

Physiology of Muscles

Three types of muscle tissues: skeletal, cardiac, and smooth

Cardiac Muscle	Skeletal Muscle	Smooth Muscle
<ul style="list-style-type: none"> • Only in heart • Striated • Involuntary pacemaker set rate of contraction; neural input can increase rate • Neural controls allow the heart to respond to changes in bodily needs • Function: responsible for coursing the blood through the body 	<ul style="list-style-type: none"> • Attach to and cover bony skeleton • Longest muscle fibers • Stripes: Striated • Voluntary • Contract rapidly; tires easily and must rest • Strong, adaptable • Responsible for overall body motility • Adaptable and can exert forces of ranging sizes • Function: responsible for all locomotion 	<ul style="list-style-type: none"> • Lines the walls of hollow, visceral organs (e.g. stomach, urinary bladder, respiratory passages) • Non-striated • Involuntary • Slow, sustained contractions • Forces food and other substances through internal body channels • Function: maintains blood pressure, and squeezes or propels substances through organs

Similarities between skeletal and smooth muscles

- Both are elongated and are called muscle fibers
- Muscle contractions are depended on two kinds of myofilaments (filaments on the myofibrils): actin and myosin
- Sarcolemma: muscle plasma membrane
- Sarcoplasm: cytoplasm of a muscle cell

Functional Characteristics of muscle tissue

- Excitability, or irritability: the ability to receive and respond to stimuli
- Contractility: the ability to shorten forcibly
- Extensibility: the ability to be stretched or extended
- Elasticity: the ability to recoil and resume the original resting length
- Maintain posture, stabilize joints and generate heat

TABLE 9.1 Structure and Organizational Levels of Skeletal Muscle

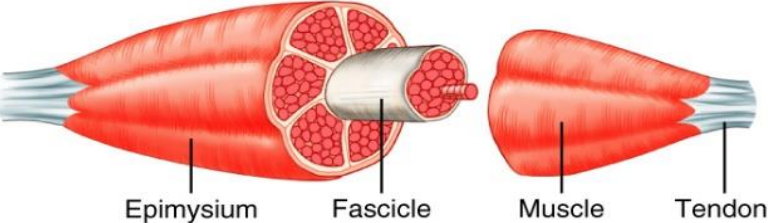
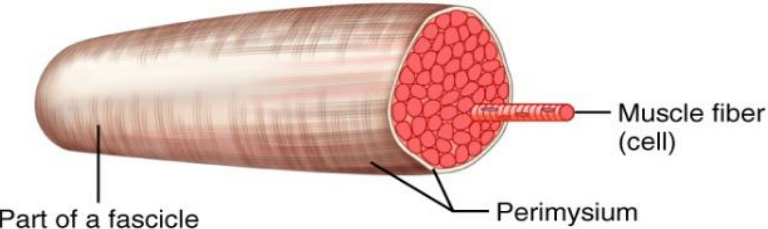
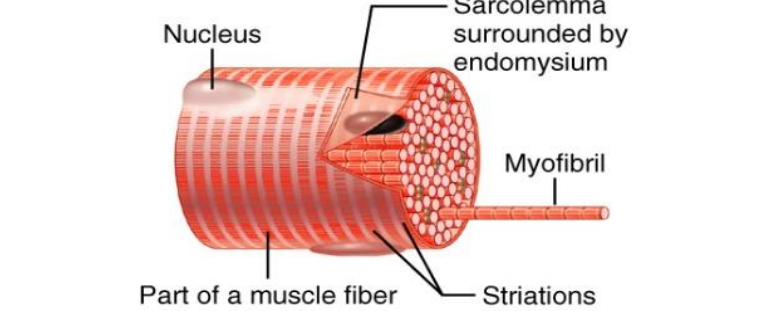
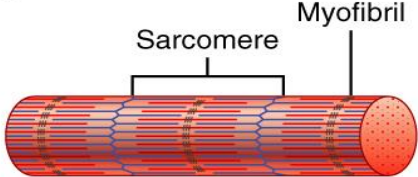
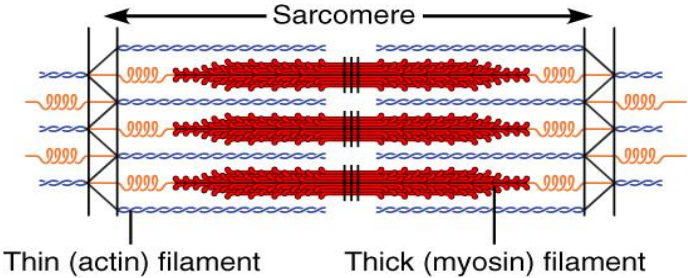
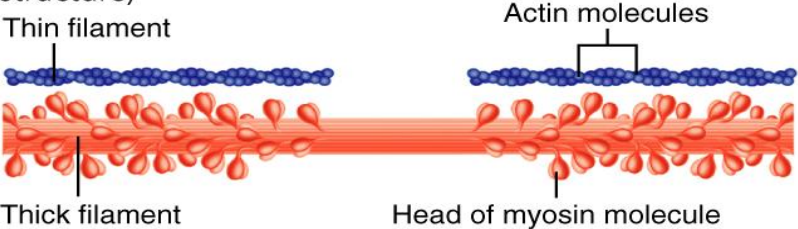
STRUCTURE AND ORGANIZATIONAL LEVEL	DESCRIPTION	CONNECTIVE TISSUE WRAPPINGS
<p>Muscle (organ)</p> 	<p>Consists of hundreds to thousands of muscle cells, plus connective tissue wrappings, blood vessels, and nerve fibers</p>	<p>Covered externally by the epimysium</p>
<p>Fascicle (a portion of the muscle)</p> 	<p>Discrete bundle of muscle cells, segregated from the rest of the muscle by a connective tissue sheath</p>	<p>Surrounded by a perimysium</p>
<p>Muscle fiber (cell)</p> 	<p>Elongated multinucleate cell; has a banded (striated) appearance</p>	<p>Surrounded by the endomysium</p>

TABLE 9.1 Structure and Organizational Levels of Skeletal Muscle

STRUCTURE AND ORGANIZATIONAL LEVEL	DESCRIPTION	CONNECTIVE TISSUE WRAPPINGS
<p>Myofibril or fibril (complex organelle composed of bundles of myofilaments)</p> 	<p>Rodlike contractile element; myofibrils occupy most of the muscle cell volume; composed of sarcomeres arranged end to end; appear banded, and bands of adjacent myofibrils are aligned</p>	
<p>Sarcomere (a segment of a myofibril)</p> 	<p>The contractile unit, composed of myofilaments made up of contractile proteins</p>	
<p>Myofilament or filament (extended macromolecular structure)</p> 	<p>Contractile myofilaments are of two types—thick and thin: the thick filaments contain bundled myosin molecules; the thin filaments contain actin molecules (plus other proteins); the sliding of the thin filaments past the thick filaments produces muscle shortening. Elastic filaments (not shown here) maintain the organization of the A band and provide for elastic recoil when muscle contraction ends</p>	

Connective tissue sheaths for skeletal muscle

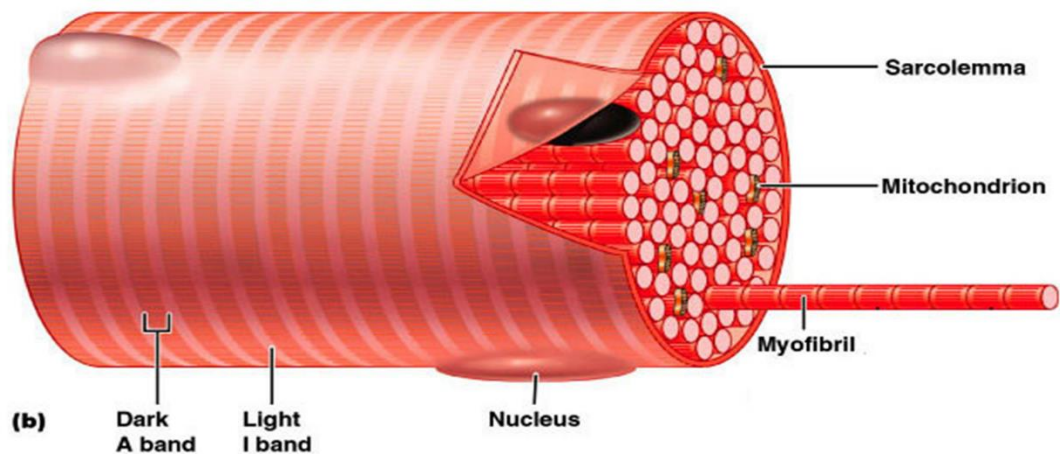
- **Epimysium:** an overcoat of dense regular connective tissue that surrounds the entire muscle
- **Perimysium:** fibrous connective tissue that surrounds groups of muscle fibers called fascicles
- **Endomysium:** fine sheath of connective tissue composed of reticular fibers surrounding each muscle fiber

Skeletal Muscle: Nerve and Blood supply

- Each muscle is served by one nerve, an artery and one or more veins
- Each skeletal muscle fiber is supplied with a nerve ending that controls contraction
- Contracting fibers require continuous delivery of oxygen and nutrients via arteries
- Wastes must be removed via veins

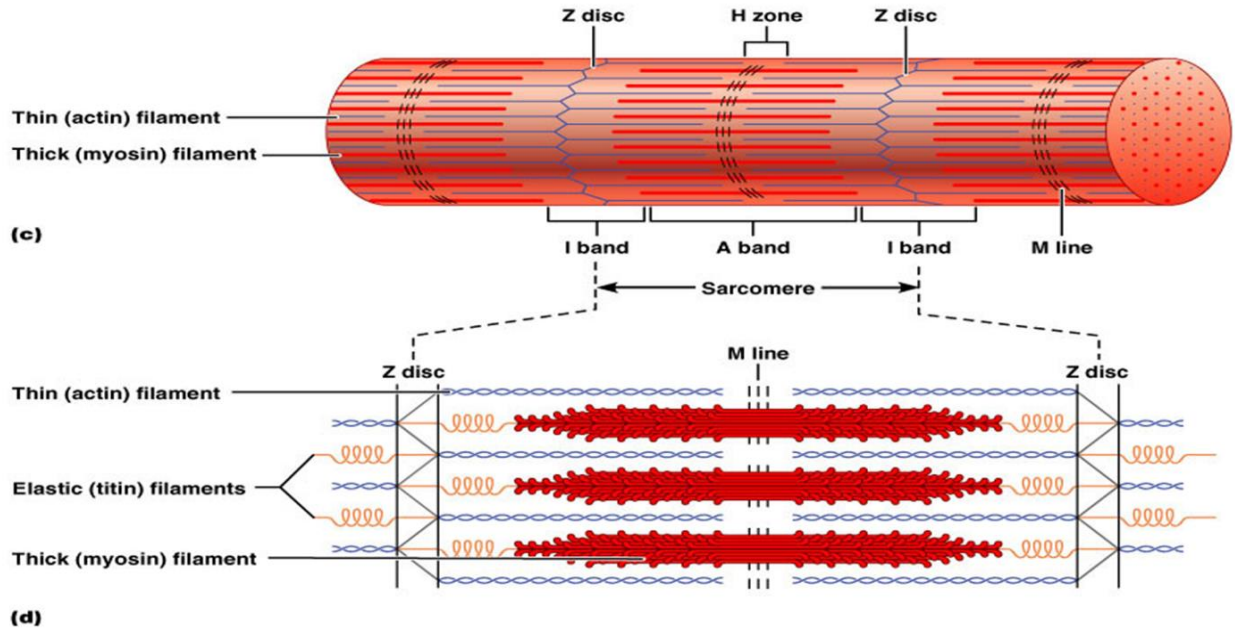
Microscopic Anatomy of a Skeletal Muscle Fiber

