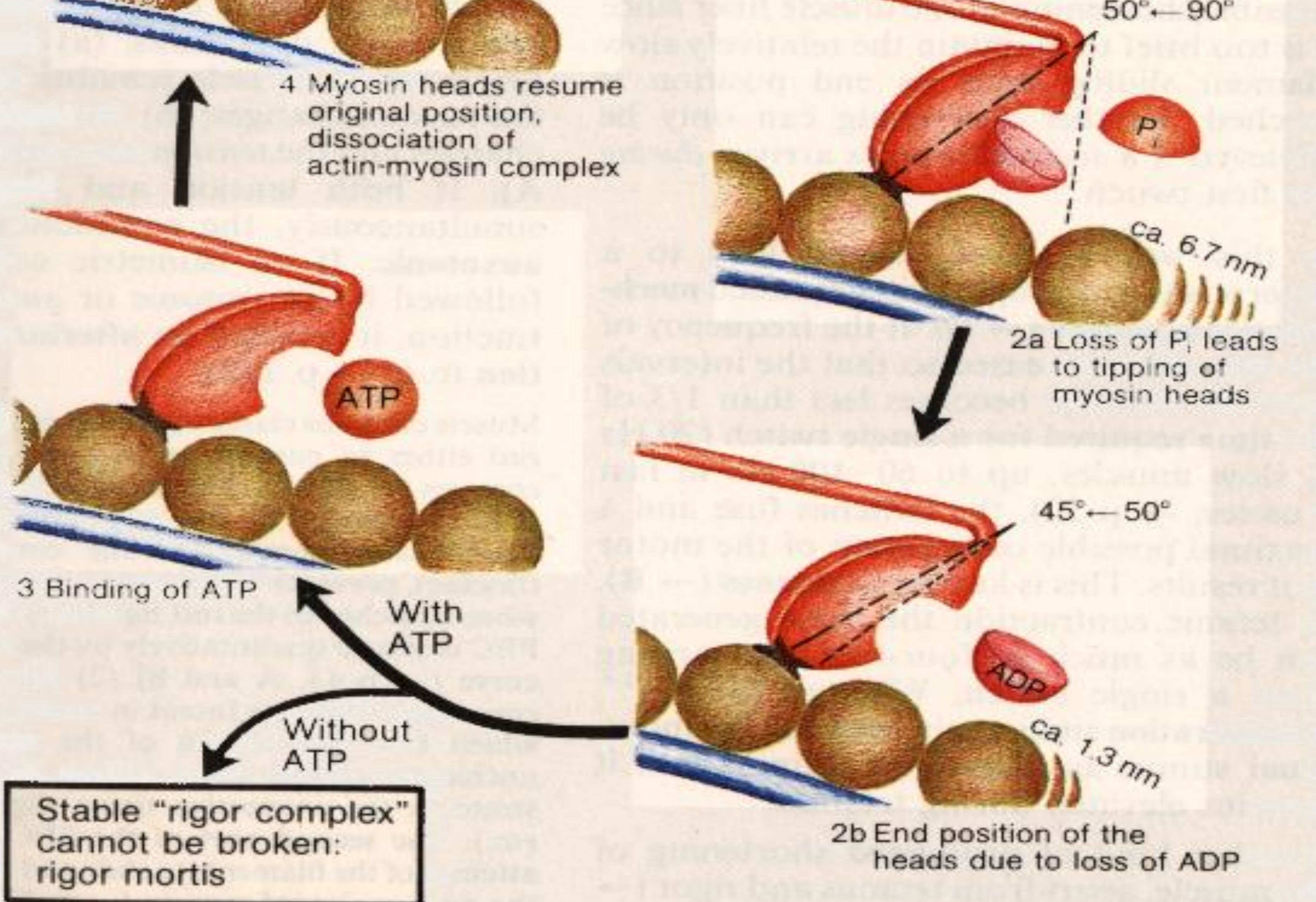
B. Ca^{2+} as mediator between electrical stimulation and contraction



C. Filament sliding



Incoming
action potential
T-system
Ca^{2+}
Longitudinal
tubules
Myosin
ATP
Tropomyosin
Actin
Troponin
Resting position
Mg^{2+}
P_i
ATP
ase
ADP
$[Ca^{2+}]_{ics}$
≤ 1 μmol/l
$[Ca^{2+}]_{ics}$
≈ 1-10 μmol/l
Ca^{2+}
45° → 90°
Relaxing effect
of ATP
ATP
1 Formation of
actin-myosin complex,
splitting of ATP
50° ← 90°
P_i
4 Myosin heads resume
original position,
dissociation of
actin-myosin complex



A. Molecular mechanisms involved in the sliding of actin and myosin filaments (isotonic contraction)

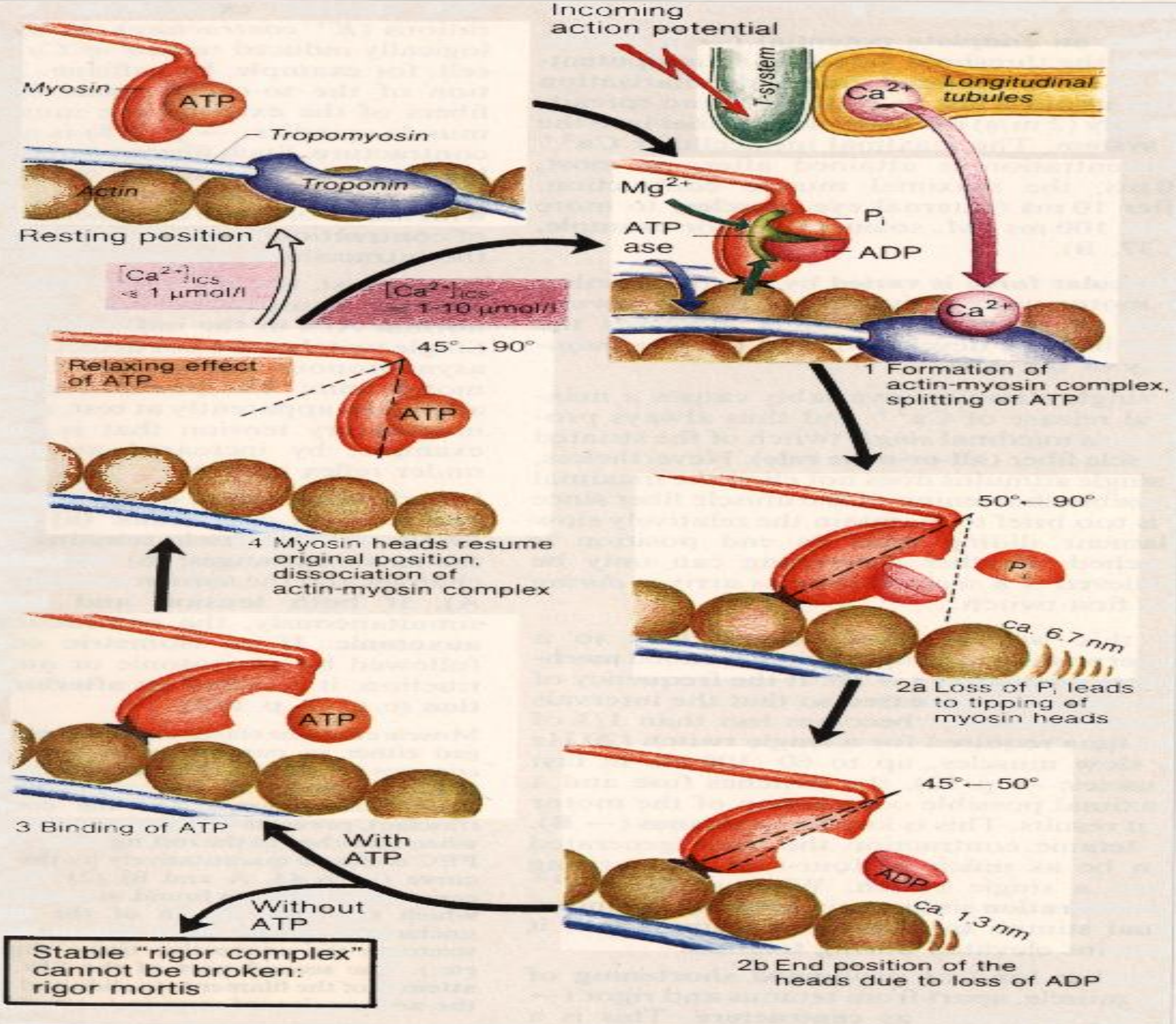
Sliding Filament Model

Muscle contracts, or shortens, when two kinds of myofilament (actin and myosin) slide past each other, increasing the amount of overlap between them.

Lengths of myofilaments do not change.

Cross bridges form between heads of myosin molecules and actin act as hooks.

Actin myofilaments are pulled toward the M line, the middle of the sarcomere.

