Chapter 1

Cell Communication

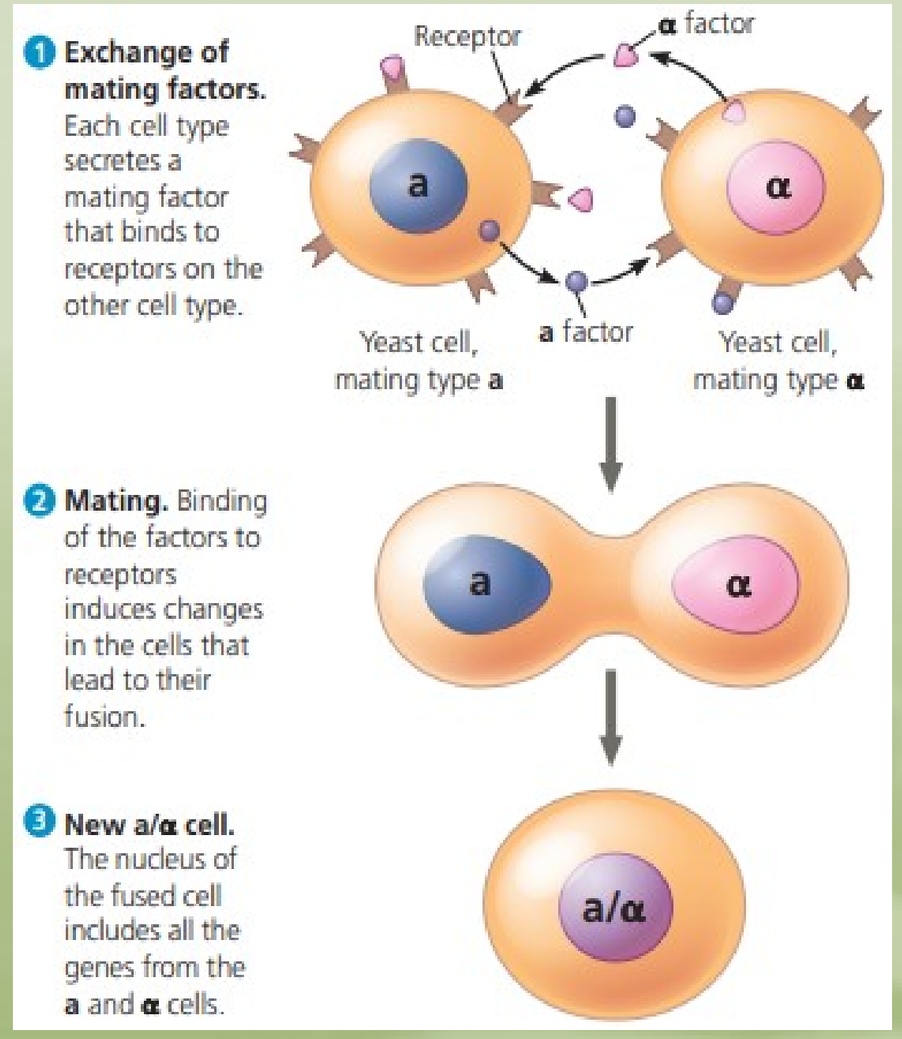
Evolution of Cell Signaling

Communication between mating yeast cells

* Each cell type secretes a mating factor that binds to receptors on the other cell type.

* The mating signal is changed, or transduced into a series of steps called a signal transduction pathway that brings about the cellular response of mating; cells change shape, grow toward each other, and fuse (mate).

* The nucleus of the fused cell (new cell) contains all the genes of both original cells.



* The molecular details of signal transduction in yeasts and mammals are strikingly similar. This suggests that early versions of cell-signaling mechanisms evolved well before the first multicellular creatures appeared on Earth.

* Scientists think that signaling mechanisms first evolved in ancient prokaryotes and single-celled eukaryotes and then were adopted for new uses by their multicellular descendants.

* Bacterial cells secrete molecules that can be detected by other bacterial cells. Sensing the concentration of such signaling molecules allows bacteria to monitor the local density of cells (quorum sensing).

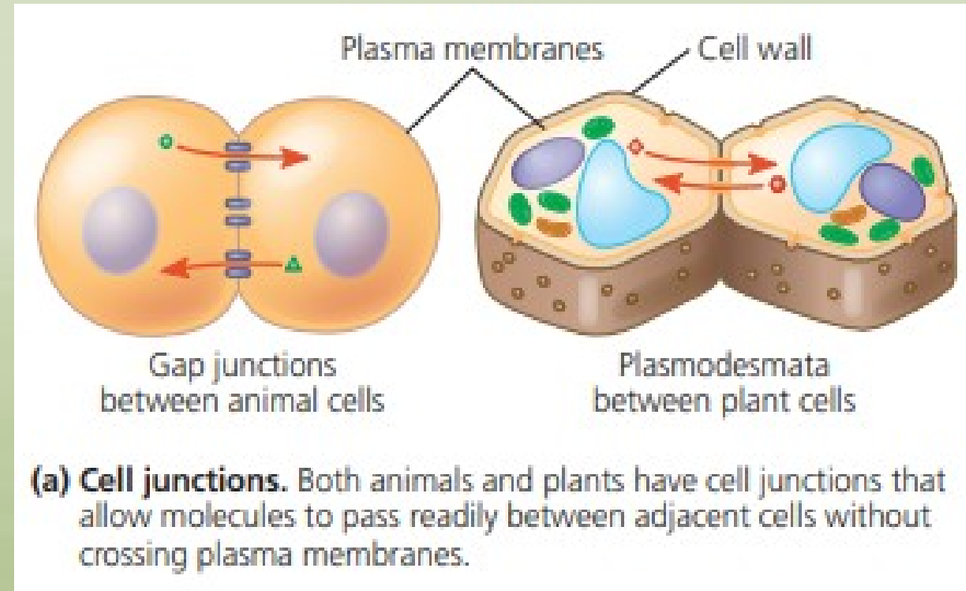
* Quorum sensing allows bacterial populations to coordinate their behaviors in activities that require a given number of cells acting synchronously. One example is formation of a biofilm, an aggregation of bacterial cells adhered to a surface. The cells in the biofilm generally derive nutrition from the surface they are on. Examples of bacterial biofilms are the slimy coating on a fallen log or on leaves and the film on your teeth each morning.

Local and Long-Distance Signaling

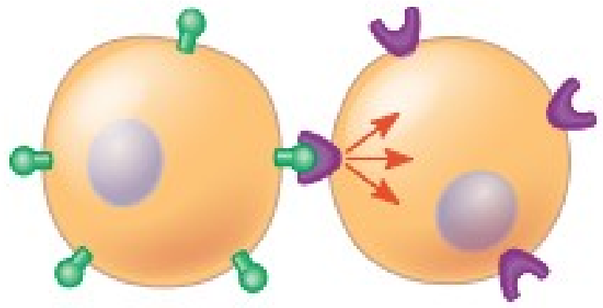
!. Local Signaling

* **Eukaryotic cells may communicate by direct contact, one type of local signaling.**

* **Both animals and plants have cell junctions that directly connect the cytoplasms of adjacent cells. In these cases, signaling substances dissolved in the cytosol can pass freely between adjacent cells.**



(a) Cell junctions. Both animals and plants have cell junctions that allow molecules to pass readily between adjacent cells without crossing plasma membranes.



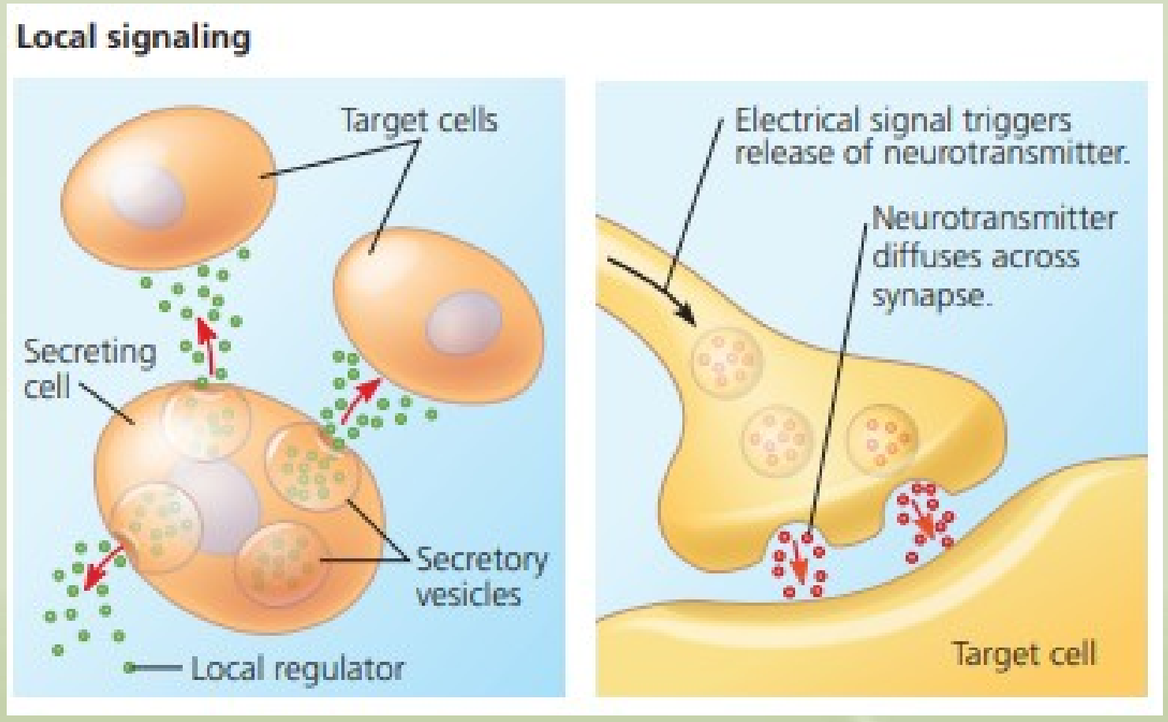
(b) Cell-cell recognition. Two cells in an animal may communicate by interaction between molecules protruding from their surfaces.

* **Animal cells may communicate via direct contact between membrane-bound cell-surface molecules in a process called cell-cell recognition.**

* **This sort of local signaling is especially important in embryonic development and immune response.**

* **Paracrine signaling:** A secreting cell acts on **nearby** target cells by secreting molecules of a local regulator (e.g. growth factor).

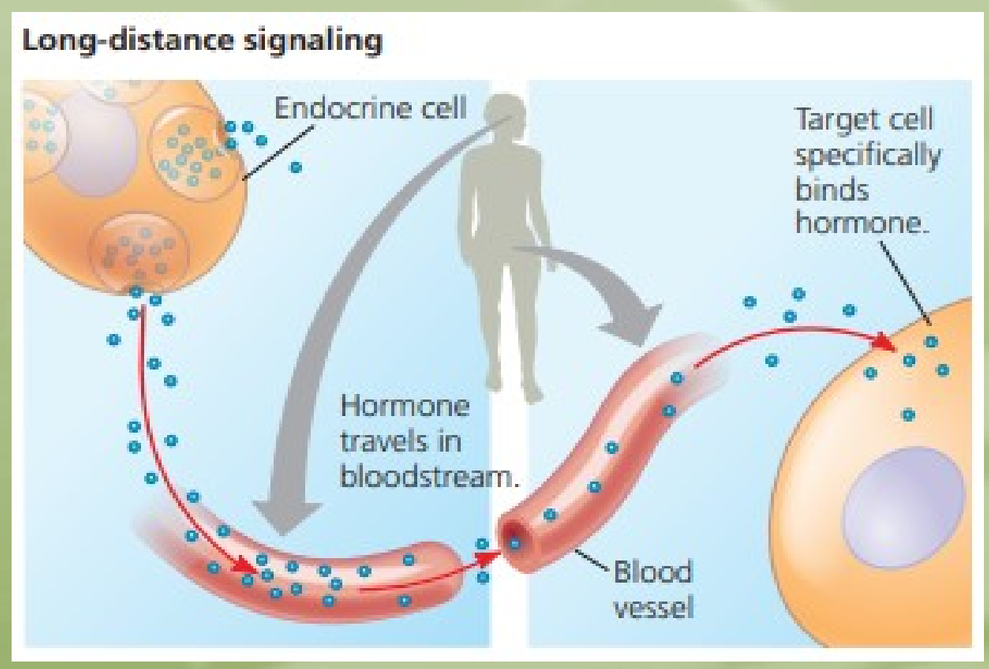
* **Synaptic signaling:** A nerve cell releases neurotransmitter molecules into a **synapse**, stimulating target cell, such as a muscle or nerve cell.



2. Long-Distance Signaling

* Both animals and plants use hormones for long-distance signaling.

* In hormonal signaling in animals (endocrine signaling), specialized cells release hormone, which travels via the **circulatory system** to its target cell.



* Plant hormones (**plant growth regulators**) reach their targets by moving through **cells or by diffusing through the air as a gas**.

* Hormones vary in size and type e.g. the plant hormone ethylene, a gas that promotes fruit ripening and helps regulate growth, is a hydrocarbon of only six atoms (C2H4). In contrast, the mammalian hormone insulin, which regulates blood glucose, is a protein with thousands of atoms.

The Three Stages of Cell Signaling: A Preview

1. Reception

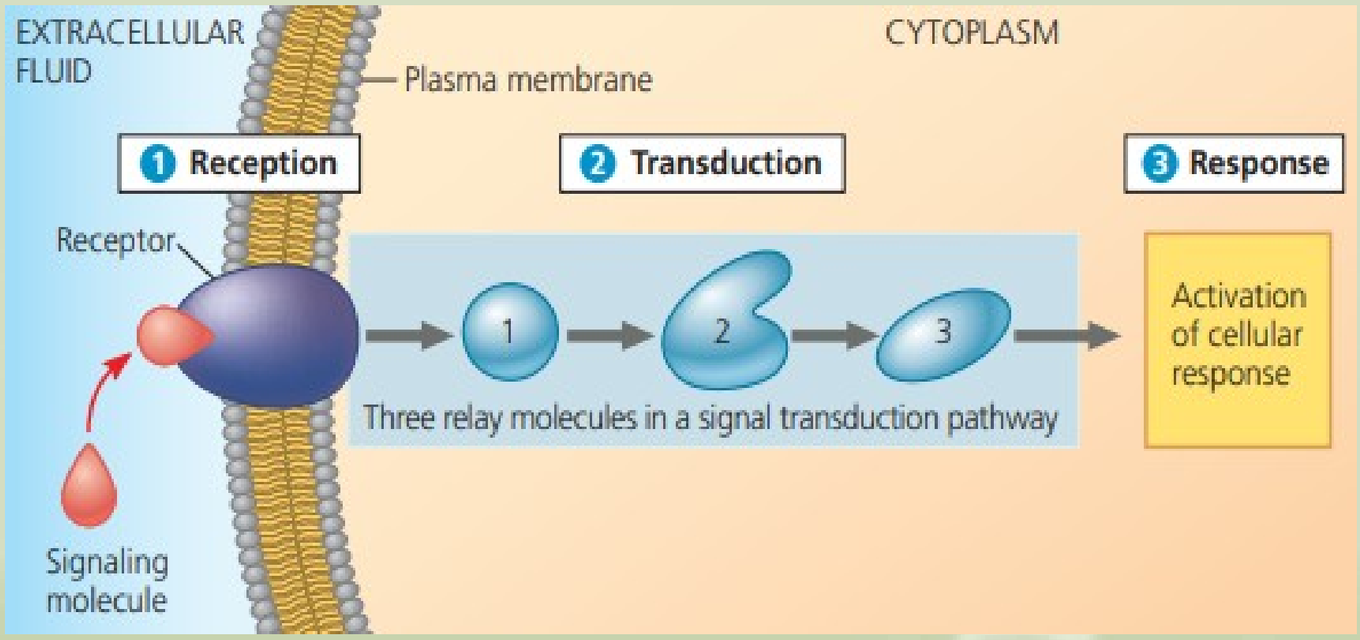
* Reception is the target cell's detection of a signaling molecule coming from outside the cell.
* A chemical signal is "detected" when the signaling molecule binds to a receptor protein located at the cell's surface or inside the cell.

2. Transduction

* Binding of signaling molecule changes the receptor protein in some way, initiating the process of transduction which occurs in a sequence of changes with a series of different molecules (a signal transduction pathway). The molecules in the pathway are called relay molecules.

3. Response

* The transduced signal finally triggers a specific response which is a cellular activity e.g. catalysis by an enzyme, rearrangement of the cytoskeleton, or activation of specific genes in the nucleus.



1. Reception: A signaling molecule binds to a receptor protein, causing it to change shape

* The signaling molecule (ligand) is complementary in shape to a specific site on the receptor and attaches there, like a key in a lock.

* Ligand binding causes a receptor protein to undergo a change in shape ⟶ receptor activation ⟶ interact with other cellular molecules.

I. Receptors in the Plasma Membrane

*** The three major types of cell-surface transmembrane receptors are G protein-coupled receptors (GPCRs), receptor tyrosine kinases, and ion channel receptors.**

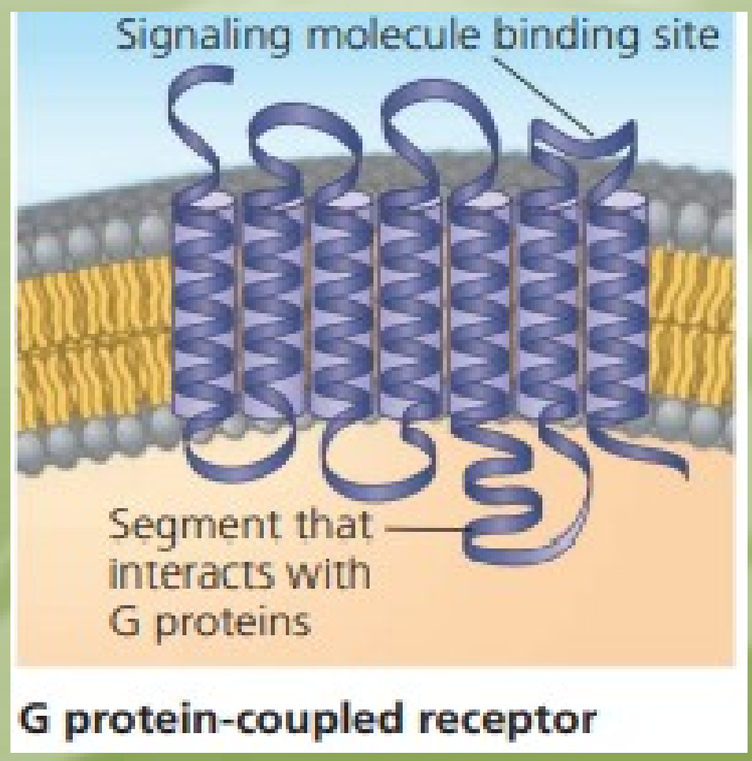
*** Malfunctions of cell-surface receptors are associated with many human diseases, including cancer, heart disease, and asthma.**

1. G Protein-Coupled Receptors (GPCR)

*** GPCR is a cell-surface transmembrane receptor that works with help of G protein (a protein binds GTP).**

*** Many different signaling molecules e.g. yeast mating factors, epinephrine and neurotransmitters use GPCRs.**

*** GPCR is a single polypeptide which has seven transmembrane α helices. The loops form binding sites for signaling molecules outside the cell and G proteins on the cytoplasmic side.**

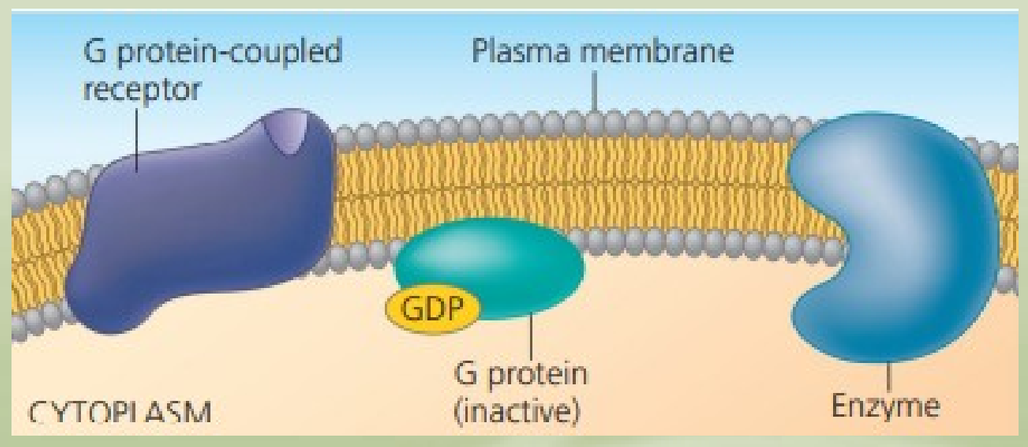


G protein-coupled receptor

* GPCR-based signaling systems are **widespread and diverse** in their functions e.g. in humans, vision, smell, and taste depend on GPCRs.

* Malfunctions of G proteins are involved in many **human diseases** e.g. bacterial infections like cholera, pertussis (whooping cough), and botulism.

Mechanism of action of G proteins

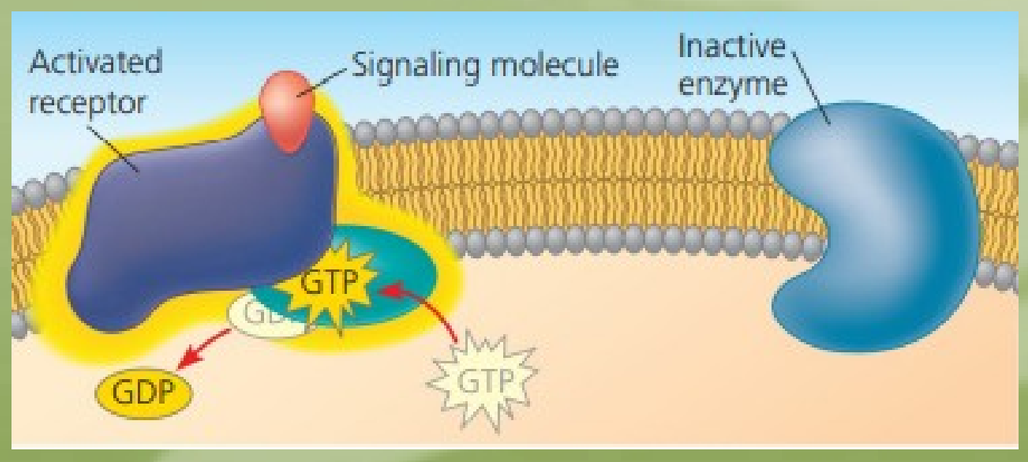


* The loosely attached G-protein to the cytoplasmic side of the membrane functions as a molecular switch that is either on or off, depending on which of two guanine nucleotides is attached, GDP or GTP.

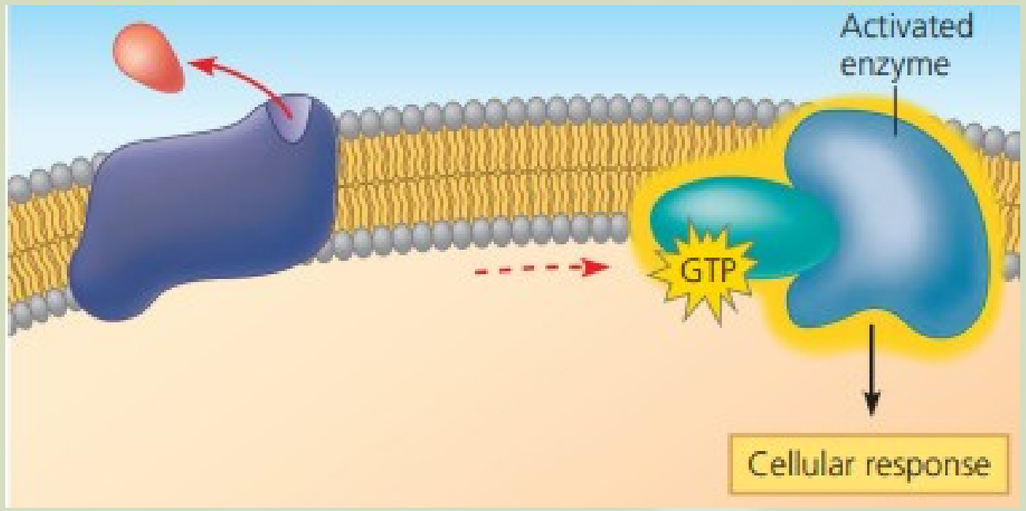
* When GDP is bound to the G protein, the G protein is **inactive (off)**.

* When signaling molecule binds to the extracellular side of the receptor, the receptor is activated and changes shape.

* Its cytoplasmic side then binds an inactive G protein, causing a GTP to displace GDP. This activates the G protein.

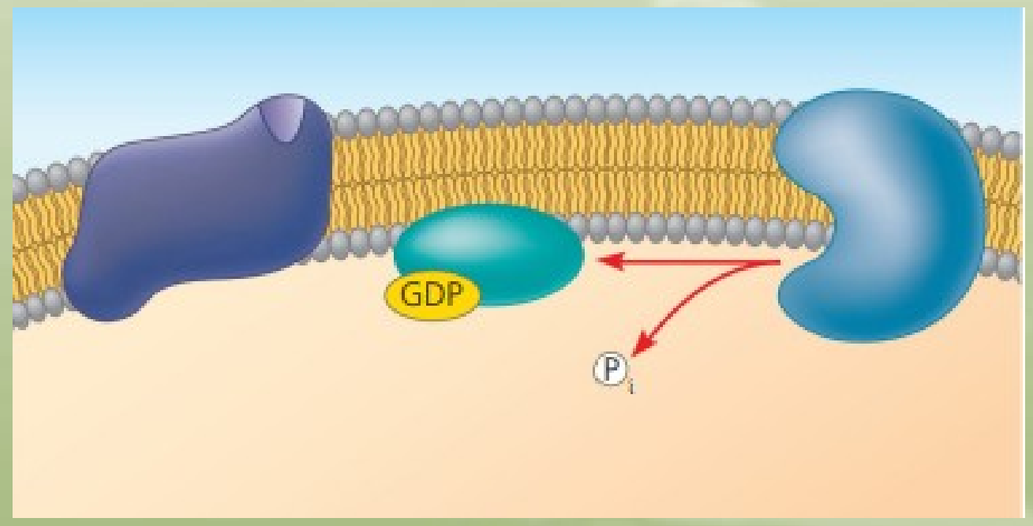


* The activated G protein dissociates (α subunit), diffuses along the membrane, and then binds to an enzyme, altering enzyme's activity ⟶ cellular response.



* Binding of signaling molecules is reversible.

* The changes in the enzyme and G protein are only temporary because G protein also functions as a GTPase i.e. it hydrolyzes its bound GTP to GDP and Pi. Now inactive again, the G protein leaves the enzyme, which returns to its original state. The G protein is now available for reuse.



2. Receptor Tyrosine Kinases (RTKs)

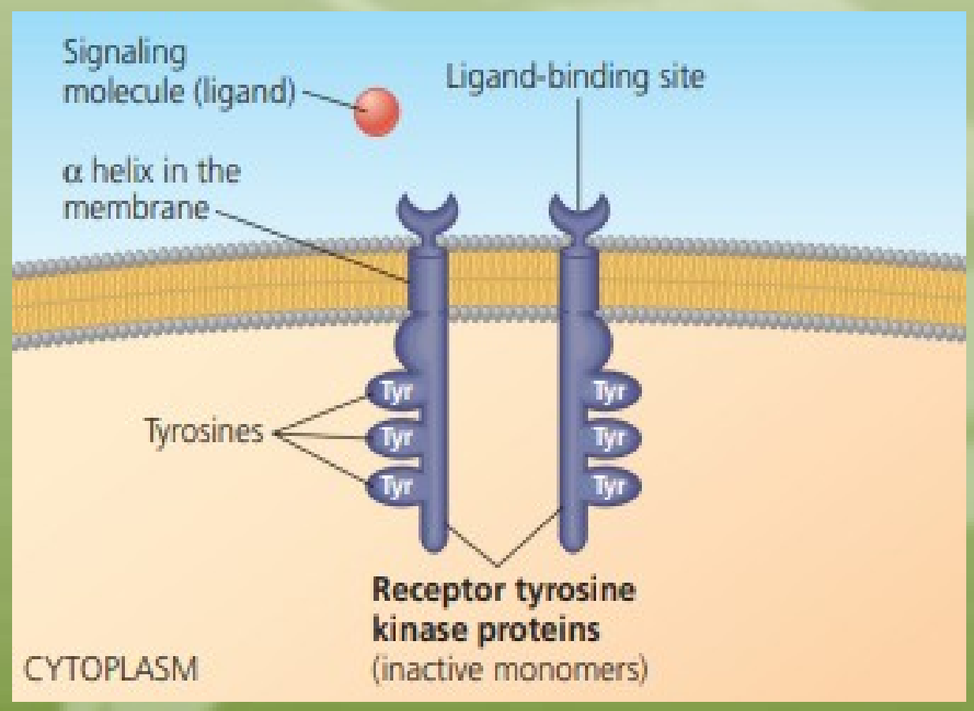
* RTKs are plasma membrane receptors with enzymatic activity.

* The part of the receptor protein extending into the cytoplasm functions as a tyrosine kinase, an enzyme that phosphorylates the amino acid tyrosine.

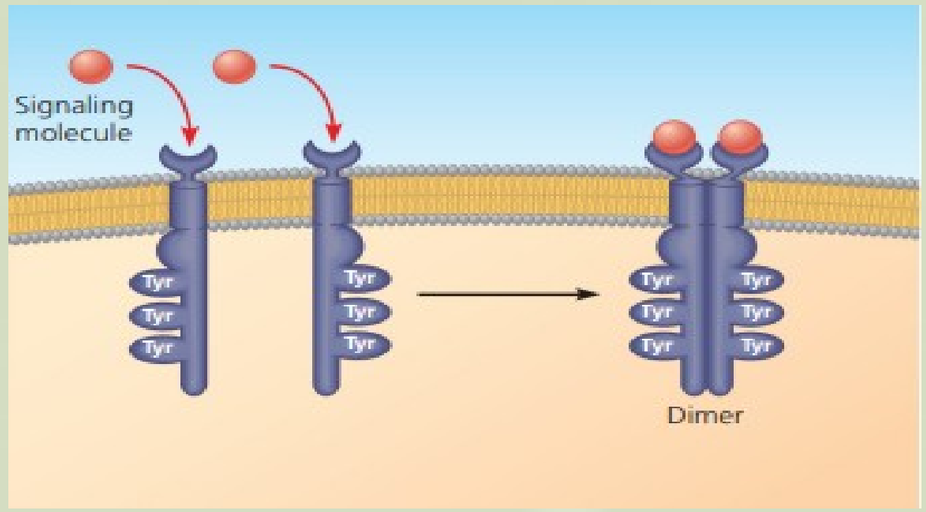
* One RTK may activate many transduction pathways and cellular responses while one GPCR activate a single transduction pathway.

* Abnormal functioning of RTKs is associated with many kinds of cancers e.g. breast cancer.

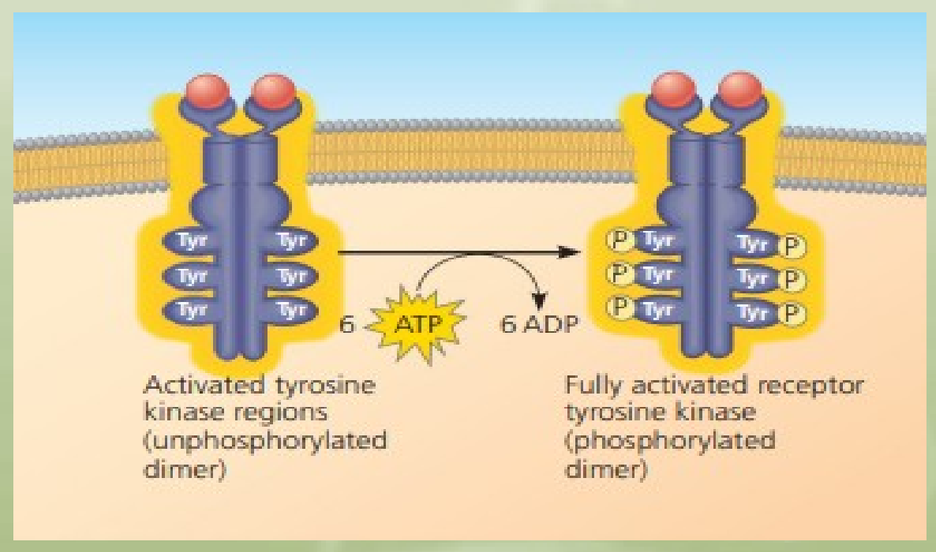
* Before the signaling molecule binds, the receptors exist as individual units (monomers). Each has an extracellular ligand-binding site, an α helix spanning the membrane, and an intracellular tail containing multiple tyrosines.



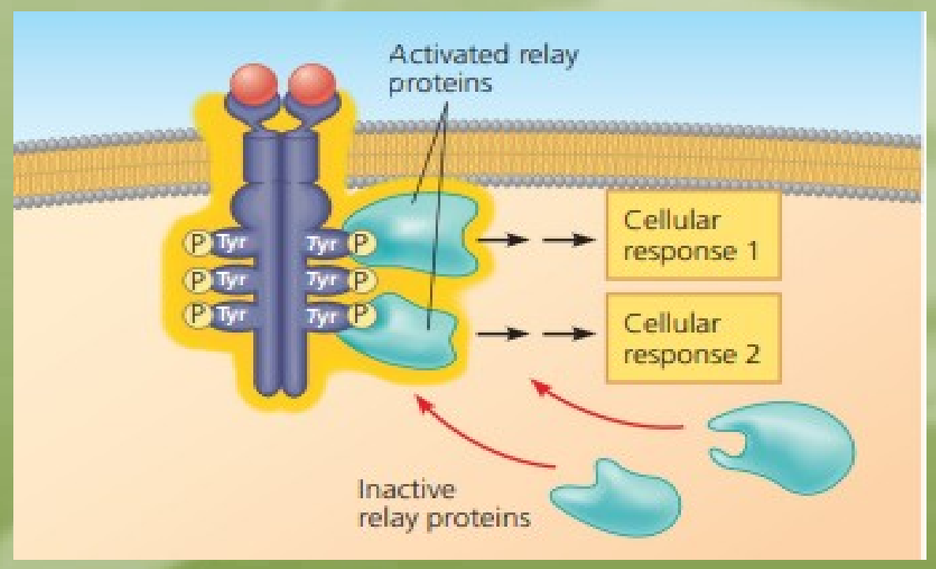
* Binding of a signaling molecule e.g. growth factor causes two receptor monomers to associate closely with each other, forming a complex called a dimer (dimerization).



* Dimerization activates tyrosine kinase region of each monomer; each tyrosine kinase adds a phosphate from an ATP molecule to a tyrosine on the tail of the other monomer.



* Now the receptor is fully activated, it is recognized by specific relay proteins inside the cell. Each such protein binds to a specific phosphorylated tyrosine, undergoing a structural change that activates the bound protein. Each activated protein triggers a transduction pathway, leading to a cellular response.