- Each muscle fiber is a long, cylindrical cell with multiple nuclei just beneath the sarcolemma and many myofibrils
- Each cell is a syncytium (containing several nuclei) produced by fusion of embryonic cells
- Sarcoplasm has numerous glycosomes (organelle) and myoglobin (oxygen-binding protein)
- The muscle fibers have the usual organelles, myofibrils, sarcoplasmic reticulum, and T tubules



Myofibrils

- Densely packed, rod-like, contractile elements
- Make up most of muscle volume
- Arrangement of myofibrils within a fiber is such that a perfectly aligned repeating series of dark A bands and light I bands is evident
- Within the A band section, there is a lighter region called the H zone. The H zone is bisected by a dark line called M line formed by the molecules of the protein myomesin
- Within each I band, a midline interruption is there called the Z disc

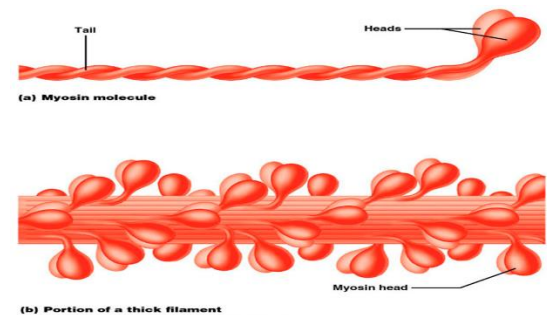


Myofilaments: Banding pattern

- Thick filament: (myosin) extend the entire length of an A band
- Thin filament (actin): extend across the I band and partway into the A band
- The Z-disc: coin shaped sheet of proteins (connectins) that anchor the thin filaments and connects myofibrils to one another
- Thin filaments do not overlap the thick filaments in the lighter H zone
- M line appears darker due to the presence of protein desmin

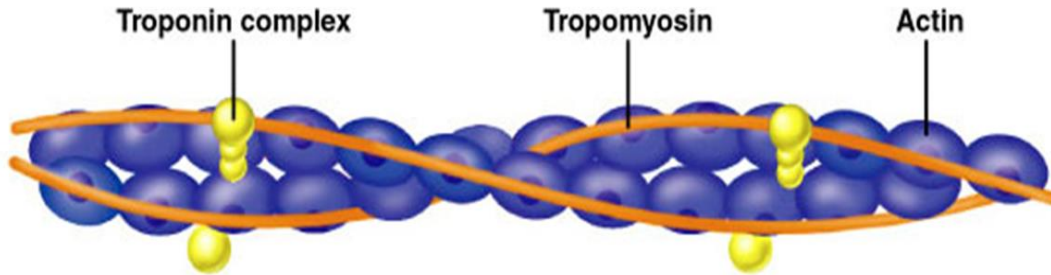
Thin Filament

- Composed of the protein myosin
- Each myosin molecule has a rod-like tail and two globular heads
- Tails: two interwoven, heavy polypeptide chains
- Heads-two smaller, light polypeptide chains called cross bridges



Thin Filaments:

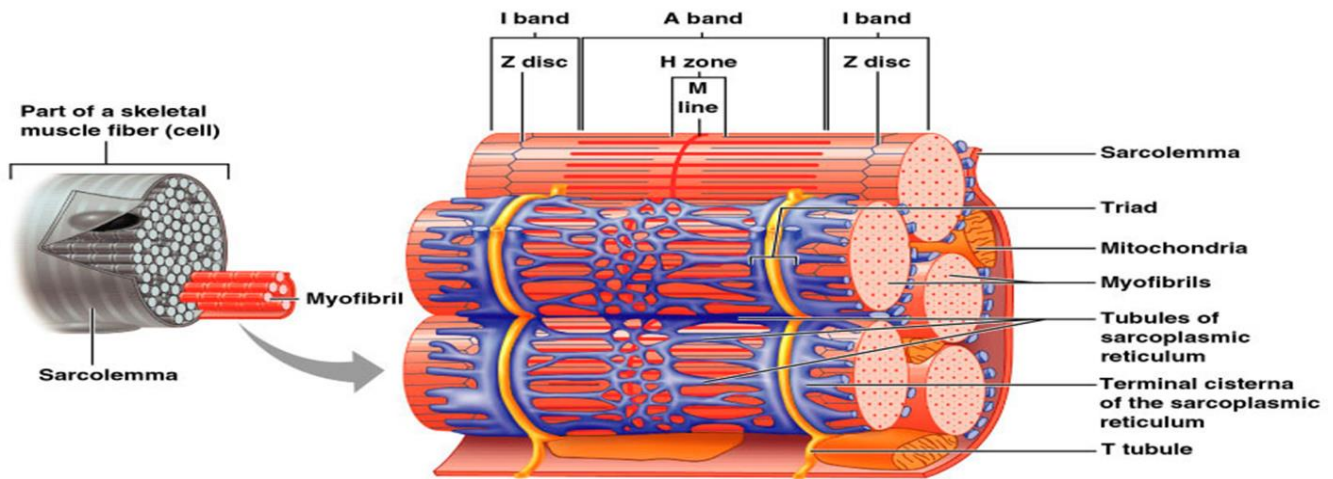
- Composed of the protein actin
- Each actin molecules is a helical polymer of globular subunits called G actin
- The subunits contain the active sites to which myosin heads attach during contraction
- Tropomyosin and troponin are regulatory subunits bound to actin



(c) Portion of a thin filament

Sarcoplasmic Reticulum (SR)

- An elaborate, smooth endoplasmic reticulum that mostly runs longitudinally and surrounds each myofibril
- Paired terminal cisternae form perpendicular cross channels
- Functions in the regulation of intracellular calcium levels.
- Elongated tubes called T-tubules penetrate into the cell's interior at each A band- I band junction
- T-tubules associate with the paired terminal cisternae to form triads



T- Tubules

- Continuous with the sarcolemma
- They conduct impulses to the deepest regions of the muscle
- These impulses signal for the release of Ca^{2+} from adjacent terminal cisternae

Triad Relationship

- T-tubules and Terminal cisterns of the SR
 - T-tubules and SR provide tightly linked signals for muscle contraction
 - A double zipper of integral membrane proteins protrudes into the intermembrane space
 - T-tubule proteins act as voltage sensors
 - SR foot proteins are receptors that regulate Ca^{2+} release from the SR cisternae

Sliding Filament Model of Contraction

- Thin filaments slide past the thick ones so that the actin and myosin filaments overlap to a greater degree
- In the relaxed state, thin and thick filaments overlap only slightly
- Upon stimulation, myosin heads bind to actin and sliding begins
- Each myosin head binds and detaches several times during contraction, acting like a ratchet to generate tension and propel the thin filaments to the center of the sarcomere which causes the muscle to shorten

Skeletal Muscle Contraction

- In order to contract, a skeletal muscle must:
 - Be stimulated by a nerve ending
 - Propagate an electrical current, or action potential, along its sarcolemma
 - Have a rise in intracellular Ca^{2+} levels, the final trigger for contraction
- Linking the electrical signal to the contraction is excitation-contraction coupling
- Muscle fiber shortens because sarcomeres shorten; filaments remain same length
- Contracted: thin filaments penetrate more deeply into A band- Z discs pulled toward thick filaments
- Note: cross bridge attachment to actin requires Ca^{++}
- Nerve impulses increases concentration of Ca^{++}

Nerve Stimulus of Skeletal Muscle

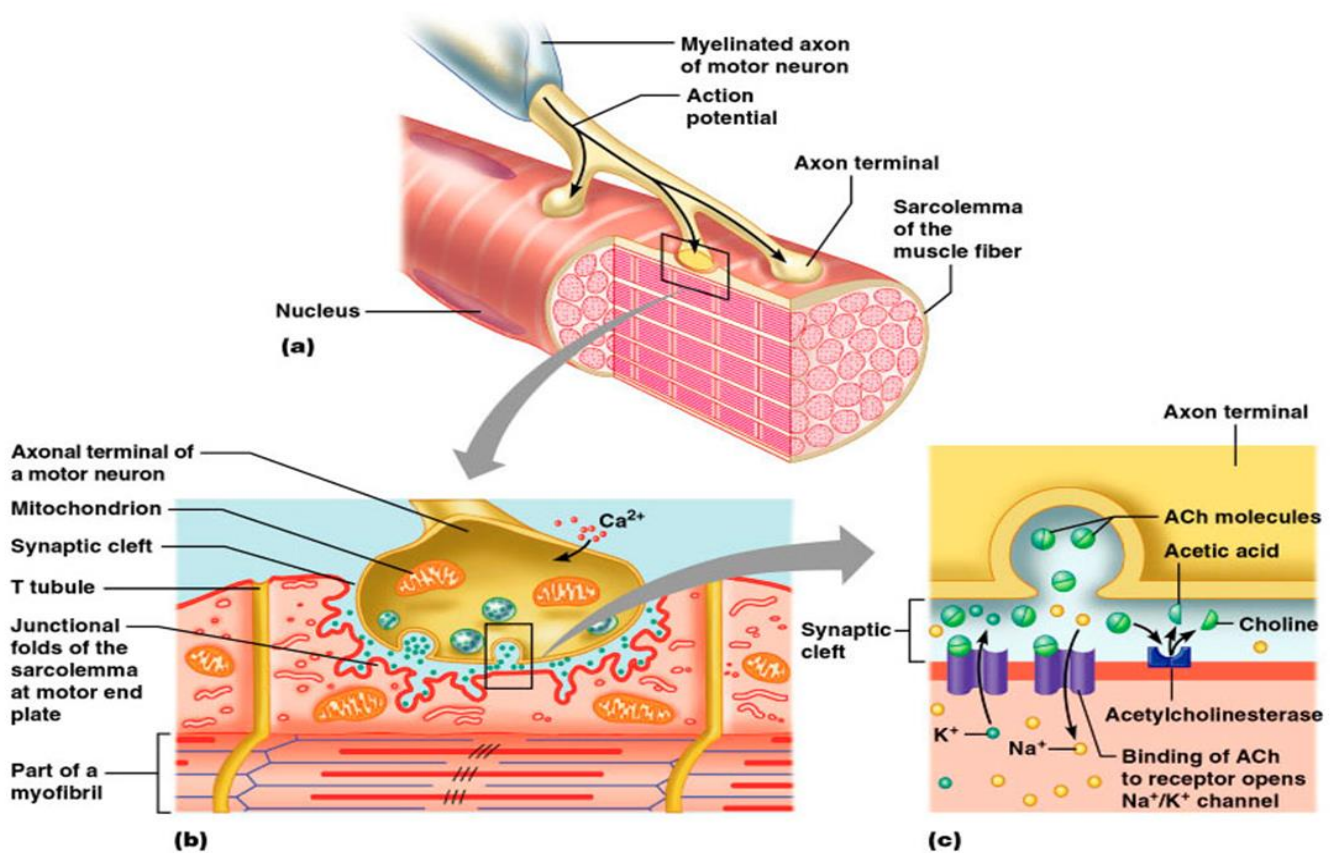
- Skeletal muscles are stimulated by motor neurons of the somatic nervous system
- Axons of these neurons travel in nerves to muscle cells
- Axons of motor neurons branch profusely as they enter muscles
- Each axonal branch forms a neuromuscular junction with a single muscle fiber

Neuromuscular Junction

- The neuromuscular junction is formed from:
 - Axonal endings, which have small membranous sacs (synaptic vesicles) that contain the neurotransmitter acetylcholine (ACh)
 - The motor end plate of a muscle, which is a specific part of the sarcolemma that contains ACh receptors and helps form the neuromuscular junction
- Though exceedingly close, axonal ends and muscle fibers are always separated by a space called the synaptic cleft
- When a nerve impulse reaches the end of an axon at the neuromuscular junction:
 - Voltage-regulated calcium channels open and allow Ca^{2+} to enter the axon
 - Ca^{2+} inside the axon terminal causes axonal vesicles to fuse with the axonal membrane. This fusion releases ACh into the synaptic cleft via exocytosis
 - ACh diffuses across the synaptic cleft to ACh receptors on the sarcolemma
 - Binding of ACh to its receptors initiates an action potential in the muscle