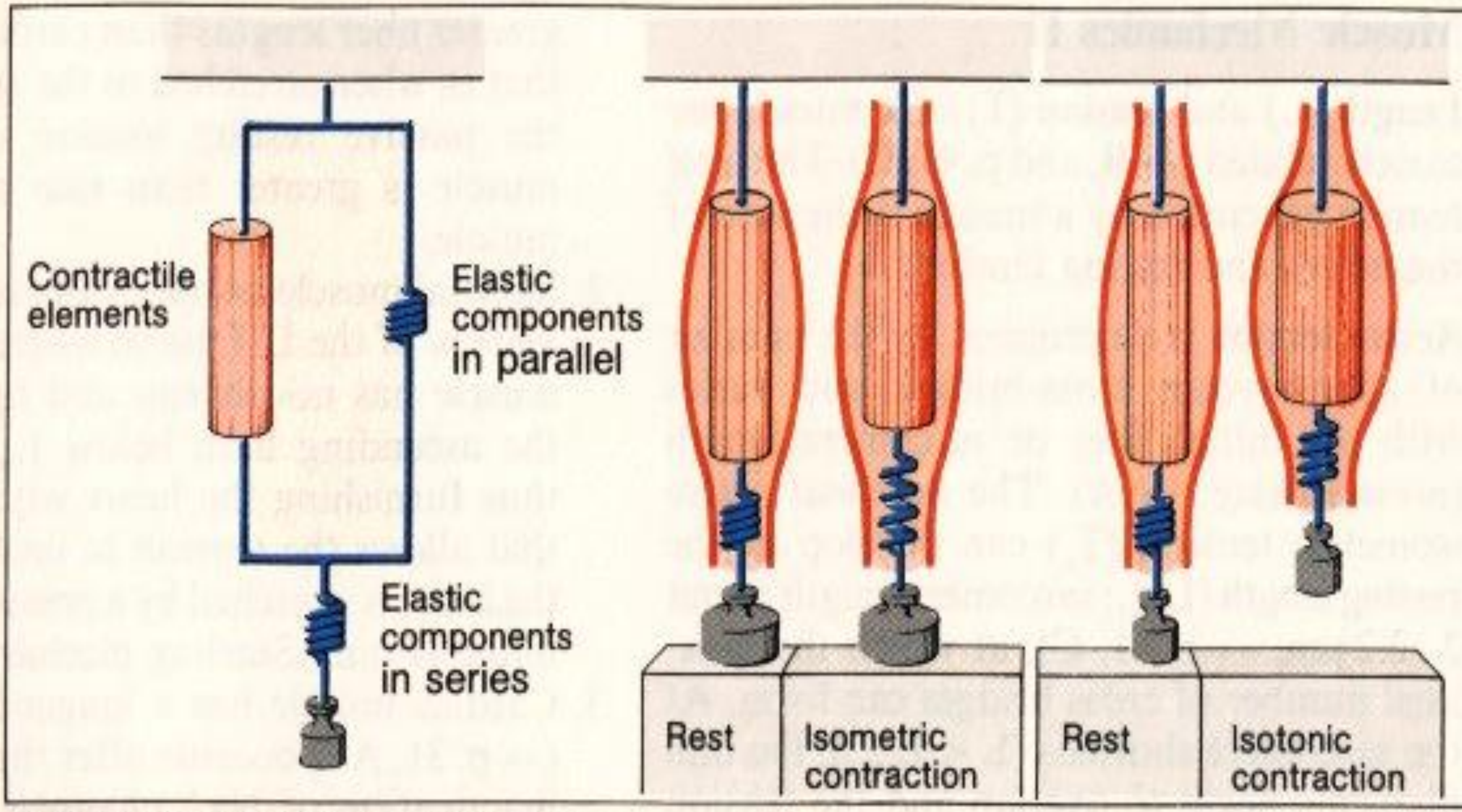


A. Molecular mechanisms involved in the sliding of actin and myosin filaments (isotonic contraction)

Summary of Excitation-Contraction Coupling

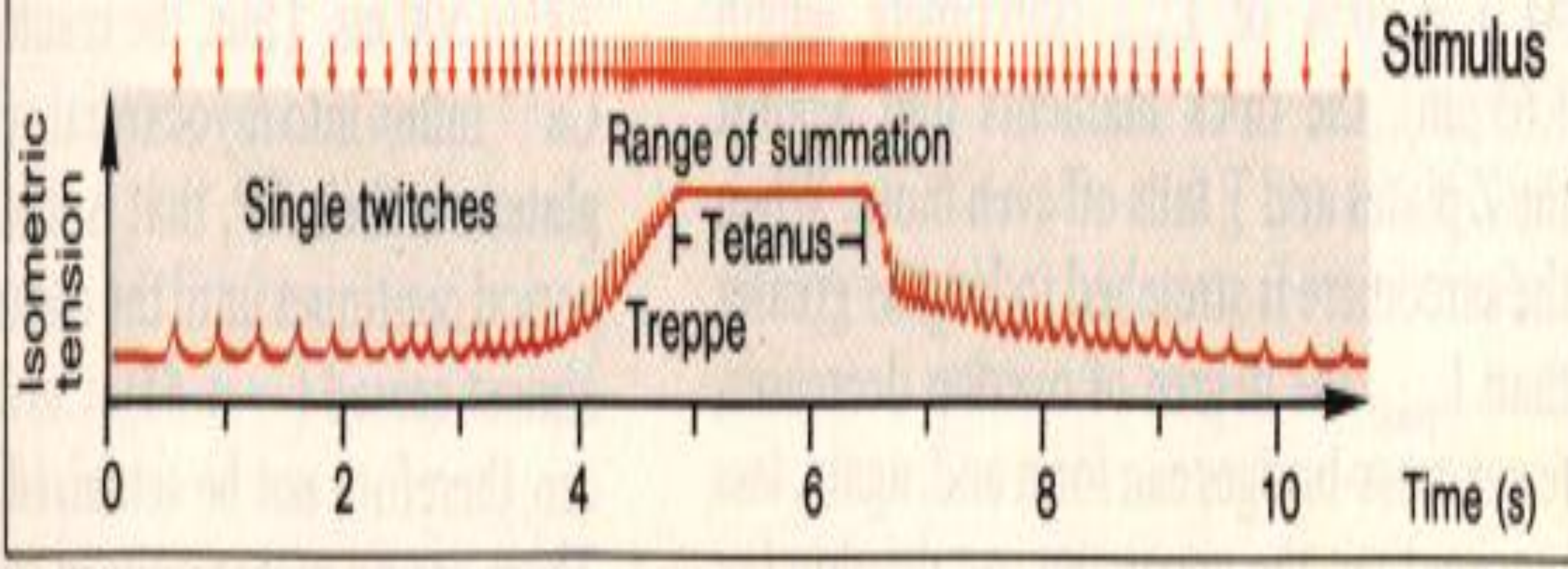
1. Powered by the hydrolysis of ATP.
2. **Actin** myofilaments contain actin, tropomyosin, and troponin complex arranged in thin, twisted strands.
3. **Myosin** myofilaments composed of myosin molecules which have oval-shaped "heads" and long "tails."
4. **Tropomyosin** blocks binding sites on actin from combining with myosin - no cross bridges.
5. Myosin heads are in low energy configuration.
6. When action potential reaches the T tubules, Ca2+ is released from the sarcoplasmic reticulum.
7. Ca2+ binds to troponin complex on the actin myofilament, causing the complex to shift and move the tropomyosin strand away from its blocking position. This leaves the active
8. binding site on the actin exposed.
9. Myosin heads bind to actin, i.e. cross bridges are formed.
10. Cross bridge binding allows myosin to act as an enzyme and split the ATP stored on the myosin heads into ADP and inorganic phosphate. Energy is released and used to move the myosin heads toward the actin myofilaments.
11. Myosin head tilts, pulling the actin myofilament along so that myosin and actin myofilaments slide past each other.
12. Actin myofilaments from opposite ends of the sarcomere move toward each other and the muscle contracts.
13. As myofilaments slide, cross bridges detach from one site and attach to the next site. May occur as often as 100 times a second.

Mechanical Features of Skeletal and Cardiac Muscle



A. Model of muscle contraction

Maximal force when minimal shortening (isometric pushing or drugging).
More energy is consumed and more heat produced with fast (light weight) and frequent isotonic contractions



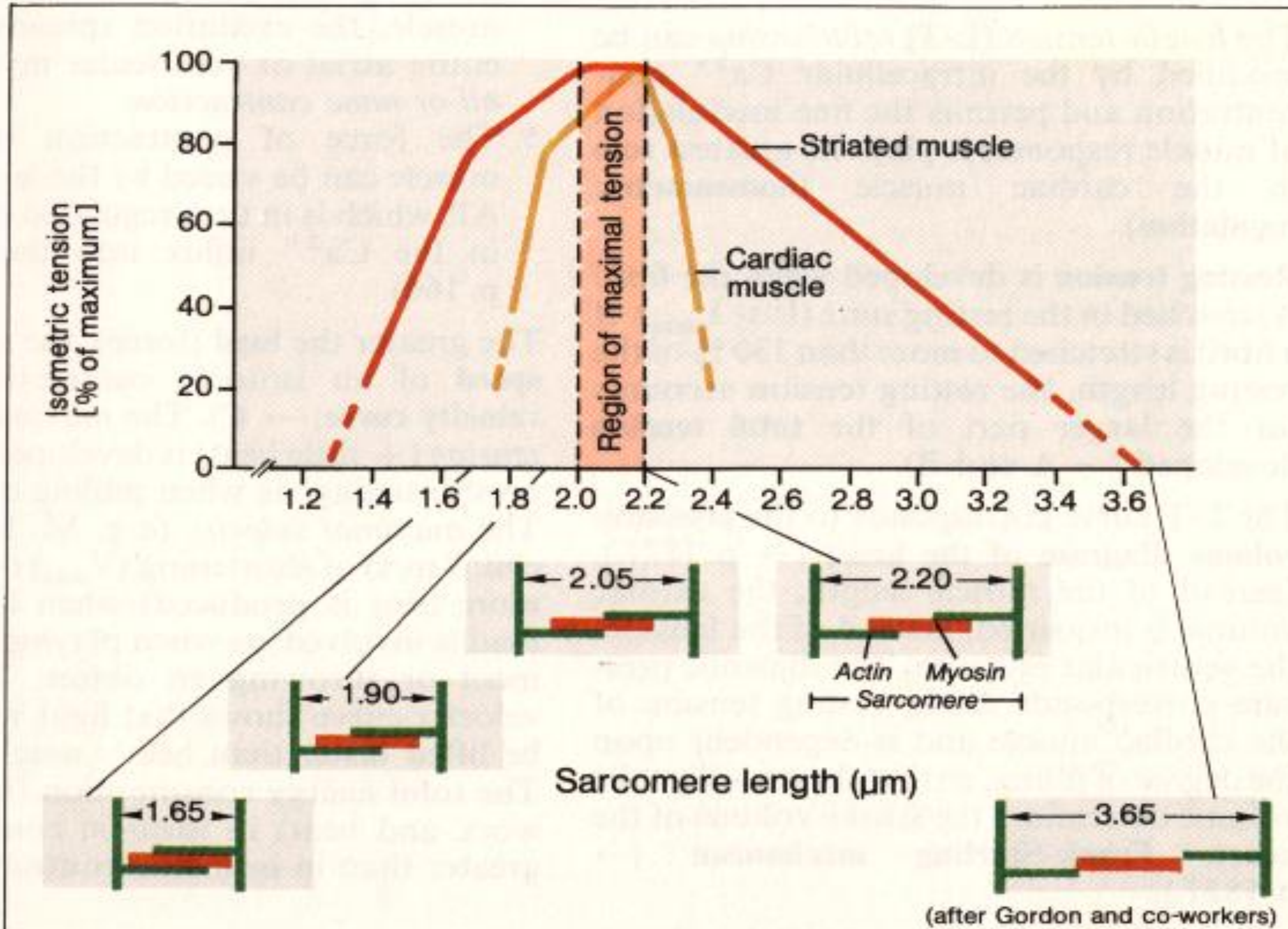
B. Stimulus frequency and muscle tension

Muscular force depends on :
-- number of cross-bridges formed in a single muscle fiber
-- degree of Motor Units recruitment
-- frequency of Action potentials

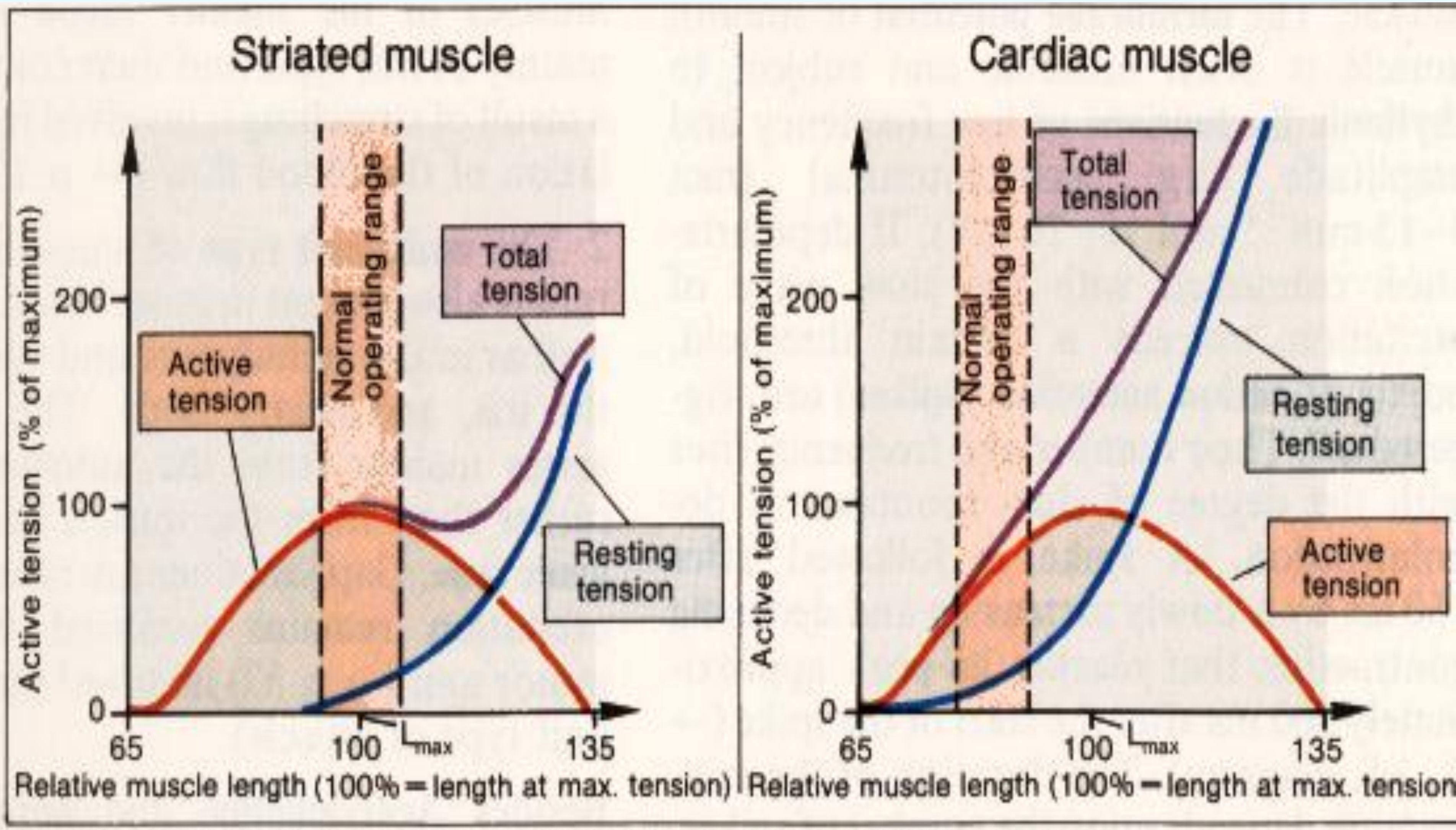
Single stimulus → single twitch (F)
Two stimuli in short interval → mechanical summation
Many stimuli at high frequency → tetanus (4xF) - ?underlying mechanism

Muscle Relaxation

1. ACh broken down by AChE which is released from the plasma membrane of the muscle fiber prevents further stimulation of the muscle fiber by the motor neuron.
2. Ca2+ moves away from the myofilaments actively transported back into the sarcoplasmic reticulum by Ca-ATPase.
3. Troponin and tropomyosin once again block the binding sites so cross bridges can't form. Sarcomeres return to regular resting length.