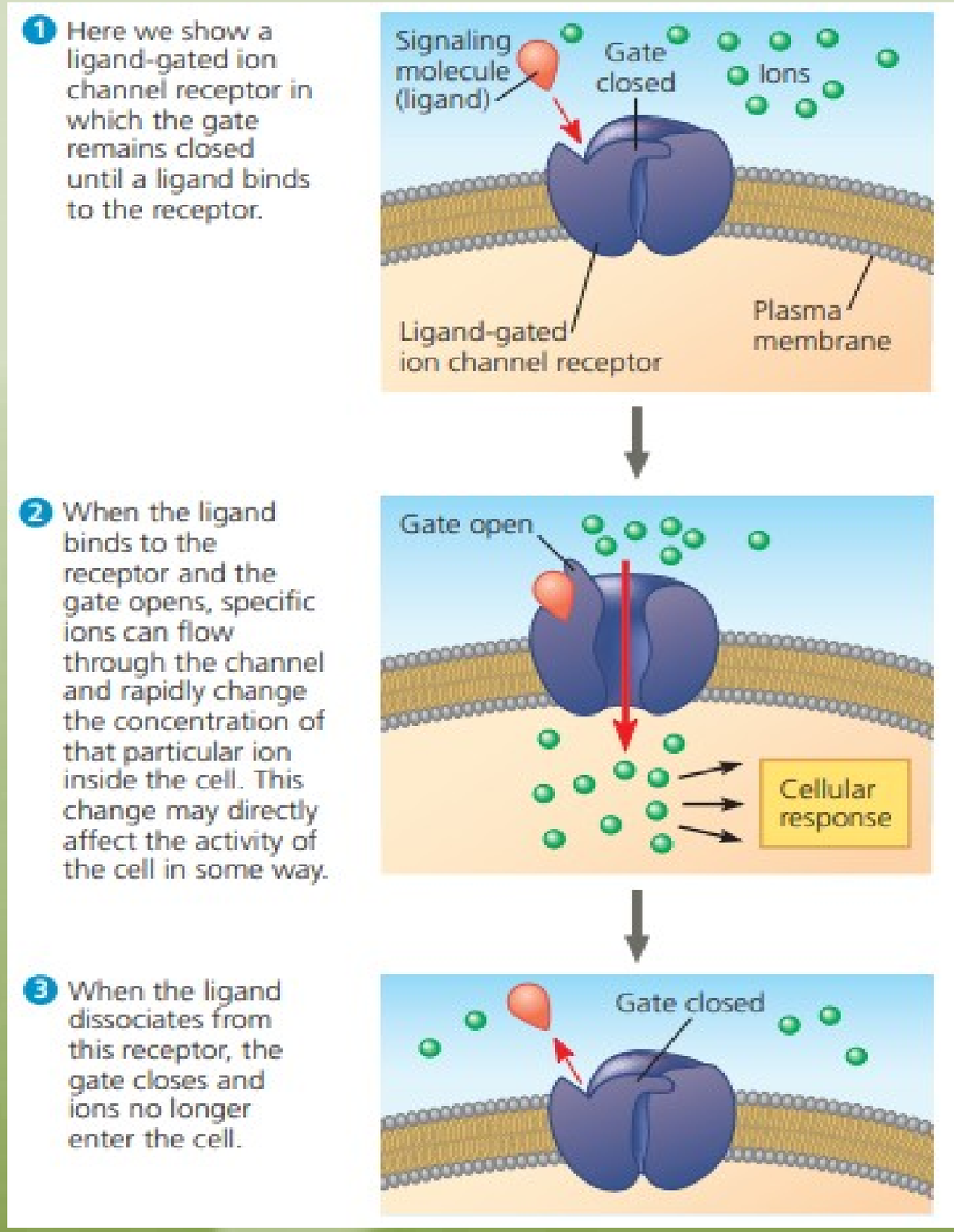


3. Ligand-gated Ion Channel

* A ligand-gated ion channel is a type of membrane receptor with a "gate" e.g. acetylcholine receptor channel.

* Binding of acetylcholine (ligand) with its channel protein causes conformational change in the protein molecule that opens the gate of acetylcholine channel that allows sodium ions to pass through.

* Acetylcholine channel is important for transmission of nerve signals from one nerve cell to another (synapse) and from nerve cells to muscle cells (neuromuscular junction) to cause muscle contraction.



II. Intracellular Receptors

* Intracellular receptors are found in either cytoplasm or nucleus.

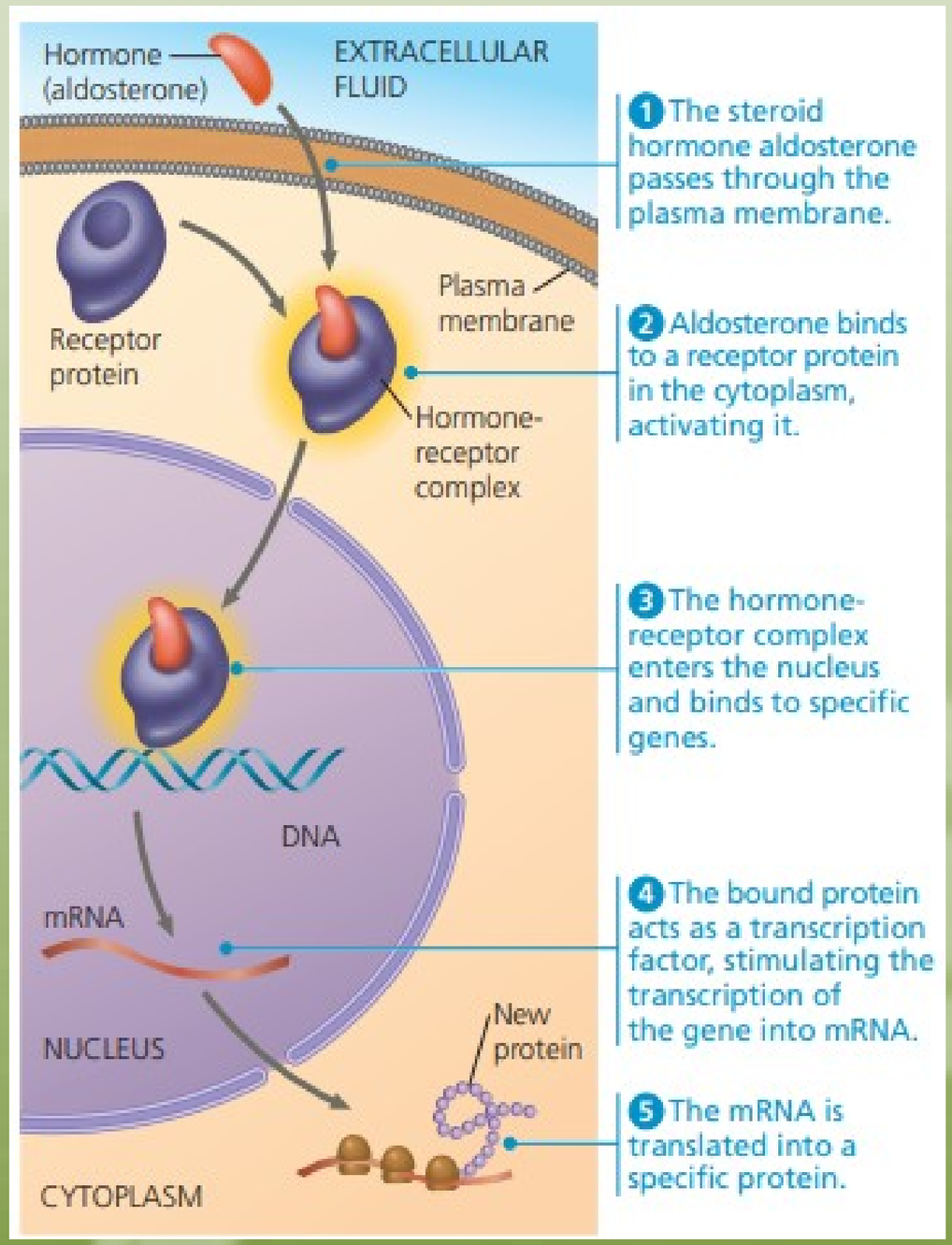
* To reach such a receptor, a signaling molecule is either hydrophobic e.g. steroid and thyroid hormones or small e.g. nitric oxide to cross plasma membrane.

* Example: Aldosterone is a steroid hormone secreted by adrenal gland.

* Aldosterone passes through plasma membrane, binds its receptor in cytoplasm of kidney cell and activating it.

* The aldosterone-receptor complex (transcription factor) enters nucleus and binds to specific genes, stimulating transcription of the gene into mRNA.

* The mRNA leaves the nucleus and is translated into a specific protein that stimulates Na+ reabsorption and K+ secretion in renal distal tubules.



2. Transduction: Cascades of molecular interactions relay signals from receptors to target molecules in the cell

* When receptors are plasma membrane proteins, the transduction stage of cell signaling is usually a multistep pathway.

* Steps often include activation of proteins by phosphorylation or dephosphorylation or release of other small molecules or ions that act as messengers.

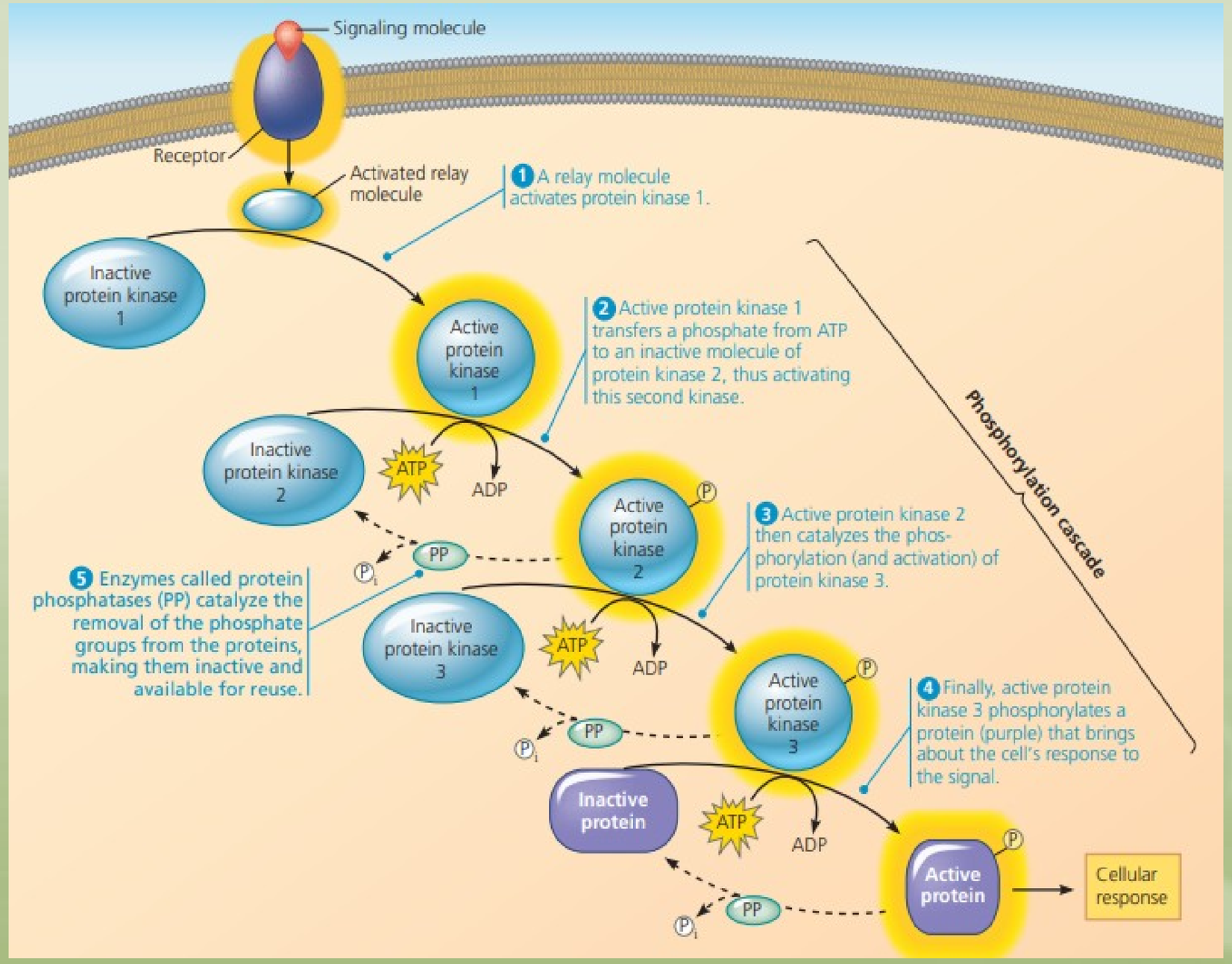
* Benefits of multistep pathways are amplifying a signal and providing more opportunities for coordination and control than do simpler systems, allowing regulation of the response.

Signal Transduction Pathways

1. Protein Phosphorylation and Dephosphorylation

* An enzyme that transfers phosphate groups from ATP to a protein is called a protein kinase (phosphorylation) and an enzyme that removes phosphate groups from proteins is called protein phosphatases (dephosphorylation).

* In a **phosphorylation cascade** (similar to that triggered in yeast by mating factors and in animal cells by growth factors), each **active** protein kinase adding a phosphate group to the next **inactive** one, causing its **shape change and activating it**.



* shape change is due interaction of the newly added phosphate groups with charged or polar amino acids on the protein being phosphorylated .

* Protein kinases regulate the activity of proteins that regulate **cell division**. Thus, abnormal activity of such **kinases** may contribute to the development of **cancer**.

* Protein kinases are inactivated by protein phosphatases (dephosphorylation). Thus phosphatases 1) provide the mechanism for turning off the signal transduction pathway when the initial signal is no longer present, and 2) make the protein kinases available for reuse, enabling the cell to respond again to an extracellular signal. The phosphorylation-dephosphorylation system acts as a molecular switch in the cell, turning activities on or off, or up or down, as required.

2. Small Molecules and Ions as Second Messengers

A. Cyclic AMP

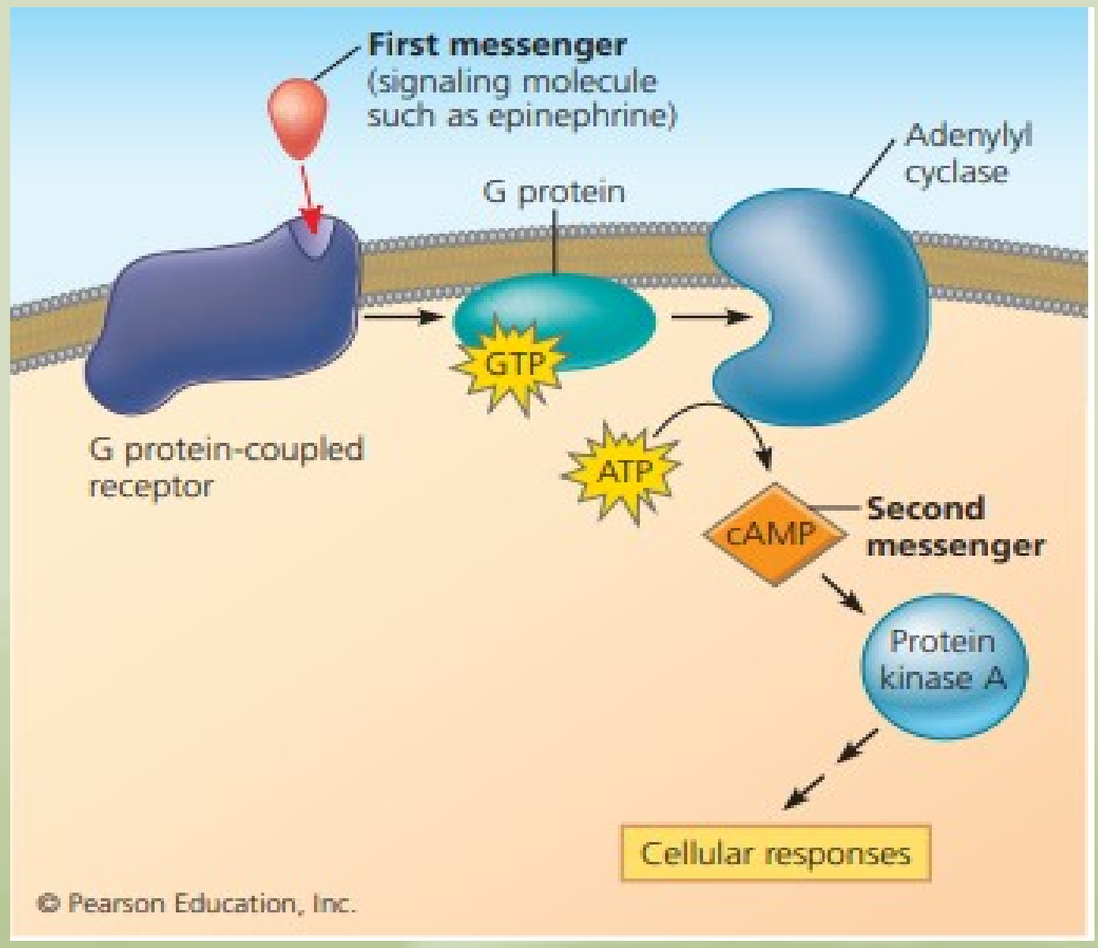
* Epinephrine causes glycogen breakdown of a liver or muscle cell without passing through the plasma membrane. How?

- Binding of epinephrine to plasma membrane of liver cell activates a G-protein coupled receptor which activates stimulatory G-protein (Gs) that activates an enzyme embedded in plasma membrane called adenylyl cyclase which converts ATP to cyclic adenosine monophosphate (cAMP).

- The cAMP acts as a second messenger and activates protein kinase A which phosphorylates other proteins, leading to cellular response.

- The cAMP does not persist for long in absence of epinephrine because another enzyme called phosphodiesterase converts cAMP to AMP.

- Further regulation of cell metabolism is provided by other G protein systems that inhibit adenylyl cyclase. In these systems, a different signaling molecule activates a different receptor, which in turn activates an inhibitory G protein (Gi) that inhibits adenylyl cyclase.



How cholera bacterium, *Vibrio cholerae*, cause cholera?

Cholera toxin is an enzyme that modifies a G protein involved in regulating salt and water secretion. Because the modified G protein is unable to hydrolyze GTP to GDP, it remains active, continuously stimulating adenylyl cyclase to make cAMP. The resulting high concentration of cAMP causes intestinal cells to secrete large amounts of salts into intestine, with water following by osmosis, resulting in diarrhea which causes death if untreated.

B. Calcium Ions and Inositol Trisphosphate (IP3)

* Calcium is more widely used than cAMP as a second messenger.

* Increasing cytosolic concentration of Ca2+ causes many responses in animal cells, including muscle cell contraction, secretion of certain substances, and cell division.

* In plant cells, a wide range of hormonal and environmental stimuli can cause brief increases in cytosolic Ca2+ concentration, triggering various signaling pathways, such as the pathway for greening in response to light.

* Cells use Ca2+ as a second messenger in pathways triggered by both G protein-coupled receptors and receptor tyrosine kinases.

* Ca2+ can function as a second messenger because its concentration in cytosol is normally much lower than outside cell.

* In response to a signal, cytosolic Ca2+ level may rise, usually by a mechanism that releases Ca2+ from the cell's ER.

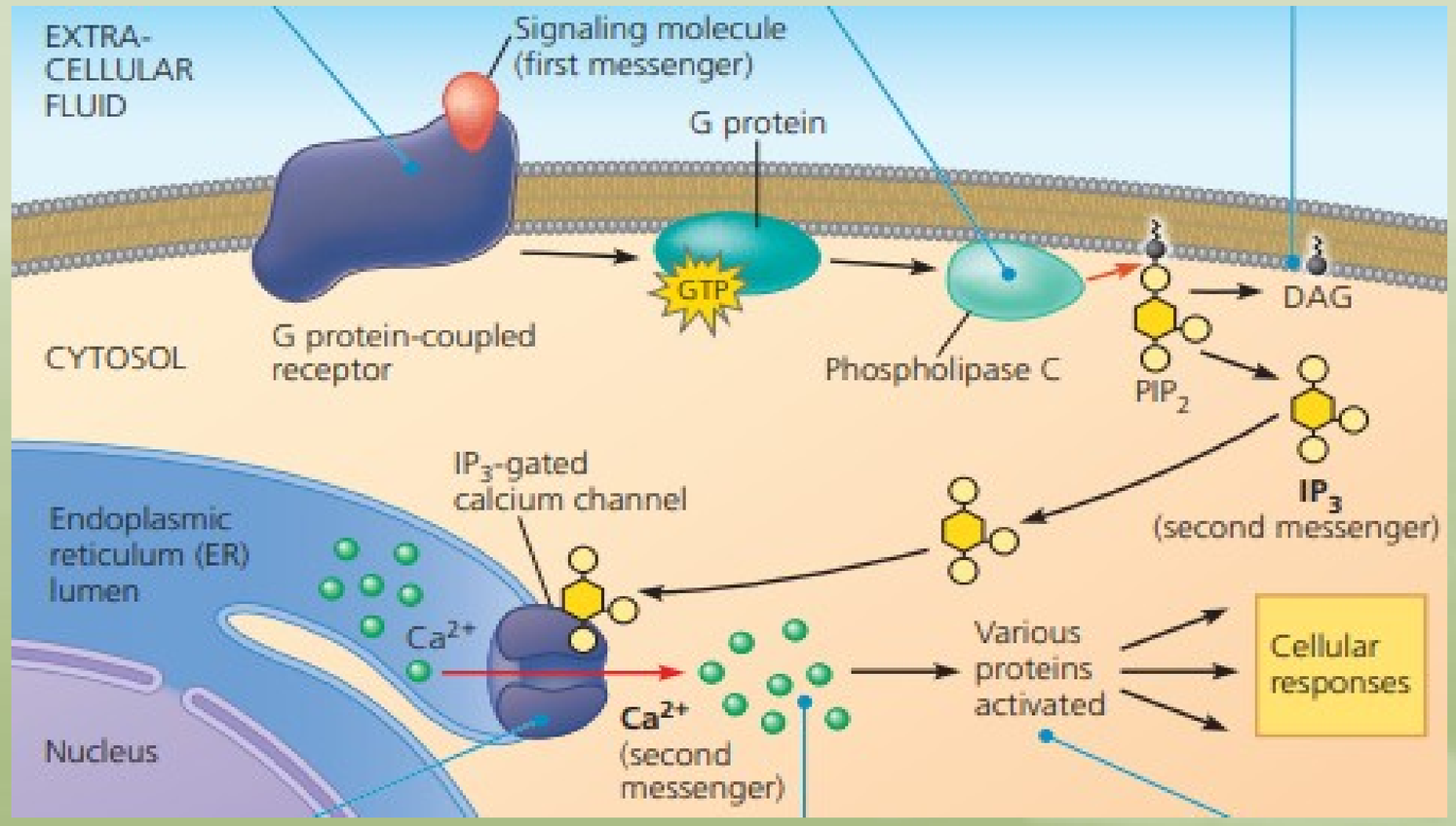
* The pathways leading to Ca2+ release involve two other second messengers, inositol trisphosphate (IP3) and diacylglycerol (DAG).

* These two messengers are produced by cleavage of phospholipid in plasma membrane called Phosphatidylinositol 4,5-bisphosphate (PIP2).

* A signaling molecule binds to a receptor, leading to activation of G-protrin that activates phospholipase C.

* Phospholipase C cleaves PIP2 into DAG and IP3.

* DAG functions as a second messenger in other pathways.



* IP3 quickly diffuses through the cytosol and binds to an IP3- gated calcium channel in the ER membrane, causing it to open.

* Calcium ions diffuse out of the ER, raising the Ca2+ level in the cytosol.

* Calcium ions activate various proteins causing cellular responses.

3. Nuclear and Cytoplasmic Responses

A. Nuclear Responses

* Many signaling pathways ultimately regulate protein synthesis, usually by turning specific genes on or off in the nucleus.

Example 1. activation of a specific gene by aldosterone.

Example 2. activation of a specific gene by a growth factor.

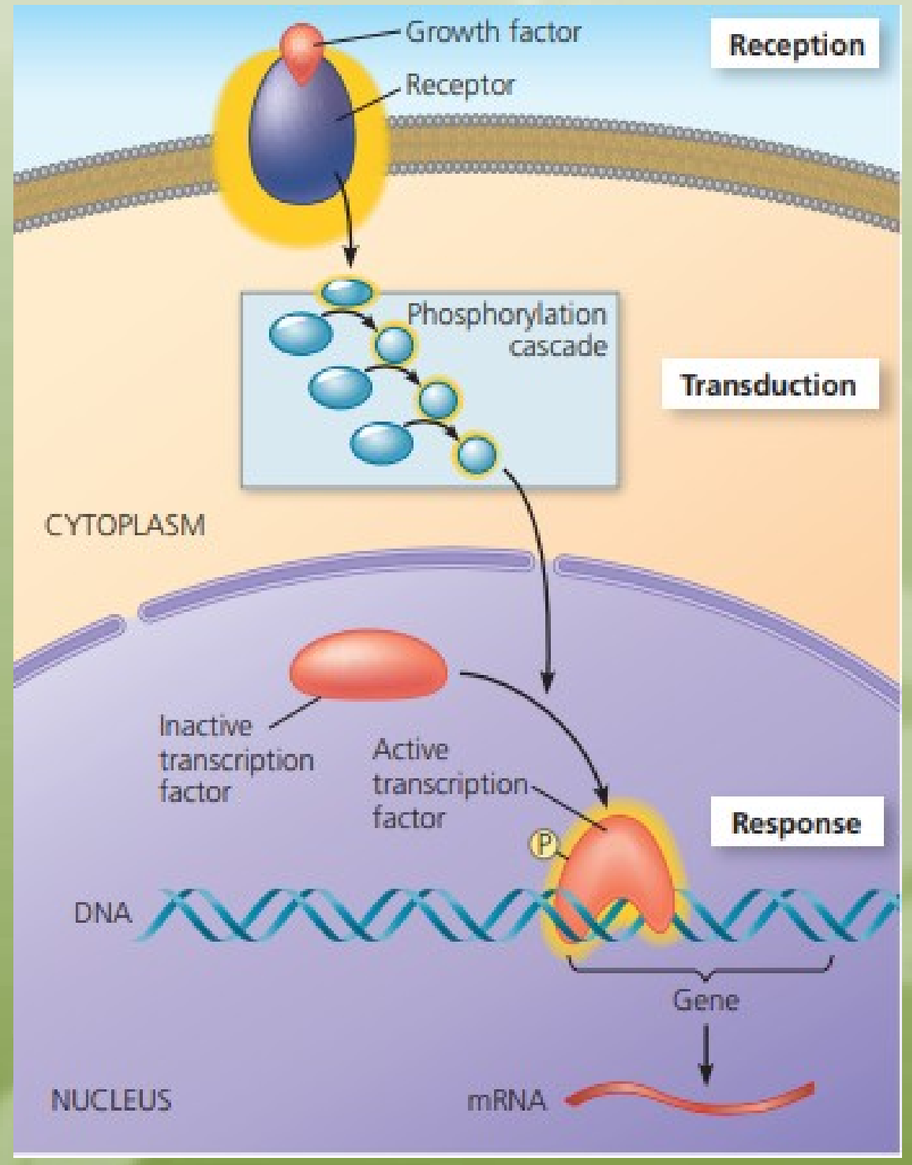
* The initial signaling molecule, a growth factor, triggers a phosphorylation cascade.

* Once phosphorylated, the last kinase in the sequence enters the nucleus and activates a gene-regulating protein, a transcription factor.

* The transcription factor stimulates transcription of a specific gene (or genes).

* The resulting mRNAs then direct the synthesis of a particular protein in the cytoplasm.

* Malfunctioning of growth factor pathways involving in cell division can contribute to development of cancer.



B. Cytoplasmic Responses

* The signaling pathway regulates the activity of cytoplasmic proteins rather than causing their synthesis.

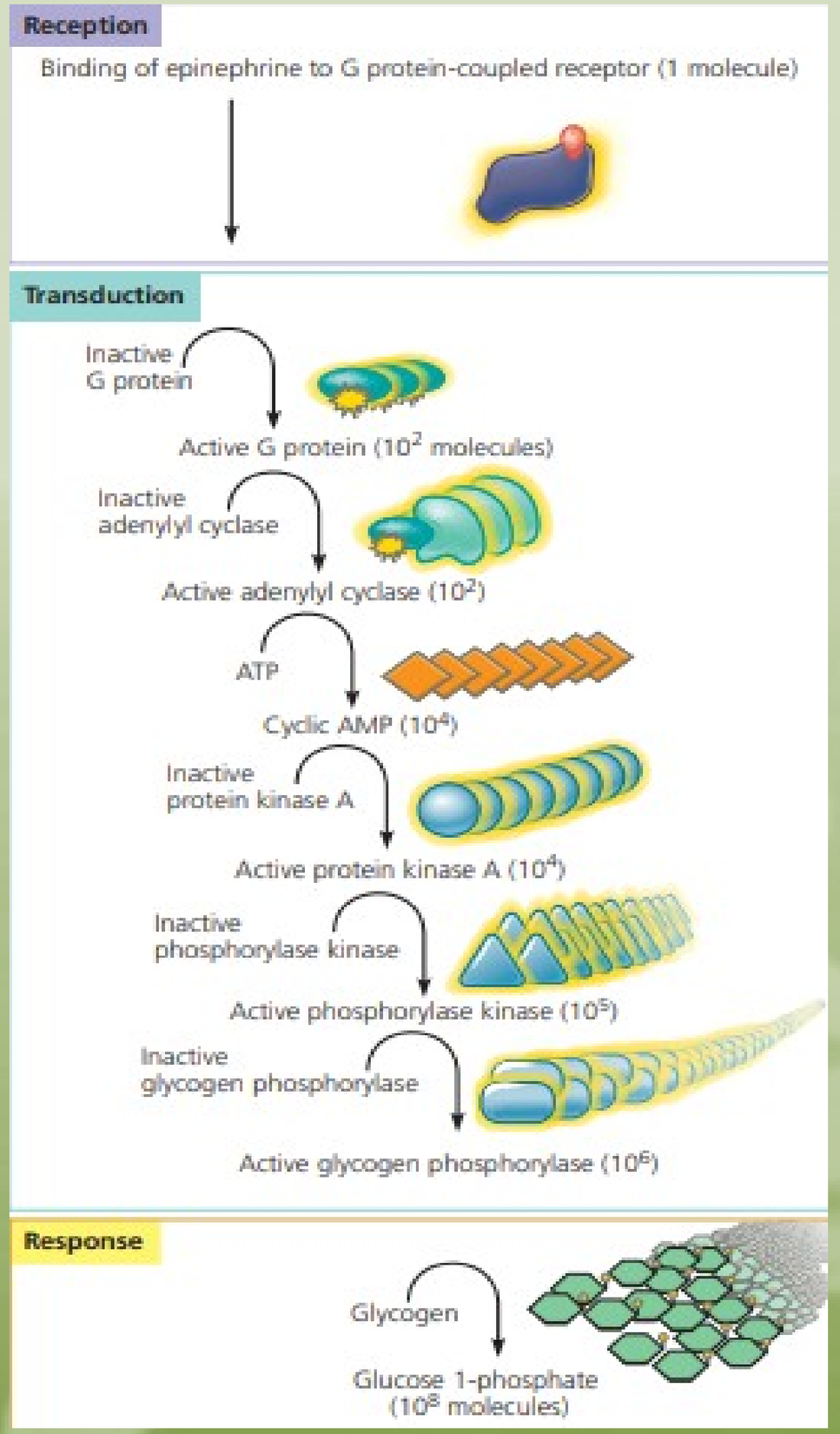
* Example 1: opening or closing of an ion channel in plasma membrane.

* Example 2: stimulation of glycogen breakdown by epinephrine in liver cell cytoplasm.

- Epinephrine acts through a G protein-coupled receptor to activate a succession of relay molecules, including cAMP and two protein kinases.

- The final protein activated is the enzyme glycogen phosphorylase, which uses inorganic phosphate to release glucose monomers from glycogen in the form of glucose 1-phosphate.

- This pathway amplifies hormonal signal.



Regulation of the Response

The extent and specificity of the response are regulated in multiple ways through 4 aspects of regulation.

1. Signal Amplification

Enzyme cascades amplify the cell's response to a signal. At each catalytic step in the cascade, the number of activated products can be much greater than in the preceding step.

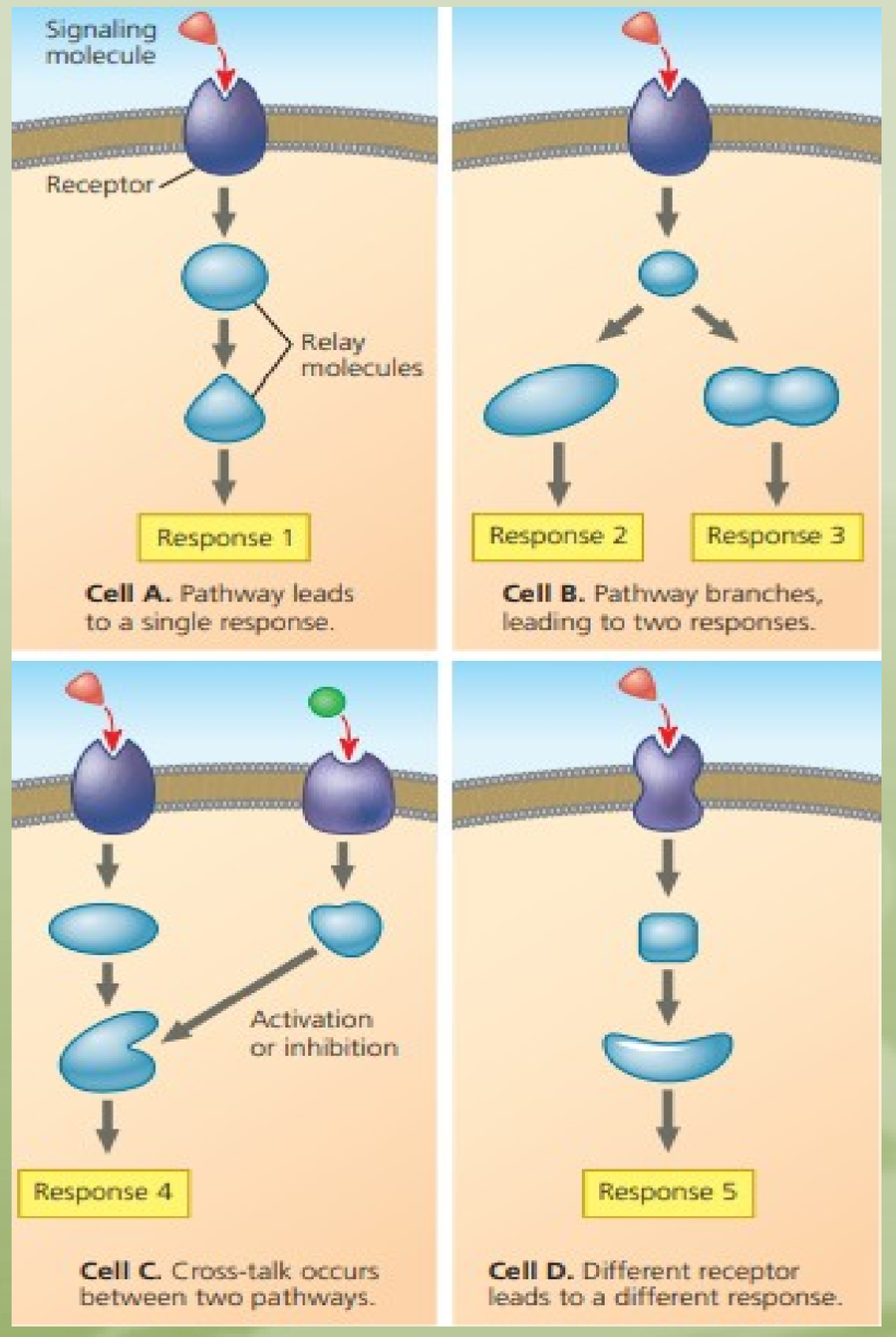
Example: stimulation of glycogen breakdown by epinephrine.