Role of Acetylcholine

- ACh binds its receptors at the motor end plate
- Binding opens chemically (ligand) gated channels
- Na^+ and K^+ diffuse out and the interior of the sarcolemma becomes less negative
- This event is called depolarization



Destruction of Acetylcholine

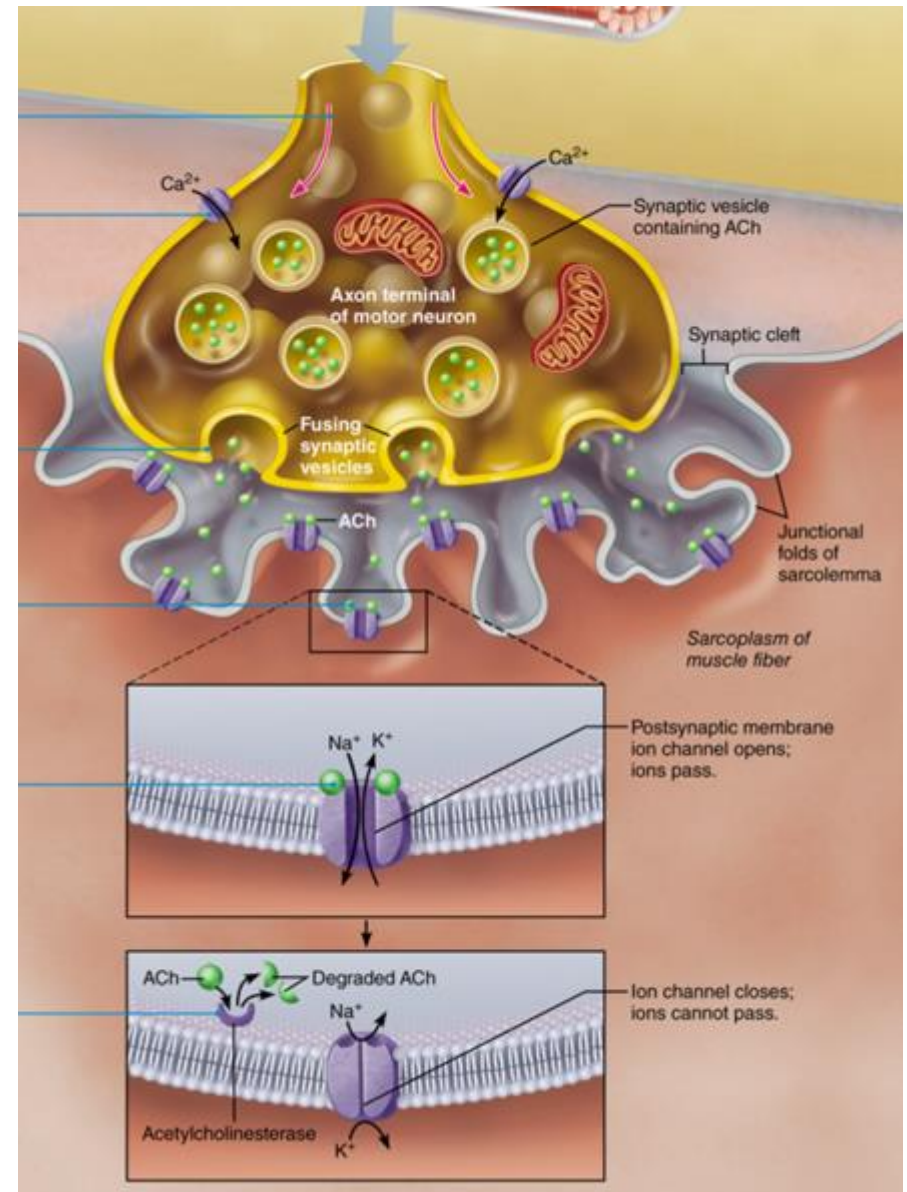
- ACh bound to ACh receptors is quickly destroyed by the enzyme acetylcholinesterase
- This destruction prevents continued muscle fiber contraction in the absence of additional stimuli

Action Potential

- A transient depolarization event that includes polarity reversal of a sarcolemma (or nerve cell membrane) and the propagation of an action potential along the membrane

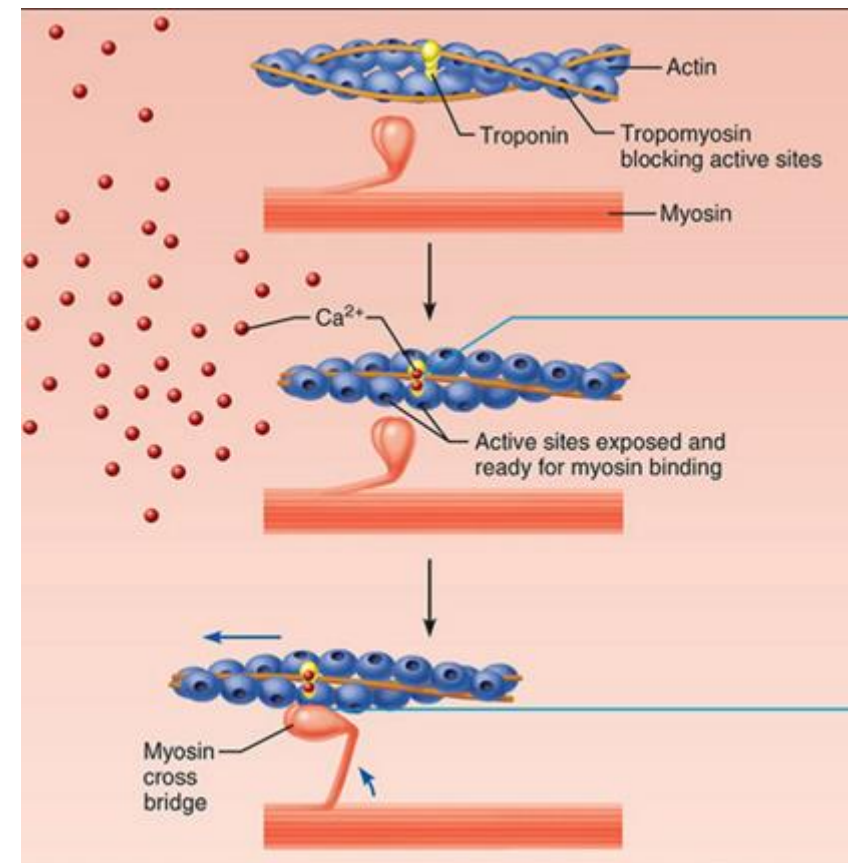
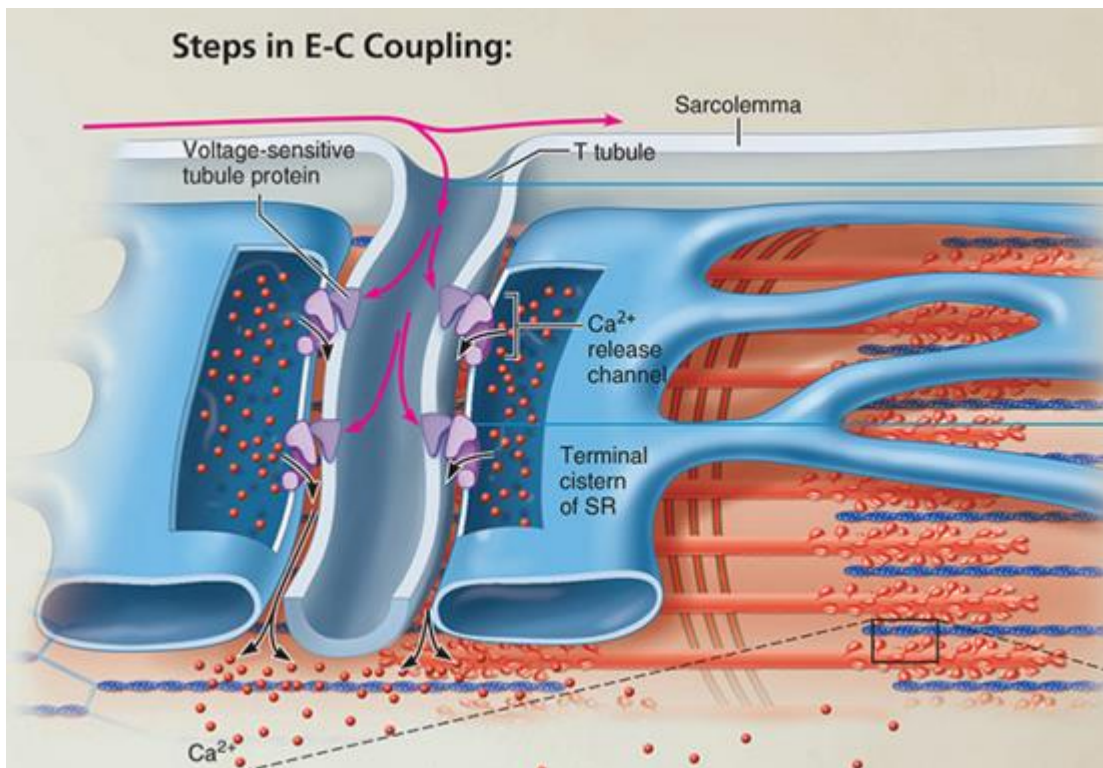
Summary of the Neuromuscular Junction

1. Action potential arrives at axon terminal of motor neuron
2. Voltage-gated Ca^{2+} enters the axon terminal, moving down its electrochemical gradient
3. Ca^{2+} entry causes ACh (a neurotransmitter) to be released by exocytosis
4. ACh diffuses across the synaptic cleft and binds to its receptors on the sarcolemma
5. ACh binding opens ion channels in the receptors that allow simultaneous passage of Na^+ into the muscle fiber and K^+ out of the muscle fiber. More Na^+ ions enter than K^+ ions exit, which produces a local change in the membrane potential called the end plate potential
6. ACh effect are terminated by its breakdown in the synaptic cleft by acetylcholinesterase and diffusion away from the junction



Summary of the Excitation-Contraction Coupling

1. The action potential propagates along the sarcolemma and down the T-tubules
2. Calcium ions are released. Transmission of the action potential along the T-tubules of the triads causes the voltage-sensitive tubule proteins to change shape. This shape change opens the Ca^{2+} release channels in the terminal cisterns of the sarcoplasmic reticulum (SR), allowing Ca^{2+} to flow into the cytosol.
3. Calcium binds to troponin and removes the blocking action of tropomyosin. When Ca^{2+} binds, troponin changes shapes, exposing binding sites for myosin (active site) on the thin filaments
4. Contraction begins: Myosin binding to actin forms cross bridges and contraction (cross bridge cycling) begins. At this point, E-C coupling is over.