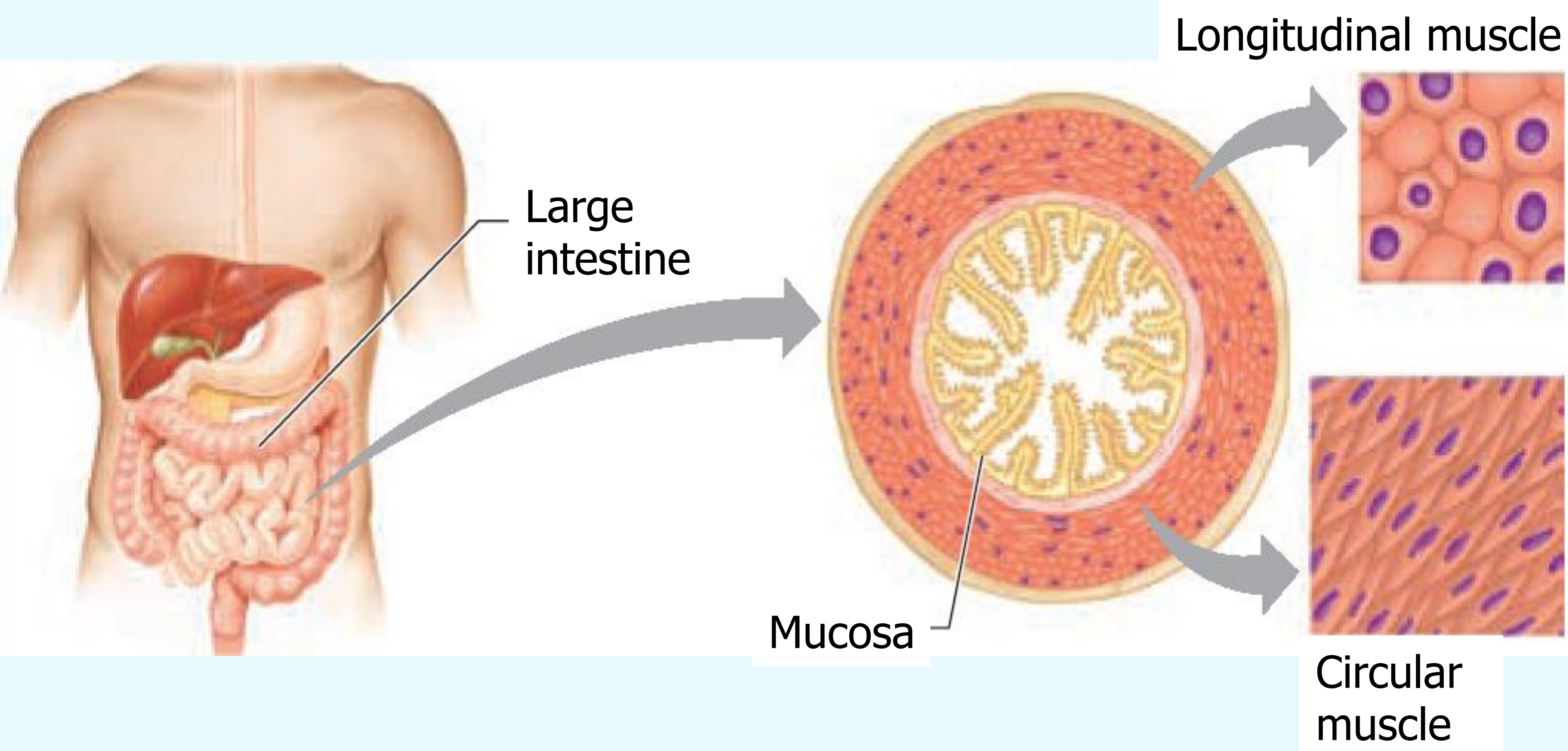
C. Isometric tension relative to sarcomere length



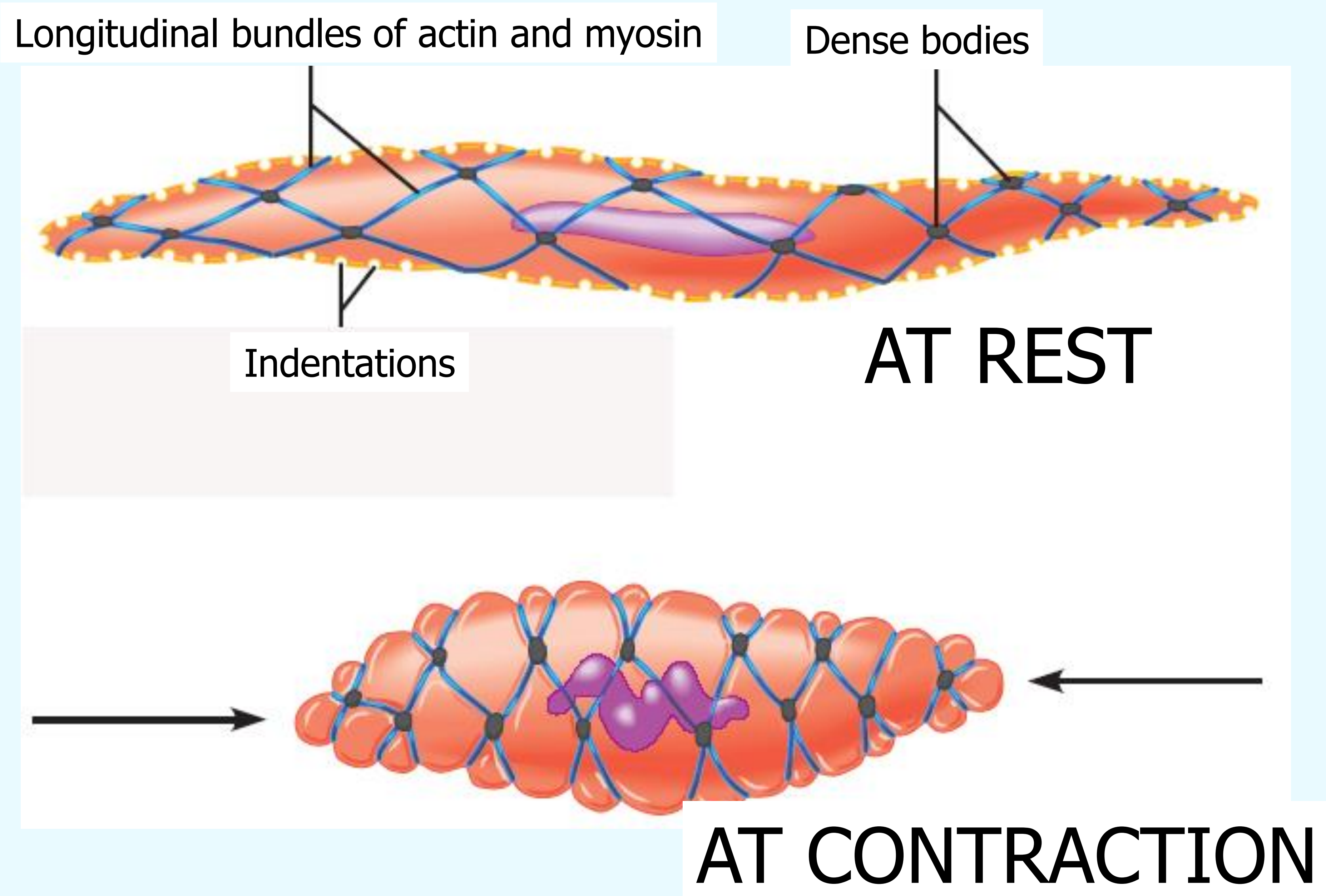
B. Length-tension curves for striated and cardiac muscle

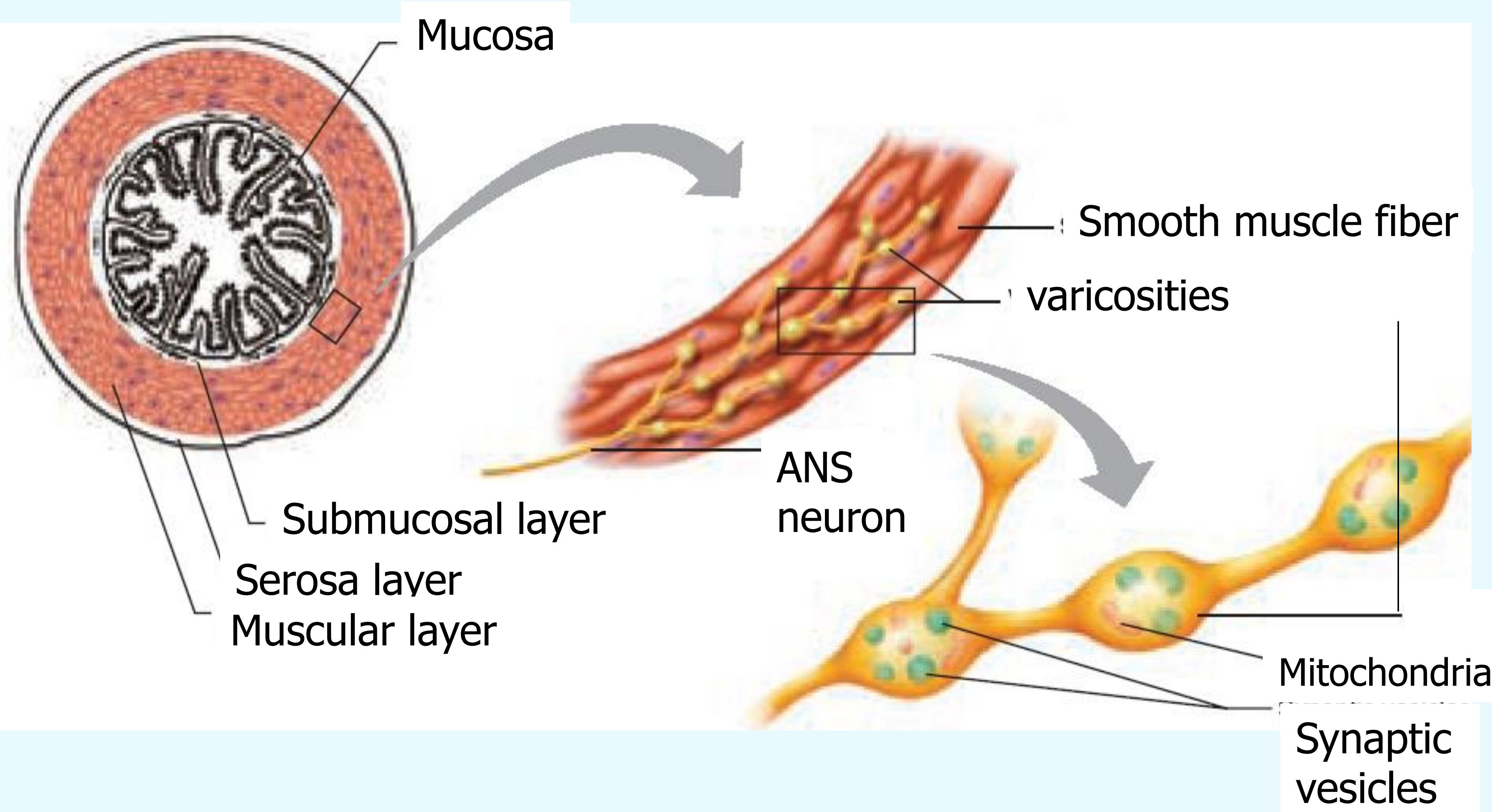
See Frank-Starling mechanism

Smooth Muscle



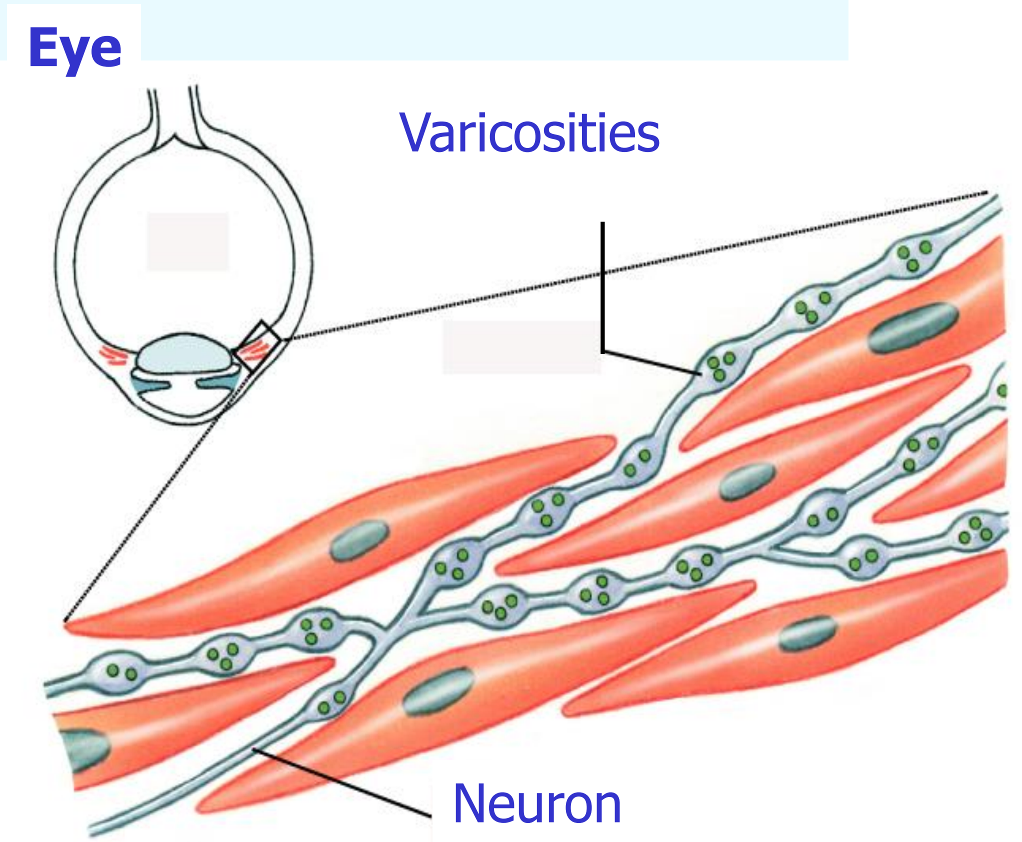
SMOOTH MUSCLE
fibers on the wall of hollow organs