*** Each adenylyl cyclase molecule catalyzes the formation of about 100 cAMP molecules, each molecule of protein kinase A phosphorylates about 10 molecules of the next kinase in the pathway, and so on.**

*** As a result of the signal's amplification, a small number of epinephrine molecules binding to receptors on the surface of a liver or muscle cell can lead to the release of hundreds of millions of glucose molecules from glycogen.**

2. The Specificity of Cell Signaling and Coordination of the Response

* The response of a particular cell to a signal depends on its receptor proteins, relay proteins, and proteins needed to carry out the response. A liver cell, for example responds appropriately to epinephrine by having their proteins cascade needed for glycogen breakdown. Thus, two cells that respond differently to the same signal differ in proteins that handle and respond to the signal.



* Example: cells A, B, and C use the same receptor protein for red signaling molecule; differences in other proteins account for their differing responses.

* In cell D, different receptor protein is used for the same signaling molecule, leading to another response.

* In cell B, a pathway that is triggered by a single kind of signal diverges to produce two responses; such branched pathways often involve receptor tyrosine kinases (which can activate multiple relay proteins) or second messengers (which can regulate numerous proteins).

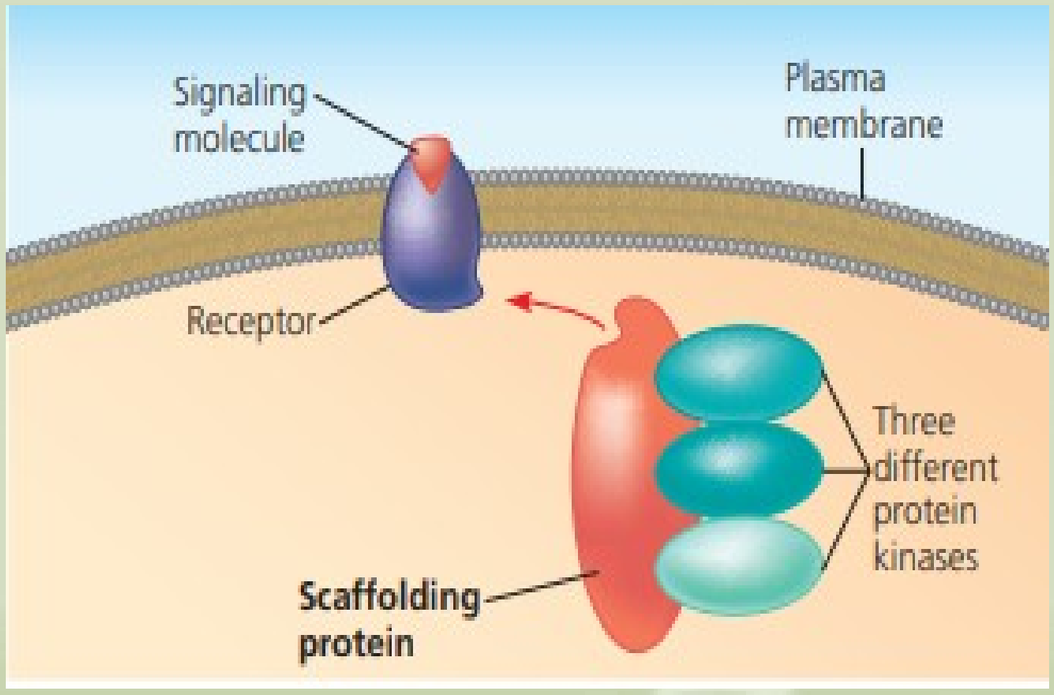
* In cell C, two pathways triggered by separate signals converge to modulate a single response. Branching of pathways and “cross-talk” (interaction) between pathways are important in regulating and coordinating a cell’s responses to information coming in from different sources in the body. An example of a signal that leads to a complex, coordinated cellular response can be found in the processes leading to the mating of yeast cells described earlier.

3. Signaling Efficiency: Scaffolding Proteins and Signaling Complexes

* Signaling pathways would operate inefficiently because most relay molecules are proteins, and proteins are too large to diffuse quickly through the viscous cytosol.

* The efficiency of signal transduction is increased by the presence of scaffolding proteins, large relay proteins to which several other relay proteins are simultaneously attached.

* Example, one scaffolding protein isolated from mouse brain cells holds three protein kinases and carries these kinases with it when it binds to an appropriately activated membrane receptor; it thus facilitates a specific phosphorylation cascade.



* Scaffolding proteins in brain cells hold together networks of signaling pathway proteins at synapses and this enhances the speed and accuracy of signal transfer between cells.

* The importance of relay proteins that serve as points of branching or intersection in signaling pathways is highlighted by the problems arising when these proteins are defective or missing e.g. in an inherited disorder called Wiskott-Aldrich syndrome (WAS), absence of a single relay protein in cells of immune system leads to such diverse effects as abnormal bleeding, eczema, and a predisposition to infections and leukemia.

4. Termination of the Signal

* In cholera, if the modified G protein is unable to hydrolyze GTP to GDP, it remains active, continuously stimulating adenylyl cyclase to make cAMP. The resulting high concentration of cAMP causes intestinal cells to secrete large amounts of salts into intestine, with water following by osmosis, resulting in diarrhea causing death if untreated.

* The ability of a cell to receive new signals depends on reversibility of changes produced by prior signals.

* Cellular response occurs only when concentration of receptors with bound signaling molecules is above a certain threshold. When the number of active receptors falls below that threshold, the cellular response ceases.

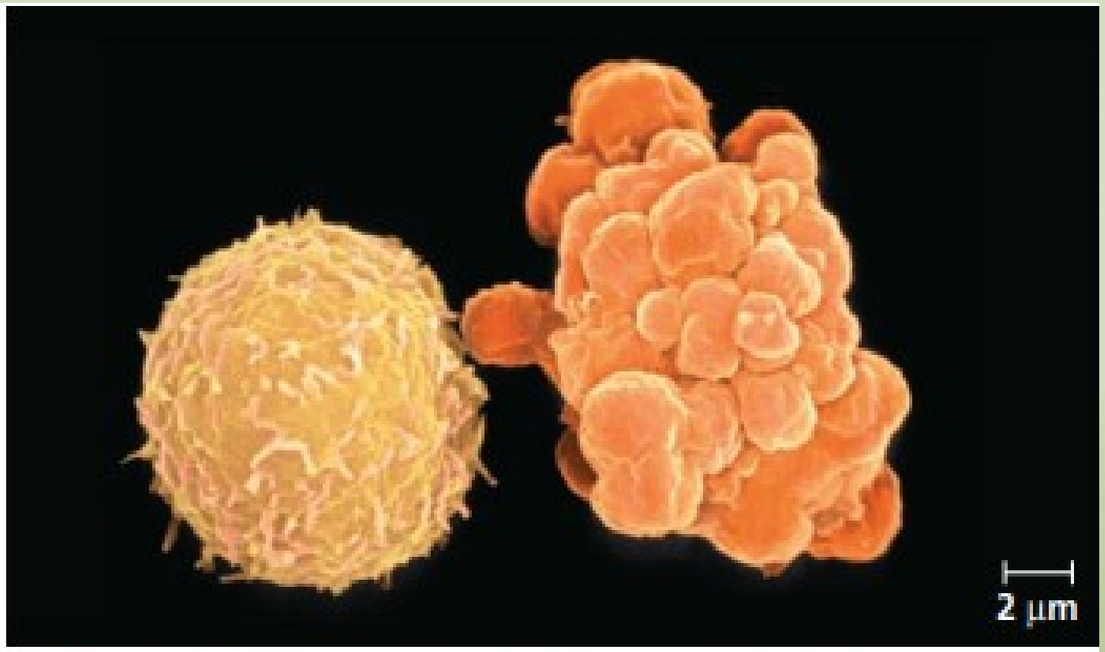
* Then, the relay molecules return to their inactive forms: The GTPase activity intrinsic to a G protein hydrolyzes its bound GTP; phosphodiesterase converts cAMP to AMP and phosphatases inactivate phosphorylated kinases. As a result, cell is soon ready to respond to a fresh signal.

Apoptosis integrates multiple cell-signaling pathways

* **Apoptosis means programmed cell death or controlled cell suicide.**

* **During apoptosis, cellular agents chop up the DNA and fragment the organelles and other cytoplasmic components. The cell shrinks and becomes lobed (blebbing), and the cell's parts are packaged up in vesicles that are engulfed and digested by specialized scavenger cells.**

* **Apoptosis protects neighboring cells from damage caused by a dying cell digestive enzymes.**



▲ **Figure 11.19 Apoptosis of a human white blood cell.** On the left is a normal white blood cell, while on the right is a white blood cell undergoing apoptosis. The apoptotic cell is shrinking and forming lobes ("blebs"), which eventually are shed as membrane-bounded cell fragments (colorized SEMs).

* **The signal that triggers apoptosis come from either outside or inside the cell. Outside the cell, signaling molecules released from other cells can initiate a signal transduction pathway that activates the genes and proteins responsible for carrying out cell death. Within a cell whose DNA has been irretrievably damaged, a series of protein-protein interactions can pass along a signal that similarly triggers cell death.**

Apoptosis in the Soil Worm *Caenorhabditis elegans*

*** In worms and other species, apoptosis is triggered by signals that activate a cascade of "suicide" proteins in the cells destined to die.**

*** Genetic research on *C. elegans* initially revealed two key apoptosis genes, called ced-3 and ced-4 (ced stands for "cell death"), which encode proteins essential for apoptosis.**

*** The proteins are called Ced-3 and Ced-4, respectively and are continually present in inactive form.**

*** In *C. elegans*, a protein in the outer mitochondrial membrane, called Ced-9 (the product of the ced-9 gene), serves as a master regulator of apoptosis, acting as a brake in the absence of a signal promoting apoptosis.**

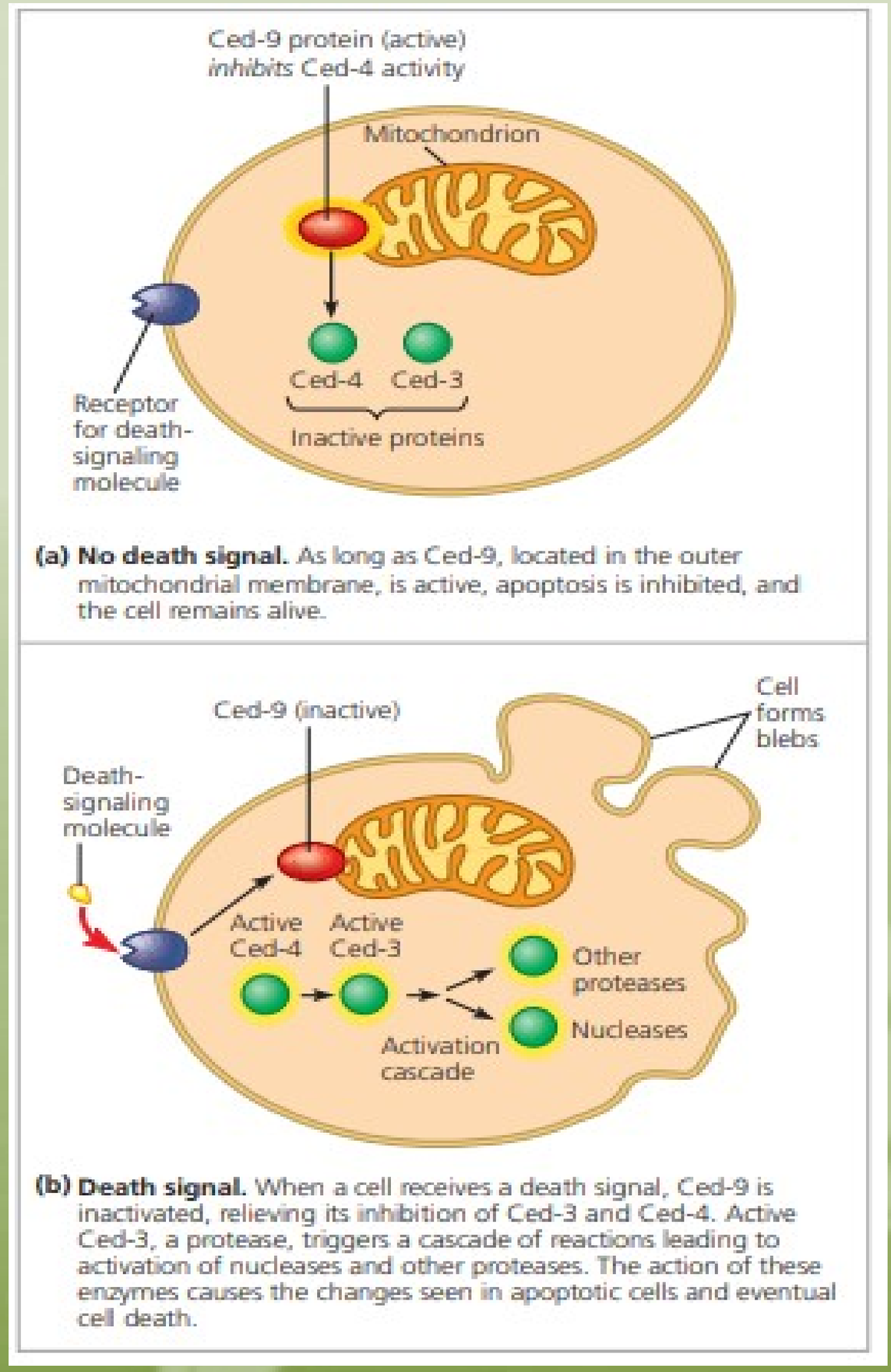
* When a death signal is received by the cell, signal transduction involves a change in Ced-9 that disables the brake, and the apoptotic pathway activates proteases and nucleases, enzymes that cut up the proteins and DNA of the cell.

* The main proteases of apoptosis are called caspases; in the nematode, the chief caspase is the Ced-3 protein.

Apoptotic Pathways and the Signals That Trigger Them

* In humans and other mammals, several different pathways, involving about 15 different caspases, can carry out apoptosis.

* The pathway that is used depends on the type of cell and on the particular signal that initiates apoptosis.



1. One major pathway involves certain mitochondrial proteins that form molecular pores in the mitochondrial outer membrane, causing it to leak and release other proteins that promote apoptosis. They may include cytochrome c, which functions in mitochondrial electron transport in healthy cells but acts as a cell death factor when released from mitochondria.

*** The process of mitochondrial apoptosis in mammals uses proteins similar to nematode proteins Ced-3, Ced-4, and Ced-9. These can be thought of as relay proteins capable of transducing apoptotic signal.**

2. Death-signaling molecule is an external ligand released by a neighboring cell and binds to a cell-surface receptor leading to activation of caspases and other enzymes that carry out apoptosis, without involving the mitochondrial pathway.

3. Two other types of alarm signals that can lead to apoptosis originate from inside cell rather than from cell-surface receptor:

A. One signal comes from the nucleus, generated when the DNA has suffered irreparable damage.

B. The second comes from the endoplasmic reticulum when excessive protein misfolding occurs.

**** Mammalian cells make life-or-death "decisions" by somehow integrating the death signals and life signals they receive from these external and internal sources.***

*** Apoptosis is essential for normal morphogenesis of hands and feet. Failure of appropriate apoptosis can result in webbed fingers and toes.**

*** In Alzheimer's disease, an accumulation of aggregated proteins in neurons activates an enzyme that triggers apoptosis, resulting in loss of brain function.**

*** Cancer can result from a failure of apoptosis; melanoma for example, have been linked to faulty forms of the human version of the *C. elegans* Ced-4 protein.**

Chapter 4

Membrane Potentials and Action Potentials

Membrane Potentials and Action Potentials

* Electrical potentials exist across membranes of all cells.

* The inside surface of the membrane is negatively charged in relation to the outside and the outside surface is positively charged in relation to the inside.

* Membrane potential is measured by small pipette filled with an electrolyte solution (Silver-silver chloride solution) and inserted into fiber interior. Another electrode called indifferent electrode is placed in extracellular fluid and potential difference between the inside and outside of the fiber is measured using a voltmeter.

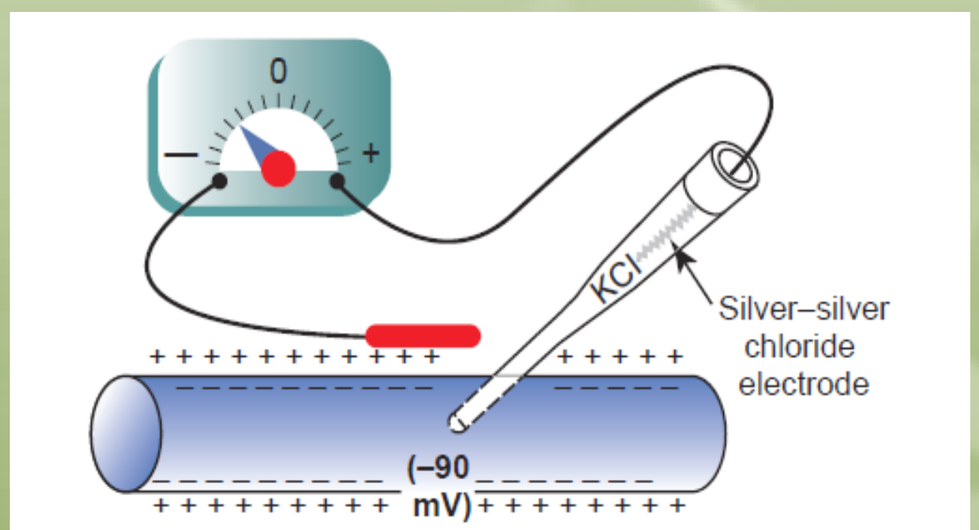


Figure 5-2. Measurement of the membrane potential of the nerve fiber using a microelectrode.

* Membrane potential across the nerve fiber at rest was found to be −90 mV and is called resting membrane potential (RMP) i.e. The potential inside the fiber is 90 mV more negative than the potential in the extracellular fluid on the outside of the fiber.

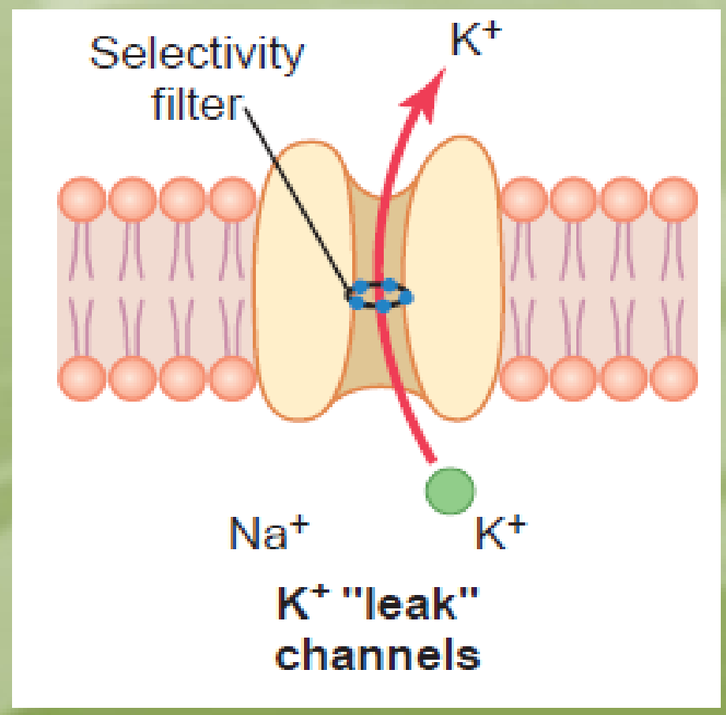
Resting membrane potential

* **Definition:** RMP is a potential across the nerve fiber at rest and it is equal −90 mV.

* **Origin of RMP:**

1. Potassium leak channel:

- It leaks potassium ions to the outside even in a resting cell.
- It may also leak sodium ions to the inside, but are about 100 times more permeable to potassium than to sodium.
- It contributes to -86 mV of the RMP



2. Na/K pump

- Continually pumps three sodium ions to outside for every two potassium ions to cell inside leading to continual loss of positive charges from inside, creating an additional degree of negativity (contributes to about −4 mV additional) on the inside.

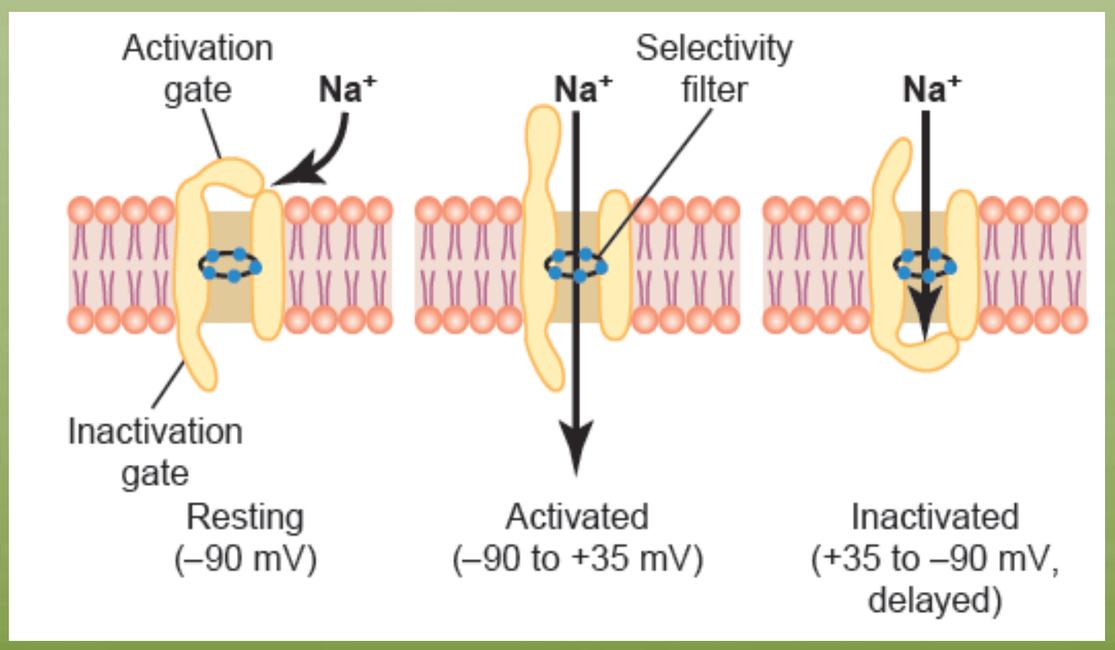
- Therefore, K leak channels and Na/K pump give a net membrane potential of −90 mV.

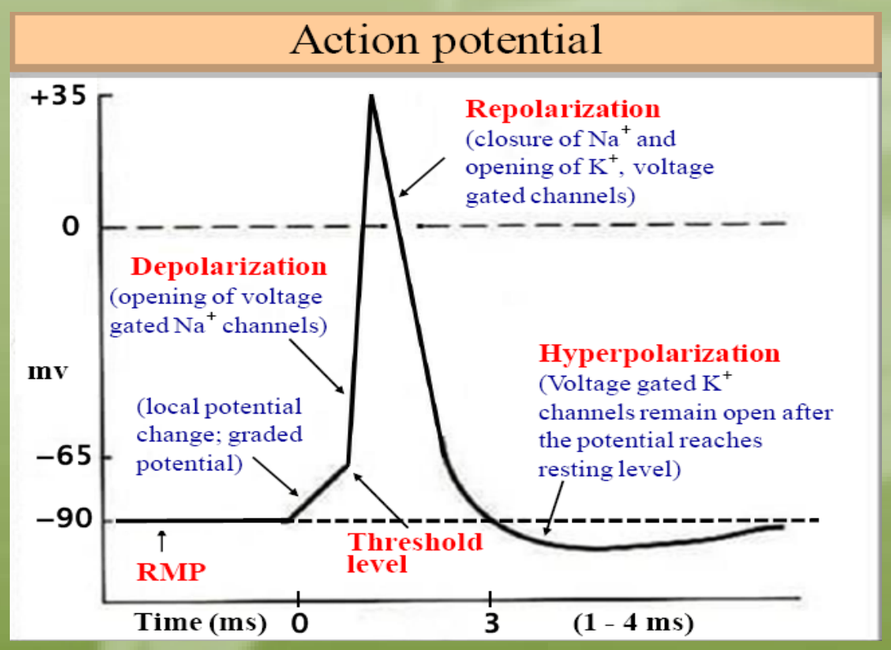
Local potential (Graded potential)

*** Definition:** **Local potential is a local change in the membrane potential that can not spread along the nerve fiber membrane.**

*** Generation of local potential:**

When a subthreshold stimulus is applied to a nerve fiber ⟶ conformational changes in activation gates of small number of voltage-gated sodium channels ⟶ flipping gates all the way to the open position membrane ⟶ sodium ions pour inward through channels ⟶ membrane potential becomes less negative and rising from RMP of −90 mV to somewhere between −70 and −50 mV returns to RMP without spreading along the nerve fiber membrane i.e. local potential.





Action potential

* **Definition:** Action potential is a rapid change in the membrane potential that spread rapidly along the nerve fiber membrane.

* **Generation of action potential:**

When a threshold stimulus is applied to a nerve fiber the following successive stages of action potential occur:

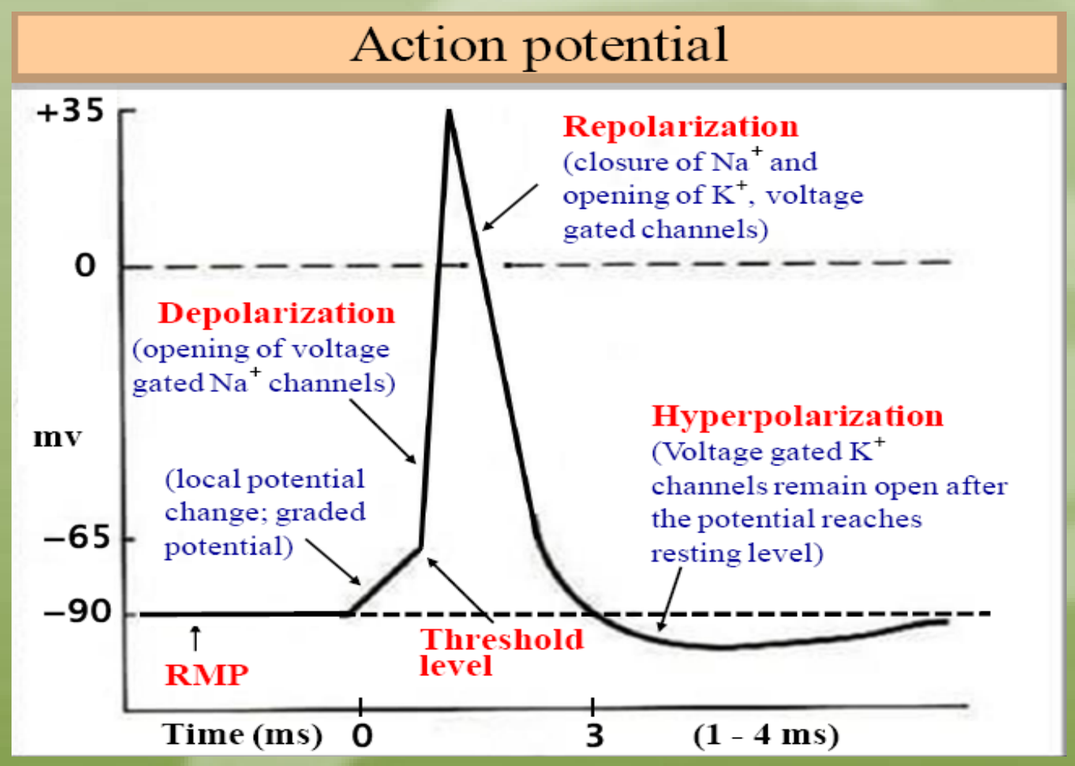
1. Depolarization stage:

Membrane potential becomes less negative than during the resting state

⟶ rising from −90 mV toward zero ⟶ reaches a voltage −70 to −50 mV

⟶ **sudden** conformational change in activation gates of **large number** of voltage-gated sodium channels

⟶ flipping gates all the way to open position ⟶ sodium ions pour inward through channels, increasing membrane permeability to sodium as much as 500- 5000 fold.



- The membrane potential at which most of voltage-gated sodium channels open (about −65 mV) is called **threshold potential or firing level.**

- In large nerve fibers, the great excess of positive sodium ions moving to the inside causes the membrane potential to "overshoot" beyond the zero level and to become positive.

- At a membrane potential +35 mV, the inactivation gate of voltage-gated sodium channels closes about 1 msec after the activation gate opens.

2. Repolarization stage:

When voltage-gated sodium channels close ⟶ conformational opening of the gate of voltage gated potassium ⟶ increased potassium diffusion outward through the channel ⟶ return membrane potential to −90 mV in about 2 msec i.e. full recovery of RMP.

3. Hyperpolarization stage:

- Hyperpolarization stage is caused by continual opening or delayed closure of voltage-gated potassium channels rendering the membrane potential to exceed the RMP i.e. more negative inside the fiber.

- Hyperpolarization stage is called after potential and it lasts for about 4 msec.

* A Positive-Feedback Cycle Opens Sodium Channels

Stimulation of a nerve fiber → rising membrane potential from −90 mV towards Zero level → opening of many voltage-gated sodium channels → rapid inflow of sodium ions → further rise in membrane potential → opening more voltage-gated sodium channels and so on (Positive-feedback cycle).

* **Re-establishment of RMP:** Performed by Na/K pump (recharging of the nerve) and required energy that derived from ATP.

* **Refractory periods of Action Potential**

1. Absolute Refractory Period (ARP):

- ARP is the period at which the nerve fiber does not respond whatever was the strength of the stimulus.
- ARP coincides with depolarization stage of action potential.

2. Relative Refractory Period (RRP):

- RRP is the period at which the nerve fiber responds at the condition that the stimulus was strong i.e. maximum stimulus.
- RRP coincides with repolarization stage of action potential.

* **All-or-Nothing Principle:** means that once an action potential has been elicited, the depolarization process travels over the entire membrane. Therefore, action potential does not change in shape and amplitude on propagation across a nerve fiber.

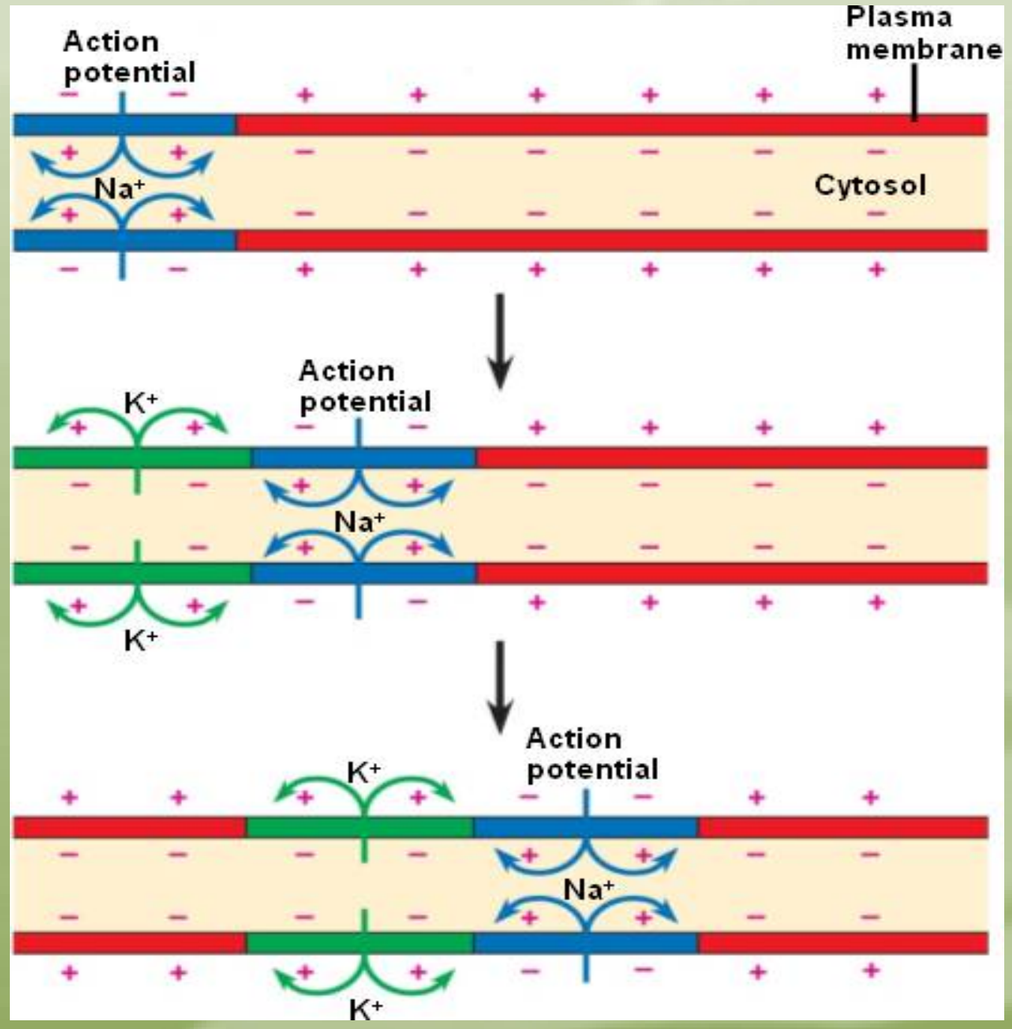
Propagation of Action Potential

* Action potential is conducted across a nerve fiber in two ways:

1. Point to point conduction: Occurs in unmyelinated nerve fibers

Mechanism:

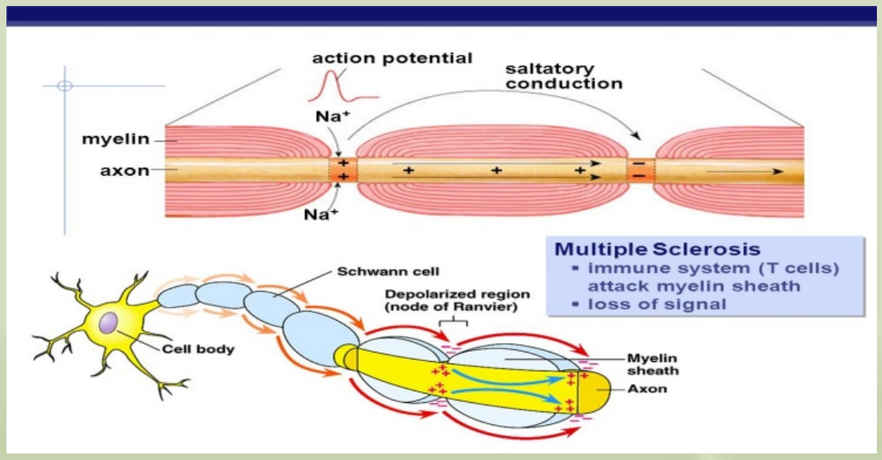
The action potential is generated in nerve fiber segment in response to threshold stimulus ⟶ attraction between positive and negative charges of the adjacent segment ⟶ local circuit currents (sink current) ⟶ opening of voltage-gated sodium channels of the adjacent segment ⟶ depolarization and generation of action potential in the adjacent segment and so on.