Contraction of Skeletal Muscle Fibers

- Contraction – refers to the activation of myosin’s cross bridges (force-generating sites)
- Shortening occurs when the tension generated by the cross bridge exceeds forces opposing shortening
- Contraction ends when cross bridges become inactive, the tension generated declines, and relaxation is induced

Contraction of skeletal Muscle (Organ Level)

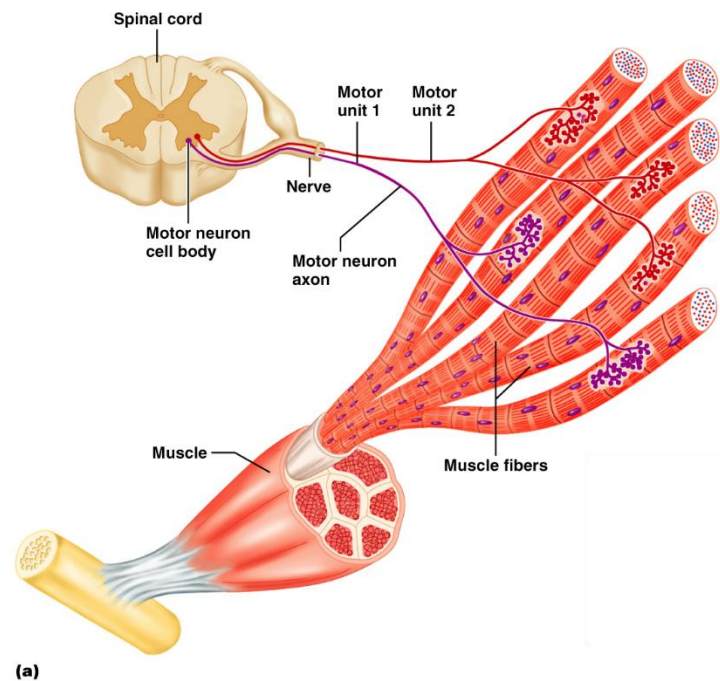
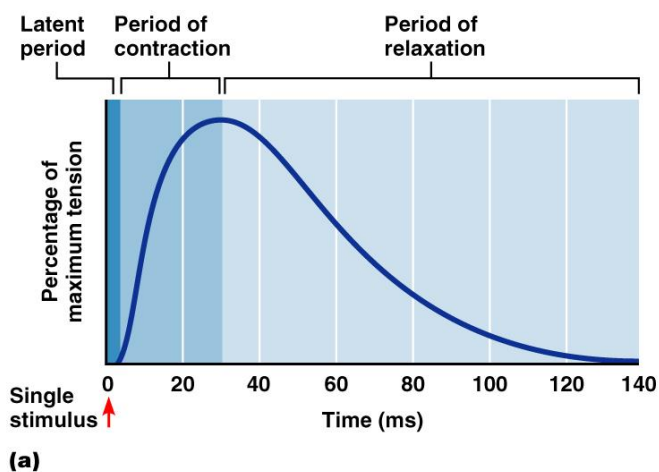
- Contraction of muscle fibers (cells) and muscles (organs) is similar
- The two types of muscle contractions are:
 - Isometric contraction – increasing muscle tension (muscle does not shorten during contraction)
 - Isotonic contraction – decreasing muscle length (muscle shortens during contraction)

Motor Unit: The nerve-Muscle Functional Unit

- A motor unit is a motor neuron and all the muscle fibers it supplies
- The number of muscle fibers per motor unit can vary from four to several hundred
- Muscles that control fine movements (fingers, eyes) have small motor units
- Large weight-bearing muscles (thighs, hips) have large motor units
- Muscle fibers from a motor unit are spread throughout the muscle; therefore, contraction of a single motor unit causes weak contraction of the entire muscle

Muscle Twitch

- A muscle twitch is the response of a muscle to a single, brief threshold stimulus
- There are three phases to a muscle twitch
 - Latent period: First few msec after stimulus; EC coupling taking place
 - Period of contraction: Cross bridges from muscle shortens
 - Period of relaxation: Ca^{2+} reabsorbed; muscle tension goes to zero

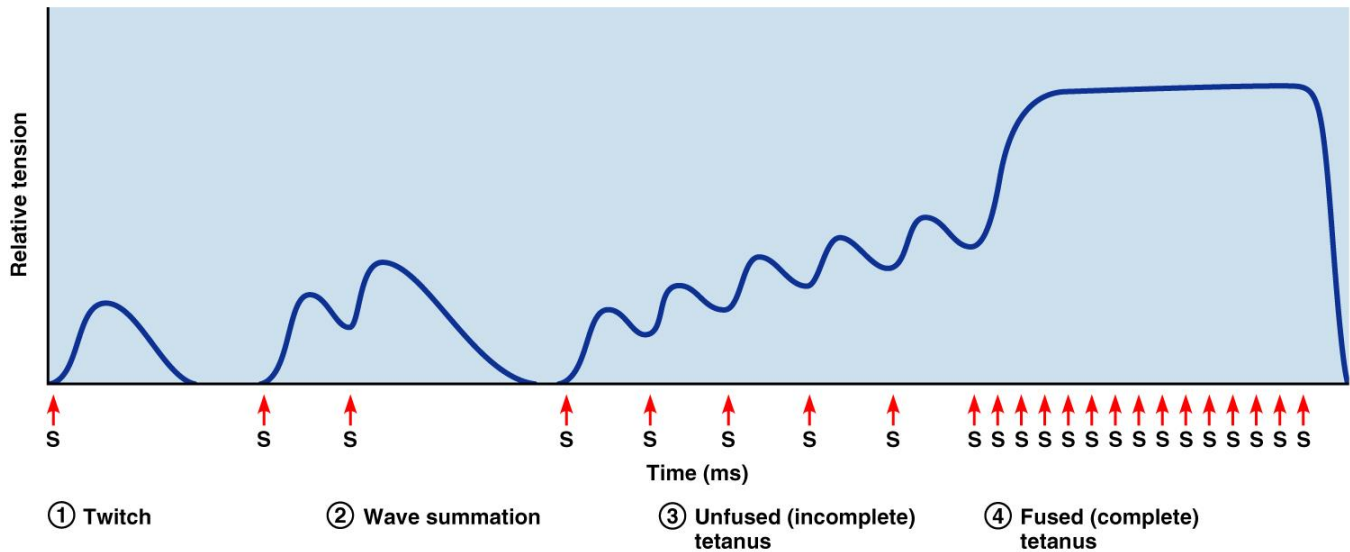


Graded Muscle Responses

- Graded muscle responses are:
 - Variations in the degree of muscle contraction
 - Required for proper control of skeletal movement
- Responses are graded by:
 - Changing the frequency of stimulation
 - Changing the strength of the stimulus

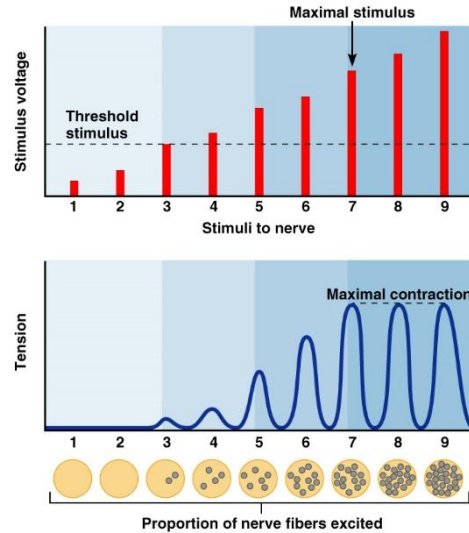
Muscle Response to Varying stimuli

- A single stimulus results in a single contractile response – a muscle twitch
- Frequently delivered stimuli (muscle does not have time to completely relax) increases contractile force – wave summation
- More rapidly delivered stimuli result in incomplete tetanus
- If stimuli are given quickly enough, complete tetanus results



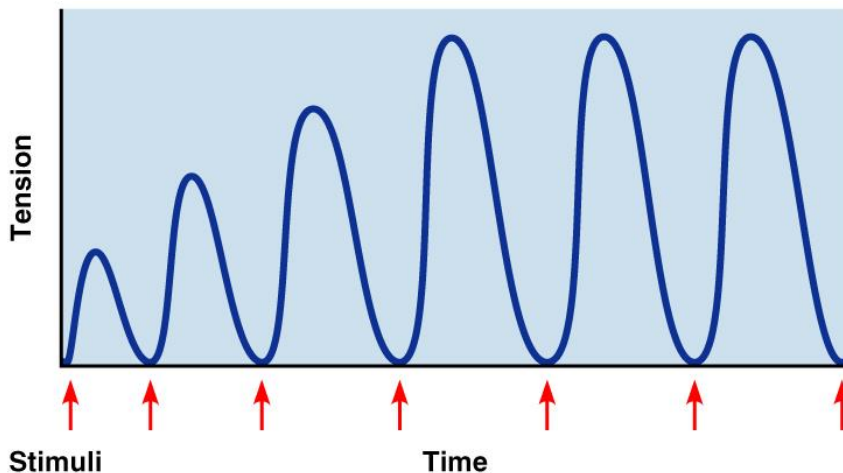
Muscle Response: Stimulation Strength

- Threshold stimulus – the stimulus strength at which the first observable muscle contraction occurs
- Beyond threshold, muscle contracts more vigorously as stimulus strength is increased
- Force of contraction is precisely controlled by multiple motor unit summation
- This phenomenon, called recruitment, brings more and more muscle fibers into play



Treppe: The Staircase Effect

- Staircase – increased contraction in response to multiple stimuli of the same strength
- Contractions increase because:
 - There is increasing availability of Ca^{2+} in the sarcoplasm
 - Muscle enzyme systems become more efficient because heat is increased as muscle contracts



Muscle Tone

- The constant, slightly contracted state of all muscles, which does not produce active movements
- Keeps the muscles firm, healthy, and ready to respond to stimulus
- Spinal reflexes account for muscle tone by:
 - Activating one motor unit and then another
 - Responding to activation of stretch receptors in muscles and tendons

Isotonic Contractions

- The muscle changes in length (decreasing the angle of the joint) and moves the load
- The two types of isotonic contractions are concentric and eccentric
 - Concentric contractions – the muscle shortens and does work
 - Eccentric contractions – the muscle contracts as it lengthens

Isometric Contractions

- Tension increases to the muscle's capacity, but the muscle neither shortens nor lengthens
- Occurs if the load is greater than the tension the muscle is able to develop

Muscle Metabolism: Energy for Contraction

- ATP is the only source used directly for contractile activity
- As soon as available stores of ATP are hydrolyzed (4-6 seconds), they are regenerated by:
 - The interaction of ADP with creatine phosphate (CP)
 - Direct phosphorylation (coupled reaction of creatine phosphate (CP) and ADP)
 - Anaerobic glycolysis
 - When muscle contractile activity reaches 70% of maximum:
 - Bulging muscles compress blood vessels
 - Oxygen delivery is impaired
 - Pyruvic acid is converted into lactic acid
 - The lactic acid: Diffuses into the bloodstream, gets picked up and used as fuel by the liver, kidneys, and heart, then converted back into pyruvic acid by the liver
 - Aerobic respiration: Krebs Cycle

Energy Systems used during different physical activities

- Weight lifting, diving, sprinting: uses ATP stored in muscles & CP that form ATP since this form requires a surge of power for only a few seconds
- Tennis, Soccer: almost entirely anaerobic because this form requires a slightly longer burst of activity
- Marathon runs, jogging: mainly aerobic since it's a prolonged activity where however anaerobic may function until aerobic reaches full efficiency.