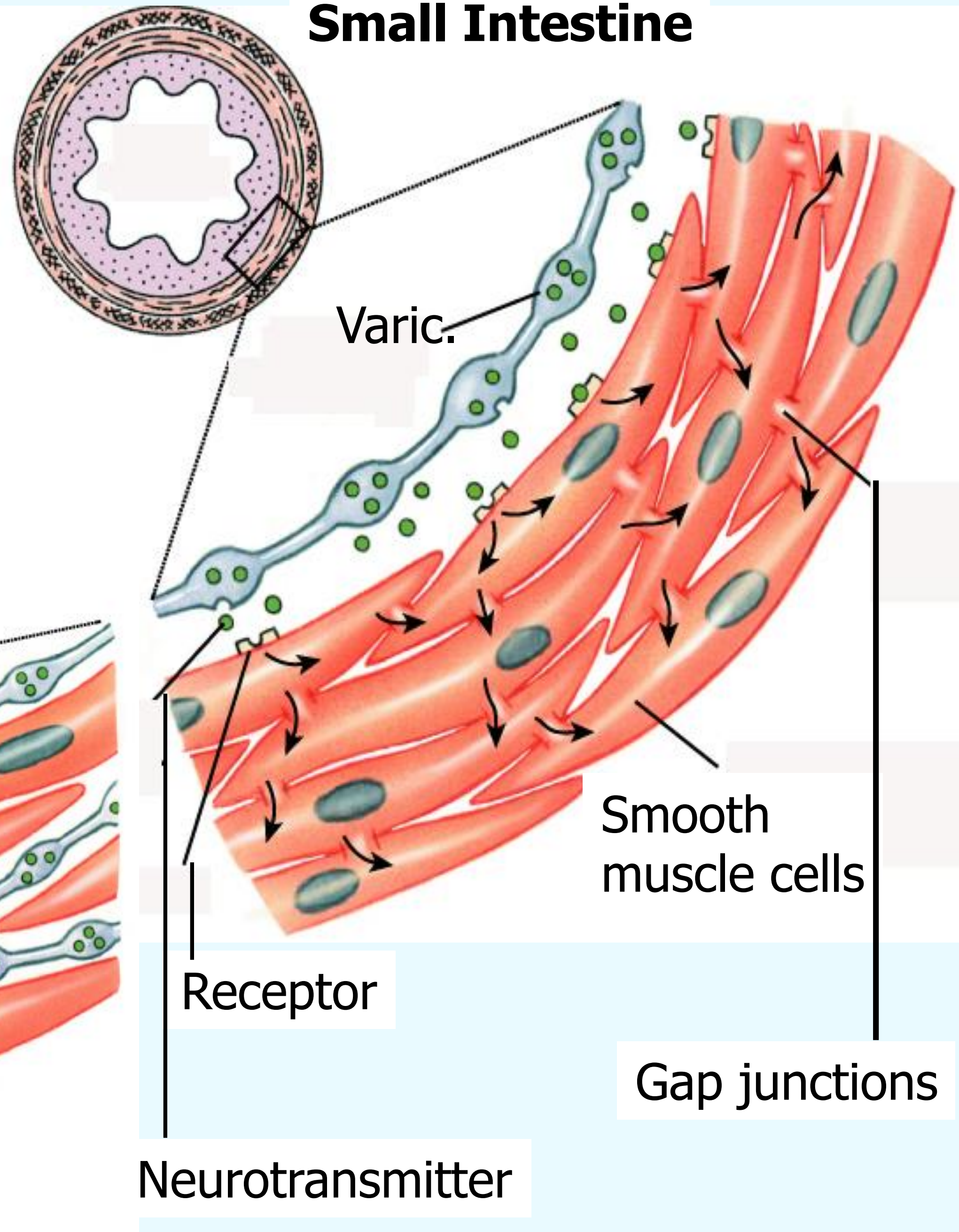

Longitudinal bundles of actin and myosin
Dense bodies
Indentations
AT REST
AT CONTRACTION

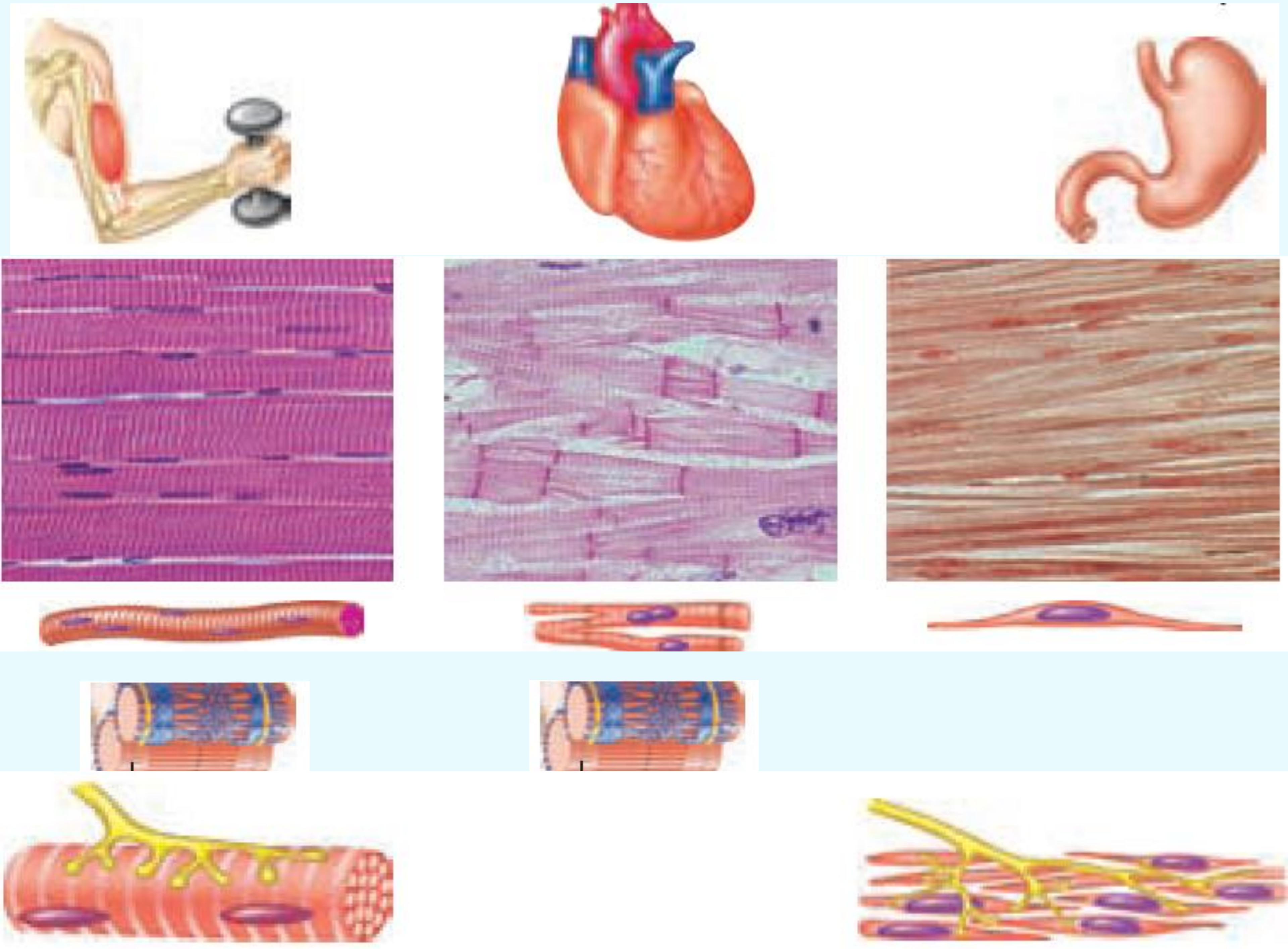

Mucosa
Smooth muscle fiber
varicosities
ANS
neuron
Submucosal layer
Serosa layer
Muscular layer
Mitochondria
Synaptic
vesicles

Singular type of smooth muscle

Multiunit type of smooth muscle







Smooth Muscle

- Not striated, so appears smooth.
- **Involuntary muscle** - controlled by autonomic nervous system.
- Found in circulatory, digestive, respiratory, and urogenital systems.
- Not connected to bones.
- Generally forms sheets in walls of large, hollow organs and walls of some blood vessels.

Properties of Smooth Muscle

- Contraction and relaxation periods are **slower** than those of any other type of muscle.
- . Contractions can last for 30 s or more but **does not tire** easily.
- Action is **rhythmical.**
- **Can stretch** far beyond resting state.

Structure of Smooth Muscle

•Cells are called fibers. Long, spindle-shaped, and slender.
•Single nucleus, usually near center of fiber at its widest point.
•Contain actin, myosin (chemically different from that in skeletal muscle), tropomyosin, but lack troponin.
•Poorly developed SR. T tubules and Z lines missing.
•Different contraction mechanism triggered by Ca++.

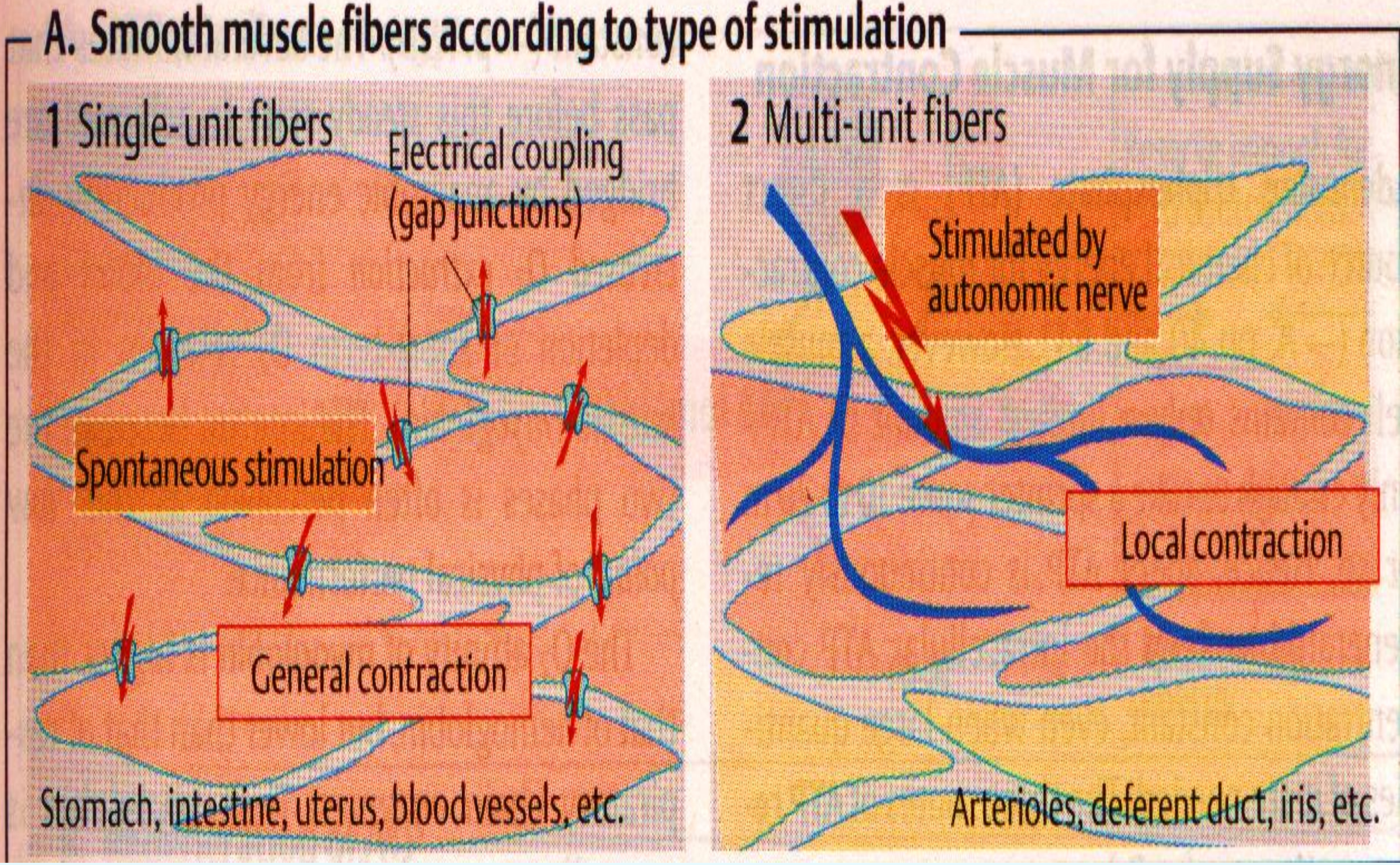
Smooth Muscle Fibers

•Actin and myosin are arranged in long bundles that extend diagonally around the periphery of the cell.
•Become globular rather than just shorter when contract.
•Actin filaments attached to **dense bodies**, protein in cytoplasm that is analogous to Z disks. More actin relative to myosin than in skeletal muscles.
•Myosin entirely covered by myosin heads. Isoform of type found in skeletal muscles.