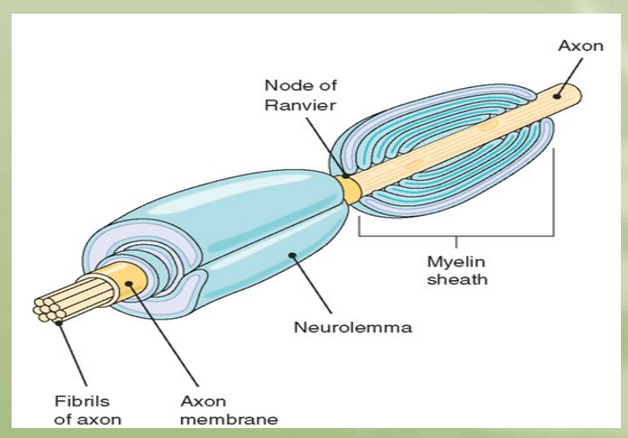


2. Saltatory conduction: Occurs in myelinated nerve fibers

Mechanism:

The action potential is generated in nerve fiber at node of Ranvier (formed by multiple layers of Schwann cell rotating around the axon and containing sphingomyelin) in response to threshold stimulus





⟶ attraction between positive and negative charges of the adjacent node ⟶ local circuit currents (sink current) ⟶ opening of voltage-gated sodium channels of the adjacent segment ⟶ depolarization and generation of action potential in the adjacent node and so on.

Saltatory conduction is 5-50 times faster than point to point conduction.

Plateau of Action potential in heart muscle fibers

* The plateau of action potential in heart muscle lasts for 0.2-0.3 second and causes contraction of heart muscle to last for this same long period.

* The plateau of action potential in heart muscle coincides with ARP which is a safety factor for the heart.

* Ion channels responsible for plateau in heart muscle include:

1. In depolarization stage:

A. Voltage-gated sodium channels, fast opening channels: allow sodium ions to enter the fiber and cause spike portion of action potential.

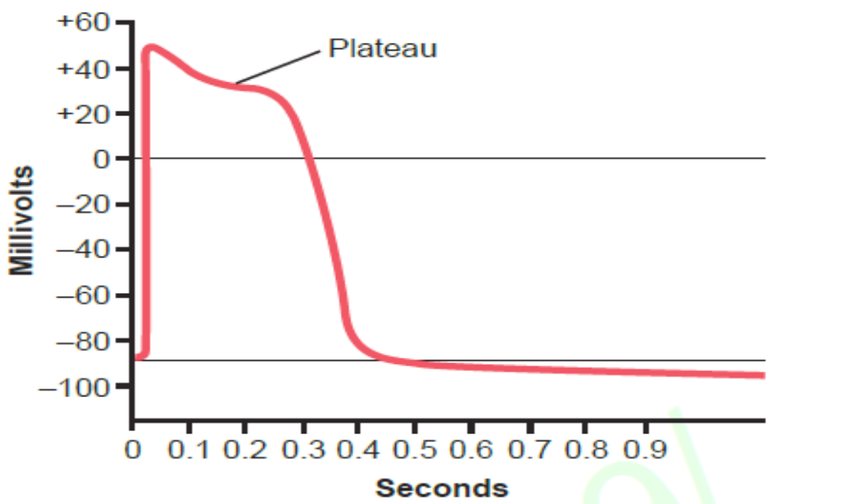


Figure 5-13. Action potential (in millivolts) from a Purkinje fiber of the heart, showing a plateau.

B. Voltage-gated calcium channels, L-type calcium channels, slow opening channels: allows calcium ions to enter the fiber and cause most of the plateau of action potential.

2. In repolarization stage:

A. Voltage-gated potassium channels, slow opening channels: allow potassium ions to exit from the fiber and partly responsible for the plateau in being delay the return of the membrane potential toward RMP.

Rhythmicity of Some Excitable Tissues—Repetitive Discharge

*** Rhythmicity or repetitive discharges occurs in:**

1. Heart e.g. rhythmical heart beat.

2. Smooth muscle e.g. rhythmical peristalsis of intestine.

3. Neurons e.g. rhythmical control of breathing.

*** rhythmicity occur when the membrane is permeable enough to sodium or calcium ions through L-type calcium channels to allow automatic membrane depolarization.**

*** The RMP in rhythmical control center of the heart is only −60 to −70 mV, which is not enough negative voltage to keep sodium and calcium channels totally closed.**

* **Therefore, the following sequence occurs:**

Some sodium and calcium ions flow inward → increases membrane voltage in positive direction → further increases in membrane permeability → depolarization → repolarization → Hyperpolarization which gradually disappears, allowing the membrane potential to increase up to the threshold for depolarization again and a new action potential occurs spontaneously (rhythmicity).

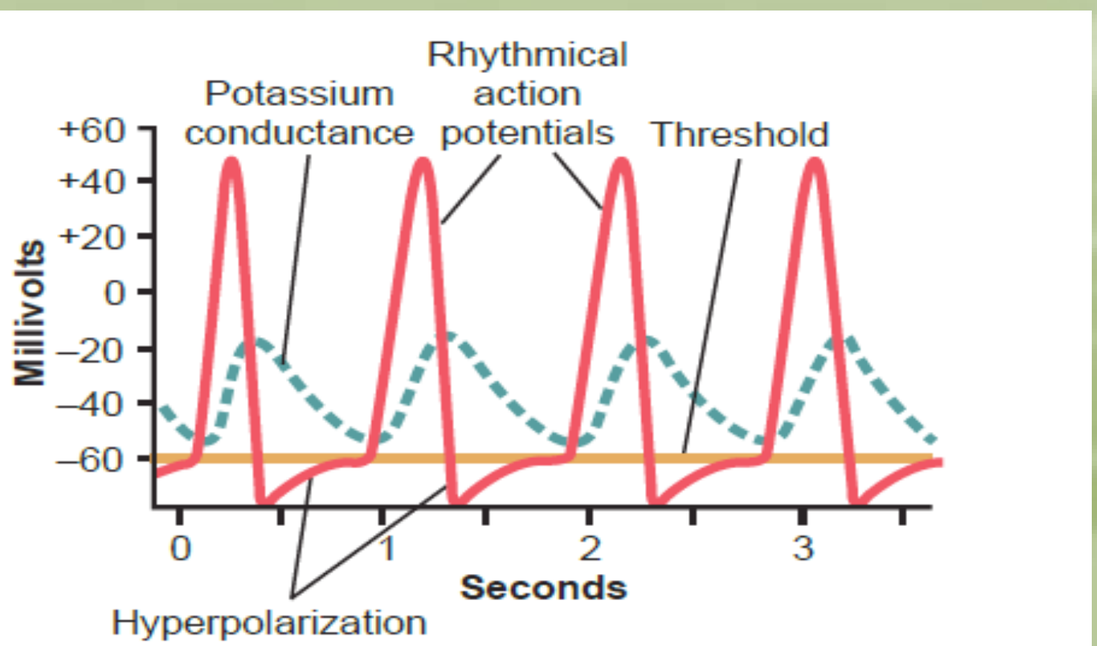


Figure 5-14. Rhythmical action potentials (in millivolts) similar to those recorded in the rhythmical control center of the heart. Note their relationship to potassium conductance and to the state of hyperpolarization.

Chapter 5

Skeletal Muscle: Neuromuscular Transmission and Contraction

TABLE 10.4

Summary of the Major Features of the Three Types of Muscular Tissue

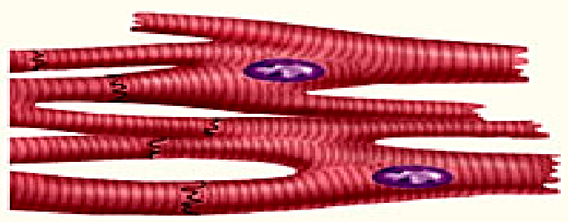
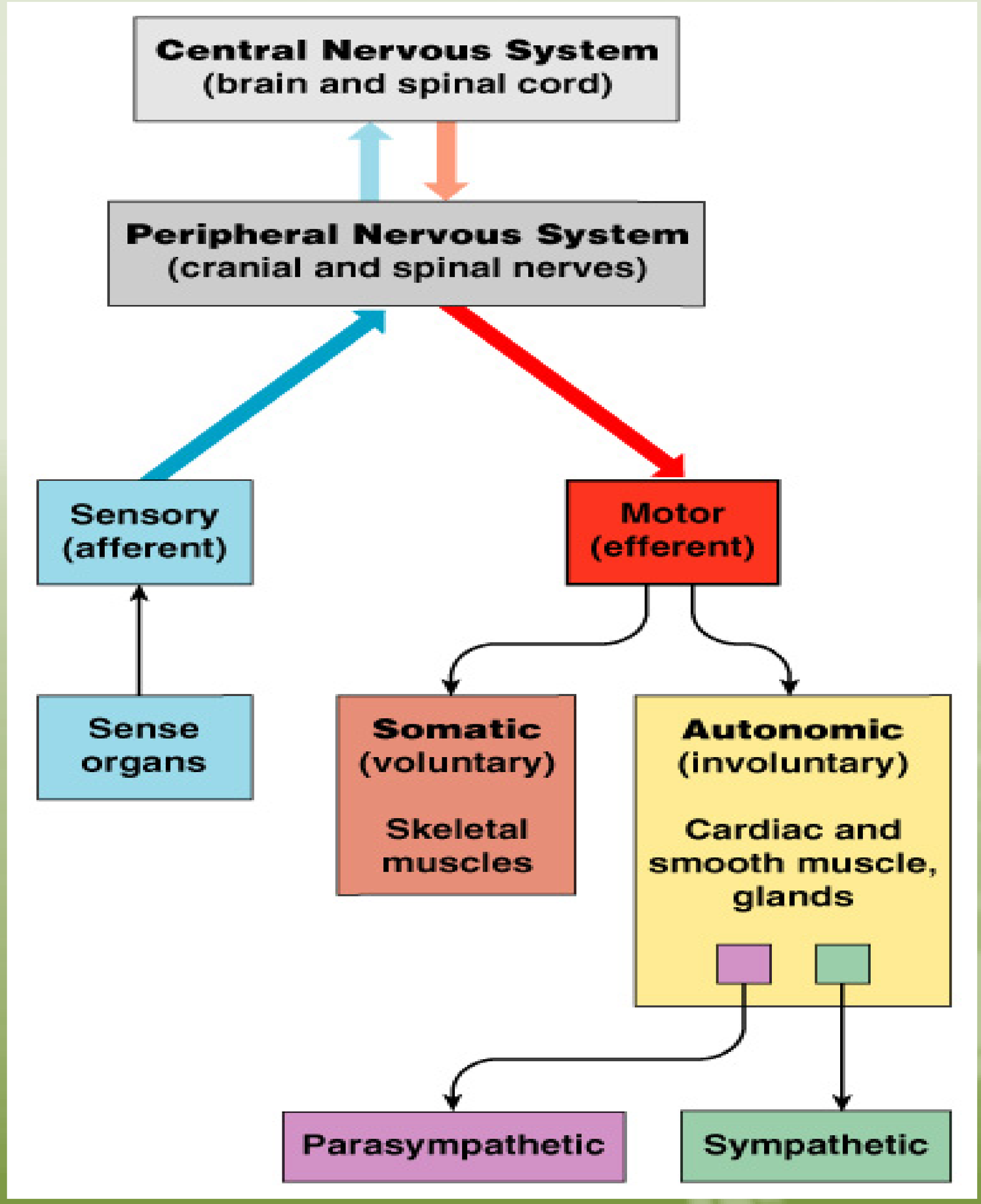
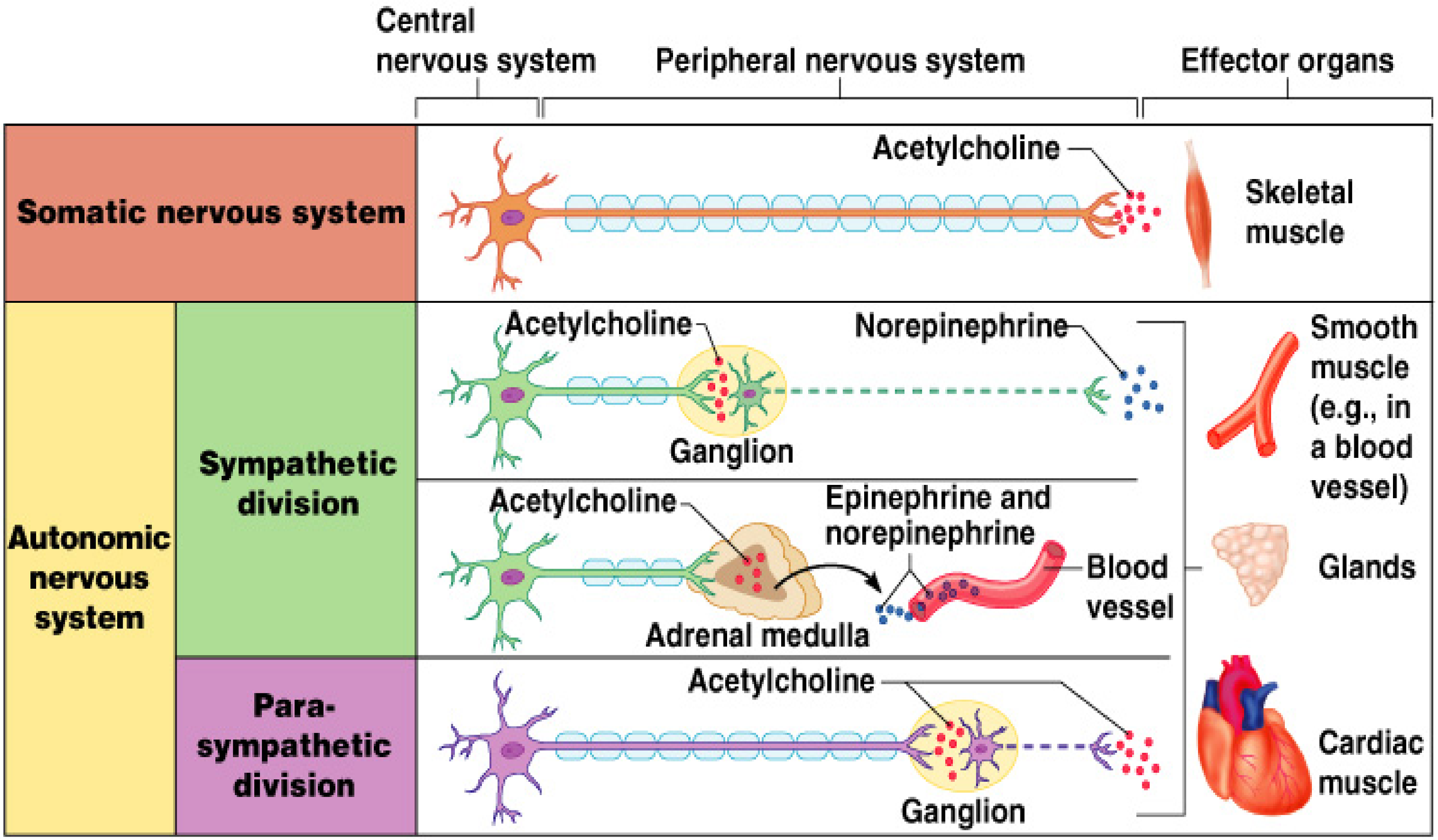
CHARACTERISTIC	SKELETAL MUSCLE	CARDIAC MUSCLE	SMOOTH MUSCLE
Microscopic appearance and features	Long cylindrical fiber with many peripherally located nuclei; striated. 	Branched cylindrical fiber with one centrally located nucleus; intercalated discs join neighboring fibers; striated. 	Fiber is thickest in middle, tapered at each end, and has one centrally positioned nucleus; not striated. 
Location	Most commonly attached by tendons to bones.	Heart.	Walls of hollow viscera, airways, blood vessels, iris and ciliary body of eye, arrector pili muscles of hair follicles.
Fiber diameter	Very large (10–100 μm).	Large (10–20 μm).	Small (3–8 μm).
Connective tissue components	Endomysium, perimysium, and epimysium.	Endomysium and perimysium.	Endomysium.
Fiber length	100 μm–30 cm.	50–100 μm.	30–200 μm.
Contractile proteins organized into sarcomeres	Yes.	Yes.	No.
Sarcoplasmic reticulum	Abundant.	Some.	Very little.
Transverse tubules present	Yes, aligned with each A–I band junction.	Yes, aligned with each Z disc.	No.
Junctions between fibers	None.	Intercalated discs contain gap junctions and desmosomes.	Gap junctions in visceral smooth muscle; none in multiunit smooth muscle.
Autorhythmicity	No.	Yes.	Yes, in visceral smooth muscle.
Source of Ca^{2+} for contraction	Sarcoplasmic reticulum.	Sarcoplasmic reticulum and interstitial fluid.	Sarcoplasmic reticulum and interstitial fluid.
Regulator proteins for contraction	Troponin and tropomyosin.	Troponin and tropomyosin.	Calmodulin and myosin light chain kinase.
Speed of contraction	Fast.	Moderate.	Slow.
Nervous control	Voluntary (somatic nervous system).	Involuntary (autonomic nervous system).	Involuntary (autonomic nervous system).
Contraction regulated by:	Acetylcholine released by somatic motor neurons.	Acetylcholine and norepinephrine released by autonomic motor neurons; several hormones.	Acetylcholine and norepinephrine released by autonomic motor neurons; several hormones; local chemical changes; stretching.
Capacity for regeneration	Limited, via satellite cells.	Limited, under certain conditions.	Considerable, via pericytes (compared with other muscle tissues, but limited compared with epithelium).

Table 10.04 Tortora - PAP 12/e


Central Nervous System
(brain and spinal cord)
Peripheral Nervous System
(cranial and spinal nerves)
Sensory
(afferent)
Motor
(efferent)
Sense
organs
Somatic
(voluntary)
Skeletal
muscles
Autonomic
(involuntary)
Cardiac and
smooth muscle,
glands
Parasympathetic
Sympathetic


Central nervous system
Peripheral nervous system
Effector organs
Somatic nervous system
Acetylcholine
Skeletal muscle
Autonomic nervous system
Sympathetic division
Acetylcholine
Norepinephrine
Smooth muscle (e.g., in a blood vessel)
Ganglion
Acetylcholine
Epinephrine and norepinephrine
Blood vessel
Glands
Adrenal medulla
Para-sympathetic division
Acetylcholine
Cardiac muscle
Ganglion
KEY:
Preganglionic axons (sympathetic)
Postganglionic axons (sympathetic)
Myelination
Preganglionic axons (parasympathetic)
Postganglionic axons (parasympathetic)

Skeletal Muscle

Skeletal Muscle Fiber

* Skeletal muscle is composed of numerous muscle fibers.

* Each muscle fiber extends the entire length of the muscle and is usually innervated by only one nerve ending, located near the middle of the fiber.

* The muscle fiber is surrounded by a thin membrane called sarcolemma.

* Each muscle fiber contains several hundred to several thousand myofibrils.

* Each myofibril is composed of about 1500 myosin filaments and 3000 actin filaments.

* Myosin and actin filaments are partially interdigitate and thus cause the myofibril to have alternate light and dark bands.

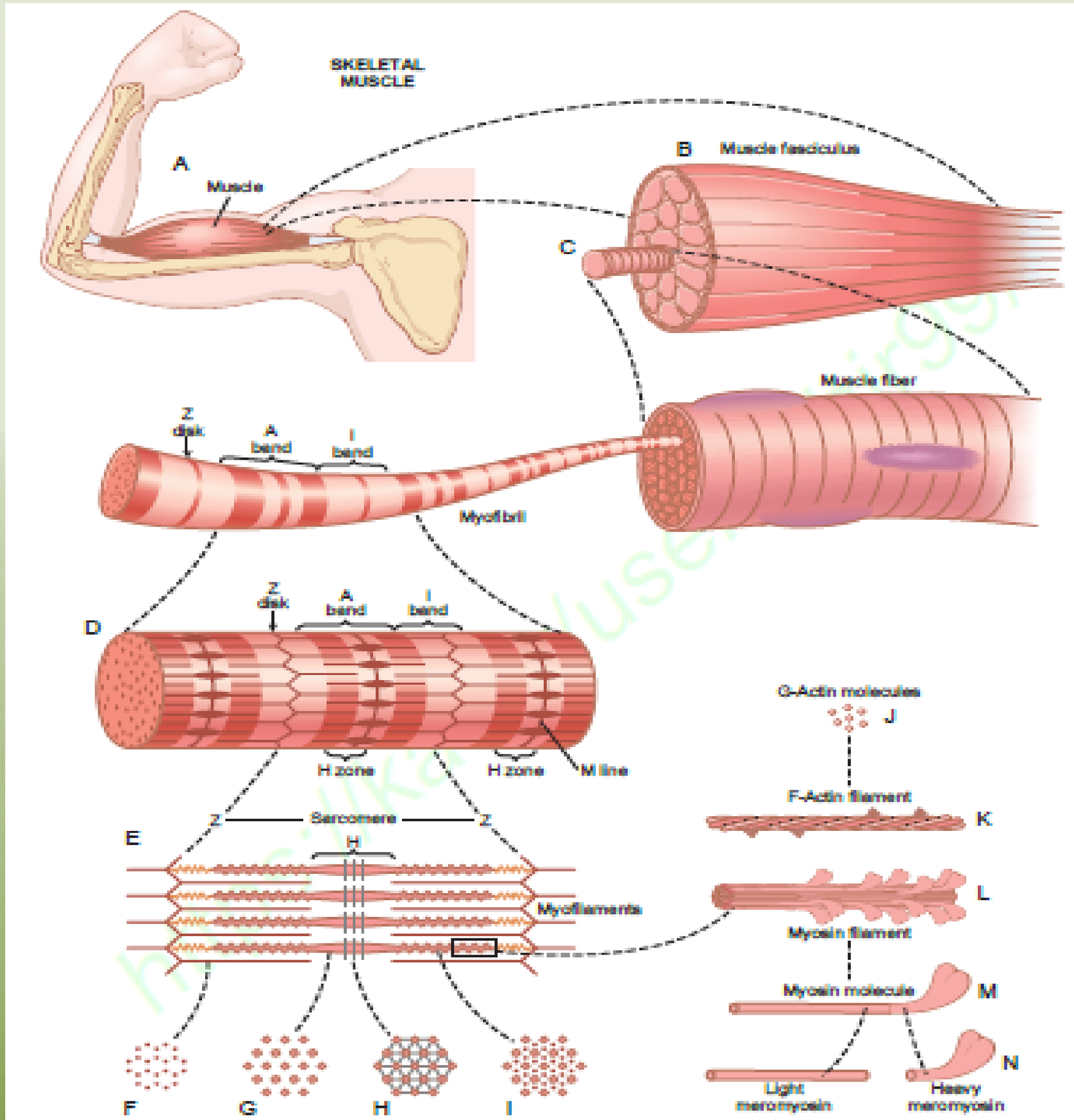


Figure 6-1. Organization of skeletal muscle, from the gross to the molecular level. *F, G, H,* and *I* are cross sections at the levels indicated.

* The light bands contain only actin filaments and are called I bands.

* The dark bands contain myosin filaments, as well as the ends of the actin filaments where they overlap the myosin, and are called A bands.

* Light and dark bands give skeletal and cardiac muscle their striated appearance (Striated muscles).

* The ends of the actin filaments are attached to a Z disk which is composed of filamentous proteins different from the actin and myosin filaments.

* The portion of the myofibril (or of the whole muscle fiber) that lies between two successive Z disks is called a sarcomere.

* When muscle fiber is contracted, the length of the sarcomere is shorten and actin filaments overlap myosin filaments.

* **Titin protein**

- Titin is a filamentous springy protein with a molecular weight of about 3 million (one of the largest protein molecules in the body) that Keep myosin and actin filaments in Place.

- One end of the titin molecule is elastic and is attached to the Z disk, acting as a spring and changing length as the sarcomere contracts and relaxes.

- The other part of the titin molecule tethers it to the myosin thick filament.

- The titin molecule also appears to act as a template for initial formation of myosin.

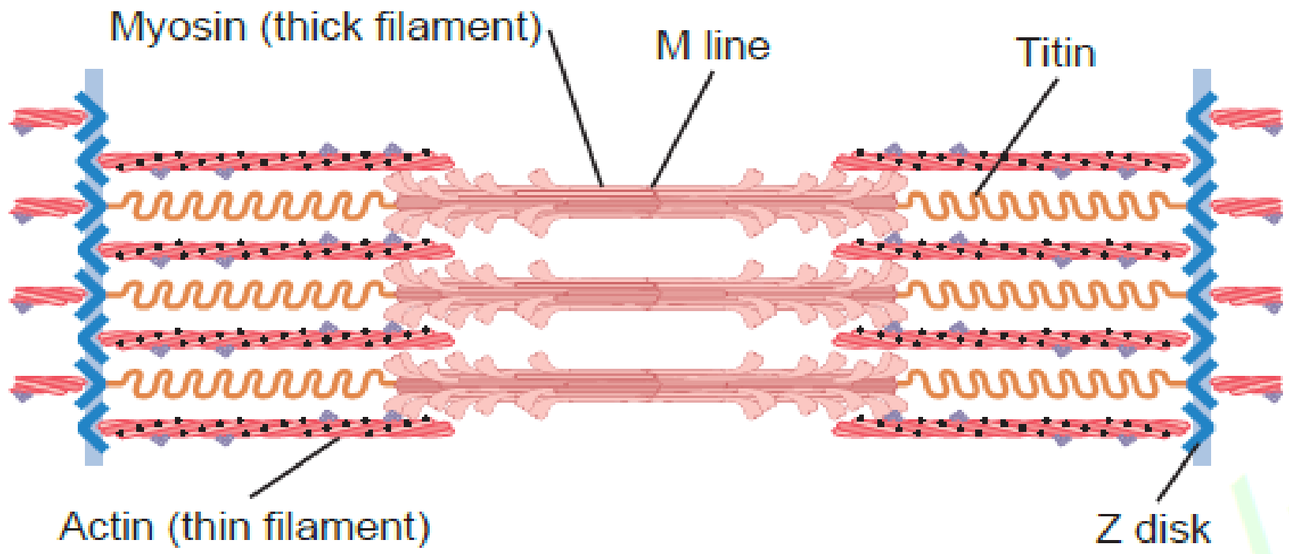


Figure 6-3. Organization of proteins in a sarcomere. Each titin molecule extends from the *Z disk* to the *M line*. Part of the titin molecule is closely associated with the myosin thick filament, whereas the rest of the molecule is springy and changes length as the sarcomere contracts and relaxes.

- **Nebulin protein : inelastic protein, is a giant skeletal muscle protein of about 6669 amino acids which forms an integral part of the sarcomeric thin filament**
  - *Alignment of A & M*

*** Sarcoplasm is the intracellular fluid between myofibrils and contains large quantities of potassium, magnesium, phosphate, multiple protein enzymes and tremendous number of mitochondria that supply the contracting myofibrils with large amounts of energy in the form of ATP.**

*** Sarcoplasmic reticulum (SR) is a specialized ER of skeletal muscle that regulates calcium storage, release and reuptake and therefore muscle contraction.**

Molecular Characteristics of Contractile Filaments

*** Myosin molecule: is composed of six polypeptide chains:**

- Two heavy chains: wrap spirally around each other to form a double helix which is called tail of myosin molecule. The end of each heavy chain is folded into a globular myosin head. Thus, there are two heads at one end of myosin molecule.

- Four light chains: are also part of myosin head, two to each head.

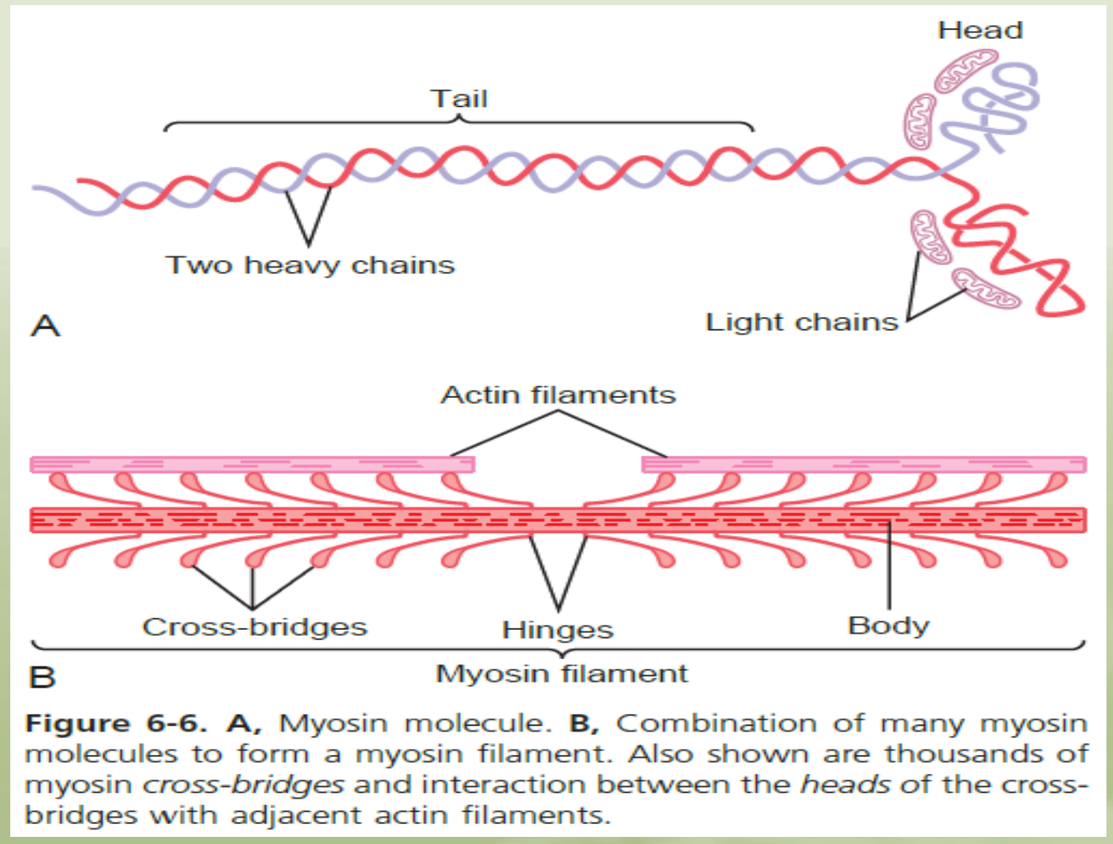
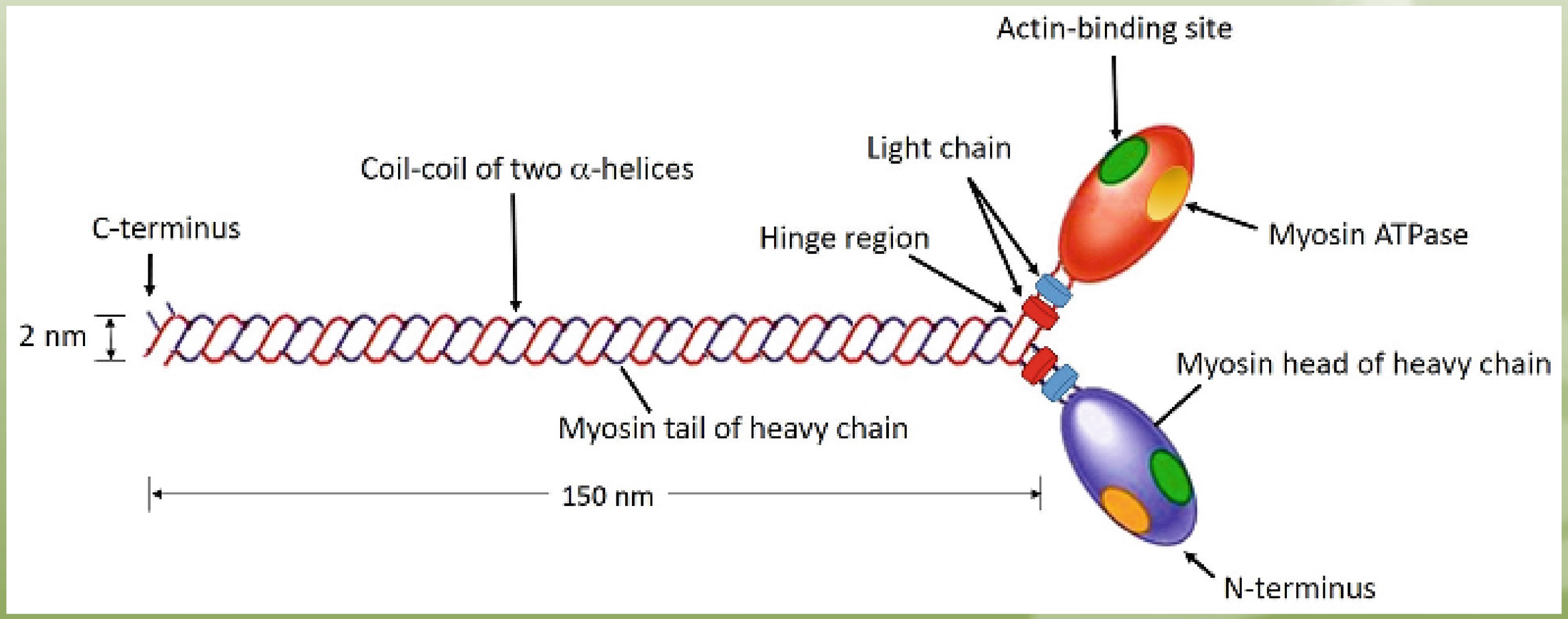


Figure 6-6. A, Myosin molecule. **B,** Combination of many myosin molecules to form a myosin filament. Also shown are thousands of myosin *cross-bridges* and interaction between the *heads* of the cross-bridges with adjacent actin filaments.

*** The tails of myosin molecules bundled together to form the body of the filament and then extend as arms with the heads hang outward to the sides of the body.**

* The protruding arms and heads together are called cross-bridges. Each cross-bridge is flexible at two points called hinges—one where the arm leaves the body of myosin filament, and the other where the head attaches to the arm.

* Myosin head functions as an adenosine triphosphatase (ATPase) enzyme.



* The protruding arms and heads together are called cross-bridges. Each cross-bridge is flexible at two points called hinges—one where the arm leaves the body of myosin filament, and the other where the head attaches to the arm.

* Myosin head functions as an adenosine triphosphatase (ATPase) enzyme.

* Actin filaments: Composed of actin, tropomyosin and troponin:

1. Actin filament

- composed of two helical strands of F-actin protein molecules.

- Each strand is composed of polymerized G-actin molecules, to each of which attached one molecule of ADP.

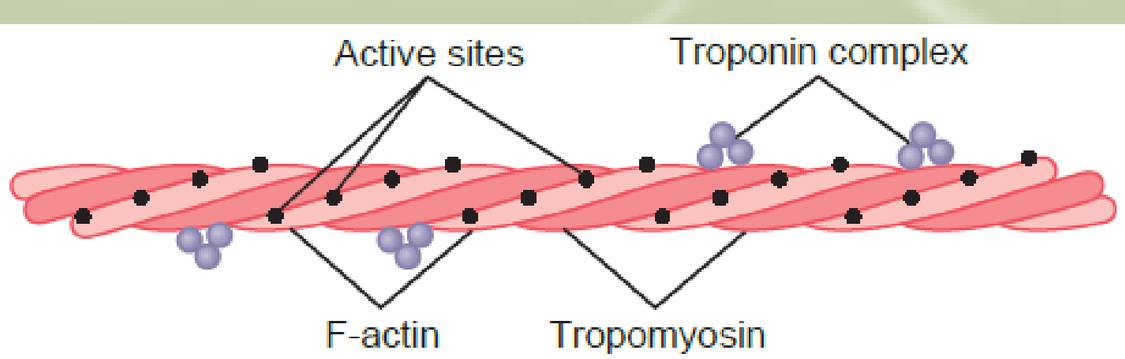


Figure 6-7. Actin filament, composed of two helical strands of *F-actin* molecules and two strands of *tropomyosin* molecules that fit in the grooves between the actin strands. Attached to one end of each tropomyosin molecule is a *troponin* complex that initiates contraction.