Muscle Fatigue:

- The muscle is in a state of physiological inability to contract
- Muscle fatigue occurs when:
 - ATP production fails to keep pace with ATP use
 - There is a relative deficit of ATP, causing contractures
 - Lactic acid accumulates in the muscle
 - Ionic imbalances are present
- Intense exercise produces rapid muscle fatigue (with rapid recovery)
- Na^+ - K^+ pumps cannot restore ionic balances quickly enough
- Low-intensity exercise produces slow-developing fatigue
- SR is damaged and Ca^{2+} regulation is disrupted

Oxygen Debt: aka Excess post-exercise oxygen consumption (EPOC)

- Oxygen debt – the extra amount of O_2 needed for the above restorative processes
- EPOC: the difference between the amount of oxygen needed for totally aerobic muscle activity and the amount actually used.
- Vigorous exercise causes dramatic changes in muscle chemistry
- For a muscle to return to a resting state:
 - Oxygen reserves must be replenished
 - Lactic acid must be converted to pyruvic acid
 - Glycogen stores must be replaced

- ATP and CP reserves must be resynthesized

Heat production during Muscle Activity:

- Only 40% of the energy released in muscle activity is useful as work
- The remaining 60% is given off as heat
- Dangerous heat levels are prevented by releasing heat from the skin by sweating

Force of Muscle Contraction

The force is affected by:

- The number of muscle fibers contracting – the more motor fibers in a muscle, the stronger the contraction
 - The relative size of the muscle – the bulkier the muscle, the greater its strength
 - Degree of muscle stretch – muscles contract strongest when muscle fibers are 80-120% of their normal resting length

Homeostasis:

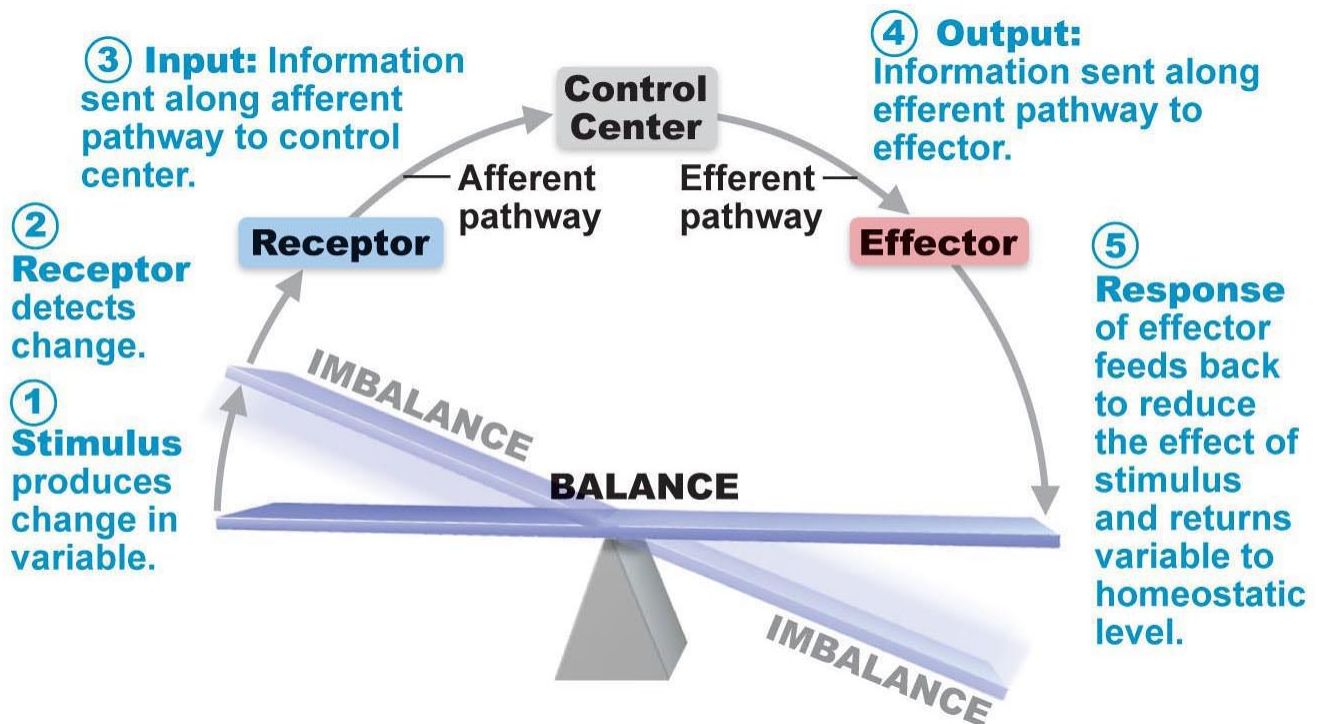
Ability of the body to maintain relatively stable internal conditions even though there is continuous change in the outside world

Ex: maintaining body temperature, blood levels, and making using wastes are not accumulating.

Essential components of a homeostatic control mechanism

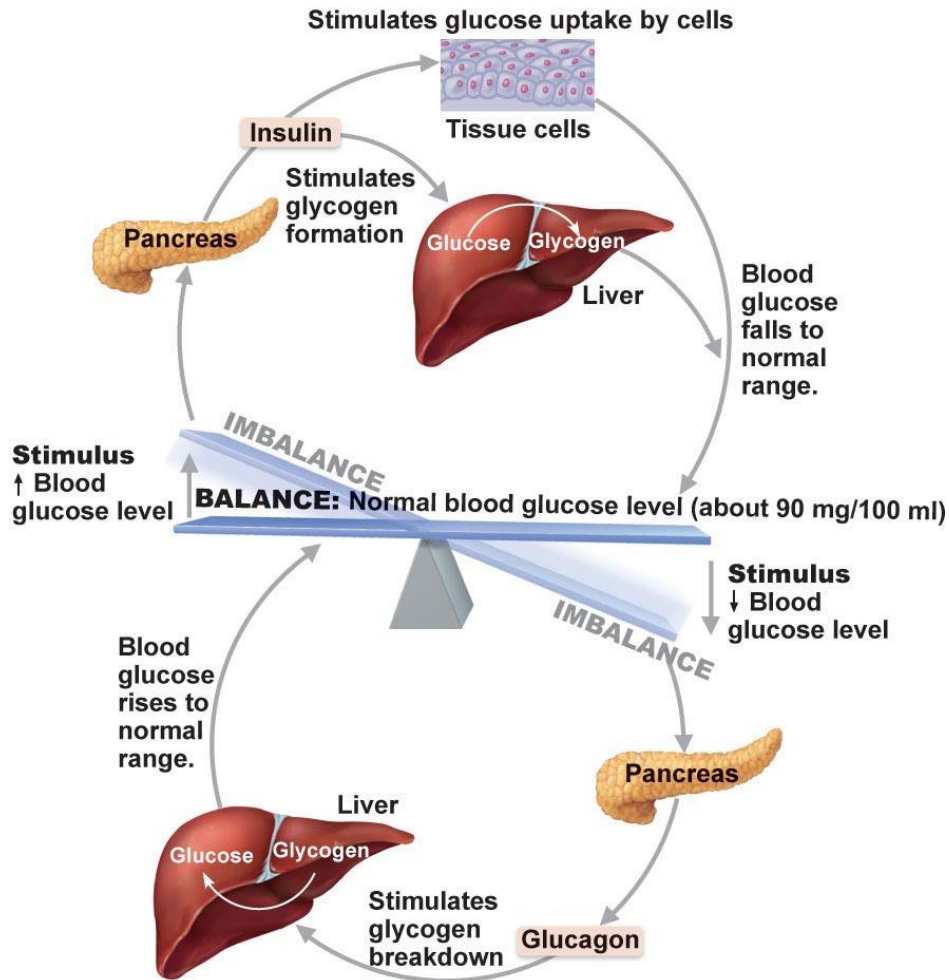
1. Receptor: senses change (stimulus) and send info (afferent pathway) to control center
2. Control center: determines set point for variable maintenance; analyzes information and determines correct response
3. Effector: provides means for response (output along efferent pathway)

Feedback (negative/positive) allows for regulation within a range/enhanced response.



Negative Feedback Mechanism:

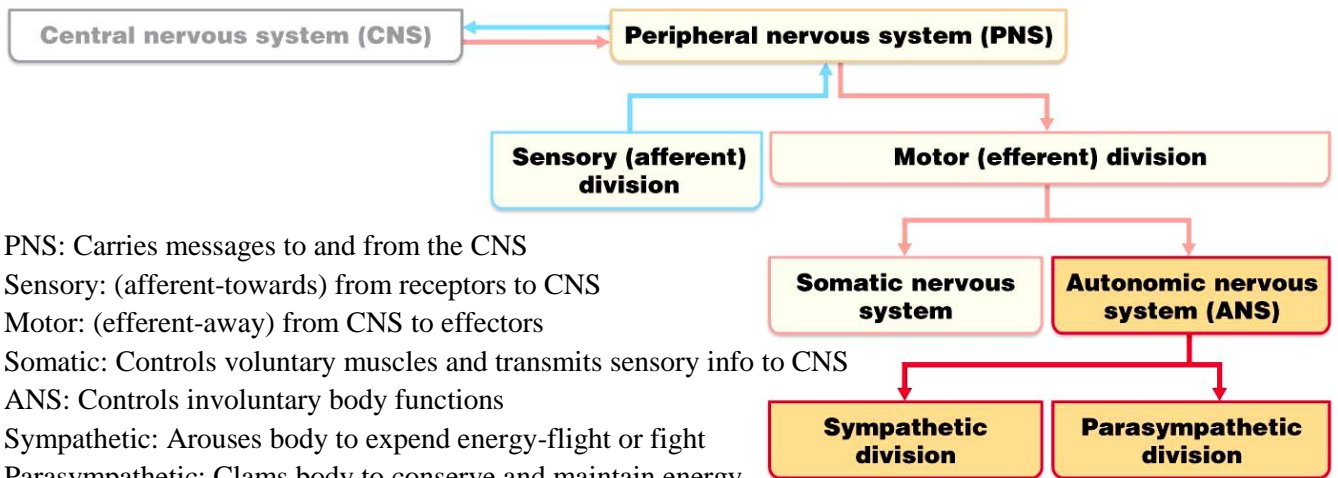
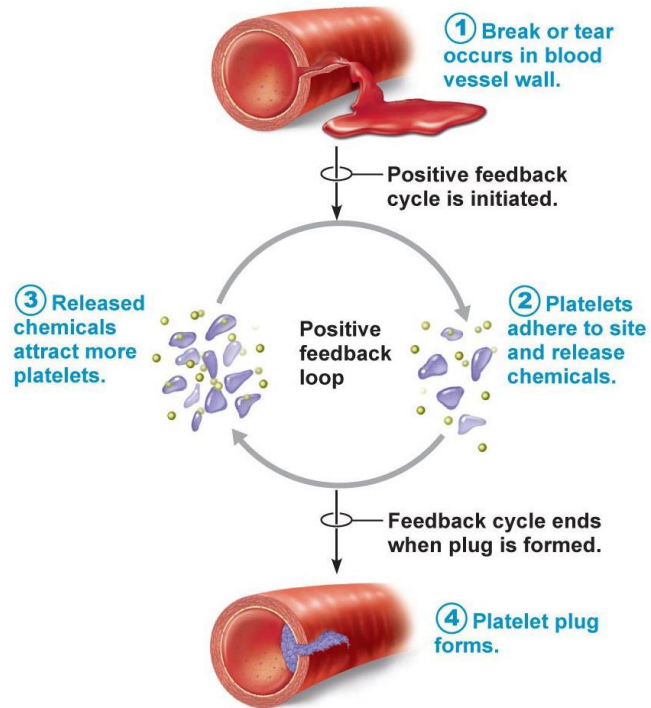
- The output reduces or shuts off stimulus. The goal is to prevent sudden, severe changes.
- Ex: the regulation of blood glucose levels and regulation of body temperature



Positive Feedback Mechanism:

Response of the mechanism enhances original stimulus (i.e. the output is further stimulated)

Ex: Blood clotting



- PNS: Carries messages to and from the CNS
- Sensory: (afferent-towards) from receptors to CNS
- Motor: (efferent-away) from CNS to effectors
- Somatic: Controls voluntary muscles and transmits sensory info to CNS
- ANS: Controls involuntary body functions
- Sympathetic: Arouses body to expend energy-flight or fight
- Parasympathetic: Clams body to conserve and maintain energy

Autonomic Nervous System:

- Sensory and motor neural pathways
- Fast response

1. Parasympathetic Division:

- Active in non-stressful situation (resting and digesting)
- Keeps the body's energy use low while regulation
- Pre-ganglionic fibers are longer than the post-ganglionic fibers