Types of Smooth Muscle

Single-unit (visceral) smooth muscle – most prevalent. Muscle fibers electrically coupled by gap junctions. Action potentials can spread rapidly throughout a sheet of tissue. Graded contractions depend on amount of Ca2+ that enters cell.

Multi-unit smooth muscle – found in iris and ciliary body of eye, part of male reproductive tract, and uterus except just prior to labor and delivery. Cells not linked electrically. Each muscle fiber associated with an axon terminal or varicosity. Allows fine control of contraction by number of units activated.


A. Smooth muscle fibers according to type of stimulation
1 Single-unit fibers
Electrical coupling
(gap junctions)
Spontaneous stimulation
General contraction
Stomach, intestine, uterus, blood vessels, etc.
2 Multi-unit fibers
Stimulated by
autonomic nerve
Local contraction
Arterioles, deferent duct, iris, etc.

Energy Supply for Muscle Contraction

Sources of ATP

Enough ATP present in a resting muscle to allow it to contract for a few seconds.

Primary source of extra ATP is from transfer of phosphate from **creatine phosphate** to ADP during a muscle contraction. Only enough for a few additional seconds of contraction.

For sustained contractions, ATP comes from breakdown of stored muscle glycogen into glucose and subsequent breakdown of glucose by cellular metabolism. Also break down fats and amino acids.

Return to Resting State

- Skeletal muscle at rest produces more ATP than it needs.
    - ATP transfers energy to creatine phosphate.
    - **ATP + creatine --> ADP + creatine phosphate**
- Breakdown of glucose to form ATP continues until resting level of creatine phosphate is restored.
    - **Where does this occur?**
    - Glycolysis in cytoplasm (2 ATP)
    - Oxidative phosphorylation in mitochondria (34 ATP)
- Glucose then used to replenish the glycogen depleted during contractions.

Strenuous Exercise

- **Glycolysis -** glucose broken down into two molecules of pyruvic acid. Net 2 ATP.
- **Aerobic respiration -** pyruvic acid enters citric acid cycle in mitochondria. Net 34 ATP.

Pyruvate + O2 ==> CO2 + H2O + energy

Amount of oxygen supplied to muscles may not be adequate to break pyruvic acid into CO2 and H20 so pyruvic acid is reduced to **lactic acid,** **anaerobic respiration** (does not require oxygen). Allows muscles to continue contracting for short time.

Muscle Fatigue

- No change in nervous impulses, neuromuscular junctions, or stimulation of muscle fibers. Contractions become weaker and weaker until muscle stops contracting **because**

•. Insufficient ATP.

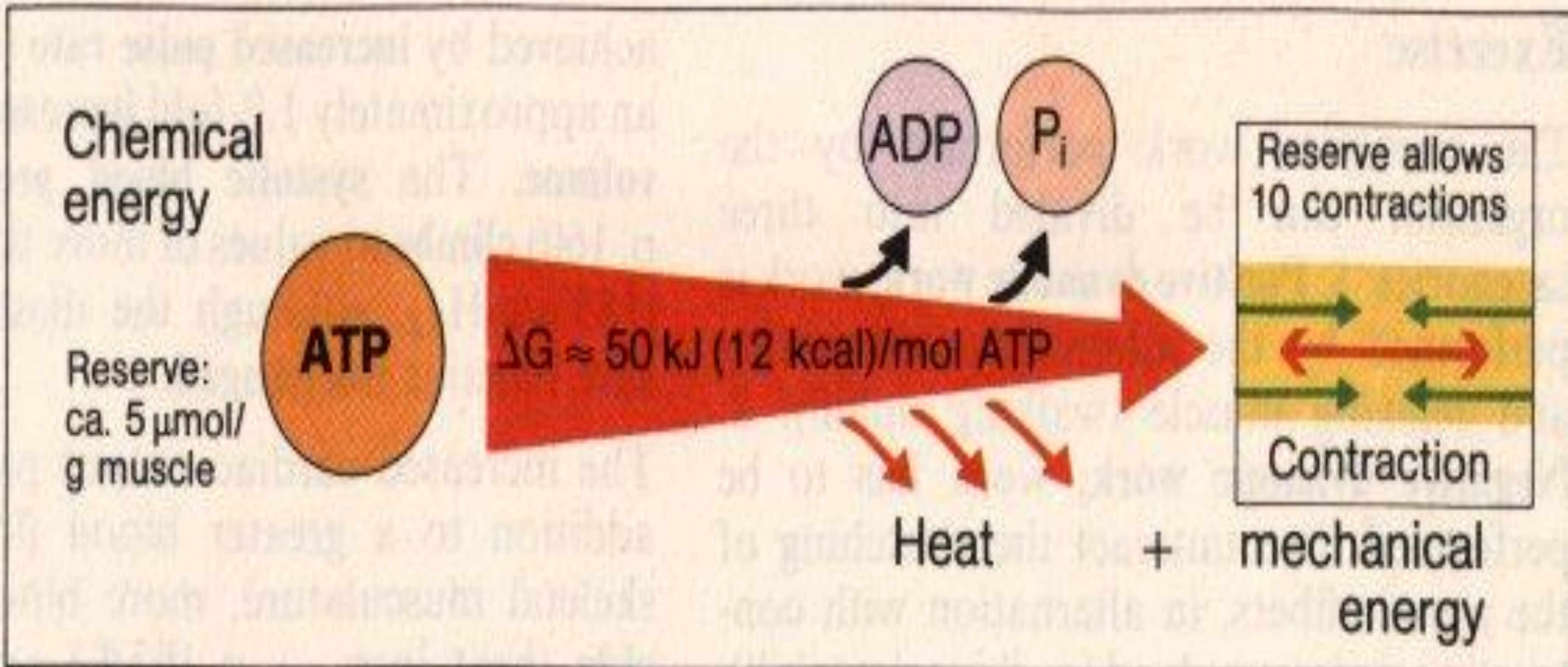
•. Accumulation of toxic products (CO_2 and lactic acid).

•. Circulatory disturbances to muscle prevent delivery of nutrients and removal of waste products.

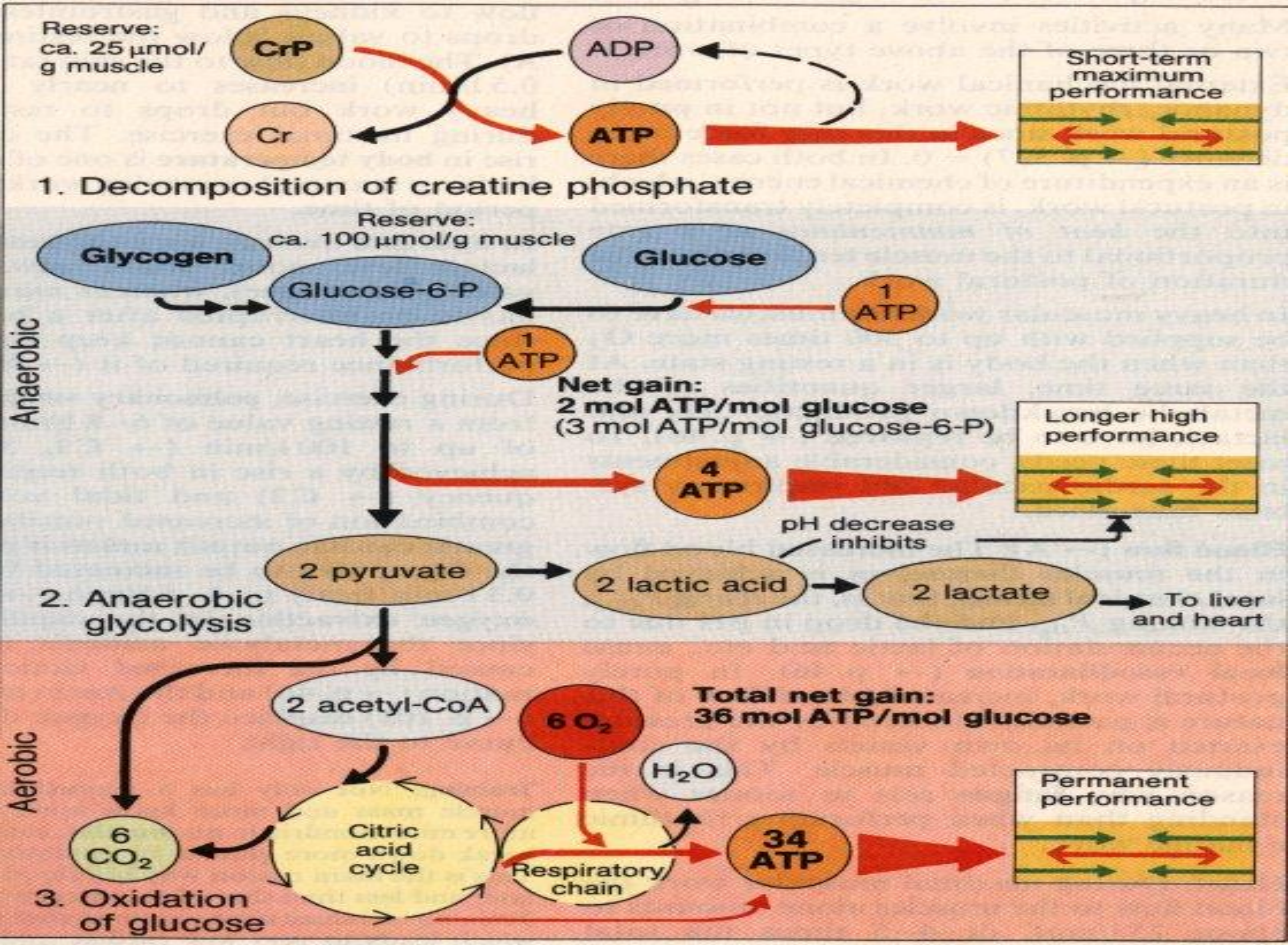
- Muscle does not contract, but does not relax either. Complete fatigue can be confused with muscle cramp. If continue to use, will convert protein in fibers for energy.

•Occurs due to **build up of lactic acid**. Lowers pH in tissue. Lactic acid must be removed from muscle fibers by converting it into CO_2 and H_2O, a process that requires oxygen. Oxygen in short supply due to strenuous exercise. Take deep, rapid breaths to provide oxygen for fatigued muscle fibers.

•**Oxygen debt** - amount of extra oxygen needed to metabolize the accumulated lactic acid and restore ATP to normal levels.



A. ATP as direct energy source



B. Regeneration of ATP

There are 2 types of muscles with a gradual variation

Fast-Twitch Muscles

•Short contraction-relaxation cycles (~30 ms), e.g. muscles that move the eyes.
•Fibers adapted to produce rapid contractions.
•Contain many mitochondria and extensive SR for plentiful supply of Ca^{2+}.
•Tire easily. Contain little **myoglobin**, oxygen-binding protein.
•Fewer capillaries than slow-twitch. Make up white muscles.

Slow-Twitch Muscles

• Long contraction-relaxation cycles, e.g. soleus muscle in leg (~3 s). Muscles in back for maintaining posture.
• Fibers adapted to produce prolonged, steady contractions. Do not tire easily.
• More mitochondria than fast-twitch. Do not have or need large supply of Ca^{2+}.
• Contain lot of **myoglobin**, oxygen-binding protein.
•Extensive capillaries. Make up red muscles.

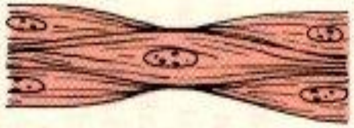
Muscle Fibers

•Most people have approximately equal numbers of fast-twitch and slow-twitch fibers in running muscles, e.g. gastrocnemius.
•Sprinters have more fast-twitch muscles and long distance runners have more slow-twitch muscles. Tests of two world class marathon runners showed that one had about 75% slow-twitch fibers and other had about 93%
•. Slow-twitch muscles take longer to reach maximal contraction, but can sustain it as long as oxygen is available.