- ADP molecules are believed to be active sites on actin filaments with which cross-bridges of myosin interact to cause muscle contraction.

2. Tropomyosin Molecules

- Tropomyosin molecules are wrapped spirally around the sides of the F-actin helix.

- In resting state, tropomyosin molecules lie on top of active sites of actin strands so that attraction cannot occur between actin and myosin filaments to cause contraction.

3. Troponin Complex

- Troponin protein complex are attached to tropomyosin molecules.

- Troponin molecule is a complex of three protein subunits:

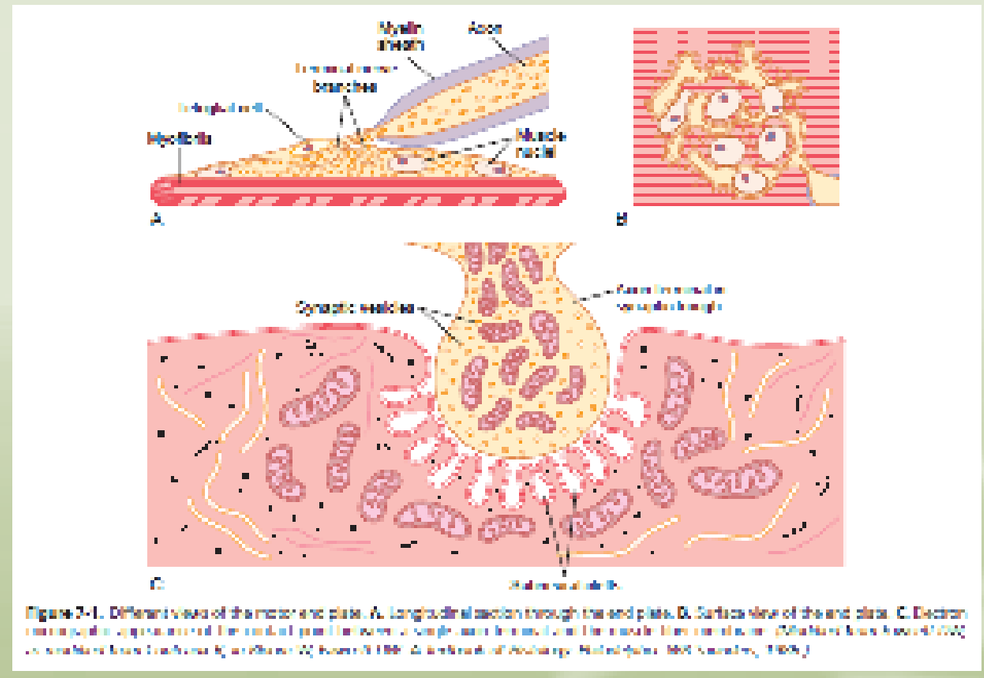
- Troponin I which has a strong affinity for actin.
- Troponin T which has a strong affinity for tropomyosin.
- Troponin C which has a strong affinity for calcium ions that initiates muscle contraction.

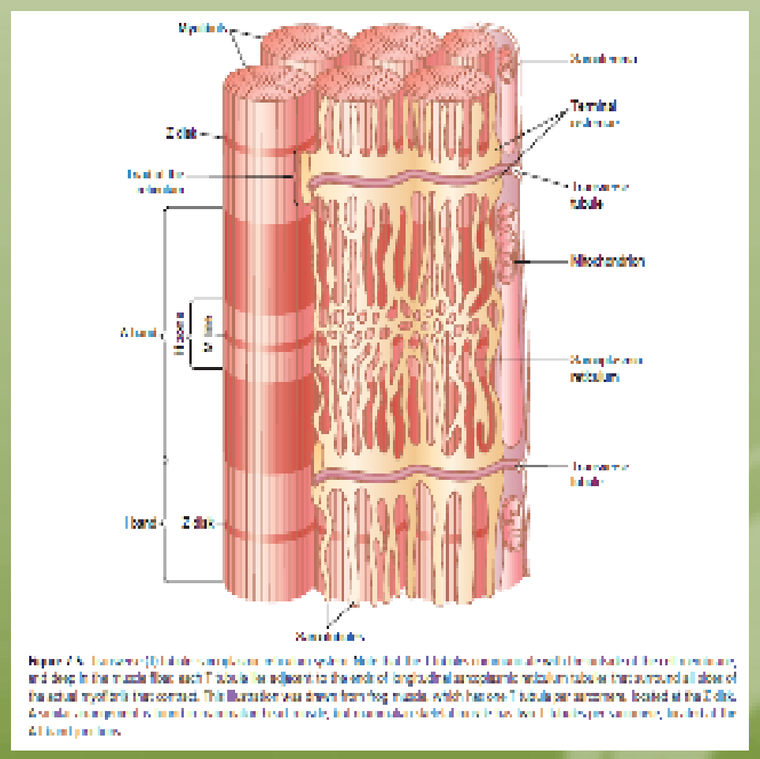
Mechanism Of Skeletal Muscle Contraction

1. Action potential travels along a motor nerve to its endings on muscle fibers (neuromuscular junction).

2. At each ending, nerve secretes neurotransmitter acetylcholine which opens acetylcholine-gated cation channels sodium ions diffuse through the channels into muscle fiber action potential

3. Action potential spreads along the muscle fiber membrane and reaches T tubule-sarcoplasmic reticulum system





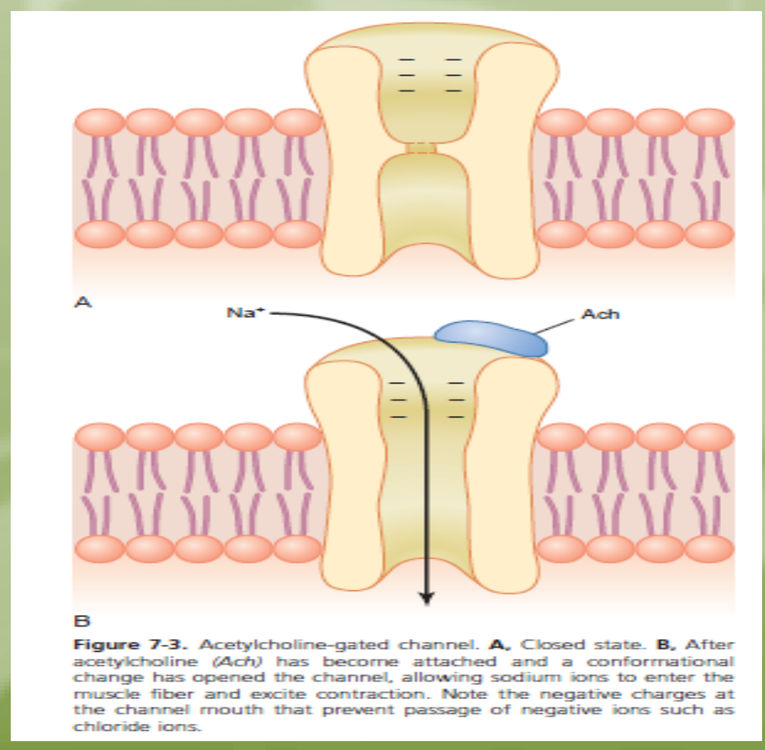


Figure 7-3. Acetylcholine-gated channel. **A,** Closed state. **B,** After acetylcholine *(Ach)* has become attached and a conformational change has opened the channel, allowing sodium ions to enter the muscle fiber and excite contraction. Note the negative charges at the channel mouth that prevent passage of negative ions such as chloride ions.

Activation of voltage sensitive dihydropyridine (DHP) receptors linked to calcium release channels (ryanodine receptor) in sarcoplasmic reticulum ⟶ opening the Ca++ release channels and permitting Ca++ to rapidly diffuse into the sarcoplasm.

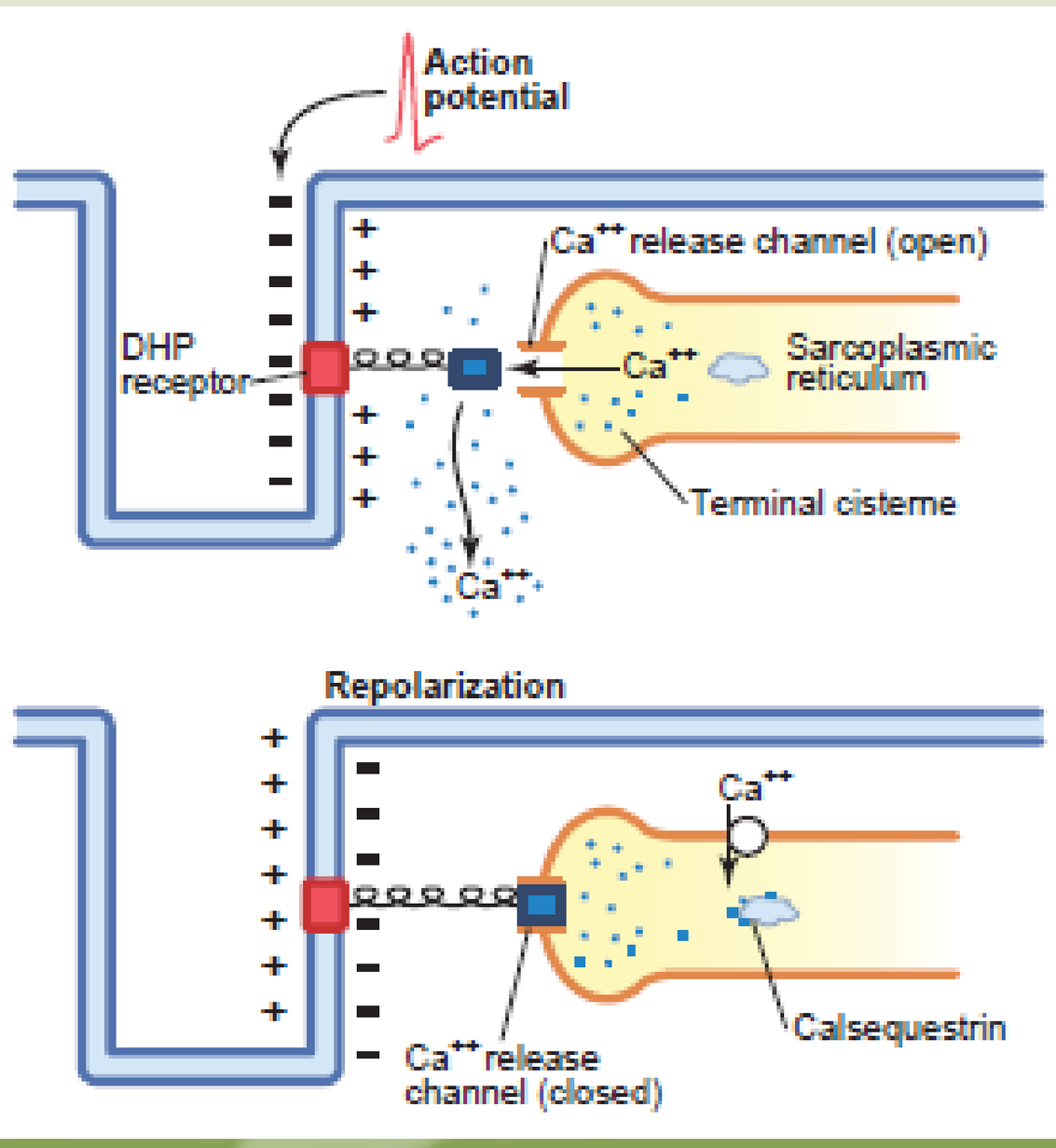


Figure 7-6. Excitation-contraction coupling in skeletal muscle. The *top panel* shows an action potential in the transverse tubule that causes a conformational change in the voltage-sensing dihydropyridine *(DHP)* receptors, opening the Ca^{++} release channels in the terminal cisternae of the sarcoplasmic reticulum and permitting Ca^{++} to rapidly diffuse into the sarcoplasm and initiate muscle contraction. During repolarization *(bottom panel)*, the conformational change in the DHP receptor closes the Ca^{++} release channels and Ca^{++} is transported from the sarcoplasm into the sarcoplasmic reticulum by an adenosine triphosphate–dependent calcium pump.

4. **At rest:** the active sites on actin filament of the relaxed muscle are inhibited or physically covered by the troponin-tropomyosin complex. Consequently, the active sites on actin filament cannot attach to the heads of myosin filaments to cause contraction.

5. **On activation:** Calcium ions released from sarcoplasmic reticulum combine with troponin C ⟶ troponin complex undergoes a conformational change that in some way tugs on tropomyosin molecule and moves it deeper into the groove between the two actin strands ⟶ uncovers active sites of actin that attract myosin cross-bridge heads and cause contraction to proceed. How?

6. The “walk-along” (or “ratchet”) theory of contraction:

- When a myosin head attaches to an active site of actin ⟶ changes in the intramolecular forces between the head and arm of its cross-bridge ⟶ the head tilts toward the arm and drags actin filament along with it (power stroke) ⟶ actin filament moves one step ⟶ the head then automatically breaks away from the active site to combine with a new active site and tilts again to cause a new power stroke and actin filament moves another step. Thus, myosin heads bend back and forth and step by step **walk along** actin filament, pulling actin filaments toward the center of myosin filament.

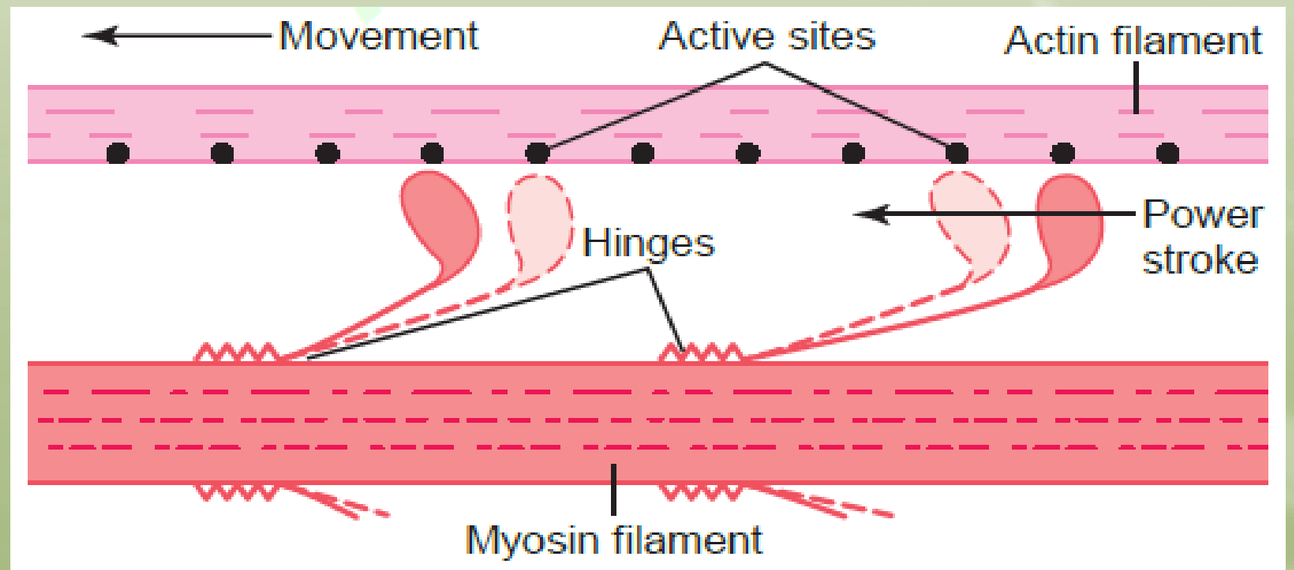


Figure 6-8. The “walk-along” mechanism for contraction of the muscle.

- Each one of the cross-bridges is believed to operate independently. Therefore, the greater the number of cross-bridges in contact with actin filament, the greater the force of contraction.

7. ATP as Energy Source for Contraction:

- Large amounts of ATP are cleaved to form ADP during contraction process.

- **Fenn effect:** The greater the amount of work performed by the muscle, the greater the amount of ATP that is cleaved.

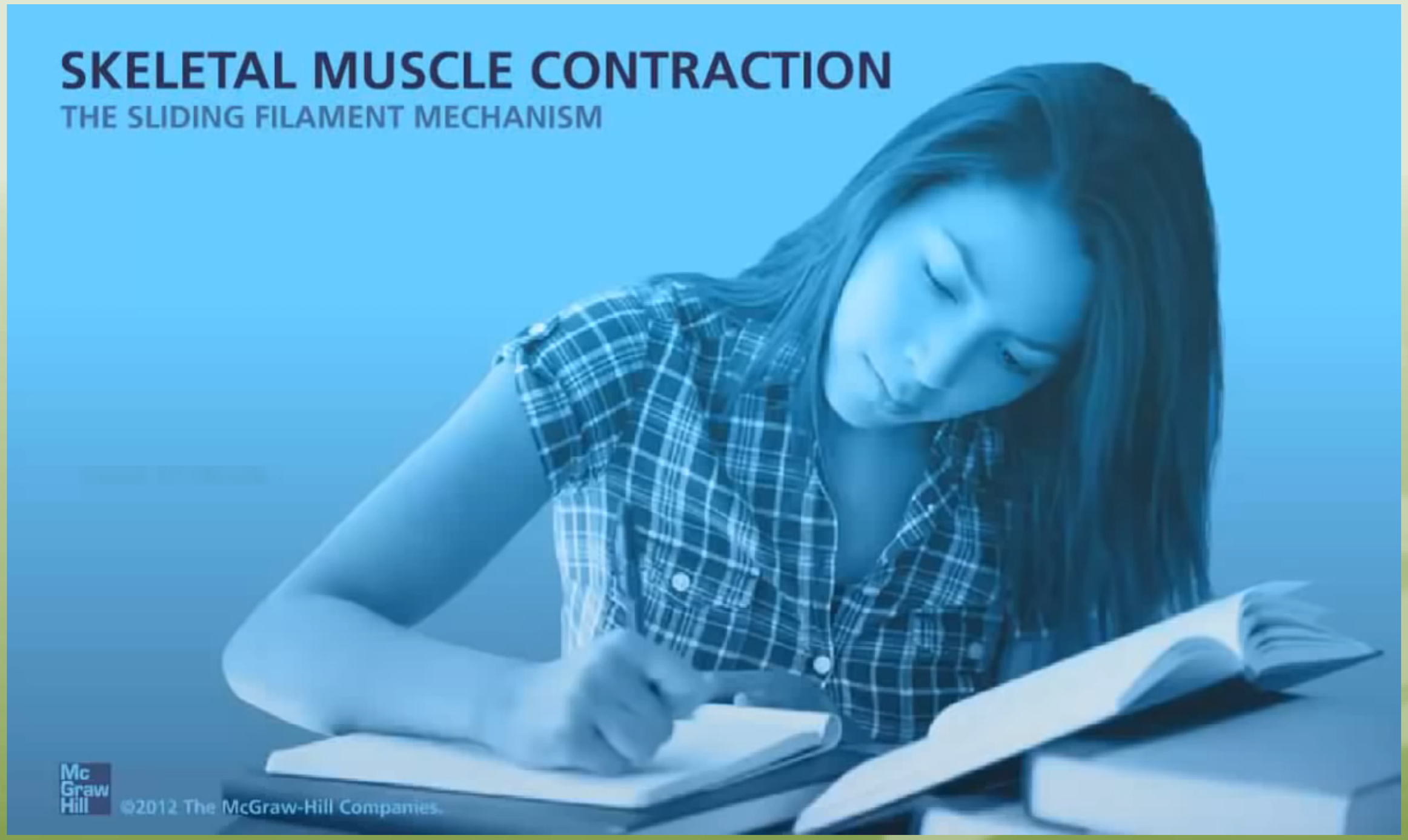
- Before contraction begins, myosin heads bind with ATP. The ATPase activity of the head immediately cleaves ATP but leaves cleavage products ADP + phosphate bound to the head and energy stored in the head.

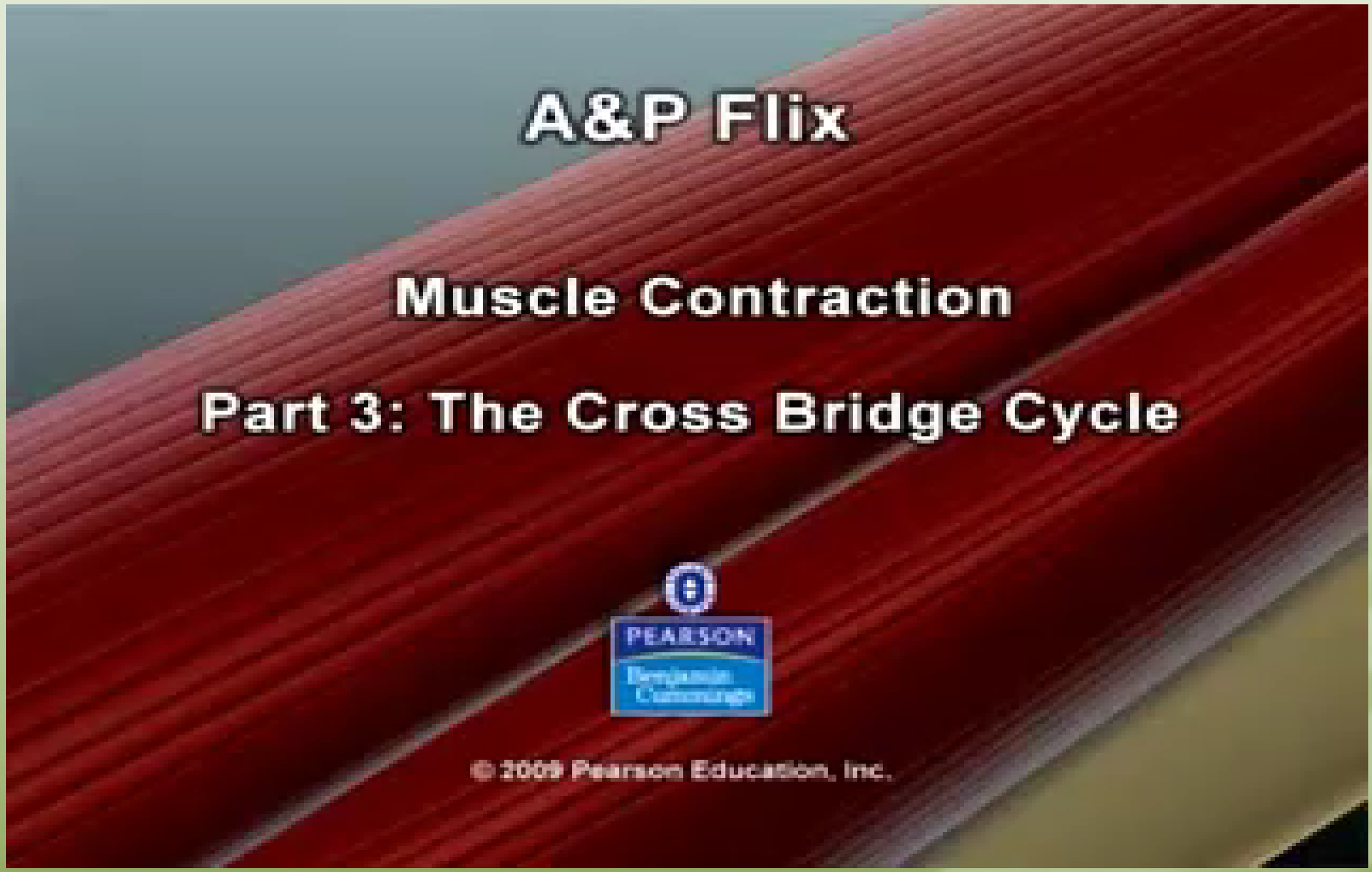
- The stored energy activates the power stroke for pulling actin filament.

- On detachment of the head from actin, ADP and phosphate that were previously attached to the head forms a new molecule of ATP which is cleaved to begin the next cycle.

8. **Muscle relaxation:** After contraction, calcium ions are actively pumped back into sarcoplasmic reticulum and muscle relaxes.

Contraction and Relaxation of Skeletal Muscle




A&P Flix
Muscle Contraction
Part 3: The Cross Bridge Cycle
PEARSON
Benjamin Cummings
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Muscle Potentials

* RMP is about −80 to −90 mV in skeletal fibers—the same as in large myelinated nerve fibers.

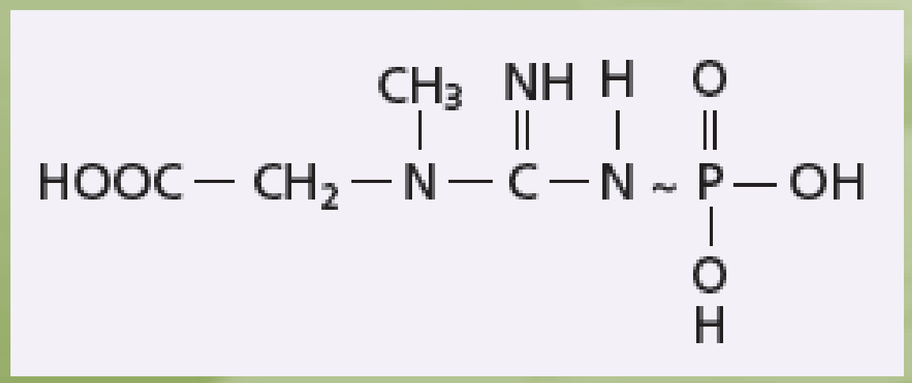
* Duration of action potential is 1 to 5 ms in skeletal muscle—about 5 times as long as in large myelinated nerves.

* Velocity of conduction is 3 to 5 m/sec—about 1/13 the velocity of conduction in the large myelinated nerve fibers that excite skeletal muscle.

Sources of Energy for Muscle Contraction

1. Phosphocreatine

- Carries a high-energy phosphate bond which has a slightly higher amount of free energy than that of each ATP bond.



Muscle Metabolism

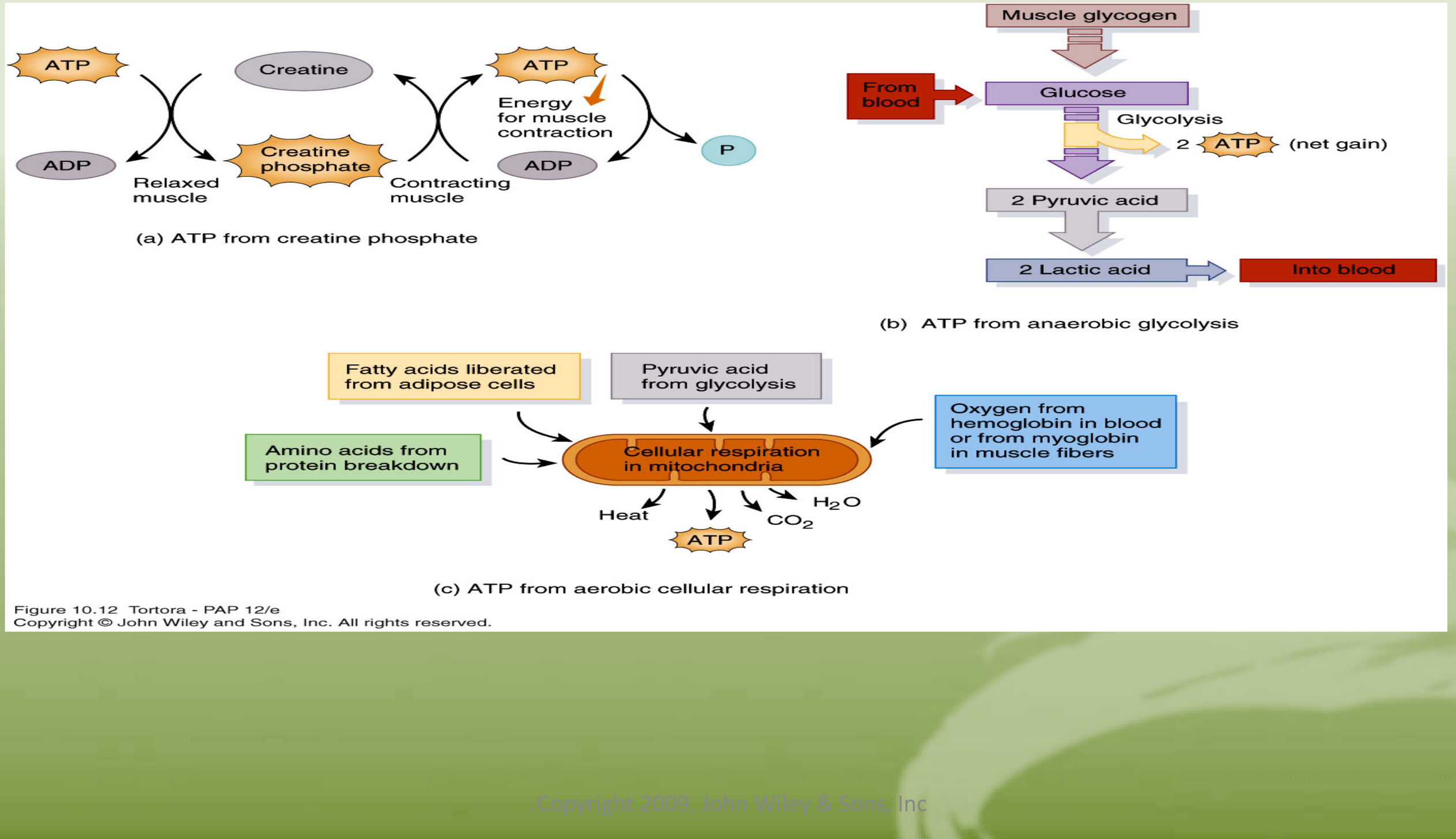


Figure 10.12 Tortora - PAP 12/e

- Phosphocreatine is instantly cleaved, and its released energy causes bonding of a new phosphate ion to ADP to reconstitute the ATP.

- The total amount of phosphocreatine in the muscle fiber is small—only about 5 times as great as ATP. Therefore, the combined energy of both stored ATP and phosphocreatine is capable of causing maximal muscle contraction for only 5-8 seconds.

2. Glycolysis

- Glycogen stored in muscle cells is rapidly breakdown to pyruvic acid and lactic acid and energy liberates which is used to convert ADP to ATP.

- The importance of this glycolysis is that a) it can occur in the absence of oxygen, so muscle contraction can be sustained up to a minute and b) the rate of formation of ATP by the glycolytic process is about 2.5 times as rapid as ATP formation in response to cellular foodstuffs reacting with oxygen.

- Accumulation of end products of glycolysis in muscle cells loses its capability to sustain maximum muscle contraction after 1 minute.

3. Oxidative metabolism

- means combining oxygen with end products of glycolysis and with various other cellular foodstuffs to liberate ATP.

- Provides more than 95 % of all energy used by the muscles for sustained, long-term contraction.

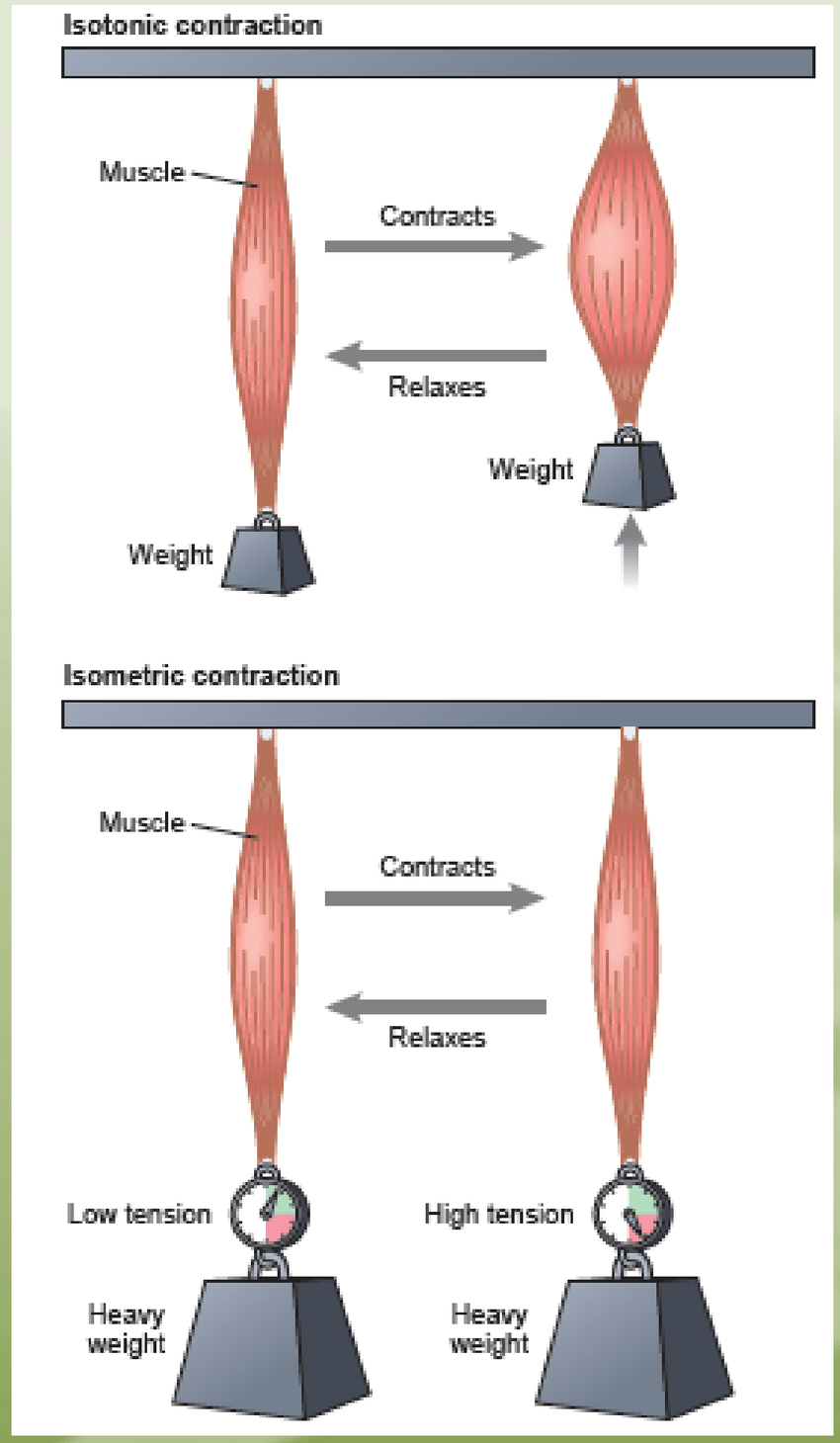
- For long-term maximal muscle activity over many hours, the greatest proportion of energy comes from fats.

- For periods of 2-4 hours, as much as one half of energy comes from stored carbohydrates.

Isometric and Isotonic Muscle Contractions

* **Isotonic contraction** occurs when the force of the muscle contraction is greater than the load and the tension on the muscle remains constant during the contraction; when the muscle contracts, it shortens and moves the load.

* **Isometric contraction** occurs when the load is greater than the force of the muscle contraction; the muscle creates tension when it contracts, but the overall length of the muscle does not change.



isometric system is often used when comparing functional characteristics of different muscle types

- Ocular muscle has a duration of isometric contraction of less than 1/50 sec: Ocular movements must be extremely rapid to maintain fixation of the eyes on specific objects to provide accuracy of vision.