2. Sympathetic Division: 'Fight or Flight' system:

- Arouses body to expend energy
- Metabolic Effect:
 - Increases metabolic rate of body cells
 - Raises blood glucose levels
 - Stimulates mobilization of fats
 - Increases mental alertness
 - Increases speed/strength of muscle contraction
- Pre-ganglionic fibers are shorter than post-ganglionic fibers

Endocrine system

Definition: Endocrine system is the collection of glands that produce hormones that regulate metabolism, growth and development, tissue function, sexual function, reproduction, sleep, and mood, among other things

Hormone: Chemical substance released into the blood stream (ductless) to regulate the metabolic function of other cells in the body

- Hormones must bind to specific receptors to influence target cell function
- Hormones are specific: level of target cell activation depends on
- Hormone concentration, target cell receptor content, affinity of hormone for receptor

It alters the level of cell activity:

- Membrane permeability/potential channels
- Synthesis of enzymes within cells
- Enzyme activation/deactivation
- Induction of secretory activity
- Stimulation of mitosis

Peptide/protein hormones:

1. Bind to cell surface receptor
2. Activate membrane-bound G protein
3. Produce 2nd messenger (cAMP)
4. Activate protein kinases to regulate activity of key enzyme

Steroid Hormone: Lipid ----Enter into nucleus and activate gene transcription

Duration of Hormone activity

- Hormones greatly influence activity
- Blood level of hormone depends on: rate of synthesis and rate of degradation/clearance from blood
- The duration can last for hours to days.
- Control of hormone release
 - **Humoral Stimuli:** Endocrine glands secrete the hormones in direct response to the changing blood levels of certain critical ions and nutrients
 - **Neural Stimuli:** Nerve fibers stimulate hormone release
 - **Hormonal Stimuli:** Endocrine glands release hormones in response to hormones produced by other endocrine organs.

Nervous system vs. Endocrine System

- Both are used to communicate with different parts of the body.
- Through the nervous system, the signals and impulses travel very quickly leading to an instantaneous response.
- Through the endocrine system, the signaling through hormones moves slower but the message lasts longer.

Major Players of the Endocrine System

Hypothalamus: Produces certain hormones that is stored in the posterior lobe and secretes hormonal releasing hormones to signal other glands to secrete stimulating hormones.

Pituitary Gland: Size of a pea. Consist of two lobes

I. **Posterior Lobe:** Hormone storage area created by Hypothalamus

1) **Oxytocin:**

Stimulated the hypothalamic neurons in response to cervical/uterine stretching and suckling of infant at breast.

2) **Antidiuretic Hormone (ADH)**

Stimulated the hypothalamic neurons in response to increased blood solute concentration or decreased blood volume. The body will then need to be adequately hydrated by telling the kidneys to reabsorb water

II. **Anterior Lobe:**

1) **Growth Hormone (GH)**

Stimulated by Growth Hormone Releasing Hormone (GHRH from Hypothalamus) which is triggered by low blood levels of GH
Stimulates growth

2) **Prolactin (PRL)**

Stimulated by decreased dopamine (PIH). Stimulates milk production

3) **Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH)**

Stimulated by the Gonadotropin Releasing Hormone (GnRH)
FSH and LH- Stimulates ovaries and testes

4) **Thyroid-Stimulating Hormone (TSH)**

Stimulated by Thyroid-Releasing Hormone (TRH) when low levels of Iodine containing compound called thyroxine is in low levels.

Stimulates the thyroid gland

5) **Adrenocorticotrophic Hormone (ACTH)**

Stimulates adrenal cortex

- III. **Thyroid Gland:** Thyroxine, Triiodothyronine, Calcitonin (lowers calcium)
- IV. **Parathyroid Gland:** Parathyroid Hormone (PT) (increases calcium)
- V. **Pancreas:** Insulin (lowers blood glucose level) and Glucagon (raises blood glucose level)
- VI. **Adrenal Medulla:** Epinephrine and Norepinephrine (raise blood glucose level. Increase metabolic rate, constrict blood vessels)
- VII. **Adrenal Cortex:** Glucocorticoids (Raise blood glucose level) and Mineralocorticoids (reabsorption of Na⁺ and excretion of K⁺ in kidneys)

Summary of Endocrine system:

- hormones released into extracellular fluid and often travel to target organs via bloodstream
- slower response time but response can be long-lived
- different chemical classes of hormones with associated mechanisms of action

Blood

Blood is a specialized connective tissue. It connects different parts of the body. It contains blood cells, and blood plasma, hormones, nutrients and etc.

- It transport (distribute) oxygen and nutrients, carbon dioxide, metabolites, nitrogenous waster products, hormones
- It regulates body temperature, fluid volume, pH
- It protects by preventing of blood loss, and preventing infections (antibodies, complement proteins)

Blood plasma:

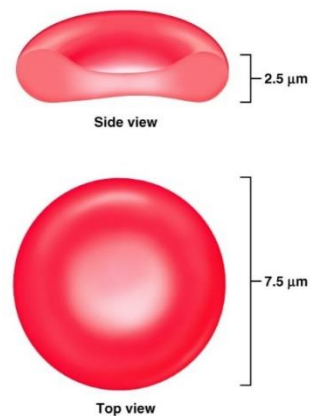
- 90% water
- Contains solutes: nutrients, respiratory gases, hormones, electrolytes, proteins (albumin, globulins), and wastes (e.g., by-products of protein breakdown)

Formed Elements

- Erythrocytes, leukocytes, and platelets
- Erythrocytes and platelets do not divide!!

Erythrocytes

- Small biconcave cells that lack nucleus and organelles
- Contain protein *spectrin* that helps RBC to be flexible, change shape, and squeeze through narrow capillaries
- Huge surface area for gas exchange
- High hemoglobin content



Hemoglobin

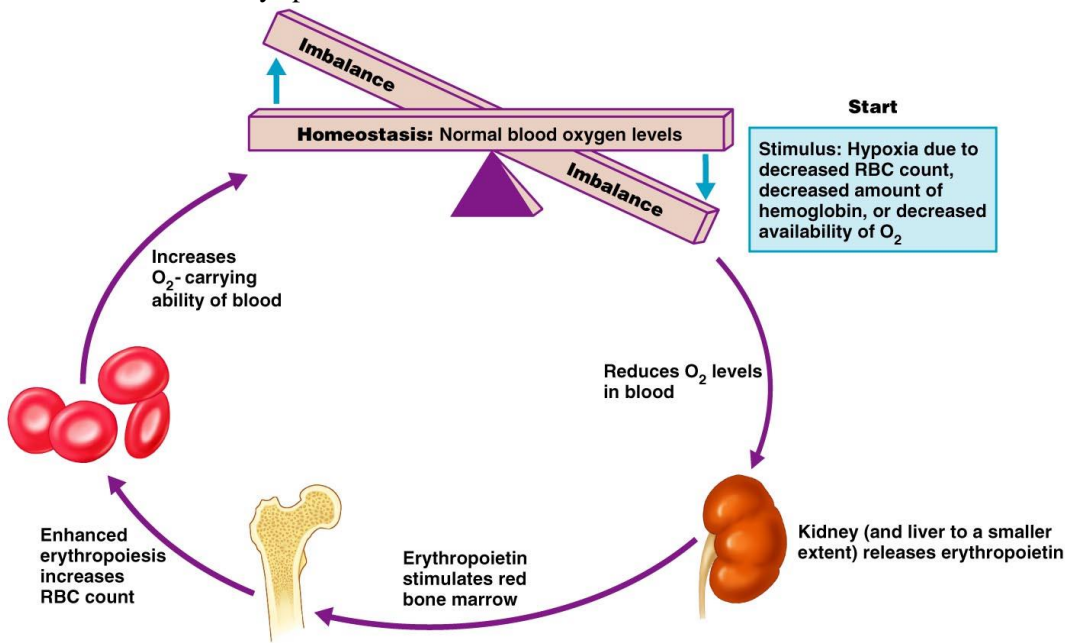
- Made up of four protein globin subunits (2 alpha, 2 beta), each bound to the iron binding red heme pigment
- Each iron atom can combine reversibly with one molecule of oxygen (there are 4 heme pigments therefore hemoglobin can carry 4 oxygen molecules)

Red Blood Cell production: Hematopoiesis

Division of cells in the red bone marrow renews red blood cells. Life span of RBC is 100-120 days

For the RBCs to produce, it requires

1. Functional hematopoietic stem cells
 2. Erythropoietin (hormone that stimulates the production of RBCs)
 3. Iron
 4. Folate
 5. Vitamin B12
- When cell O_2 falls, oxygen “sensors” in kidneys and liver (a heme protein) → stimulate transcription of EPO
 - Kidneys produce 85%-90% of EPO



Copyright © 2006 Pearson Education, Inc., publishing as Benjamin Cummings.

Life Cycle of RBC

- Most hemoglobin degradation – in the macrophages of the spleen
- Iron is reused. The most common areas of iron storage in our bodies: liver, bone marrow, intestinal mucosa and spleen
- If the body does not need iron, it is stored in the mucosal cells and lost when these cells die and are slough

Iron:

- **Heme iron** found in hemoglobin and myoglobin is found in meats. It is better absorbed than non-heme iron
- **Non-heme iron** found in vegetable, grains and supplements

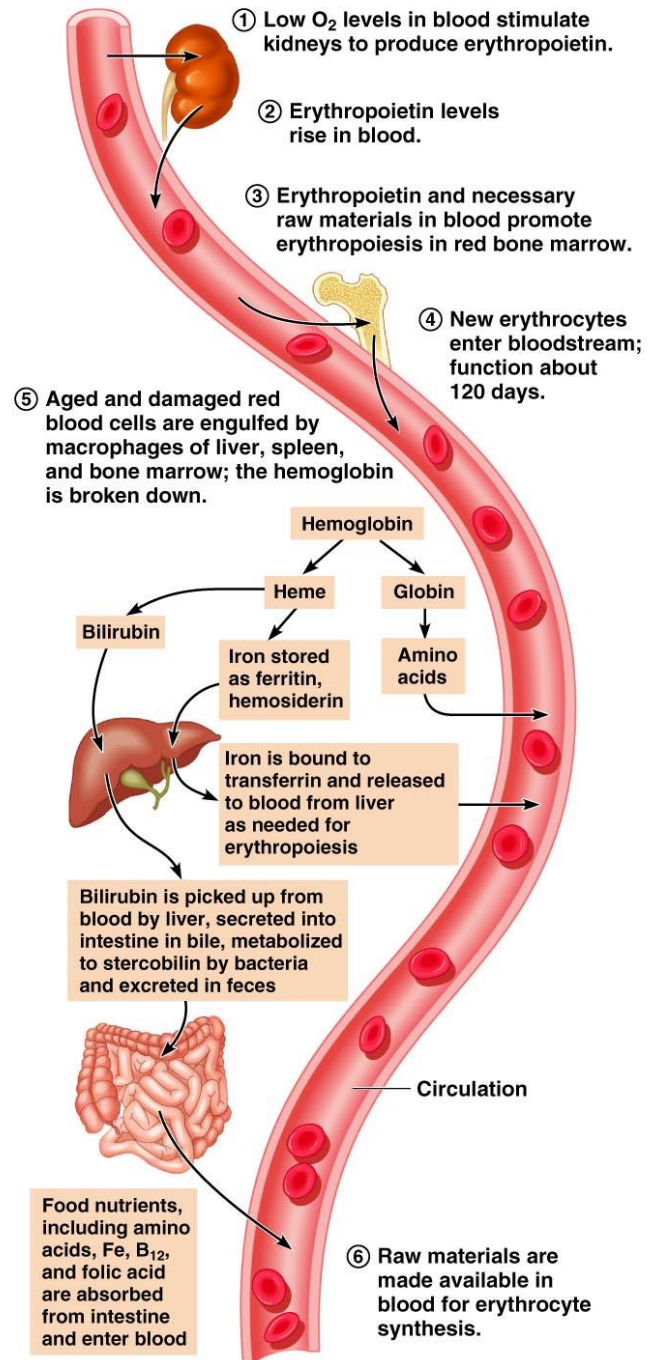
Folate

- Found in dark green leafy vegetables
- Deficiency impacts a lot

***Megaloblastic Anemia** is caused by folate or vitamin B 12 deficiency. It is when blood cells are unable to divide, leaving large, immature red blood cells.