Οξειδωτική φωσφορυλίωση

Αναερόβια γλυκόλυση

A. Structure and function of 3 classes of muscle

		Smooth muscle	Cardiac muscle	Skeletal muscle
				
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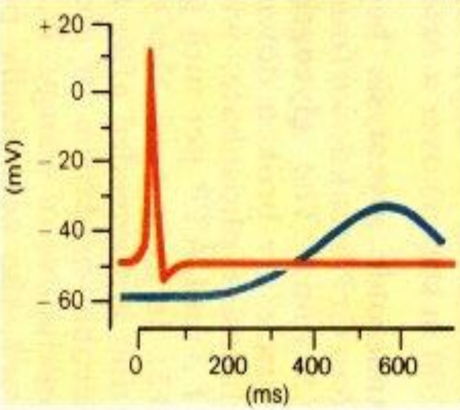
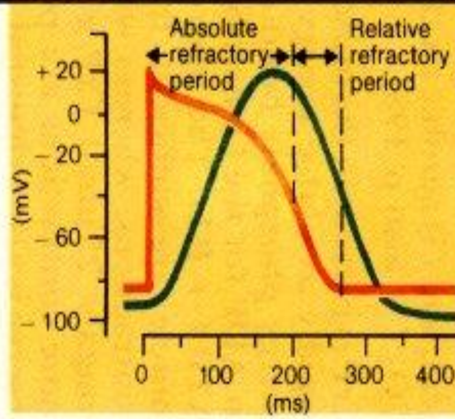
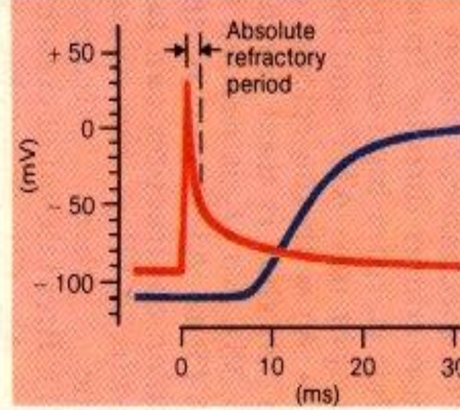
	Nucleus/fiber	1:1	1:1	Several per fiber
	Sarcomere	None	Yes-max. length 2.6 µm	Yes-max. length 3.65 µm
	Syncytium	Yes (bridges)	Yes (functional)	No
	Sarcoplasmic reticulum	Poorly developed	Well developed	Extensively developed
	ATPase	Little	Average	Much
Function	Pacemaker	Yes (slow)	Yes (fast)	No (requires neural impulse)
	Response	Graded	All or none	Graded
	Tetanus	Yes	No	Yes
	Operating range	Variable length-tension curve	On rising portion of length-tension curve	On peak of length-tension curve
Response	Potential; Mechanical tension			

Effects of Physical Activity

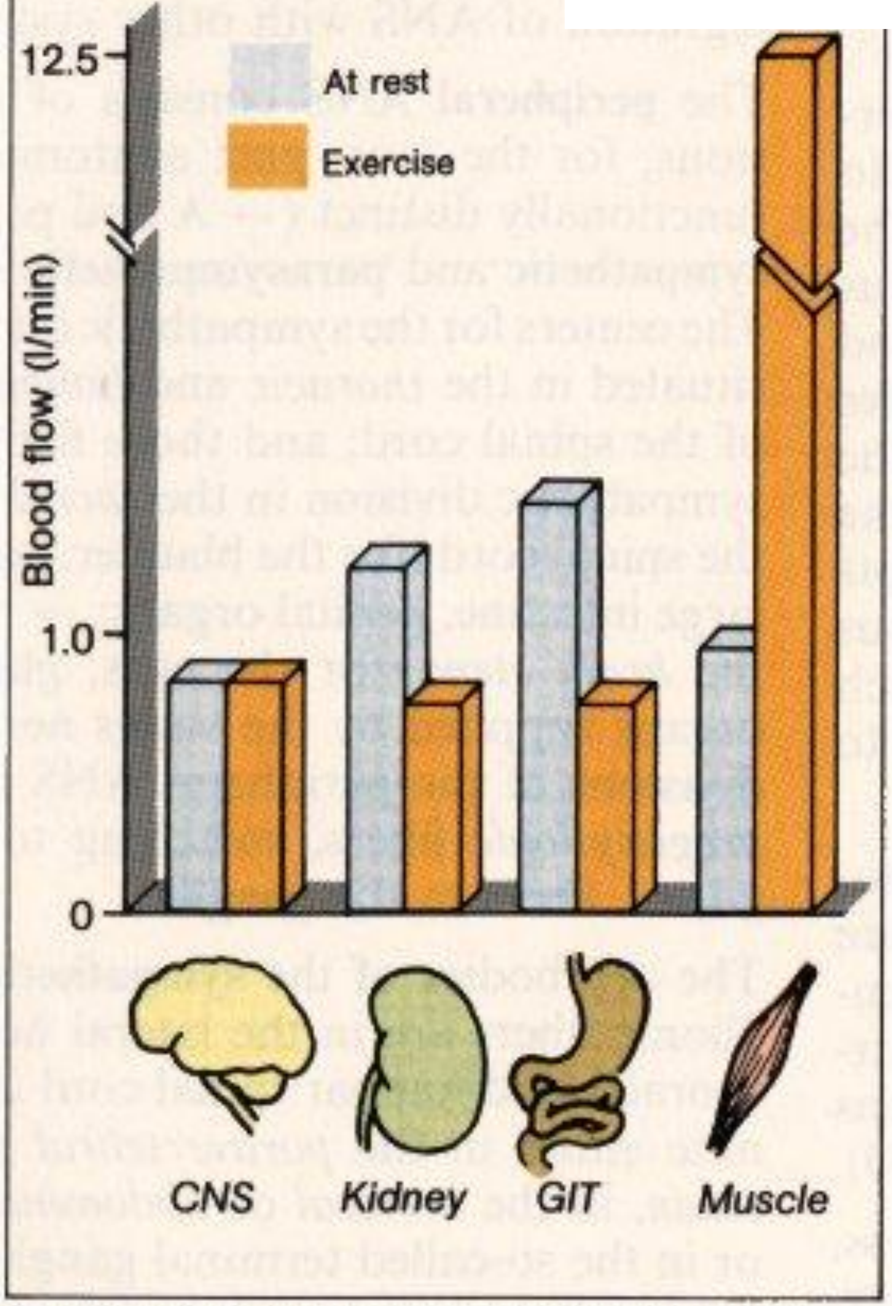
Muscular hypertrophy - as result of strenuous physical activity, **diameter** of individual fibers increases as do number of myofibrils and mitochondria, amount of SR, and blood supply.

. Exercised muscle becomes larger and stronger and uses oxygen and available energy more efficiently. Efficiency of trained athlete is about 20-25% but some have achieved 40% efficiency.

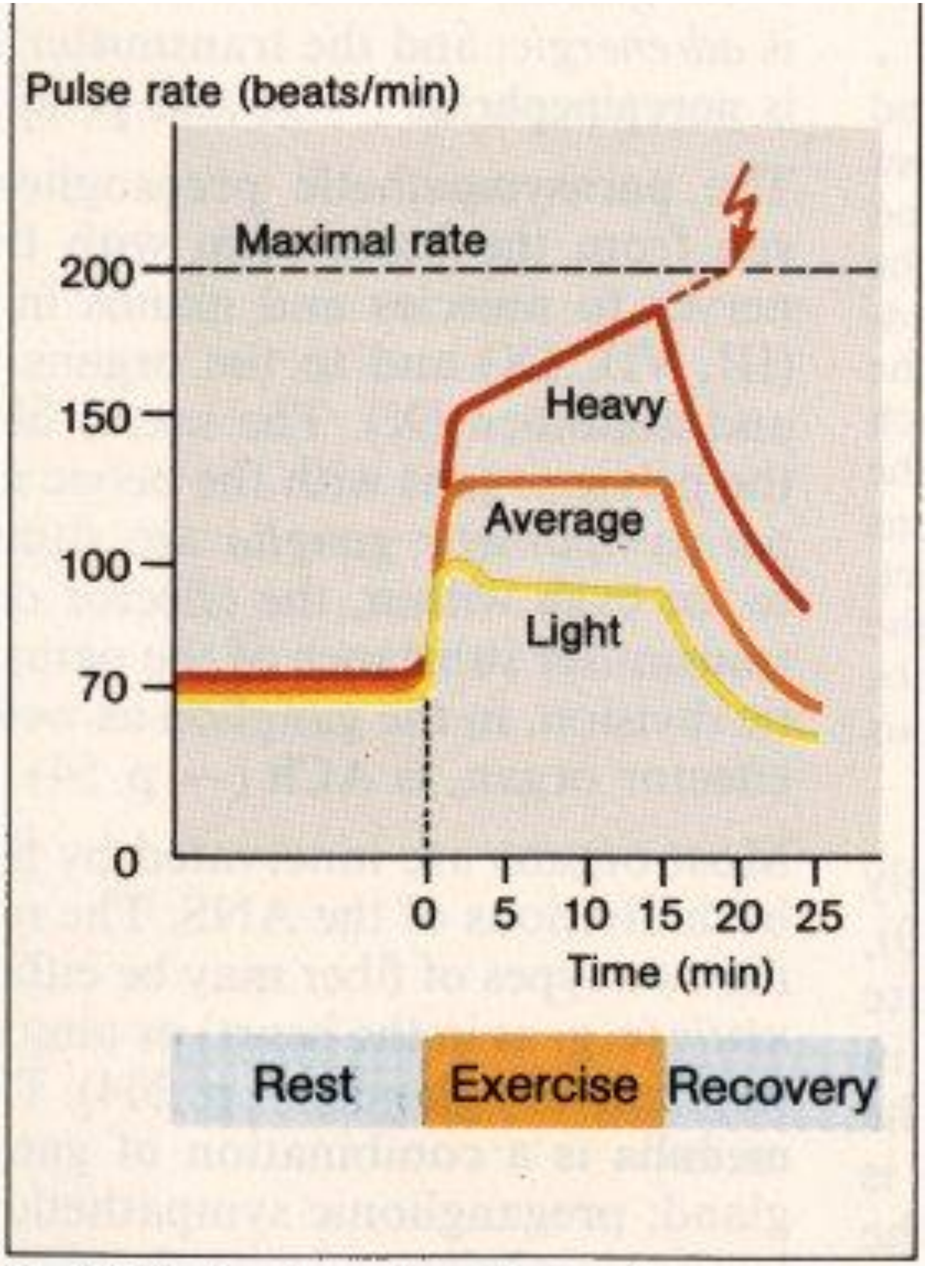
Muscular atrophy - muscles shrink and become weak if not used over a period of months. Metabolic activity decreases.

. Astronauts show decrease in muscle mass after prolonged weightlessness. About half of atrophied muscles also have damaged nerve endings which produce poor coordination.

Blood circulation in exercise

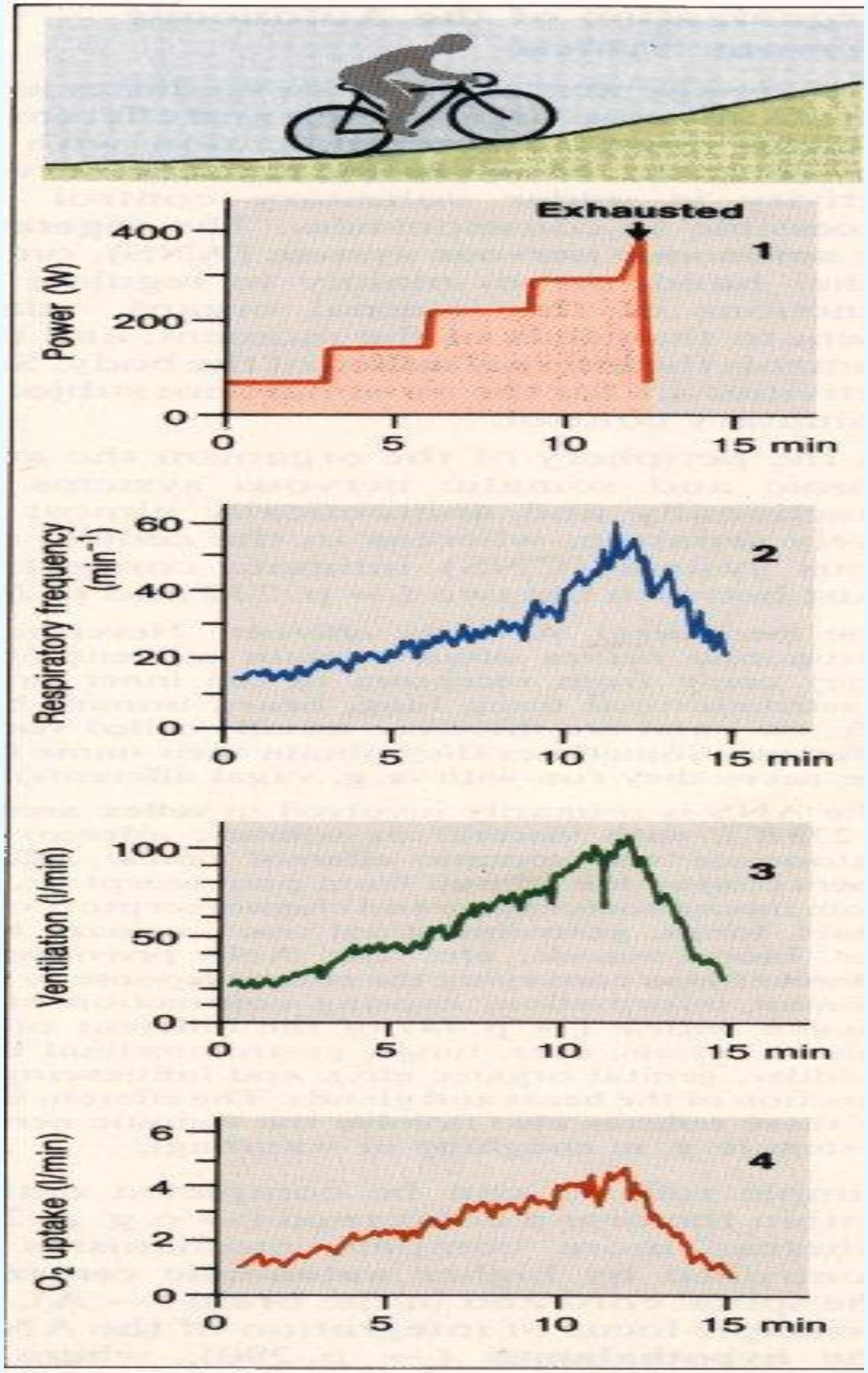


A. Blood flow response to exercise



B. Work load and pulse rate

Respiration in exercise



C. Respiration during exercise

Strength of Contraction

Number of fibers stimulated - the greater the number of motor units recruited, the greater the strength of muscle contraction.