- Gastrocnemius muscle has a duration of isometric contraction of about 1/15 sec: Gastrocnemius muscle must contract moderately rapid to provide sufficient velocity of limb movement for running and jumping.

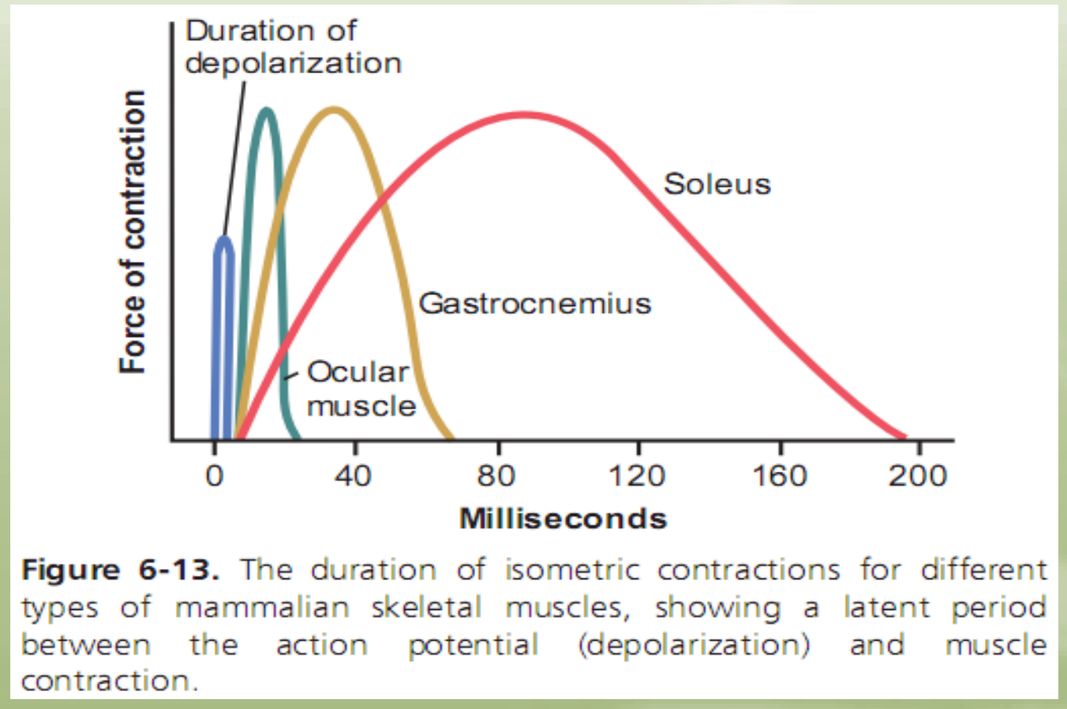


Figure 6-13. The duration of isometric contractions for different types of mammalian skeletal muscles, showing a latent period between the action potential (depolarization) and muscle contraction.

- Soleus muscle has a duration of isometric contraction of about 1/5 sec: Soleus muscle is concerned with slow contraction for continual, long-term support of the body against gravity.

Fast Versus Slow Muscle Fibers

Every muscle is composed of a mixture of fast and slow fibers: Muscle that responds rapidly (e.g. anterior tibialis) is composed mainly of fast fibers and muscle that responds slowly but with prolonged contraction (e.g. soleus) is composed mainly of slow fibers.

Fast Fibers (Type II, White Muscle)	Slow Fibers (Type 1, Red Muscle)
Larger	Smaller
Innervated by larger nerve fibers	Innervated by smaller nerve fibers
Have a less extensive blood supply because oxidative metabolism is of secondary importance.	Have a more extensive blood vessel system to supply extra amounts of oxygen.
- Have fewer mitochondria because oxidative metabolism is secondary. - Have an extensive SR for rapid release of Ca++ to initiate contraction.	Have large number of mitochondria to support high levels of oxidative metabolism.
- Deficient in red myoglobin giving it the name white muscle. - Have large amounts of glycolytic enzymes for rapid release of energy by the glycolytic process.	Contain large amounts of myoglobin which gives slow muscle a reddish appearance and hence the name red muscle.

Motor Unit

* **Motor Unit:** All the muscle fibers innervated by a single nerve fiber.

* Small muscles that require fine control e.g. laryngeal muscles have 2-3 muscle fibers per motor unit whereas large muscles that do not require fine control e.g. soleus muscle have several hundred muscle fibers per motor unit.

* Muscle fibers in motor units are overlapped in microbundles allowing motor units to contract in support of one another.

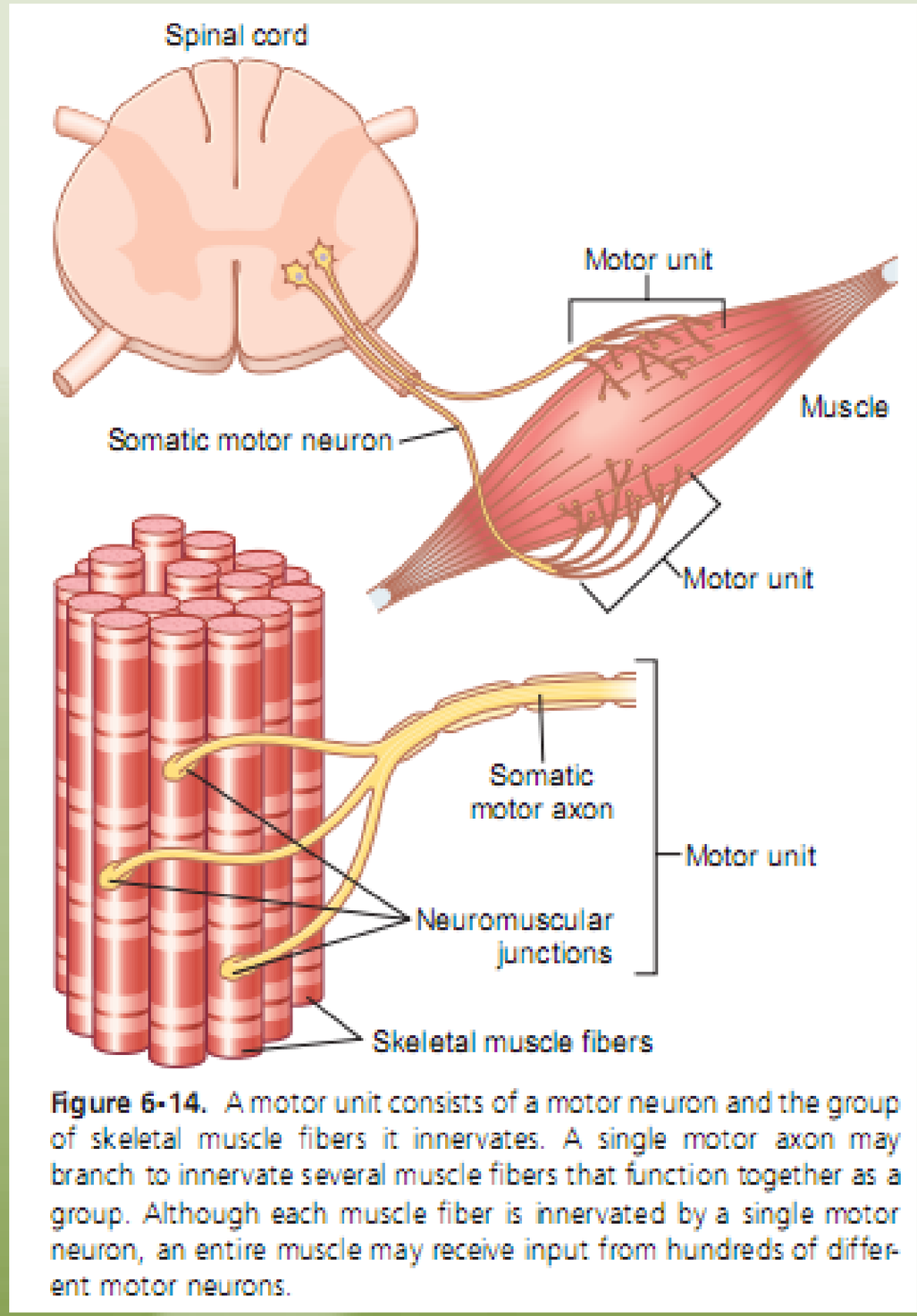


Figure 6-14. A motor unit consists of a motor neuron and the group of skeletal muscle fibers it innervates. A single motor axon may branch to innervate several muscle fibers that function together as a group. Although each muscle fiber is innervated by a single motor neuron, an entire muscle may receive input from hundreds of different motor neurons.

Multiple Fiber Summation

* When CNS sends a weak signal to a muscle, the smaller motor units are stimulated before larger motor units.

* As the strength of the signal increases, larger and larger motor units begin to be excited, with the largest motor units often having as much as 50 times the contractile force of the smallest units. This phenomenon is called the size principle and it is important because it allows the gradations of muscle force.

* Single muscle fiber obeys all or non law. However, the whole muscle contraction can be summated.

Frequency Summation and Tetanization

* Individual simple muscle twitches occurring one after another at low frequency of stimulation.

* As frequency of stimulation increases, each new contraction occurs before the preceding one is over ⟶ the second contraction is added partially to the first.

* More increasing in frequency of stimulation ⟶ rapid successive contractions that fuse together and appear to be smooth and continuous (Tetanization).

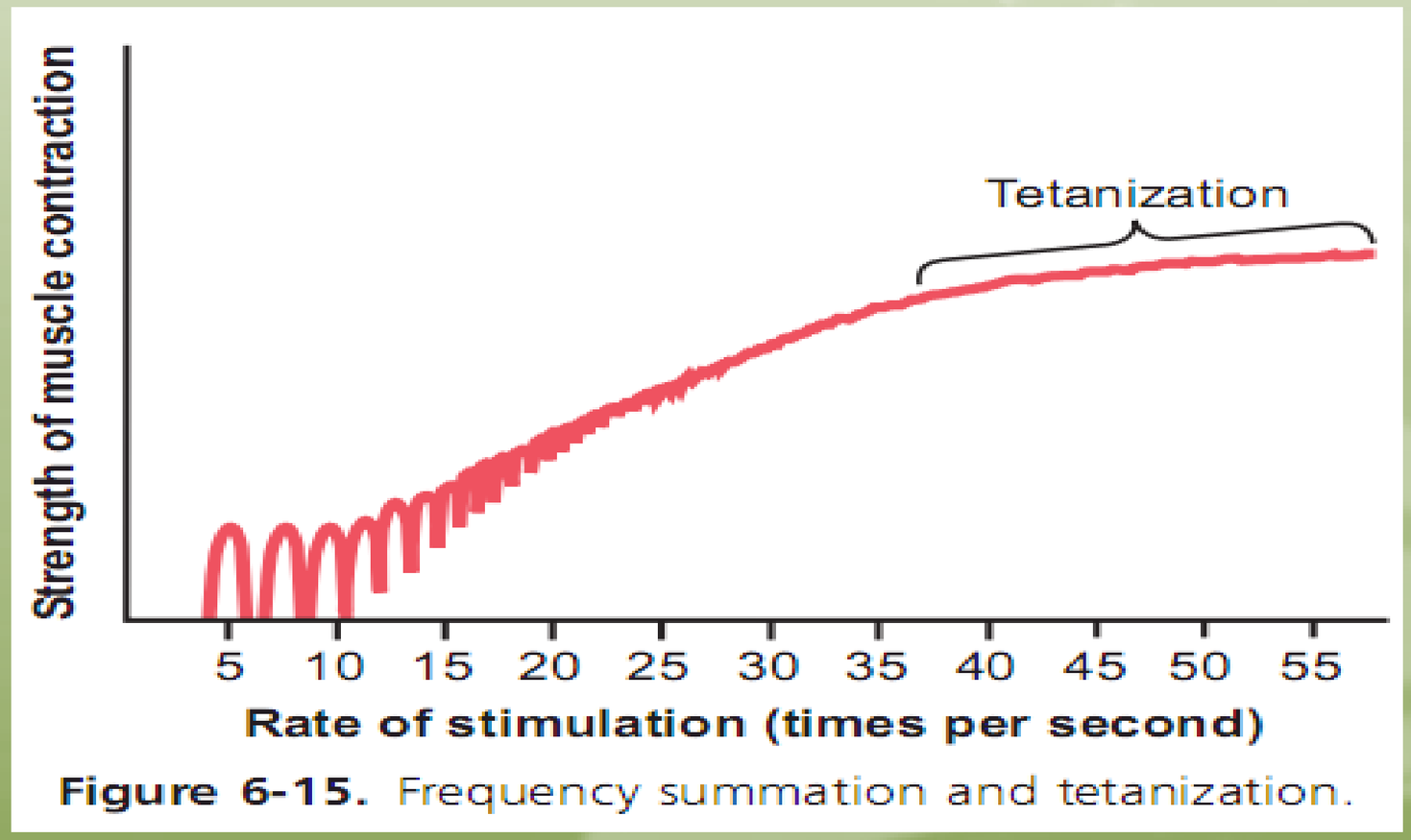


Figure 6-15. Frequency summation and tetanization.

Skeletal Muscle Tone

* Muscle tone means certain amount of tautness remains in muscle at rest.

* skeletal muscle tone results from a low rate of nerve impulses coming from the spinal cord. These nerve impulses are controlled by 1) signals transmitted from the brain to the appropriate spinal cord anterior motor neurons and by 2) signals that originate in muscle spindles located in the muscle itself.

Muscle Fatigue

* Prolonged and strong contraction of a muscle leads to muscle fatigue. Muscle fatigue may result from:

1) Inability of contractile and metabolic processes of muscle fibers to continue.

2) Decrease transmission through neuromuscular junction.

3) Interruption of blood flow through a contracting muscle.

Muscle Hypertrophy and Muscle Atrophy

Muscle hypertrophy

* means increase of the total mass of a muscle.

* results from an increase in the number of actin and myosin filaments in each muscle fiber (fiber hypertrophy).

* occurs when the muscle is loaded during the contractile process.

Muscle atrophy

*means decrease of the total mass of a muscle.

* Occurs in unused muscle for many weeks in which the rate of degradation of contractile proteins is more rapid than the rate of replacement.

* Degradation of contractile proteins occurs through ATP-dependent ubiquitin-proteasome pathway. Proteasomes are large protein complexes that degrade damaged or unneeded proteins by proteolysis. Ubiquitin is a regulatory protein that labels which cells will be targeted for proteosomal degradation.

Hyperplasia of Muscle Fibers

* means a few percent increase in the actual number of muscle fibers under extreme muscle force generation. The increase in fiber number is called fiber hyperplasia.

Muscle Denervation

* Muscle denervation causes muscle atrophy which begins immediately. After about 2 months, degenerative changes begin to appear in muscle fibers.

* If nerve supply grows back rapidly, full return of function can occur in 3 months, then, the capability of functional return becomes less and less, with no further return of function after 1-2 years.

* In final stage of denervation atrophy, most of muscle fibers are destroyed and replaced by fibrous and fatty tissue which has a tendency to continue shortening for many months (contracture).

* One problem in physical therapy is to keep atrophying muscles from contractures. This goal is achieved by daily stretching of the muscles.

Chapter 6

Organization of the Nervous System, Basic Functions of Synapses, and Neurotransmitters

The Nervous System

Neuron: The Basic Functional Unit

* The CNS contains more than 100 billion neurons.

* A typical neuron of brain motor cortex is shown in the figure.

* Incoming signals enter this neuron through synapses located on dendrites (few hundred to 200,000).

* Output signal travels by a single axon leaving the neuron. Then, this axon have many branches to other parts of the nervous system through synapses.

* A special feature of synapses is that the signal normally passes only in the forward direction, from the axon of a preceding neuron to dendrites of subsequent neurons. This feature forces the signal to travel in required directions to perform specific functions.

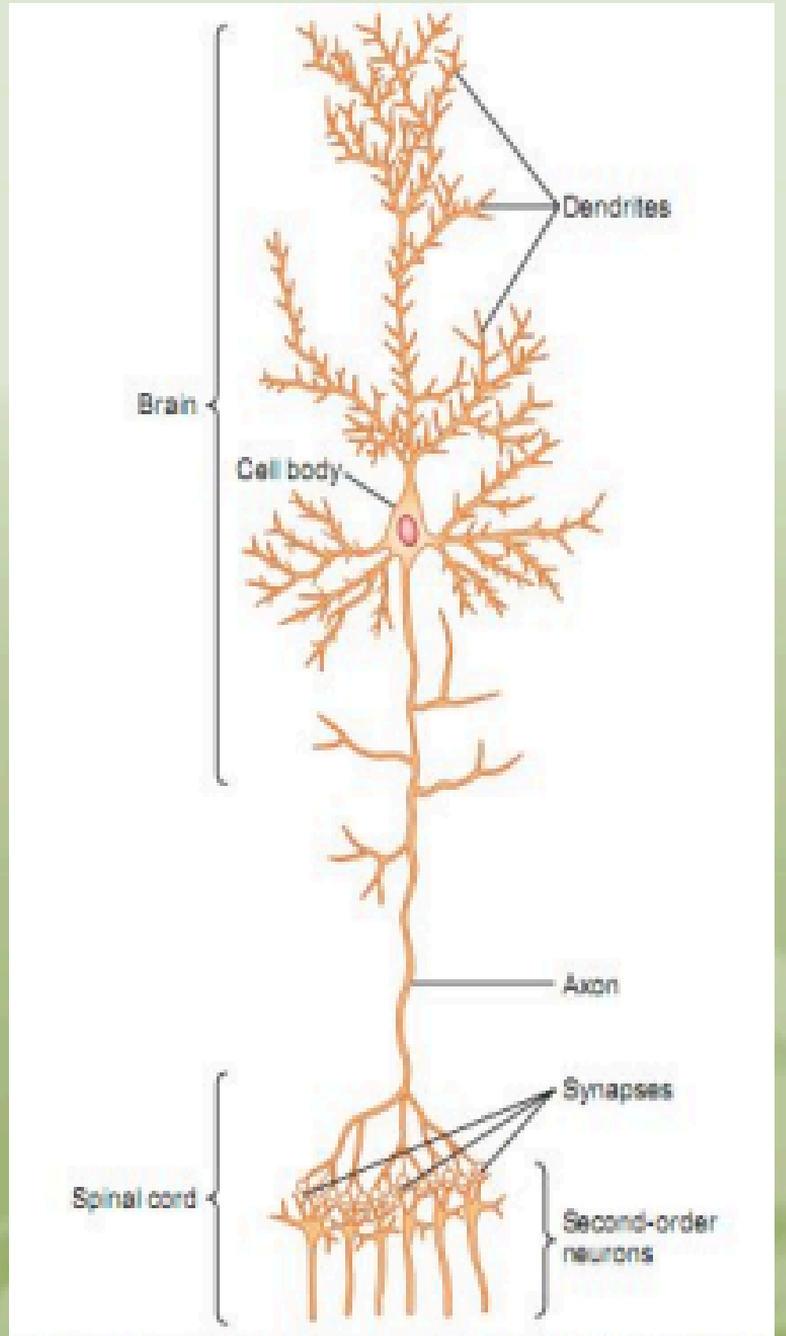


Figure 46-1. Structure of a large neuron in the brain showing its important functional parts. *(Modified from Guyton AC: Basic Neuroscience: Anatomy and Physiology. Philadelphia: WB Saunders, 1987.)*

Sensory part of the Nervous System—Sensory Receptors

* Activities of the nervous system are initiated by sensory experiences that excite sensory receptors (e.g. visual, auditory and tactile receptors).

* Sensory experiences can either cause immediate reactions from the brain or memories of experiences can be stored in brain for minutes, weeks or years and determine bodily reactions at future.

* Somatic portion of sensory system transmits sensory information from receptors of body surface and from some deep structures. This information enters

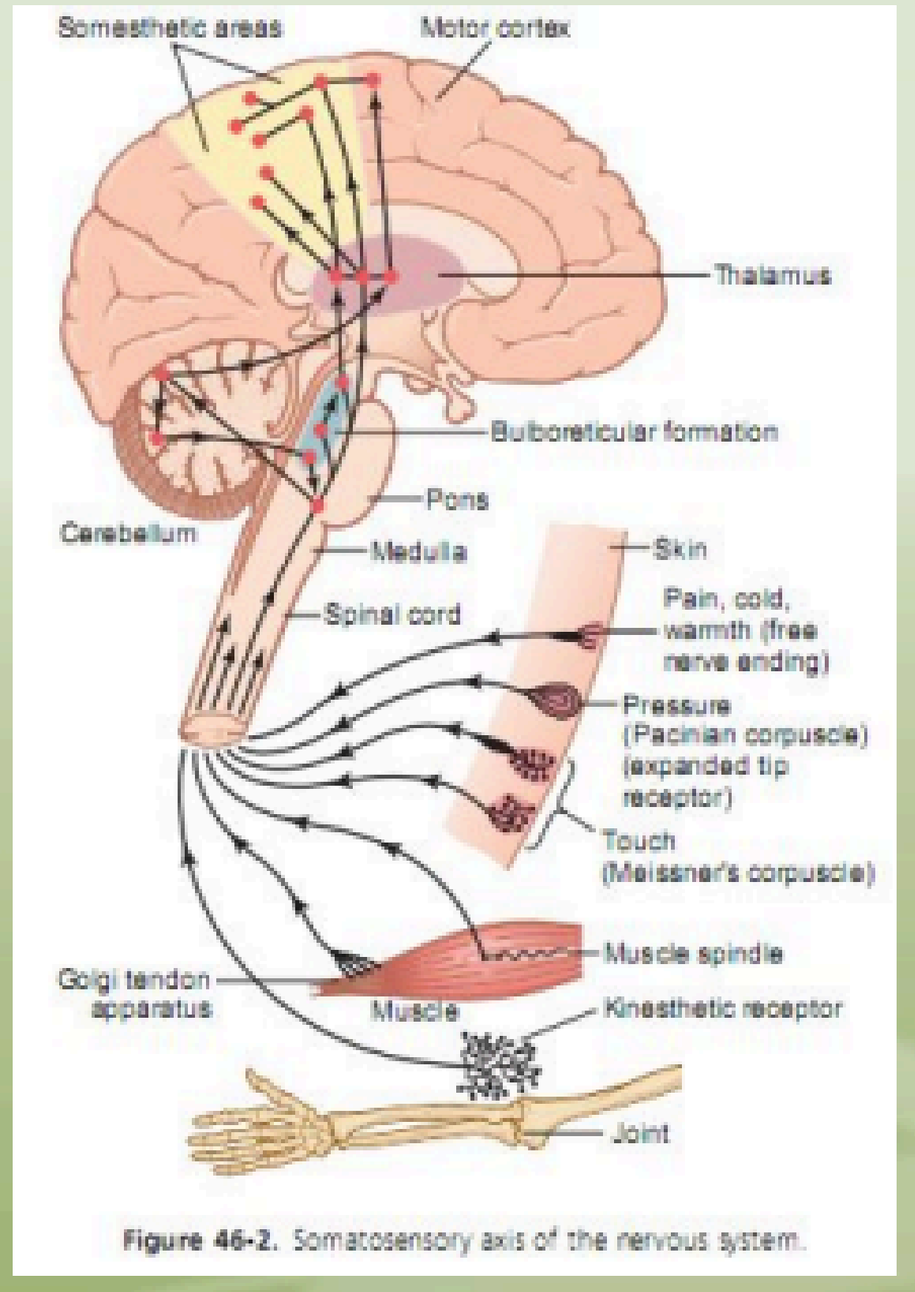


Figure 46-2. Somatosensory axis of the nervous system.

CNS through peripheral nerves to sensory areas in (1) spinal cord (2) medulla oblongata, pons and mesencephalon (3) cerebellum (4) thalamus and (5) areas of cerebral cortex

Motor Part of the Nervous System—Effectors

* The nervous system controls motor functions by controlling (1) contraction of skeletal muscles, (2) contraction of smooth muscles and (3) secretion of exocrine and endocrine glands. The muscles and glands are called effectors.

* Skeletal muscles are controlled by skeletal motor nerves from many levels of CNS including (1) spinal cord; (2) medulla oblongata, pons and mesencephalon; (3) basal ganglia; (4) cerebellum and (5) motor cortex.

* Lower regions of CNS are concerned with automatic, instantaneous muscle responses to sensory stimuli and higher regions are concerned with deliberate complex muscle movements.

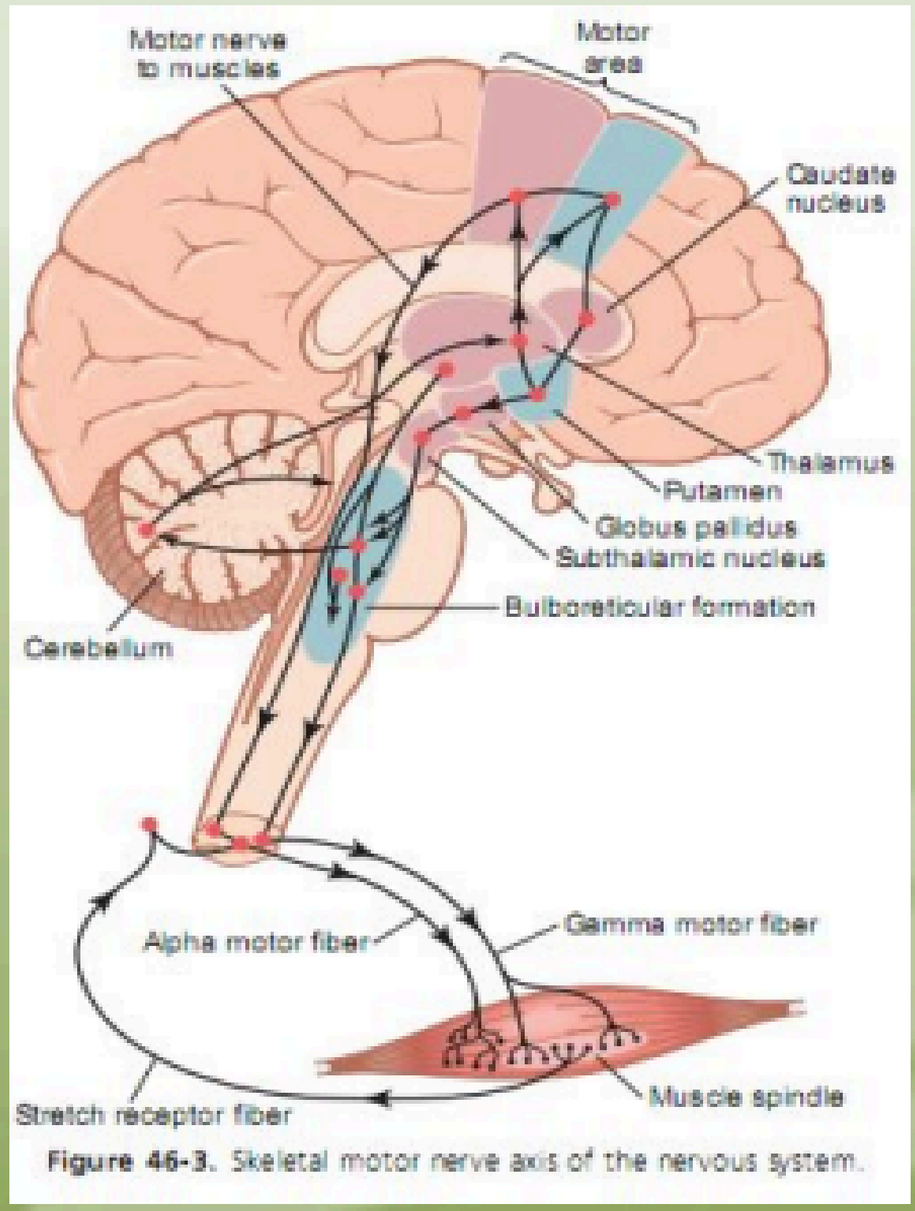


Figure 46-3. Skeletal motor nerve axis of the nervous system.

* Smooth muscles and glands are controlled by autonomic nervous system.

Major Levels of Central Nervous System Function

1. Spinal cord level

* The spinal cord is not only a conduit for signals from body to brain or from brain to body, but also performs many organized functions e.g. neuronal circuits in spinal cord can cause (1) walking movements, (2) reflexes that withdraw por tions of the body from painful objects, (3) reflexes that stiffen the legs to support the body against gravity, and (4) reflexes that control local blood vessels, gastrointestinal movements, or urinary excretion.

2. Lower brain or subcortical level

* Most of subconscious activities are controlled in lower areas of the brain including medulla, pons, mesencephalon, hypothalamus, thalamus, cerebellum, and basal ganglia e.g.

subconscious control of arterial blood pressure and respiration is achieved mainly in medulla and pons.

3. Higher brain or cortical level

* The cerebral cortex is an extremely large memory storehouse.

* The cerebral cortex never functions alone but always in association with lower brain centers. In fact, the lower brain centers initiate wakefulness in the cerebral cortex and opening its bank of memories to the thinking machinery of the brain.

Central Nervous System Synapses

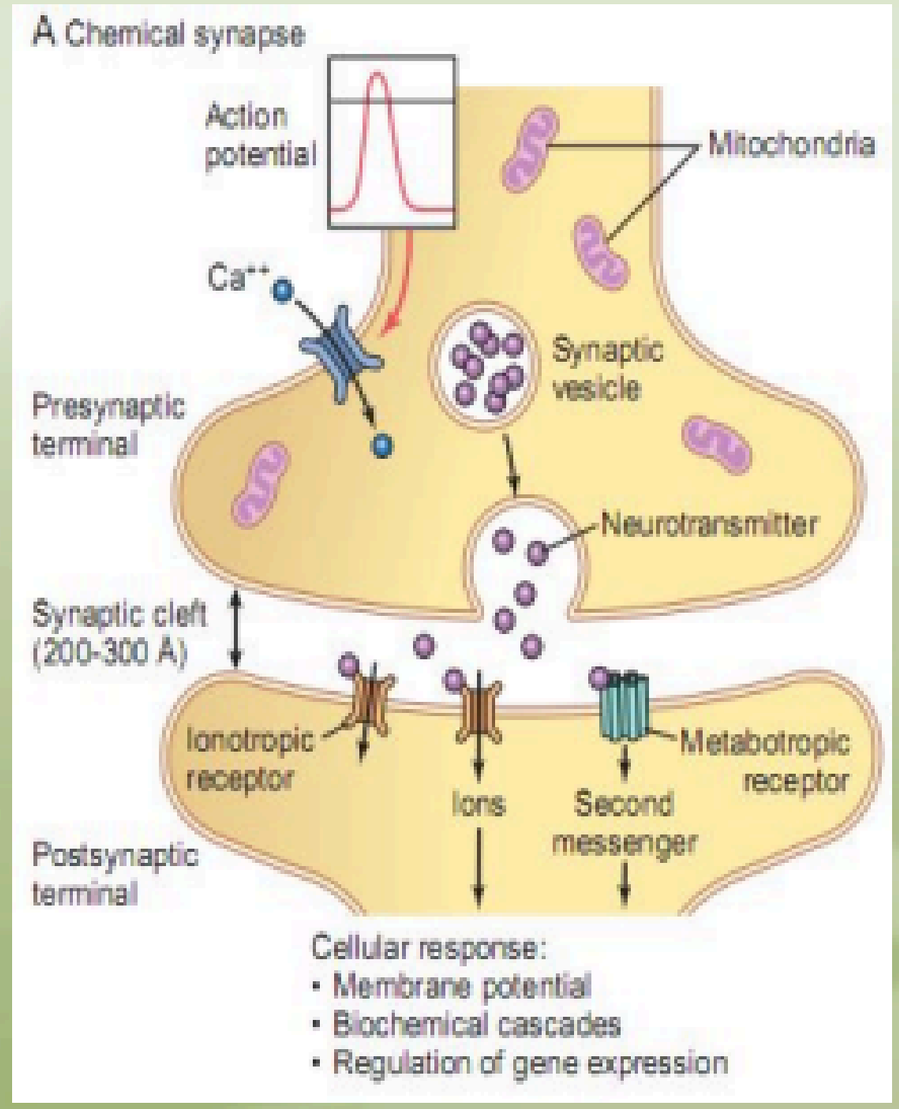
Types of synapses

1. Chemical synapses:

* Are most of the synapses in CNS.

* The presynaptic neuron secretes at its nerve ending a neurotransmitter which acts on receptor proteins in the membrane of the postsynaptic neuron to excite the neuron, inhibit it, or modify its sensitivity.

* More than 40 neurotransmitters have been discovered e.g. acetylcholine, norepinephrine, epinephrine, gamma aminobutyric acid (GABA) and glutamate.

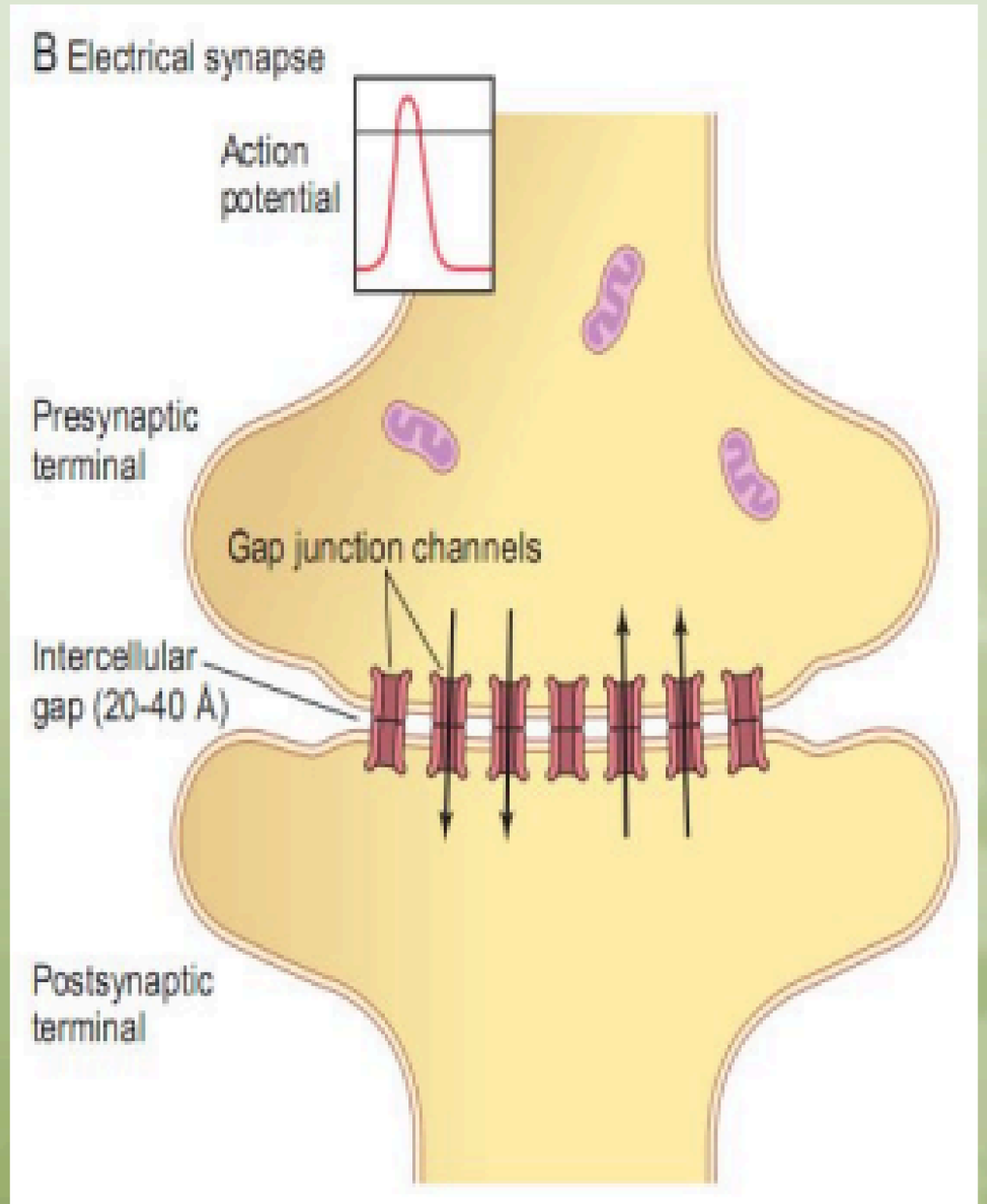


* Transmit signals in one direction from presynaptic to postsynaptic neuron (unidirectional or one-way conduction) which allows signals to be directed toward specific goals.