Vitamin B12

- Found in animal products



RBC Disorders

- **Anemia:** Deficit of RBC, Low Hb levels, abnormal hemoglobin
- **General signs and symptoms:**
 - Increased respiration and heart rate
 - Fatigue
 - Decreased activity tolerance
 - Murmur
- Perform a hematocrit (a blood test to measure the % of blood volume is occupied by RBC) to see if anemic
- **Thalassemia:**
 - Underproduction of one of the globin chains leading to abnormal hemoglobin formation and decreased RBCs survival rates.
 - Alpha strand is less severe than the beta strand
- **Sickle Cell Anemia**
 - Chronic form of hemolytic anemia (RBCs are destroyed and removed before their life span), that has a sickle shape which decreases the cell's flexibility and results in restricted movement through the blood vessels. This restricts the delivery of oxygen.
 - Avoid dehydration, infections, fever
- Both Thalassemia and Sickle Cell will be present due to homozygous recessive of the trait.
- **Polycythemia:** High RBC count and potentially caused by EPO doping

Hemostasis

- Orderly, stepwise process for stoppage of bleeding
- Platelets: bits of megakaryocyte membrane containing cytoplasm and various organelles but no nucleus
 - Thrombopoietin made by kidneys stimulates the bone marrow for the maturation of megakaryotes (large bone marrow cell) to make platelets.

Hemostasis:

Stage 1: Vessel spasm

Injury to a blood vessel causes vascular smooth muscles in the vessel wall to contract. This reduces the flow of the blood from the vessel rupture. Both local nervous reflexes and the local humoral factors contribute to the vasoconstriction. Thromboxane released from platelets causes vasoconstriction.

Stage 2: Formation of platelet plug

Immediately after vessel injury, von Willebrand factor (large plasma protein), release from the endothelium, binds to platelet receptors, causing adhesion of the platelets to the exposed collagen fibers. The exposure of collagen stimulates the platelets to swell, sticky and spiky. As the platelets adhere to the collagen fibers on the damaged vessel wall, they become activated and release ADP and TXA₂. These two attract more platelets.

Stage 3: Blood Coagulation

Reinforces platelets and acts as a "molecular glue." Blood is converted from a liquid to a gel. Fibrin form a mesh that traps red blood cells and platelets forming the clot.

Stage 4: Clot retraction

Platelets contract, exerting a pull on the surrounding fibrin strands. Serums squeezed out from clot & ruptured edges of blood vessels pulled closer.

Stage 5: Clot dissolution

The slow release of the tissue plasminogen activator converts plasminogen to plasmin, which digests the fibrin strands, causing the clot to dissolve

Platelet disorder:

- Decreased platelet count: generalized bleeding
- Increased platelet count

Hemophilia (blood doesn't clot normally)

Blood Types

- The presence of agglutinogens (antigens) tell what type of blood it is
- The agglutinins (antibodies) will react to antigens not normally present

Type A: Has A antigen. Has antibody B. Can receive from type A and O

Type B: Has B antigen. Has antibody A. Can receive from type B and O

Type AB: Has antigen A and B. No antibodies. Can receive from type A, B, AB, and O

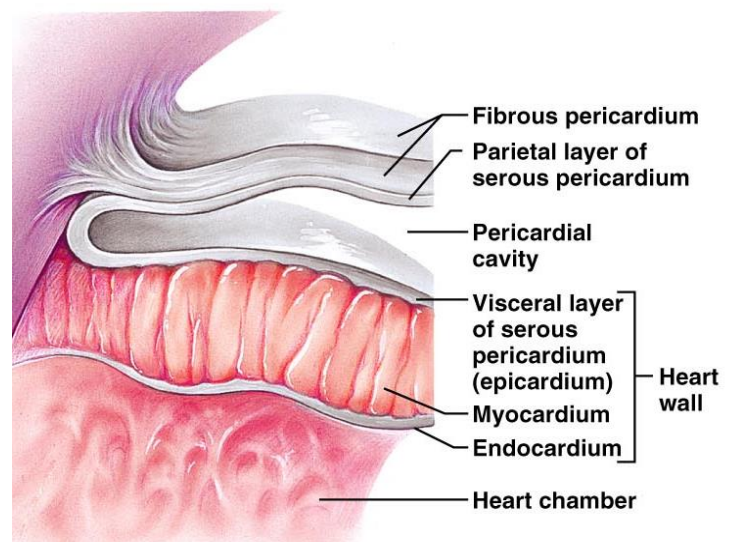
Type O: Has no antigens. Has antibodies A and B. Can only receive from type O

The Heart

Located between the lungs, in the center of the medial cavity of the thorax

It is enclosed by a tough, connective tissue layer called the pericardium.

- Pericardium protects and anchors the heart. It has two layers
 - Outer **fibrous pericardium**: loosely fitting
 - The **pericardial cavity** with the pericardial fluid in it is between the two layers. It reduces friction between the two membranes.
 - Inner **serous pericardium** (thin, slippery). Has two parts
 - **Parietal layer** : lines the internal surface of the fibrous pericardium
 - **Visceral layer**: lines the external heart surface



Layers of the heart wall:

- **Epicardium** is the visceral layer of the pericardium
- **Myocardium** is made of cardiac muscle tissue; forms a bulk of the heart.
- **Endocardium** has endothelium and connective tissue. It line the heart chambers and covers the skeleton of the valves.

The circular and spiral arrangement of cardiac muscle fibers

- Cardiac muscle cells that are branching are arranged into bundles.
- The connective tissue fibers reinforce myocardium internally and anchor cardiac muscle fibers

Blood Flow pathway

From the Superior vena cava, inferior vena cava, and from the heart itself to the right atrium, right ventricle, to the pulmonary trunk (pulmonary artery), to the lungs to get oxygen, through pulmonary vein (four pulmonary veins) to left atrium, to left ventricle to aorta

Parts of the heart

Internal fibrous Septum: separates the atria and ventricles

Interventricular Septum: Separates the lower chambers of the heart (right ventricle and left ventricle)

Right Atrium receives blood from 3 veins

- 1) Superior vena cava: systemic from regions above diaphragm
- 2) Inferior vena cava: systemic from below the diaphragm
- 3) Coronary sinus: from myocardium

It features special features:

- Fossa ovalis: thin filament that used to cover foramen ovale
- Foramen ovale (fetal development): an opening between the left and right atria

Ventricle: discharging chambers:

- The pumps of the heart; walls much thicker than in atria
- The wall of the **left ventricle** - **3x thicker** than of the right one. This is because the left ventricle needs to push the blood against resistance (pressure) to the rest of the body.
- **Right ventricle** pumps blood to **pulmonary trunk**
- **Left ventricle** pumps blood to **aorta**
- Internal walls have muscle bundles: **trabeculae carneae, papillary muscles** (valve function)

The heart pumps

- 1) **Pulmonary circuit:** blood vessels that carry blood to the lungs (deoxygenated)
- 2) **Systemic circuit:** blood vessels that carry blood to all the tissue (oxygenated)

Coronary Circulation:

Arises from the base of the aorta: it provides blood to the heart. The shortest circulation in the body. The veins join together in the coronary sinus which empties the blood to the right atrium and roughly follows the myocardial arteries

Heart Valves

➤ Atrioventricular Valves:

- ✓ **Tricuspid valve** between right atrium and right ventricle
- ✓ **Mitral valve (bicuspid valve)** between left atrium and left ventricle

The chordae tendinae (collagen cords) connects the papillary muscles to the valve and keeps the flaps of the valve pointing in the direction of blood flow. The corda tendinae by contracting as blood flows into the ventricle, prevents blood backflow into the atria

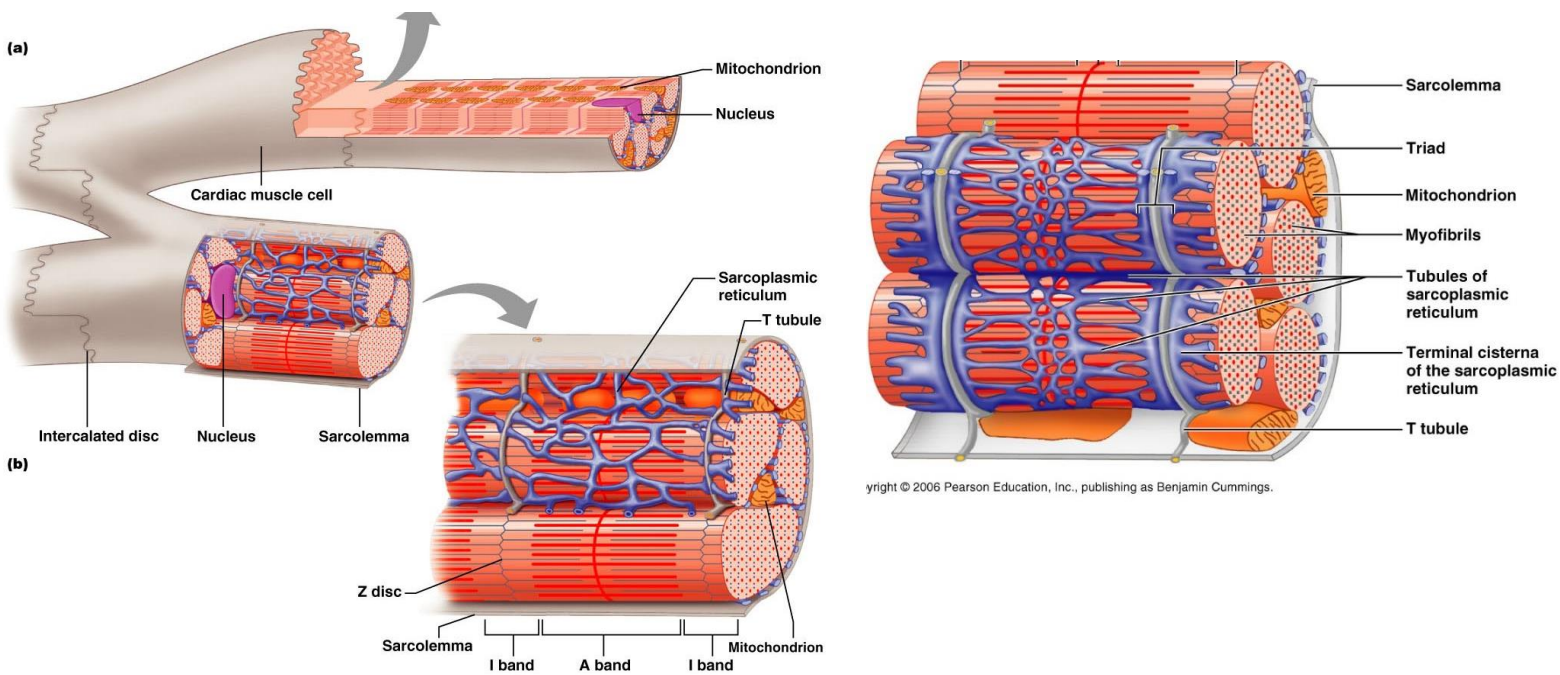
The pressure created by the contraction of the atrium flowing blood into the ventricle increases the pressure inside of the ventricle. Then the valves are forced to be “close” which in return keeps the back flow of blood into the atrium.