Muscle size - greater the muscle size (cross-sectional area), the greater the strength of contraction. Can be increased through regular exercise.

Length-tension relationship - ideal resting length is length at which greatest tension can be developed. Length at which greatest number of cross bridges form between myosin and actin. Little overlap between actin and myosin = low tension.

By-Products of Mechanical Work

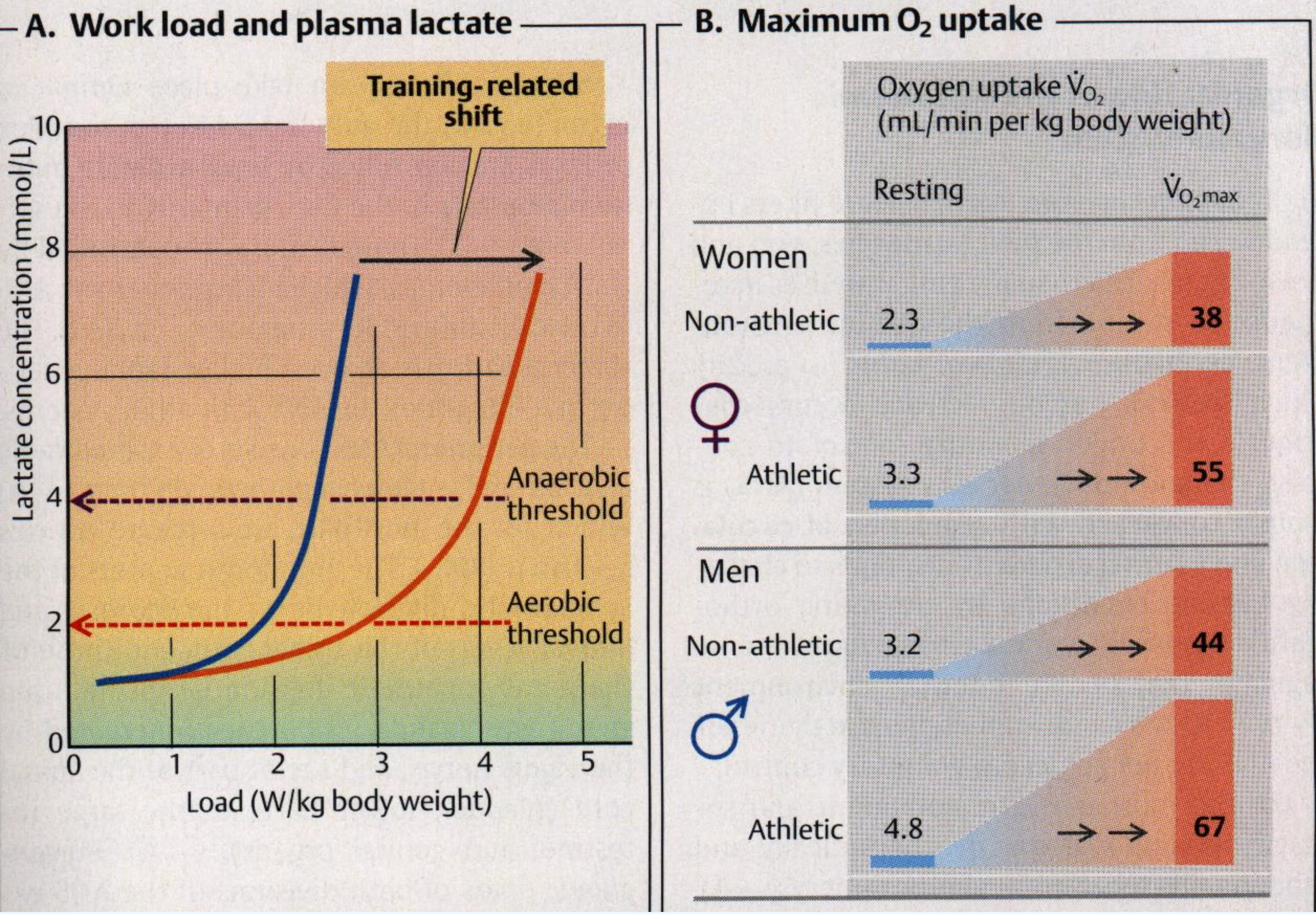
Heat production - major source of heat for temperature regulation.

. **Shivering -** muscular tremors that occur about 10-20 times a second. Also produced during heavy physical activity.

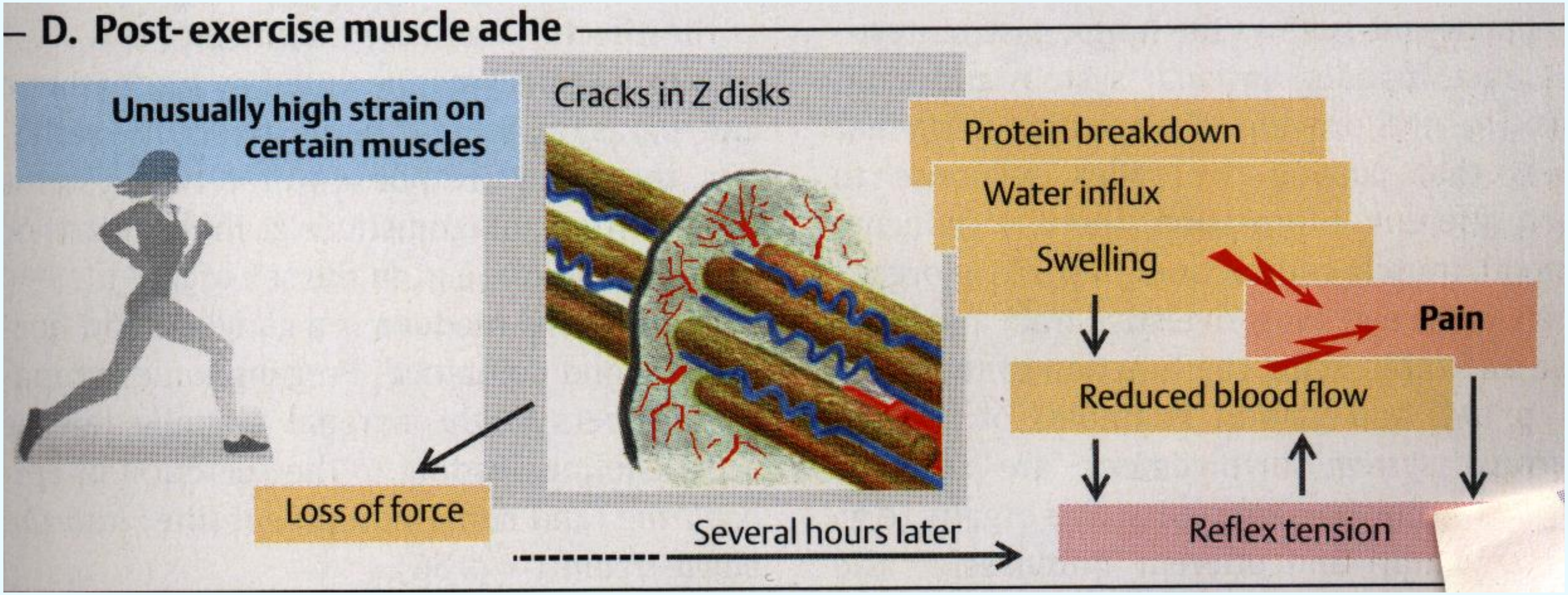
Oxygen debt - skeletal muscles use up oxygen faster than it can be supplied.

Muscle fatigue - occurs due to build up of lactic acid.

Physical Fitness and Training



A. Work load and plasma lactate
Training-related shift
Lactate concentration (mmol/L)
10
8
6
4
2
0
Anaerobic threshold
Aerobic threshold
0
1
2
3
4
5
Load (W/kg body weight)
B. Maximum O2 uptake
Oxygen uptake V̇O2 (mL/min per kg body weight)
Resting
V̇O2max
Women
Non-athletic 2.3 38
Athletic 3.3 55
Men
Non-athletic 3.2 44
Athletic 4.8 67


D. Post-exercise muscle ache
Unusually high strain on certain muscles
Cracks in Z disks
Protein breakdown
Water influx
Swelling
Pain
Reduced blood flow
Loss of force
Several hours later
Reflex tension

Cardiac Muscle

Found only in the heart.
Contains same type of myofibrils and protein components as found in skeletal muscle.
Contractile process basically same as for skeletal muscle.
Contain huge numbers of mitochondria (35% of cell compared with 2% of skeletal muscle cells), welldeveloped SR, and T tubules.

Cardiac Cells

Closely packed.
Joined end to end by special cell junctions, **intercalated disks**.
Intercalated disks contain desmosomes (spot welds) and gap junctions with channel proteins for almost instantaneous transmission of electrical signals from one cardiac cell to next.

Cardiac vs. Skeletal Muscle

SR less extensive in cardiac muscle.
Ca2+ of intact cardiac muscle > than that of skeletal muscle.
Cardiac muscle affected by calcium imbalances before skeletal muscle.
Cardiac cells can contract for longer periods than skeletal muscle cells due to large amount of Ca2+.
Long refractory period in cardiac muscle cells (200 ms vs. 1-2

Muscles and Bones

Origin - end of the muscle that is attached to the bone that does **not** move during a contraction.

Insertion - end of muscle that is attached to the bone that moves during a contraction.

Relative terms. Can be reversed with the same muscle, depending upon the action, e.g. muscles from chest to upper extremity generally move the extremity with the origin on the thoracic skeleton and the insertion on the extremity. When climbing rope, muscles pull body up so extremity is origin.

Lever Systems & Muscle Actions

Movements of most skeletal muscles accomplished through a system of levers with a rigid **lever arm** pivoting around a fixed point, the **fulcrum**.

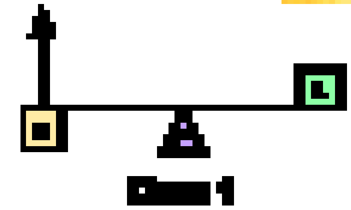
Two **forces** act on every lever -

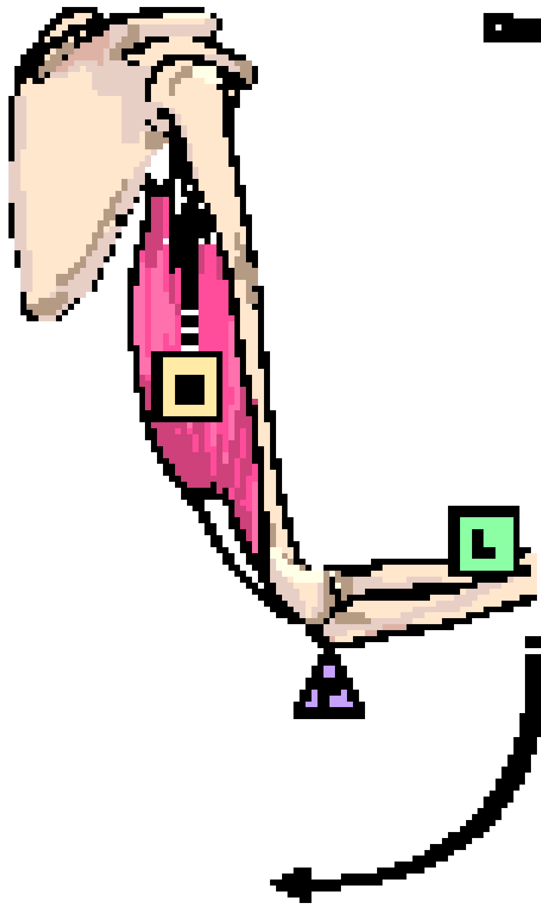
- Weight to be moved (resistance to be overcome).
- Pull or effort applied (applied force).

Bone acts as lever arm and joint as fulcrum.