2. Electrical synapses:

*** Are gap junctions connected adjacent neurons that allow free movement of ions from the interior of one neuron to the interior of the next neuron.**

*** Transmit signals in either direction (bidirectional transmission) that permits coordination of activities of large groups of interconnected neurons.**



Physiological Anatomy of the Synapse

*** A typical anterior motor neuron in the anterior horn of the spinal cord is composed of three major parts:**

1. Soma: the main body of the neuron

2. Single axon: extends from the soma into a peripheral nerve that leaves the spinal cord and

3. Dendrites: are great numbers of branching projections of the soma.

*** As many as 10,000 to 200,000 presynaptic terminals from many other neurons lie on the surfaces of the dendrites and soma of the motor neuron.**

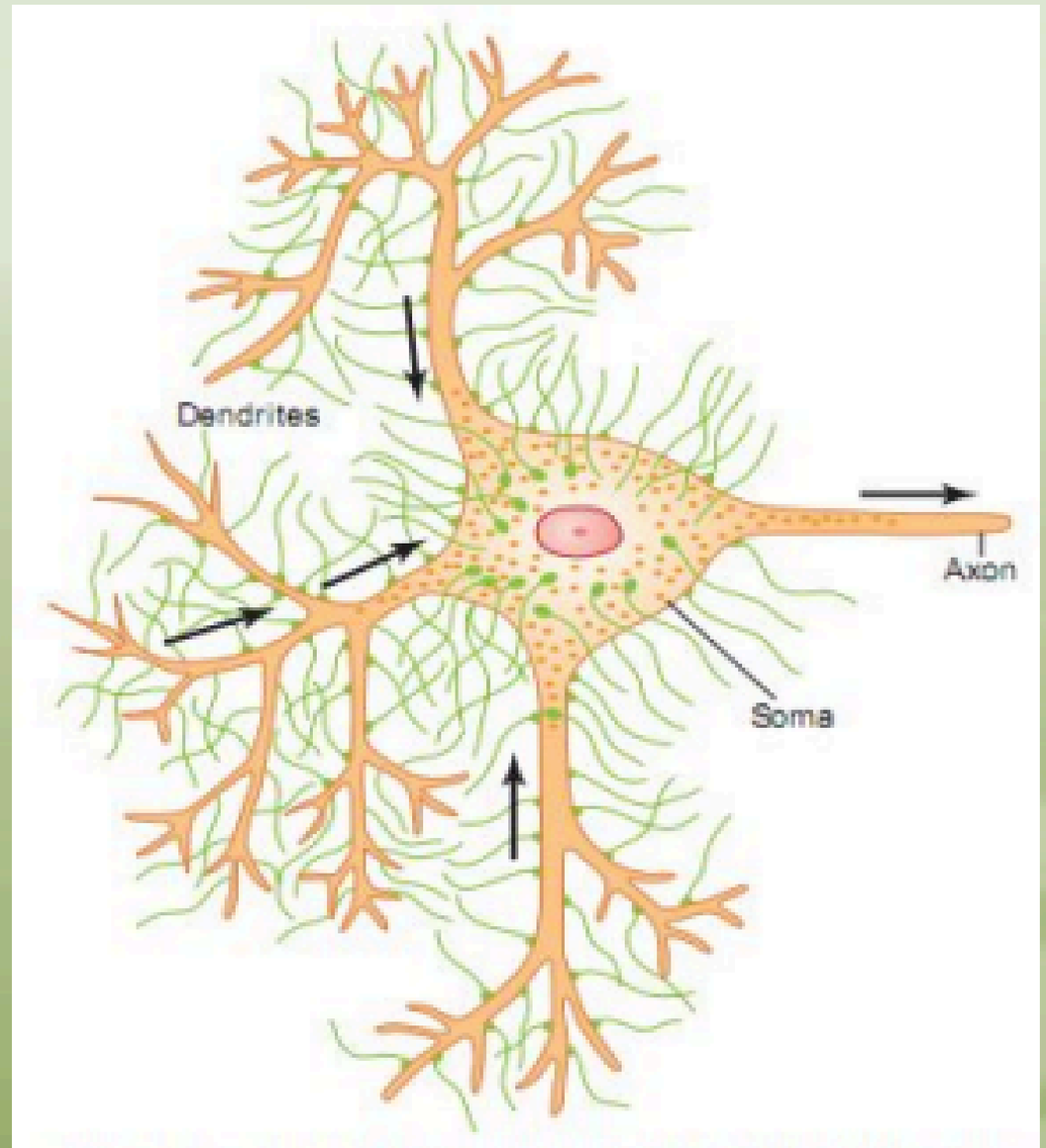


Figure 46-6. A typical anterior motor neuron showing presynaptic terminals on the neuronal soma and dendrites. Note also the single axon.

* Many of presynaptic terminals are excitatory (secrete excitatory neurotransmitter e.g. glutamate) and others are inhibitory (secrete inhibitory neurotransmitter e.g. GABA).

* Neurons differ in (1) size of cell body; (2) length, size and number of dendrites, (3) length and size of axon and (4) number of presynaptic terminals. These differences make neurons to perform different functions.

Presynaptic Terminals

* The presynaptic nerve terminal is in the form of oval knob called presynaptic knob.

* The presynaptic knob contains:

- Synaptic vesicles which contains neurotransmitter

- Mitochondria which provide ATP for synthesizing neurotransmitter.

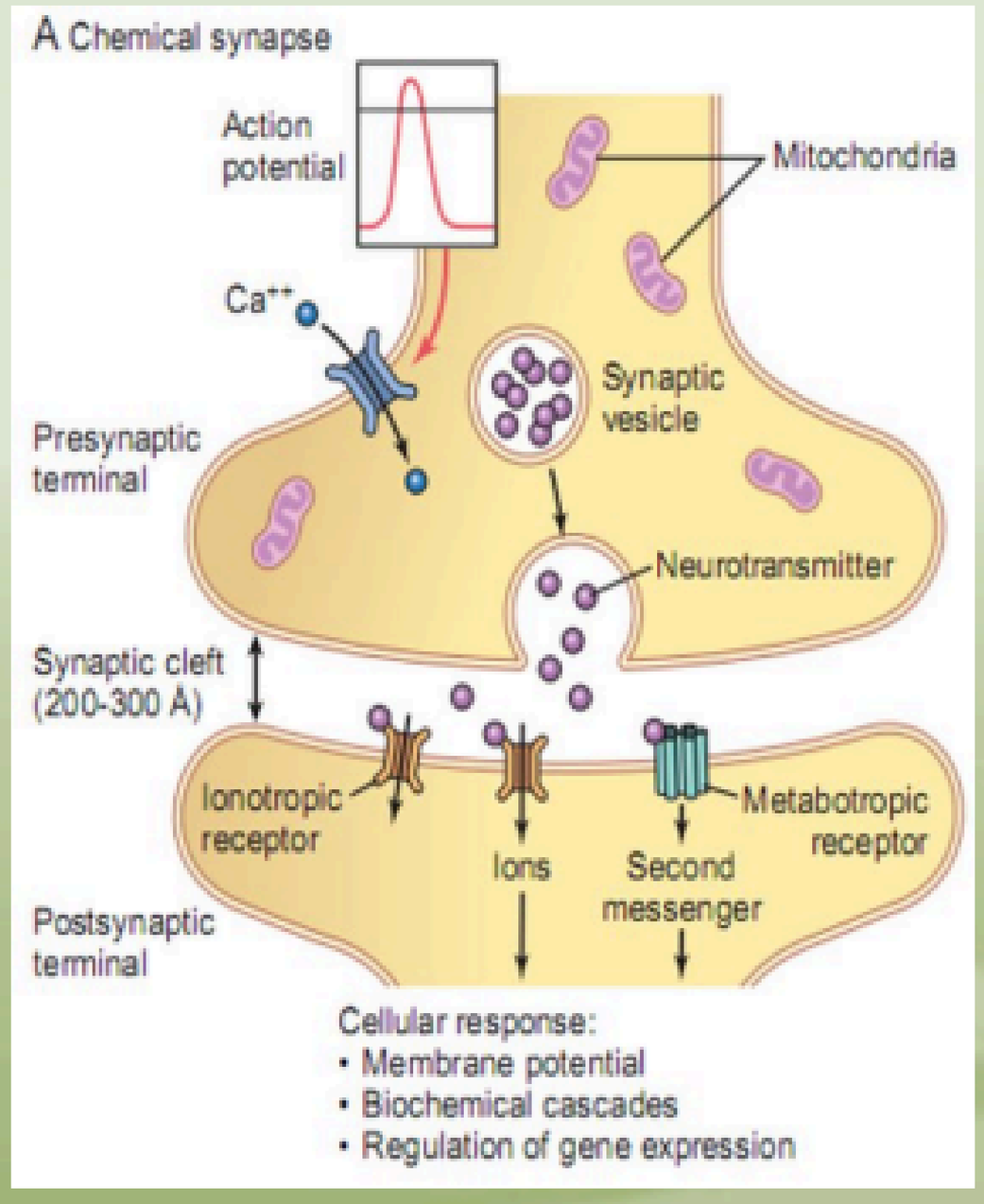
* The presynaptic knob is separated from the postsynaptic soma by a synaptic cleft (200-300 angstroms in width).

Postsynaptic Terminals

* The postsynaptic membrane contains receptor proteins, each has two components:

1. Binding component that protrudes into the synaptic cleft and binds the neurotransmitter

2. Intracellular component that passes all the way through the postsynaptic membrane.



* Neurotransmitter receptors are:

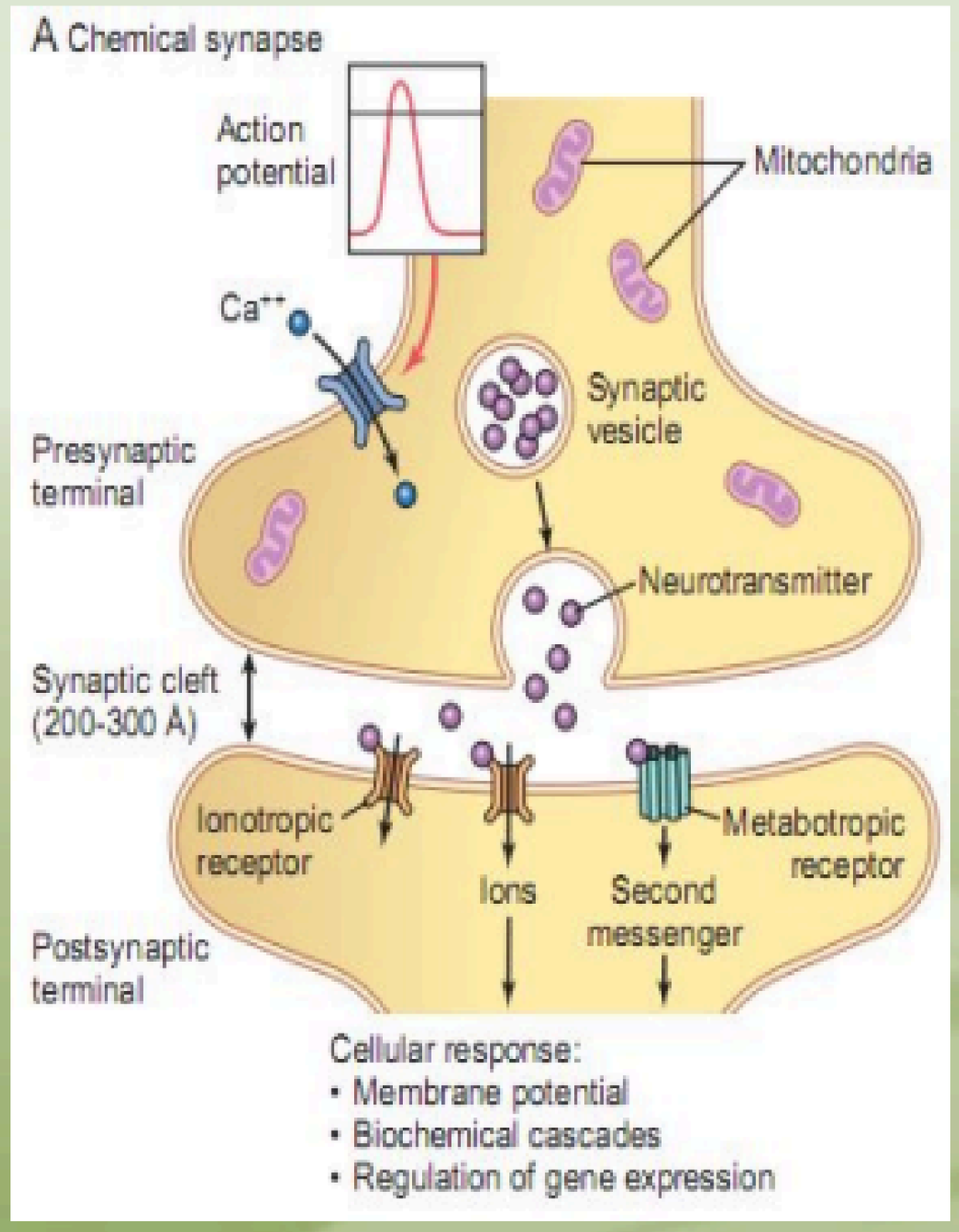
1. Ionotropic receptors which gate cation or anion channels.

2. Metabotropic receptors which act through second messenger system.

Mechanism of Synaptic Transmission

* When an action potential reach presynaptic nerve terminal ⟶ depolarization of presynaptic membrane and opening of voltage-gated calcium channels and calcium ions flow into presynaptic terminal ⟶ synaptic vesicles move and fuse with presynaptic membrane and release neurotransmitter into the cleft by exocytosis.

* The neurotransmitter binds to postsynaptic receptors which are:



1. Ionotropic receptors which gate cation or anion channels.

- Opening of cation channels e.g. sodium channels by excitatory transmitter allows sodium ions to flow into postsynaptic neuron causing depolarization and if reach threshold level ⟶ action potential in postsynaptic neuron (Excitation).

- Opening of anion channels e.g. chloride channels by inhibitory transmitter allows chloride ions to flow into postsynaptic neuron causing hyperpolarization (Inhibition).

- Opening of potassium channels allows potassium ions to flow outside postsynaptic neuron causing hyperpolarization (Inhibition).

2. Metabotropic receptors which act through second messenger system. How?

- Metabotropic receptors acting through second messenger system are believed to be involved in memory because they cause prolonged changes for seconds to months in postsynaptic neurons after the transmitter is gone.

- Ion channels are not suitable for causing prolonged postsynaptic neuronal changes because these channels close within milliseconds after the transmitter is gone.

- One of the most common types of second messenger system is that uses G proteins.

Inactive G protein complex is free in the cytosol and consists of GDP and three components: α component that is the activator portion of the G protein, β and γ components that are attached to the α component.

- When the receptor is activated by a neurotransmitter ⟶ conformational changes ⟶ α subunit releases GDP and simultaneously binds GTP while separating from β and γ portions.

- The separated α-GTP complex moves within the cytoplasm of the cell to perform one or more of the following functions:

1. Opening specific ion channels e.g. potassium channel which often stays open for a prolonged time.

2. Activation of cAMP or cGMP which stimulates metabolic pathways in the neuron.

3. Activation of one or more intracellular enzymes which can cause any one of many specific chemical functions.

4. Activation of gene transcription which causes proteins and structural changes in postsynaptic neuron.

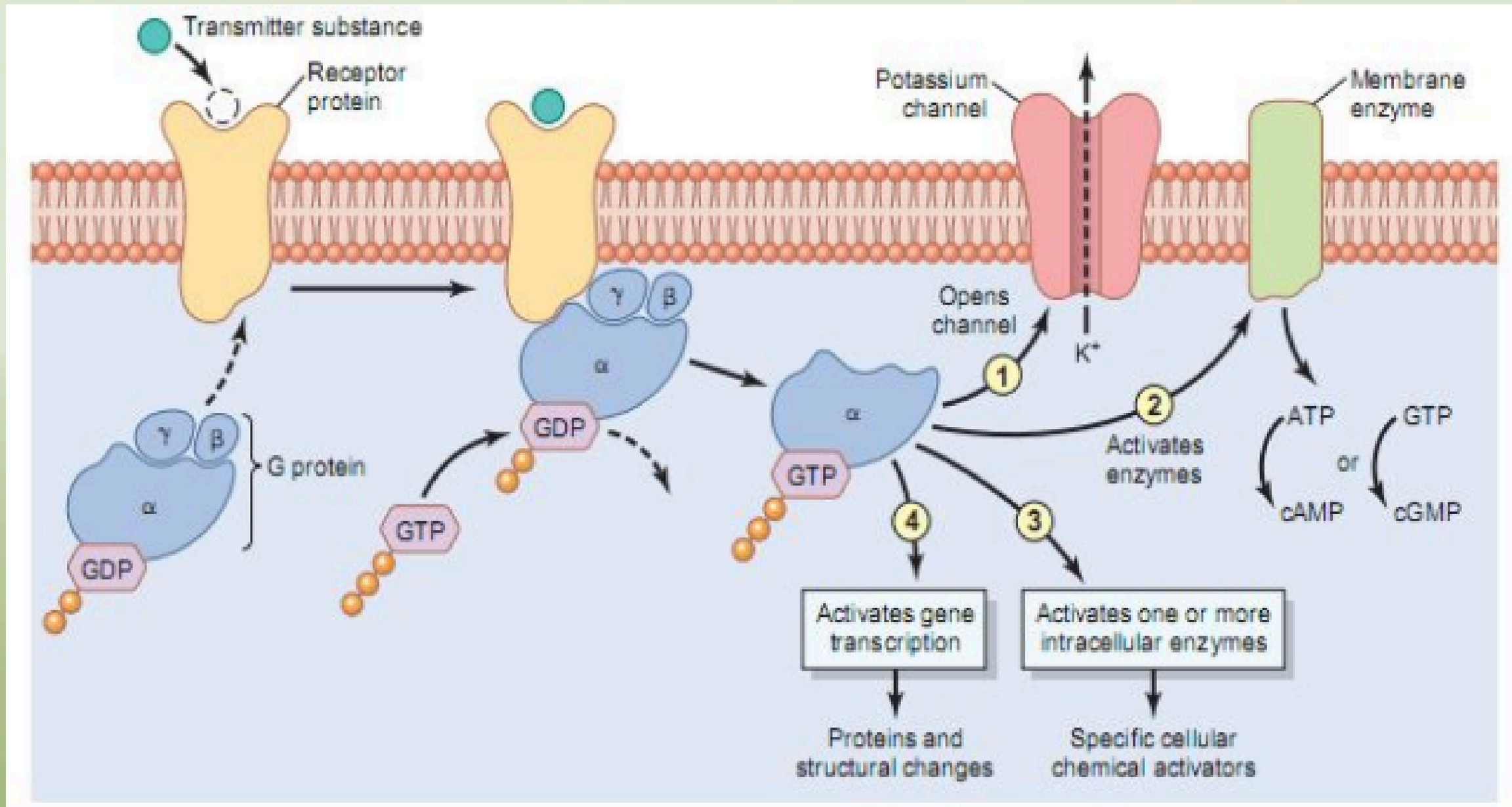


Figure 46-7. The "second messenger" system by which a transmitter substance from an initial neuron can activate a second neuron by first causing a transformational change in the receptor that releases the activated alpha (α) subunit of the G protein into the second neuron's cytoplasm. Four subsequent possible effects of the G protein are shown, including *1*, opening an ion channel in the membrane of the second neuron; *2*, activating an enzyme system in the neuron's membrane; *3*, activating an intracellular enzyme system; and/or *4*, causing gene transcription in the second neuron. Return of the G protein to the inactive state occurs when guanosine triphosphate *(GTP)* bound to the α subunit is hydrolyzed to guanosine diphosphate *(GDP)* and the β and γ subunits are reattached to the α subunit.

Synaptic Transmitters

I. Small-Molecule, Rapidly Acting Transmitters

* Synthesized in cytosol of presynaptic terminal and absorbed by active transport into transmitter vesicles.

* Transmitter vesicles release their transmitter into synaptic cleft in response to action potential within a millisecond or less.

* The subsequent action of small molecule transmitter on postsynaptic receptors also occurs within another millisecond or less.

* Transmitter vesicles are continually recycled. After fusion of vesicle with presynaptic membrane and release transmitter, the vesicle portion of the membrane invaginates back to inside of presynaptic terminal and pinches of to form a new vesicle.

* Characteristics of Some Important Small-Molecule Transmitters

1. Acetylcholine:

* Synthesized in presynaptic terminal from acetyl coenzyme A and choline in the presence of choline acetyltransferase enzyme and it is then transported into its specific vesicles.

* Vesicles release acetylcholine into synaptic cleft.

* Once finish its action on postsynaptic receptors, acetylcholine is rapidly split again to acetate and choline by cholinesterase enzyme.

* Vesicles are recycled and choline is actively transported back into presynaptic terminal to be used again for synthesis of new acetylcholine.

* Acetylcholine is secreted by:

- Terminals of the large pyramidal cells from motor cortex

- Neurons in basal ganglia
- Motor neurons that innervate skeletal muscles
- Preganglionic neurons of autonomic nervous system
- Postganglionic neurons of parasympathetic nervous system
- Some of postganglionic neurons of sympathetic nervous system.

* Acetylcholine has an excitatory effect on small intestine and inhibitory effect on heart by vagus nerve.

2. Norepinephrine:

* Secreted by terminals of many neurons in brain stem and hypothalamus to help control overall activity and mood of the mind, such as increasing the level of wakefulness.

* Also secreted by most postganglionic neurons of sympathetic nervous system, where it excites some organs e.g the heart but inhibits others e.g. the intestine.

3. Dopamine:

* Secreted by neurons that originate in the substantia nigra and terminate in basal ganglia.

* The effect of dopamine is usually inhibition.

4. Glycine

* Secreted at synapses in spinal cord and act as an inhibitory transmitter. However glycine can act as an excitatory transmitter on NMDA receptor which is believed to be involved in memory.

5. Gamma-aminobutyric acid (GABA):

* Secreted by nerve terminals in spinal cord, cerebellum, basal ganglia and many areas of the cortex.

* The effect of GABA is usually inhibition through GABA receptors:

- $GABA_A$ receptors: allow chloride ions influx.
- $GABA_B$ receptors: allow potassium ions efflux.

6. Glutamate:

* Secreted by presynaptic terminals in many sensory pathways entering CNS, as well as in many areas of cerebral cortex.

* The effect of glutamate is usually excitation through glutamate receptors:

- Ionotropic receptors: allow sodium ions influx.
- Metabotropic receptors: act through second messenger system.
- N-methyl D- aspartate (NMDA) receptors: In addition to sodium ions influx and potassium ions efflux, NMDA receptors allow calcium ions influx which are believed to be involved in memory.

7. Serotonin:

* Secreted by nuclei that originate in brain stem and project to many brain and spinal cord areas, especially to dorsal horns of spinal cord and to hypothalamus.

* Serotonin acts as an inhibitor of pain pathways in spinal cord and its inhibitor action in higher regions is believed to control the mood, perhaps even to cause sleep.

Nitric oxide:

* is especially secreted by nerve terminals in areas of the brain responsible for memory.
* is not preformed and stored in vesicles in presynaptic ter minal. Instead, it is synthesized instantly as needed and then diffuses out of presynaptic terminals to nearby postsynaptic neurons to change intracellular metabolic functions that modify neuronal excitability for seconds, minutes, or perhaps even longer.

II. Large-Molecule, Delayed Acting Neuropeptides

* Synthesized as integral parts of large protein molecules by ribosomes in neuronal cell body which enter spaces inside ER and subsequently inside Golgi apparatus, where two changes occur:

1. Neuropeptide forming protein is enzymatically split into smaller fragments, some of which are either the neuropeptide itself or a precursor of it.

2. Second, Golgi apparatus packages the neuropeptide into minute transmitter vesicles that are released into the cytoplasm and then transported all the way to axonal terminals by axonal streaming and finally release their neuropeptides in response to action potentials. However, the vesicle is autolyzed and is not reused.

* Neuropeptides are released in much smaller amounts than small molecule transmitters. However, this difference is compensated for by the more potent action of neuropeptides.

* Neuropeptides cause much more prolonged actions (Last for days, months or years) which include:

- Prolonged closure of calcium channels
- Prolonged changes in the metabolism
- prolonged change in activation or deactivation of specific genes in the cell nucleus, and/or
- Prolonged alterations in numbers of excitatory or inhibitory receptors.

Electrical Events During Neuronal Excitation

Resting Membrane Potential of the Neuronal Soma

* The RMP of a spinal motor neuron soma is about −65 mV which is somewhat less negative than the −90 mV found in large peripheral nerve fibers and in skeletal muscle fibers.

* This lower voltage of the soma allows both positive and negative control of the degree of neuronal excitability i.e. decreasing voltage to a less negative value makes neuron more excitable, whereas increasing voltage to a more negative value makes neuron less excitable.

Uniform Distribution of Electrical Potential Inside the Soma

* The interior of neuronal soma contains a highly conductive electrolytic solution and its diameter is large (10-80 micrometers) causing almost no resistance to conduction of electric current from one part to another part of the soma.

* Therefore, any change in potential in any part of the intrasomal fluid causes an almost exactly equal change in potential at all other points inside the soma. This principle plays a major role in "summation" of signals entering the neuron from multiple sources.

Effect of Synaptic Excitation or Inhibition on Postsynaptic Membrane

* **Figure A:** The RMP everywhere in the soma of postsynaptic neuron is −65 mV.

* **Figure B:** Excited postsynaptic neuron by excitatory neurotransmitter e.g. glutamate which causes positively charged sodium ions influx that neutralizes part of negativity of RMP leading to increase membrane potential in positive direction from −65 to −45 mV. This potential equals +20 mV and is called excitatory postsynaptic potential (EPSP).

- If this potential rises high enough in the positive direction, it will elicit an action potential in postsynaptic neuron.

- Discharge of a single presynaptic terminal can never increase neuronal potential from −65 mV to −45 mV.

- An increase of this magnitude requires simultaneous discharge of many terminals (summation).

* Figure C: inhibited postsynaptic neuron by inhibitory neurotransmitter e.g. GABA which causes negatively charged chloride ions influx or negatively charged potassium ions efflux leading to increase membrane potential in negative direction from −65 to −70 mV. This potential equals -5 mV and is called inhibitory postsynaptic potential (IPSP).

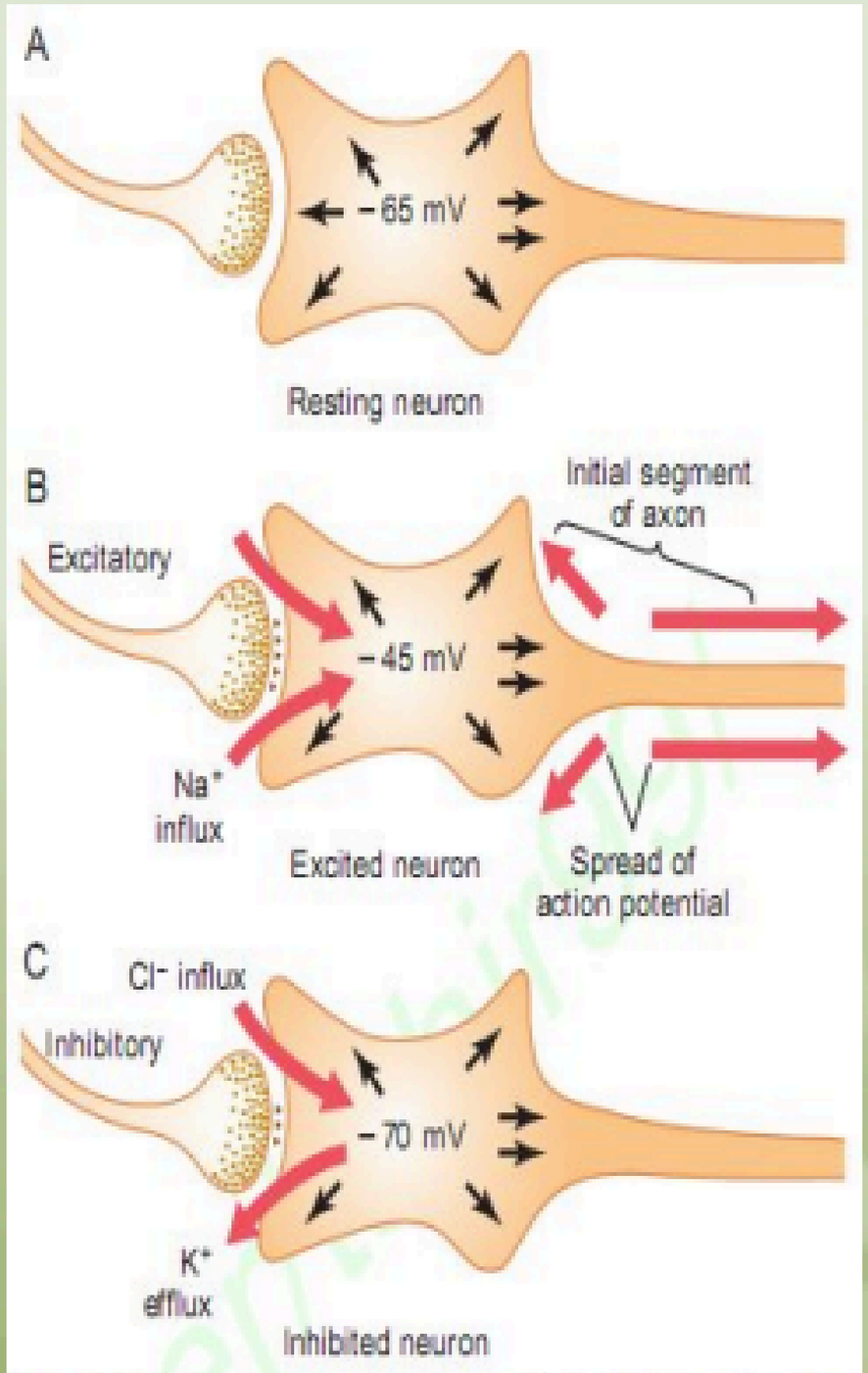


Figure 46-9. Three states of a neuron. **A,** *Resting neuron*, with a normal intraneuronal potential of –65 millivolts. **B,** Neuron in an *excited state*, with a less negative intraneuronal potential (–45 millivolts) caused by sodium influx. **C,** Neuron in an *inhibited state*, with a more negative intraneuronal membrane potential (–70 millivolts) caused by potassium ion efflux, chloride ion influx, or both.

* **Excitatory postsynaptic potential (EPSP):** is a local depolarization (sodium ions influx) of postsynaptic neuron caused by excitatory neurotransmitter e.g glutamate.

* **Inhibitory postsynaptic potential (IPSP):** is a hyperpolarization (chloride ions influx or potassium ions efflux) of postsynaptic neuron caused by inhibitory neurotransmitter e.g GABA.

Generation of Action Potentials in the Initial Segment

* When EPSP rises high enough in the positive direction, it will initiate action potential in the postsynaptic neuron which begins in the initial segment of the axon. **Why in the initial segment not in the soma?**

1. The membrane of the initial segment has seven times more voltage-gated sodium channels than the soma.

2. The EPSP that will elicit action potential in initial segment is between +10 and +20 mV while it is +30 mV or more in the soma.

* The action potential travels forward along the axon.

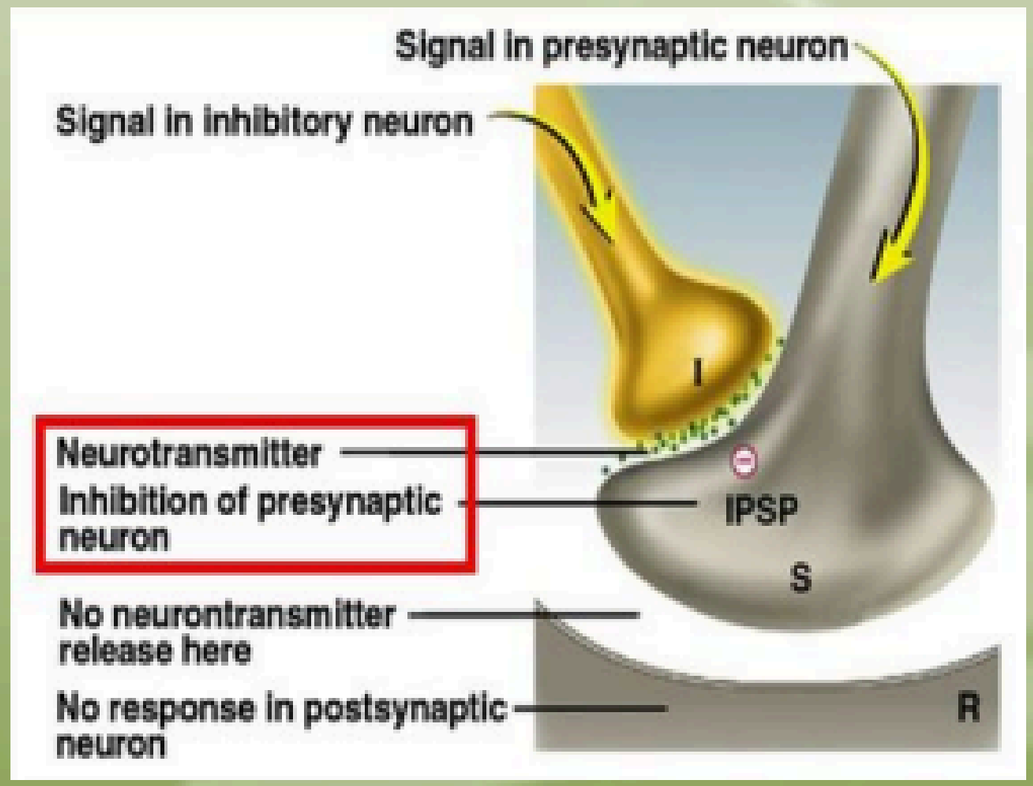
* The action potential tries to travel backward over the soma or even to dendrites but it is stopped. **Why?** because they have very few voltage-gated sodium channels.

Presynaptic Inhibition

* Occurs at presynaptic terminals before signal reaches synapse.

* Caused by release of an inhibitory transmitter e.g. GABA onto outsides of presynaptic nerve fibrils via opening chloride channels.

* Occurs in many sensory pathways in which adjacent sensory nerve fibers inhibit one another to minimize sideways spread and mixing of signals in sensory tracts.



Time course of postsynaptic potentials

* On excitation, the postsynaptic membrane becomes permeable to sodium ions for 1-2 ms and creating EPSP (blue and green curves), then this potential slowly declines over the next 15 ms.

* Simultaneous firing of only a few synapses will not cause sufficient summated potenti al to elicit an action potential but that simulta neous firing of many synapses will raise the summated potential to threshold for excitation and cause action potential.