- ✓ Pulmonary semilunar valve: between right ventricle to pulmonary artery
- ✓ Aortic semilunar valve: between left ventricle to aorta

Cardiac Muscle	Skeletal Muscle
Similarities	
<ul style="list-style-type: none"> • Striated muscle fibers with myofibrils (actin and myosin) • Sarcolemma with T-tubules • Sarcoplasmic reticulum with calcium • Action potential that initiate muscle contraction 	
Anatomical Differences	
<ul style="list-style-type: none"> • Shorter, branched cells connected by <i>intercalated discs</i> and <i>gap junctions</i> • <i>Desmosomes</i>: cell to cell adhesion for stability and prevent separation under tension • <i>Gap junction</i>: passage for small molecules. Helps with synchronized cells 	<ul style="list-style-type: none"> • elongated cells • <i>myotendinous junctions</i>
<ul style="list-style-type: none"> • Only one or two centrally located nuclei 	<ul style="list-style-type: none"> • Lots of nuclei
<ul style="list-style-type: none"> • T-tubules 5x greater in size than in skeletal muscle (only 1 T-tubule per sacromere) 	<ul style="list-style-type: none"> • T-tubules smaller but 2 per sacromere
<ul style="list-style-type: none"> • poorly developed sarcoplasmic reticulum (no terminal cisterna) 	<ul style="list-style-type: none"> • well developed sarcoplasmic reticulum holding lots of Ca^{2+}
<ul style="list-style-type: none"> • lots of mitochondria (40% of the cytoplasmic volume) 	<ul style="list-style-type: none"> • mitochondria, only 2%-6% of cytoplasm volume
<ul style="list-style-type: none"> • special electrical conduction system 	<ul style="list-style-type: none"> • motorneurons
Functional Difference	
<ul style="list-style-type: none"> • Stimulation: Autorhythmicity • Involuntary contraction • all cells contract at once synchronously (syncytium: “all or none”) ⇒ organ contraction • resting membrane potential = - 85 to -35 mV • depolarization at +20 mV • prolonged action potentials with plateau (plateau is 200-300 ms) • Prolonged absolute refractory period <u>prevents tetanic contractions</u> • Ca^{2+} from both intra- (80%) and extracellular (20%) sources • Aerobic energy sources 	<ul style="list-style-type: none"> • Motor nerve ending stimulation • voluntary contractions • fibers of stimulated motor unit contract simultaneously • resting membrane potential of -70 mV • depolarization at +35 mV • short, spike action potentials (0.4-2 ms) • Short absolute refractory period • Ca^{2+} from the sarcoplasmic reticulum only (100% intracellular) • Both aerobic and anaerobic energy sources (depend on the fiber types) • CNS stimulated contractions
<ul style="list-style-type: none"> • Polarization maintained by the $Na^+/Ca^{++}/K^+$ pump • Fast Na^+ channels open to produce a spike at the beginning of the action potential 	<ul style="list-style-type: none"> • Polarization maintained by the Na^+/K^+ pump until a stimulus causes ion gates (channels) to open

- **Slow Ca^{++}** channels open to produce *plateau depolarization*. This produces a **long absolute refractory period** which ends **as K^+ efflux is well under way** to produce repolarization

- **Fast Na^+** channels open to produce the depolarization spike associated with an action potential
- **Short refractory period** as *K^+ channels* open to *reestablish membrane polarity*
-



Copyright © 2006 Pearson Education, Inc., publishing as Benjamin Cummings.

Cardiac Cell

- Myogenic Cells “self -excitable”
- Myogenicity is the property of spontaneous depolarization and impulse generation
- Autorhythmicity: The natural rhythm of spontaneous depolarization.
- No neural or hormonal stimulation required

Mechanism of Contraction

Phase 0: Rapid upstroke (fast depolarization). Brief opening of voltage-gated fast Na^+ . Na^+ rushes in

Phase 1: dip; Na^+ influx stops

Phase 2: Plateau; Ca^{2+} flows in through slow channels----keeping and balancing membrane potential in the positive side

Phase 3: Repolarization (permeability to Ca^{2+} declines; K^+ permeability increases and K^+ moves out to repolarize.

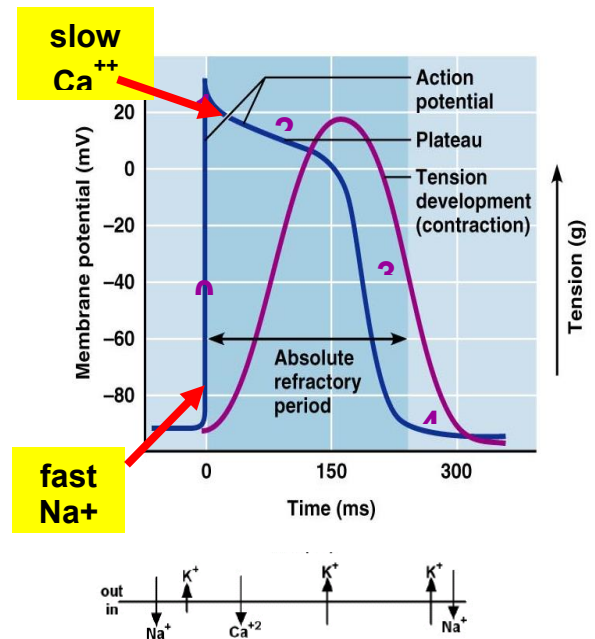
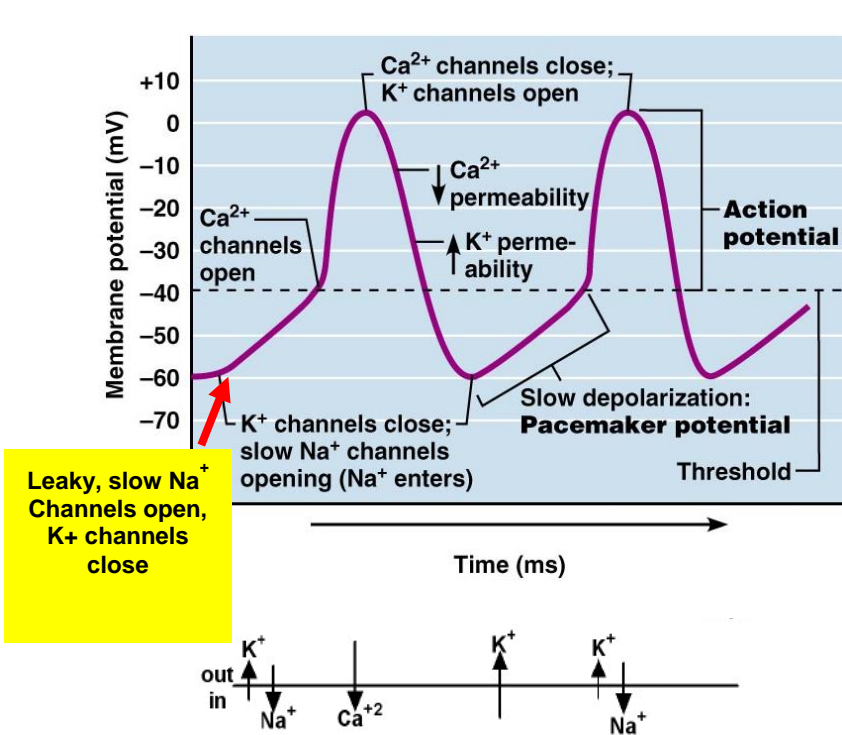
Phase 4: Resting (Ca^{2+} pumped back out into sarcoplasmic reticulum and K^+ permeability decreases

Autorhythmic cells:

- 1-2% of muscle cells
- Smaller than the contractile cells; very few myofibrils
- **Automaticity**- spontaneous depolarization towards threshold
- **Responsible for initiating and distributing the stimulus** (electrical impulses) to contract
- **Initiate action potentials**
- *Have unstable resting potentials called pacemaker potentials*
- **Use Ca^{++} influx** (rather than Na^+) for rising phase of the action potential
- Action potentials **do not have plateau**

Contractile Cells:

- 98-99% of muscle cells
- Larger, branching, striated cells with many contractile fibres (actin and myosin)
- **Need to be stimulated** by the autorhythmic cells to depolarize
- **Respond to stimulus** (electrical impulses) by contracting
- *Have stable resting potentials*
- **Use Na^+ influx** for rising phase of the action potential
- Action potentials **have plateau**



Sinoatrial (SA) Node

- Located in the posterior wall of the right atrium
- **Sinus rhythm** determines heart rate
- **Pacemaker** = usually **SA** node because it is the fastest (~100/min resting)
- **Pacemaker potentials** → **action potentials**
- SA node depolarizes and the resulting impulse spreads across the atrial myocardium and through the internodal fibers to the AV node.
- The atrial myocardium contracts in response, a physical event.

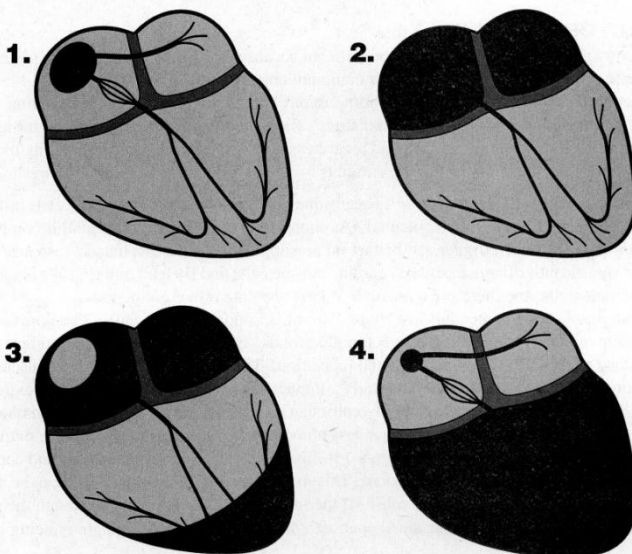
Atrio-Ventricular (AV) Node

- Located at the junction between the atria and ventricles
- Picks up the impulse and transfers it to the AV Bundle (Bundle of His)
- This produces a **0.1 second (100 msec) delay** in the cardiac cycle. It takes approximately .03 sec from SA node depolarization to the impulse reaching the AV node, and .13 sec for the impulse to get through the AV node and reach the Bundle of His.
- During this period the atria repolarize
- From the AV node the impulse travels through the bundle branches
- AV bundle splits into two pathways in the interventricular septum (bundle branches)
- **Bundle branches carry the impulse toward the apex** of the heart and through **the Purkinje fibers to the ventricular myocardium**, causing ventricular depolarization and ventricular contraction, a physical event

In Summary: the atria get excited first, then travel to the apex at the bottom then comes to the above region to excite the ventricles.

Sequence of Excitation

Regions of excitation in black



Cardiac centers are located in

The medulla oblongata of the brain stem

- **Cardioacceleratory center** innervates & stimulates
 - SA and AV nodes
 - heart muscle
 - coronary arteries through the **sympathetic neurons**
- **Cardioinhibitory center** inhibits
 - SA and AV nodes through the **parasympathetic** fibers in the vagus nerves

Heart Rate under parasympathetic stimulation

- Decreased heart rate – when ACh released by parasympathetic neurons opens chemically gated K^+ channels, leading to hyperpolarization and slower rate of spontaneous depolarization

Heart rate under sympathetic stimulation

- Increased heart rate – when NE released by sympathetic neurons increases the rate of depolarization and shortens the period of repolarization

ECG: Electrocardiography

- Record electrical activity of the heart
- Three distinguishable waves:
 - 1). **P wave** → **atria depolarization** (precedes atria contraction)
 - 2). **QRS complex** → **ventricular depolarization** (precedes ventricular contraction)
 - 3). **T wave** → **ventricular repolarization** (takes place during ventricular excitation)