First-Class Lever

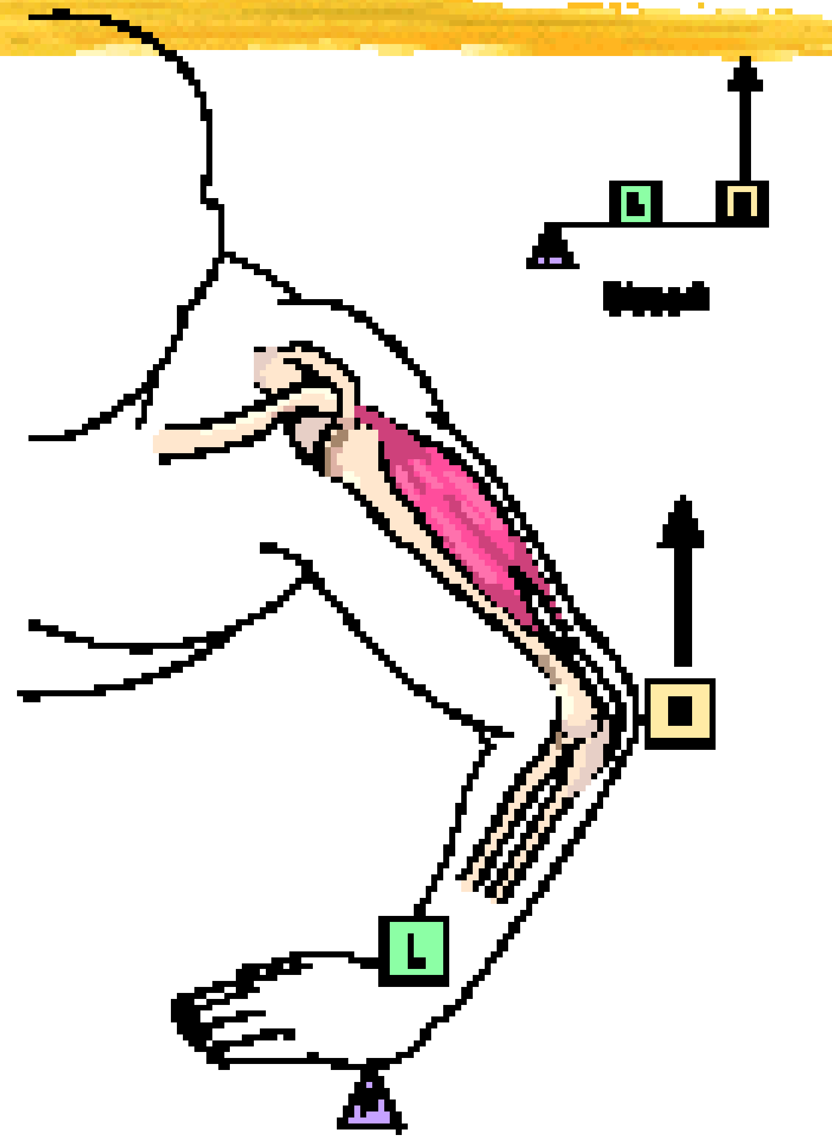
Force is applied at one end of the lever arm, the weight to be moved is at the other end, and the fulcrum is at a point between the two.



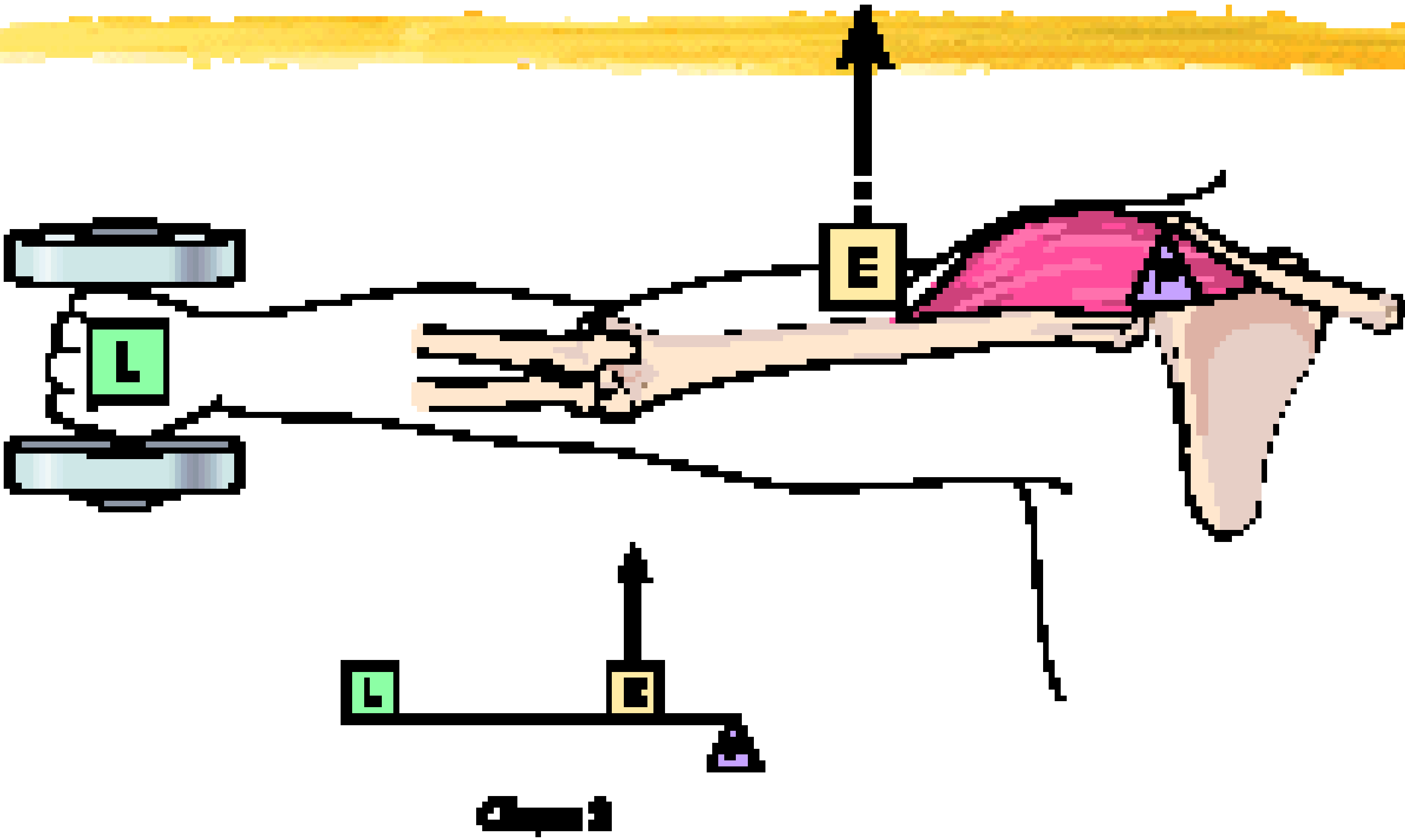


Second-Class Lever

The applied force is at one end of the lever arm, the fulcrum is at the other end, and the weight to be moved is at a joint between the two.



Third-Class Lever

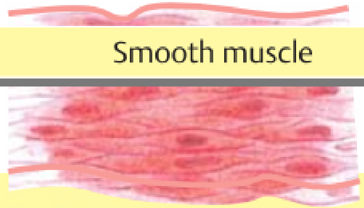


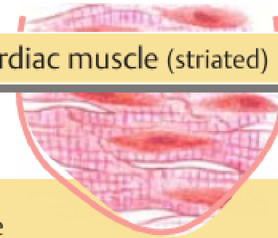
The weight to be moved is at one end of the lever arm, the fulcrum is at the other end, and the applied force to move the weight is close to the fulcrum. Most common lever in the body.

Levers in Body

- Second-class lever which raises body on ball of the foot is the only lever in the body which operates at a mechanical advantage.
- Lever system in body provides **speed of motion** at expense of great strength - evolved to run away from dangerous animals, not pick them up and throw them.
- Leverage of a muscle is improved as the distance from the insertion to the joint (fulcrum) is increased. Muscle with insertion relatively far from a joint has more force than a muscle with a closer insertion, but longer lever arm must move a greater distance so motion is slower.

A. Structure and function of heart, skeletal and smooth muscle



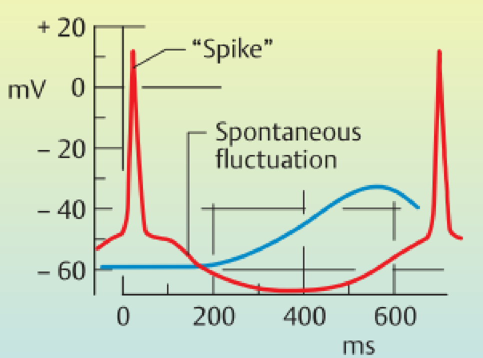


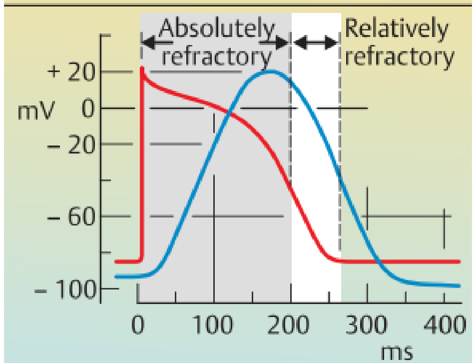
Structure and function	Smooth muscle	Cardiac muscle (striated)	Skeletal muscle (striated)
Motor end-plates	None	None	Yes
Fibers	Fusiform, short (≤ 0.2 mm)	Branched	Cylindrical, long (≤ 15 cm)
Mitochondria	Few	Many	Few (depending on muscle type)
Nucleus per fiber	1	1	Multiple
Sarcomeres	None	Yes, length ≤ 2.6 µm	Yes, length ≤ 3.65 µm
Electr. coupling	Some (single-unit type)	Yes (functional syncytium)	No
Sarcoplasmic reticulum	Little developed	Moderately developed	Highly developed
Ca^{2+} "switch"	Calmodulin/caldesmon	Troponin	Troponin
Pacemaker	Some spontaneous rhythmic activity ($1s^{-1}$ – $1h^{-1}$)	Yes (sinus nodes ca. $1s^{-1}$)	No (requires nerve stimulus)
Response to stimulus	Change in tone or rhythm frequency	All or none	Graded
Tetanizable	Yes	No	Yes
Work range	Length-force curve is variable	In rising length-force curve (see **2.15E**)	At peak of length-force curve (see **2.15E**)

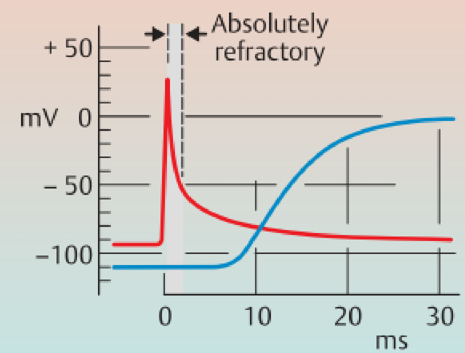
Response to stimulus

Potential

Muscle tension



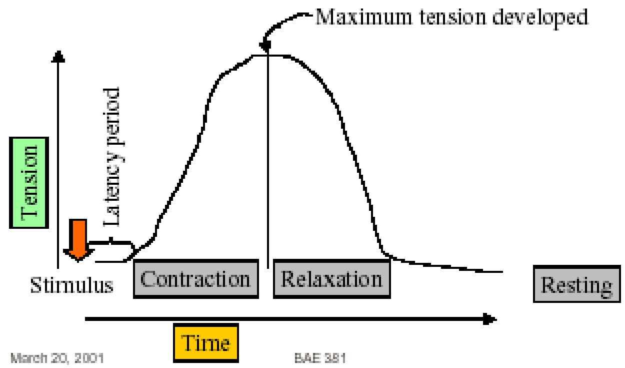




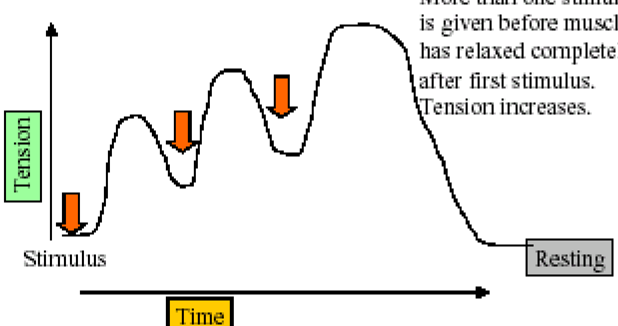
Twitch

- **Latent period** - brief period between electrical stimulus and beginning of contraction. Time during which Ca^{2+} is released from SR so that shortening is initiated. ~2 ms.
- **Contraction period** - upward part of tracing. Lasts 10 to 80 ms.
- **Relaxation period** - downward part. 10-80 ms. Active uptake of Ca^{2+} by SR.
- **Refractory periods** - 5 ms. Absolute and relative.
- Like turning a light switch on an off one time.

Twitch

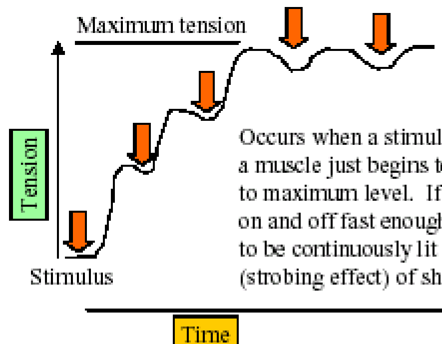


Summation



More than one stimulus is given before muscle has relaxed completely after first stimulus. Tension increases.

Incomplete Tetanus



Occurs when a stimulus is given each time a muscle just begins to relax. Tension rises to maximum level. If turn a light switch on and off fast enough, the room will seem to be continuously lit but with blinking (strobing effect) of short off periods.