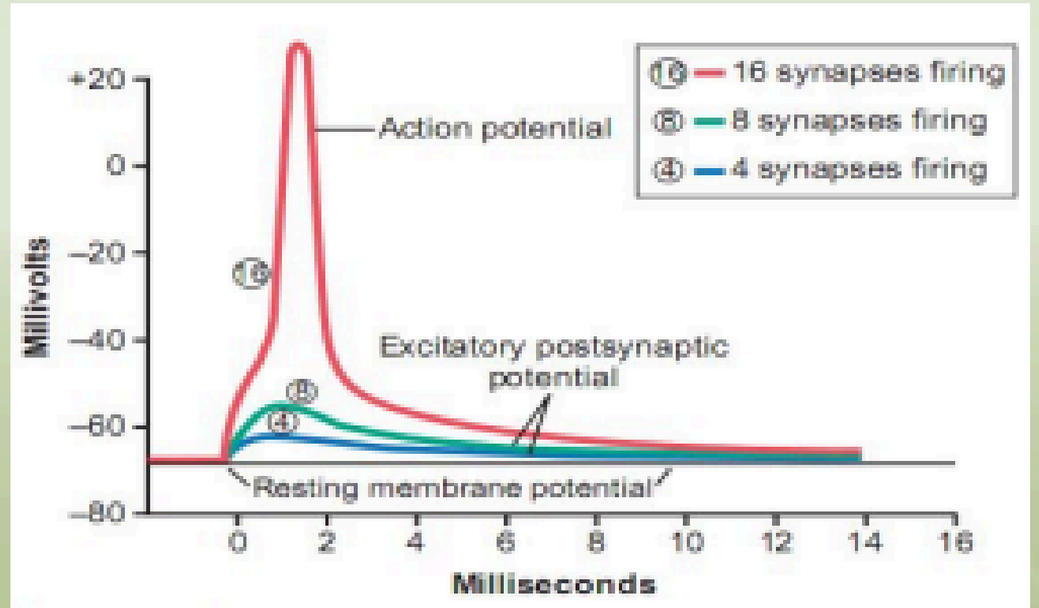


Figure 46-10. Excitatory postsynaptic potentials, showing that simultaneous firing of only a few synapses will not cause sufficient summated potential to elicit an action potential but that simultaneous firing of many synapses will raise the summated potential to threshold for excitation and cause a superimposed action potential.

* On inhibition, the postsynaptic membrane becomes permeable to chloride or potassium ions for 1-2 ms and creating IPSP, then this potential slowly declines over the next 15 ms.

* Some neuropeptides excite or inhibit the postsynaptic neuron for much longer periods.

Spatial Summation

* Excitation of a single presynaptic terminal on the surface of a neuron almost never excites the neuron because the amount of transmitter cause an EPSP no greater than 0.5-1 mV

* However, many presynaptic terminals are usually stimulated at the same time and their EPSPs can be summated until postsynaptic neu ronal action potential occurs in the initial segment (spatial summation).

Temporal Summation

* means successive discharges from a single presynaptic terminal that occur rapidly enough and its EPSPs can be summated until postsynaptic neuronal action potential occurs in the initial segment.

Simultaneous summation of IPSP and EPSP

if a neuron is being excited by an EPSP, an IPSP from another neuron can reduce postsynaptic potential to less than threshold value for excitation, thus turning of the neuron.

Facilitation of neurons

Facilitated neuron is a neuron that having its membrane potential nearer the threshold for firing than normal but is not yet at the firing level. Consequently, another excitatory signal entering the neuron from other source can then excite the neuron very easily.

Special characteristics of synaptic transmission

1. Fatigue of Synaptic Transmission

*** means that the firing rate of postsynaptic neuron becomes progressively less in succeeding ms or seconds when is repetitively stimulated at a rapid rate.**

*** is important mean by which the excess excitability of the brain during an epileptic seizure is finally subdued so that the seizure ceases. Thus, development of fatigue is a protective mechanism against excess neuronal activity.**

* The mechanism of fatigue is mainly exhaustion or partial exhaustion of stores of transmitter substance in presynaptic terminals.

2. Effect of Alkalosis or Acidosis on Synaptic Transmission

* Alkalosis greatly increases neuronal excitability e.g. a rise in arterial blood pH from 7.4 to 7.8 to 8.0 causes cerebral epileptic seizures. In a person who is predisposed to epileptic seizures, hyperventilation may cause an epileptic attack?.

* Acidosis greatly depresses neuronal activity; a fall in pH from 7.4 to below 7.0 causes a comatose state e.g. in very severe diabetic or uremic acidosis, coma develops.

3. Effect of Hypoxia on Synaptic Transmission

* Cessation of oxygen for only a few seconds can cause complete inexcitability of neurons. This effect is observed when brain's blood flow is temporarily interrupted because within 3-7 sec, the person becomes unconscious.

4. Effect of drugs on Synaptic Transmission

* **Cafeine, theophylline and theobromine**, which are found in coffee, tea and cocoa, respectively, all increase neuronal excitability, presumably by reducing threshold for excitation of neurons.

* **Strychnine** increases excitability of neurons by inhibiting the action of some inhibitory transmitter substances, especially the inhibitory effect of glycine in the spinal cord resulting in severe tonic muscle spasms.

* **Anesthetics** increase neuronal membrane threshold for excitation and thereby decrease synaptic transmission. Because many anesthetics are lipid soluble, it has been reasoned that some of them might change physical characteristics of the neuronal membranes, making them less responsive to excitatory agents.

5. Synaptic delay

* means the time consumed in transmission of a neuronal signal from a presynaptic to a postsynaptic neuron which comprised (1) discharge of transmitter by presynaptic terminal, (2) diffusion of transmitter to postsynaptic neuronal membrane, (3) action of transmitter on membrane receptor, (4) action of receptor to increase membrane permeability, and (5) inward diffusion of sodium to raise the EPSP to a high enough level to elicit action potential.

* Synaptic delay is about 0.5 ms.

* Neurophysiologists can estimate the number of neurons in the circuit from the measure of delay time.

e.g. The delay time=10 ms

The number of neurons in the circuit=10/0.5=20 neurons

Chapter 7

The Autonomic Nervous System and the Adrenal Medulla

Autonomic Nervous System

* Autonomic nervous system is the portion of the nervous system that controls most visceral functions of the body.

* One of the most striking character of autonomic nervous system is the rapidity and intensity with which it can change visceral functions e.g. within 3 to 5 seconds it can increase heart rate to twice normal.

General Organization of Autonomic Nervous System

* Autonomic nervous system is activated by centers located in spinal cord, brain stem and hypothalamus. In addition, portions of cerebral cortex, especially of limbic cortex, can transmit signals to lower centers and in this way can influence autonomic control.

* Autonomic nervous system operates through visceral reflexes.

* The efferent autonomic signals are transmitted to the various organs of the body through two major subdivisions called sympathetic and parasympathetic nervous system.

Physiological Anatomy of Sympathetic Nervous System

1. Paravertebral sympathetic chains of ganglia.
2. Prevertebral ganglia (celiac, superior mesenteric, aortico-renal, inferior mesenteric and hypogastric).
3. Nerves extending from ganglia to different internal organs.
4. Sympathetic nerve fibers originate in spinal cord along with spinal nerves between cord segments T1 and L2 and pass first into the sympathetic chain and then to different organs.

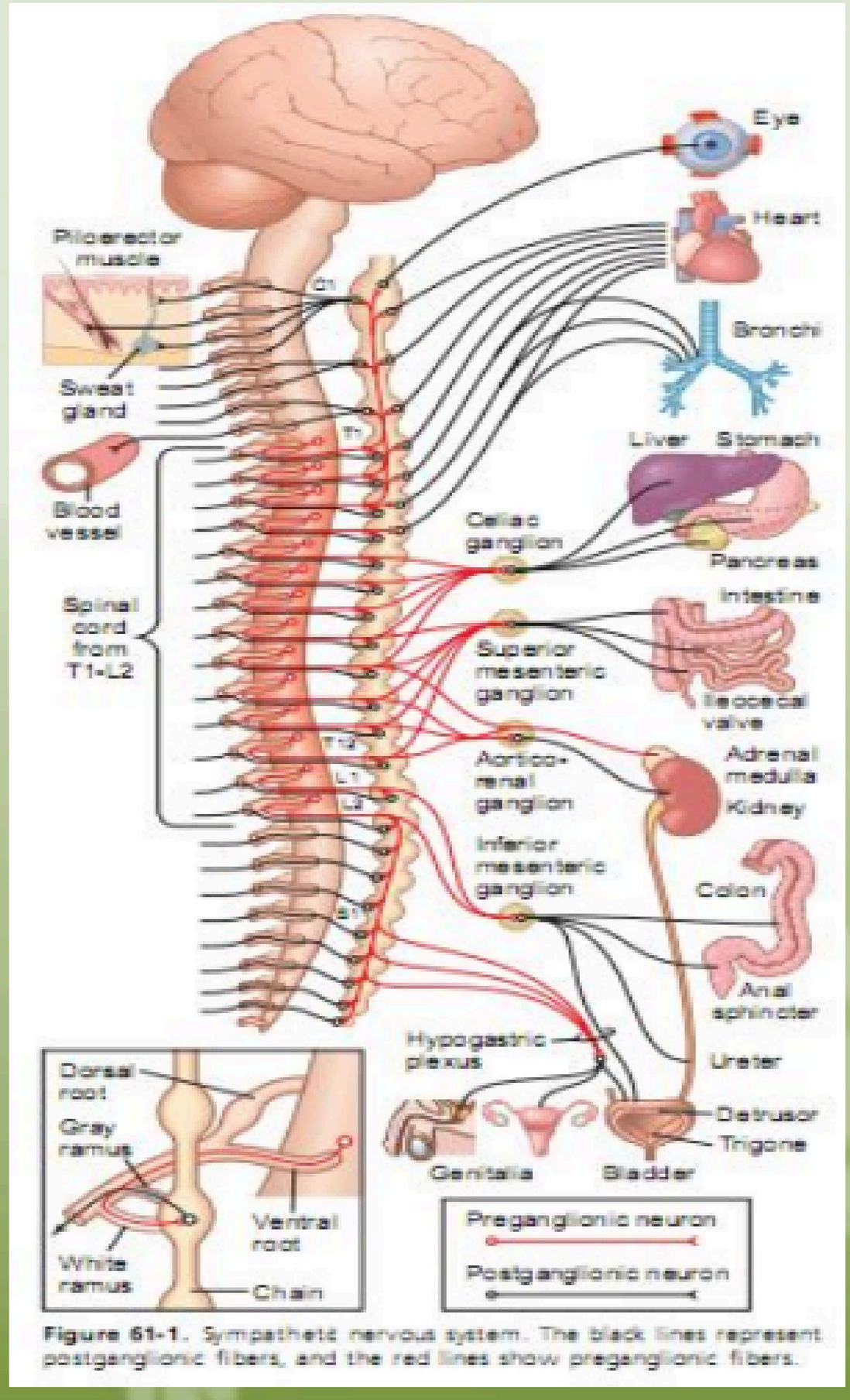


Figure 61-1. Sympathetic nervous system. The black lines represent postganglionic fibers, and the red lines show preganglionic fibers.

Preganglionic and Postganglionic Sympathetic Neurons

* The cell body of each preganglionic neuron lies in the intermediolateral horn of the spinal cord; its fiber passes through a ventral root of the cord into the corresponding spinal nerve.

* Immediately after the spinal nerve leaves the spinal canal, the preganglionic sympathetic fibers leave the spinal nerve and pass through a white ramus into one of the ganglia of the sympathetic chain.

* The fibers then can take one of the following three courses:

1. synapse with postganglionic sympathetic neurons in the ganglion.
2. Pass upward or downward in the chain and synapse in one of the other ganglia of the chain or

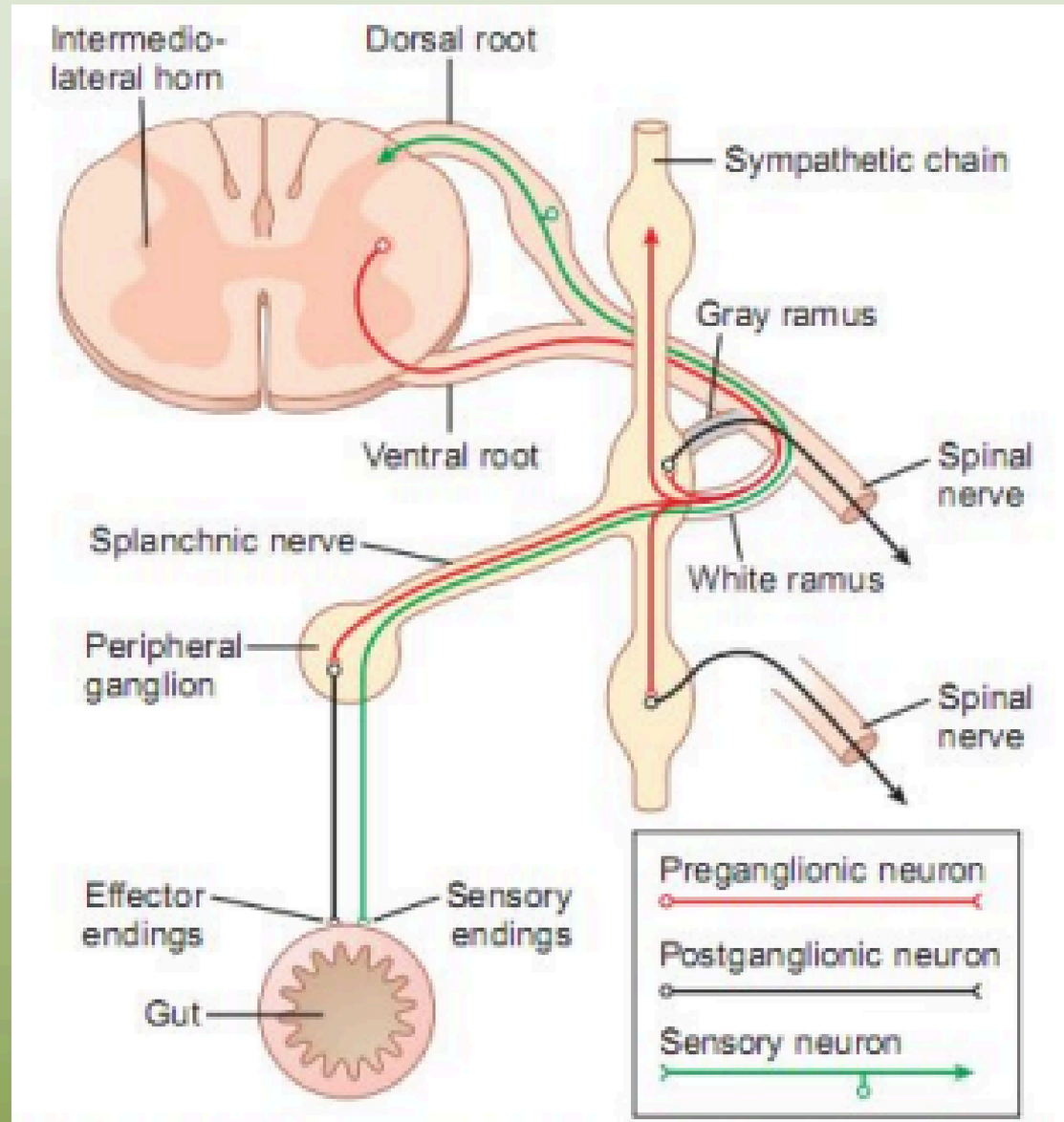


Figure 61-2. Nerve connections among the spinal cord, spinal nerves, sympathetic chain, and peripheral sympathetic nerves.

3. pass for variable distances to synapse in a peripheral sympathetic ganglion.

* Postganglionic sympathetic neuron thus originates either in one of the sympathetic chain ganglia or in one of the peripheral sympathetic ganglia. From either of these two sources, the postganglionic fibers then travel to their destinations in the various organs.

Segmental Distribution of Sympathetic Nerve Fibers

* Sympathetic fibers from spinal cord segment

- T1 pass up the sympathetic chain to terminate in the head
- T2 terminate in the neck
- T3, T4, T5, and T6 into thorax
- T7, T8, T9, T10, and T11 into abdomen
- T12, L1, and L2 into the legs.

* The distribution of sympathetic nerves to each organ is determined partly by the locus in the embryo from which the organ originated. For instance, the heart receives many sympathetic nerve fibers from the neck portion of the sympathetic chain because the heart originated in the neck of the embryo before translocating into the thorax.

Special Nature of Sympathetic Nerve Endings in Adrenal Medullae

* Preganglionic sympathetic nerve fibers pass all the way from the intermediolateral horn cells of the spinal cord, through the sympathetic chains, then through the splanchnic nerves, and finally into the two adrenal medullae.

* In the adrenal medullae, Preganglionic sympathetic nerve fibers end directly on modified neuronal cells that secrete epinephrine and norepinephrine into the blood stream. These secretory cells embryologically are derived from nervous tissue and are actually postganglionic neurons.

Physiological Anatomy of Parasympathetic Nervous System

* Parasympathetic fibers leave CNS through:

1. Cranial nerves III, VII, IX and X

2. Second and third sacral spinal nerves

3. Occasionally the first and fourth sacral nerves.

* About 75% of all parasympathetic nerve fibers are in vagus nerves (cranial nerve X). The vagus nerves supply the heart, lungs, esophagus, stomach, entire small intestine, proximal half of the colon, liver, gallbladder, pancreas, kidneys and upper portions of the ureters.

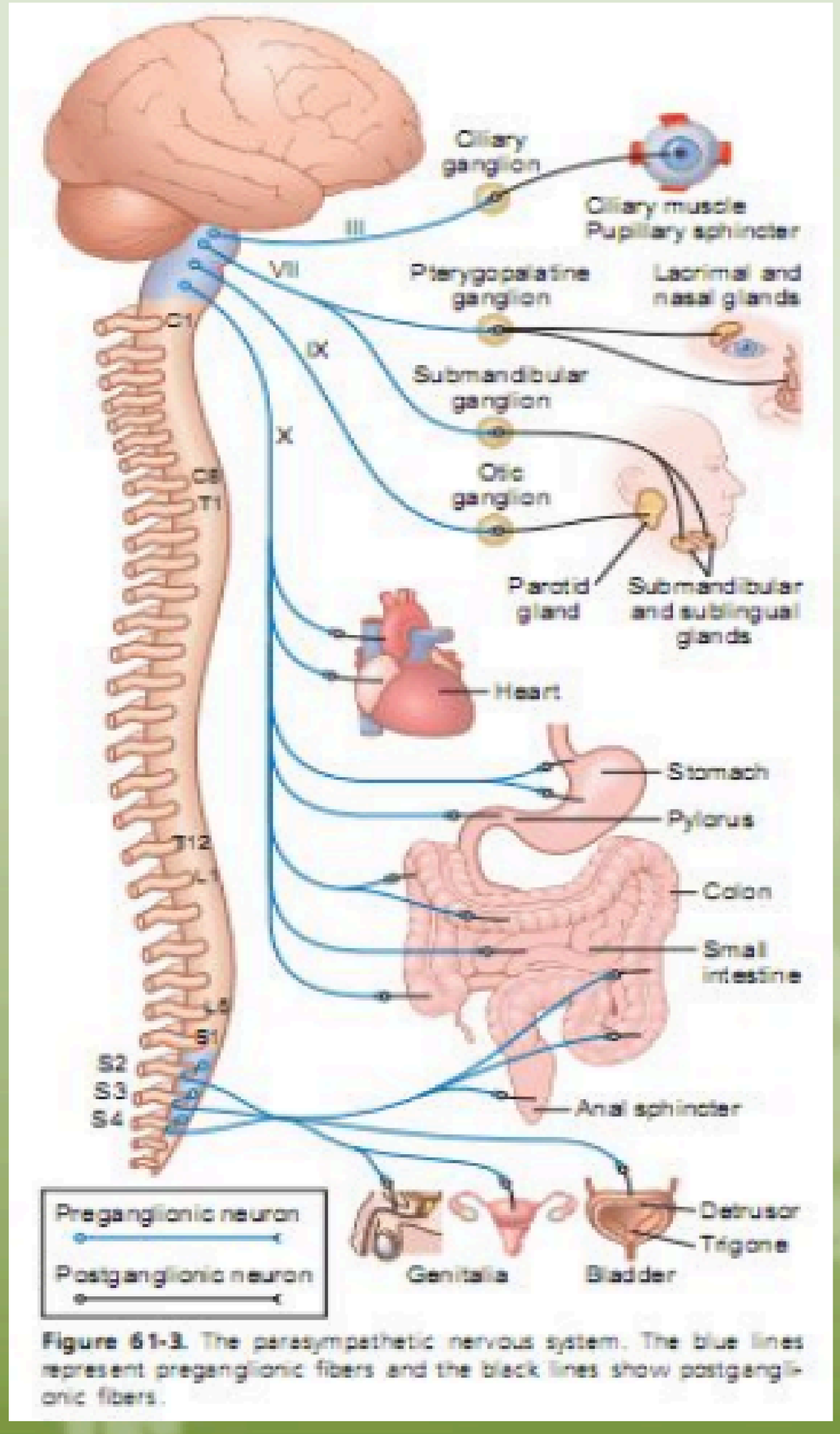


Figure 61-3. The parasympathetic nervous system. The blue lines represent preganglionic fibers and the black lines show postganglionic fibers.

* Parasympathetic fibers in the third cranial nerve go to pupillary sphincter and ciliary muscle of the eye.

* Parasympathetic fibers from the seventh cranial nerve pass to the lacrimal, nasal and submandibular glands.

* Parasympathetic fibers from the ninth cranial nerve go to the parotid gland.

* Sacral parasympathetic fibers are in pelvic nerves, which pass through the spinal nerve sacral plexus at S2 and S3 levels to supply descending colon, rectum, urinary bladder, lower portions of ureters and external genitalia to cause erection.

Preganglionic and Postganglionic Parasympathetic Neurons

* Preganglionic parasympathetic fibers are longer than preganglionic sympathetic fibers i.e. pass uninterrupted all the way to the organ, whereas postganglionic parasympathetic fibers are much shorter than postganglionic sympathetic fibers i.e. Postganglionic neurons are located in the wall of the organ.

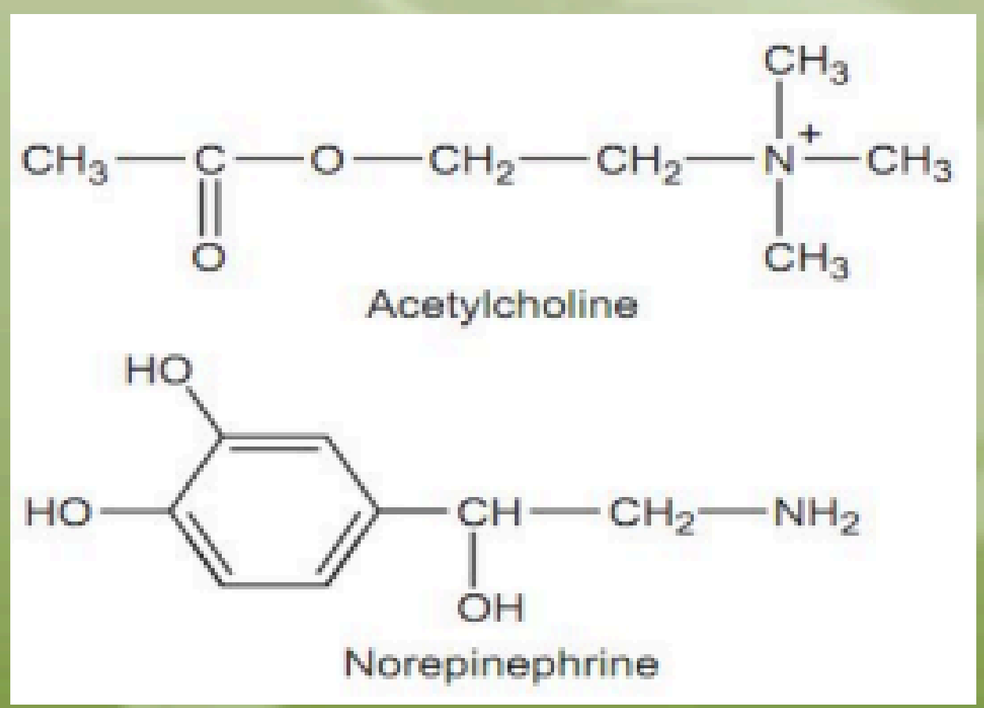
Cholinergic and Adrenergic Fibers

* All preganglionic neurons are cholinergic (secrete acetylcholine) in both sympathetic and parasympathetic nervous systems.

* All postganglionic neurons of parasympathetic system are cholinergic.

* Most of postganglionic sympathetic neurons are adrenergic (secrete norepinephrine) except postganglionic sympathetic fibers to sweat glands and perhaps to a very few blood vessels are cholinergic.

* The molecular structures of acetylcholine and norepinephrine are shown in the figure.



Mechanisms of Transmitter Secretion and Removal

* Preganglionic autonomic nerve endings have bulbous enlargements called varicosities in which transmitter vesicles of acetylcholine or norepinephrine are synthesized and stored.

* Varicosities contain large numbers of mitochondria that supply ATP required for acetylcholine or norepinephrine synthesis.

* When an action potential reach preganglionic terminals, calcium ions diffuse into varicosities and cause transmitter vesicles to empty their contents into synaptic cleft by exocytosis.

Synthesis of Acetylcholine, Its Destruction, and Its Duration of Action

* Acetylcholine is synthesized in varicosities of cholinergic nerve fibers by choline acetyltransferase enzyme and stored in vesicles.

$$\text{Acetyl-CoA} + \text{Choline} \xrightarrow[\text{acetyltransferase}]{\text{Choline}} \text{Acetylcholine}$$

* Once acetylcholine is secreted, it persists for a few seconds while performing its function. Then it is split into acetate and choline by acetylcholinesterase enzyme that is found on postganglionic neuronal membrane. The formed choline is then transported back into preganglionic nerve ending, where it is used again for synthesis of new acetylcholine.

Synthesis of Norepinephrine, Its Removal and Its Duration of Action

* Synthesis of norepinephrine begins in the varicosities of adrenergic nerve fibers and is completed inside the transmitter vesicles.

* Steps involved in the sysnthesis of norepinephrine are the followings:

Synthesis of Norepinephrine, Its Removal and Its Duration of Action

* Synthesis of norepinephrine begins in the varicosities of adrenergic nerve fibers and is completed inside the transmitter vesicles.

* Steps involved in the synthesis of norepinephrine are the followings:

1. Tyrosine $\xrightarrow{\text{Hydroxylation}}$ Dopa
2. Dopa $\xrightarrow{\text{Decarboxylation}}$ Dopamine
3. Transport of dopamine into the vesicles
4. Dopamine $\xrightarrow{\text{Hydroxylation}}$ Norepinephrine

* In adrenal medulla, this reaction goes still one step further to transform about 80 % of norepinephrine into epinephrine, as follows:

5. Norepinephrine $\xrightarrow{\text{Methylation}}$ Epinephrine

*** Norepinephrine is secreted by nerve terminals to do its action on its receptors and then it is removed by three ways:**

1. Reuptake into adrenergic nerve endings by active transport, accounting for removal of 50-80% of secreted norepinephrine.

2. Diffusion away from nerve endings into surrounding body fluids and then into blood, accounting for removal of most of the remaining norepinephrine

3. Destruction of small amounts by monoamine oxidase and catechol-O-methyl transferase enzymes.

Acetylcholine Receptors

1. Muscarinic receptors

- Activated by muscarine (a poison from toadstools) and by acetylcholine.

- Use G proteins for signaling.

- Found on all effector cells that are stimulated by postganglionic cholinergic neurons of either parasympathetic or sympathetic system.

2. Nicotinic receptors

- Activated by nicotine in small dose and acetylcholine.

- are ligand-gated ion channels.

- Found in autonomic ganglia at synapses between preganglionic and postganglionic neurons of both sympathetic and parasympathetic systems as well as at neuromuscular junctions in skeletal muscle.

Adrenergic Receptors

1. Alpha Receptors

- Divided into alpha1 and alpha2 receptors.
- Use G proteins for signaling.

2. Beta Receptors

- Divided into beta1, beta2 and beta3 receptors.
- Use G proteins for signaling.

* Norepinephrine excites mainly alpha receptors but excites beta receptors to a lesser extent as well.
* Epinephrine excites both types of receptors approximately equally.
* A synthetic hormone chemically similar to epinephrine and norepinephrine, isopropyl norepinephrine, has an extremely strong action on beta receptors but essentially no action on alpha receptors.

Table 61-2 Autonomic Effects on Various Organs of the Body

Organ	Effect of Sympathetic Stimulation	Effect of Parasympathetic Stimulation
Eye		
Pupil	Dilated	Constricted
Ciliary muscle	Slight relaxation (far vision)	Constricted (near vision)
Glands Nasal Lacrimal Parotid Submandibular Gastric Pancreatic	Vasoconstriction and slight secretion	Stimulation of copious secretion (containing many enzymes for enzyme-secreting glands)
Sweat glands	Copious sweating (cholinergic)	Sweating on palms of hands
Apocrine glands	Thick, odoriferous secretion	None
Blood vessels	Most often constricted	Most often little or no effect
Heart		
Muscle	Increased rate Increased force of contraction	Slowed rate Decreased force of contraction (especially of atria)
Coronaries	Dilated (β_2); constricted (α)	Dilated

Note: Sympathetic and parasympathetic affect the heart mainly by increasing or decreasing specific actions of Sinoatrial node (SAN). Very strong vagal parasympathetic stimulation can stop the heart for a few seconds and cause temporary loss of arterial pressure (Vagal attack).

Lungs		
Bronchi	Dilated	Constricted
Blood vessels	Mildly constricted	? Dilated
Gut		
Lumen	Decreased peristalsis and tone	Increased peristalsis and tone
Sphincter	Increased tone (most times)	Relaxed (most times)
Liver	Glucose released	Slight glycogen synthesis
Gallbladder and bile ducts	Relaxed	Contracted
Kidney	Decreased urine output and increased renin secretion	None
Bladder		
Detrusor	Relaxed (slight)	Contracted
Trigone	Contracted	Relaxed
Penis	Ejaculation	Erection

Note: Sympathetic and parasympathetic affect gastrointestinal activity mainly by increasing or decreasing specific actions in the gastrointestinal intramural plexus (intrinsic set of nerves located in the walls of the gut)

Systemic arterioles		
Abdominal viscera	Constricted	None
Muscle	Constricted (adrenergic α) Dilated (adrenergic β_2) Dilated (cholinergic)	None
Skin	Constricted	None
Blood		
Coagulation	Increased	None
Glucose	Increased	None
Lipids	Increased	None
Basal metabolism	Increased up to 100%	None
Adrenal medullary secretion	Increased	None
Mental activity	Increased	None
Piloerector muscles	Contracted	None
Skeletal muscle	Increased glycogenolysis Increased strength	None
Fat cells	Lipolysis	None

Function of Adrenal Medulla

* Stimulation of sympathetic nerves to adrenal medulla causes large quantities of epinephrine (80%) and norepinephrine (20%) to be released into blood.

* Adrenal medullary epinephrine and norepinephrine have almost the same effects as direct sympathetic stimulation, except that their effects are prolonged, lasting 2-4 minutes after stimulation is over.

* Epinephrine causes almost the same effects as norepinephrine, but the effects differ in the following respects:

1. Epinephrine, because of its greater effect in stimulating beta receptors, has a greater effect on cardiac stimulation than does norepinephrine.

2. Epinephrine causes only weak constriction of blood vessels in muscles, in comparison with much stronger constriction caused by norepinephrine. Therefore, norepinephrine greatly increases peripheral resistance (PR) and elevates arterial pressure, whereas epinephrine raises arterial pressure to a lesser extent but increases cardiac output (CO) more.

3. Epinephrine has 5-10 times as great a metabolic effect as norepinephrine.

* The organs are actually stimulated in two ways: directly by sympathetic nerves and indirectly by adrenal medullary hormones. The two means of stimulation support each other and either can, in most instances, substitute for the other i.e. a safety factor.

* Adrenal medullary epinephrine and norepinephrine stimulate structures of the body that are not innervated by direct sympathetic fibers e.g. metabolic rate of almost every cell is increased by these hormones, especially by epinephrine.

Sympathetic and Parasympathetic "Tone"

* Normally, sympathetic and parasympathetic systems are continually active, and the basal rates of activity are known, respectively, as sympathetic tone and parasympathetic tone.

* This tone allows sympathetic or parasympathetic to both increase and decrease the activity of a stimulated organ. Examples:

1. Sympathetic tone normally keeps systemic arterioles constricted to about one-half their maximum diameter. By increasing the degree of sympathetic stimulation, these vessels can be constricted even more; conversely, by decreasing the stimulation, the arterioles can be dilated.

2. Parasympathetics tone in gastrointestinal tract. Surgical removal of parasympathetic supply to gut by cutting vagus nerves can cause gastric and intestinal "atony" immediately with resulting blockage of gastrointestinal propulsion and constipation. Gastrointestinal tone can be controlled by the brain. However, later

* intrinsic compensation soon develops to return the function of the organ almost to its normal basal level.

* Much of the overall tone of sympathetic nervous system results from basal secretion of epinephrine and norepinephrine from adrenal medulla, in addition to the tone resulting from direct sympathetic stimulation.

Autonomic Reflexes

1. Cardiovascular Autonomic Reflex: e.g. Regulation of arterial blood pressure - baroreceptor system (previously discussed).

2. Gastrointestinal Autonomic Reflexes: e.g. the uppermost part of gastrointestinal tract autonomic reflex. Smell of appetizing food or presence of food in the mouth initiates signals from nose and mouth to vagal, glossopharyngeal and salivatory nuclei of brain stem which transmit signals through parasympathetic nerves to secretory glands of mouth and stomach, causing secretion of digestive juices sometimes even before food enters the mouth.

3. Defecation and micturition Reflexes: Stretching of rectum or urinary bladder sends impulses to sacral cord, which in turn causes reflex contraction of rectum or bladder and relaxation of sphincters, thereby promoting defecation or micturition.

4. sexual reflexes: initiated by psychic stimuli from brain and impulses converge on sacral cord and, in male, result first in erection, mainly a parasympathetic function, and then ejaculation, partially a sympathetic function.

"Alarm" or "Stress" Response of Sympathetic Nervous System

* Mass discharge means large portions of sympathetic nervous system discharge at the same time.

* Mass discharge increases the ability of the body to perform vigorous muscle activity in many ways:

1. Increased arterial pressure

2. Increased blood flow to active muscles concurrent with decreased blood flow to organs such as gastrointestinal tract and kidneys that are not needed for rapid motor activity

3. Increased rates of cellular metabolism

4. Increased blood glucose concentration

5. Increased glycolysis in liver and in muscle

6. Increased muscle strength

7. Increased mental activity

8. Increased rate of blood coagulation

* Mass discharge provides extra activation of the body in stress and is called sympathetic stress response e.g. sympathetic alarm reaction or fight-or-flight reaction which is elicited by stimulating hypothalamus then signals are transmitted downward through reticular formation of brain stem and into spinal cord to cause massive sympathetic discharge. The animal in this state decides instantly whether to stand and fight or to run.

Brain Stem control of autonomic nervous system

* Many neuronal areas in brain stem control different autonomic functions e.g. arterial pressure, heart rate and respiratory rate are controlled in brain stem.

* Transection of brain stem above midpontine level allows basal control of arterial pressure to continue but prevents its modulation by higher centers e.g. hypothalamus.

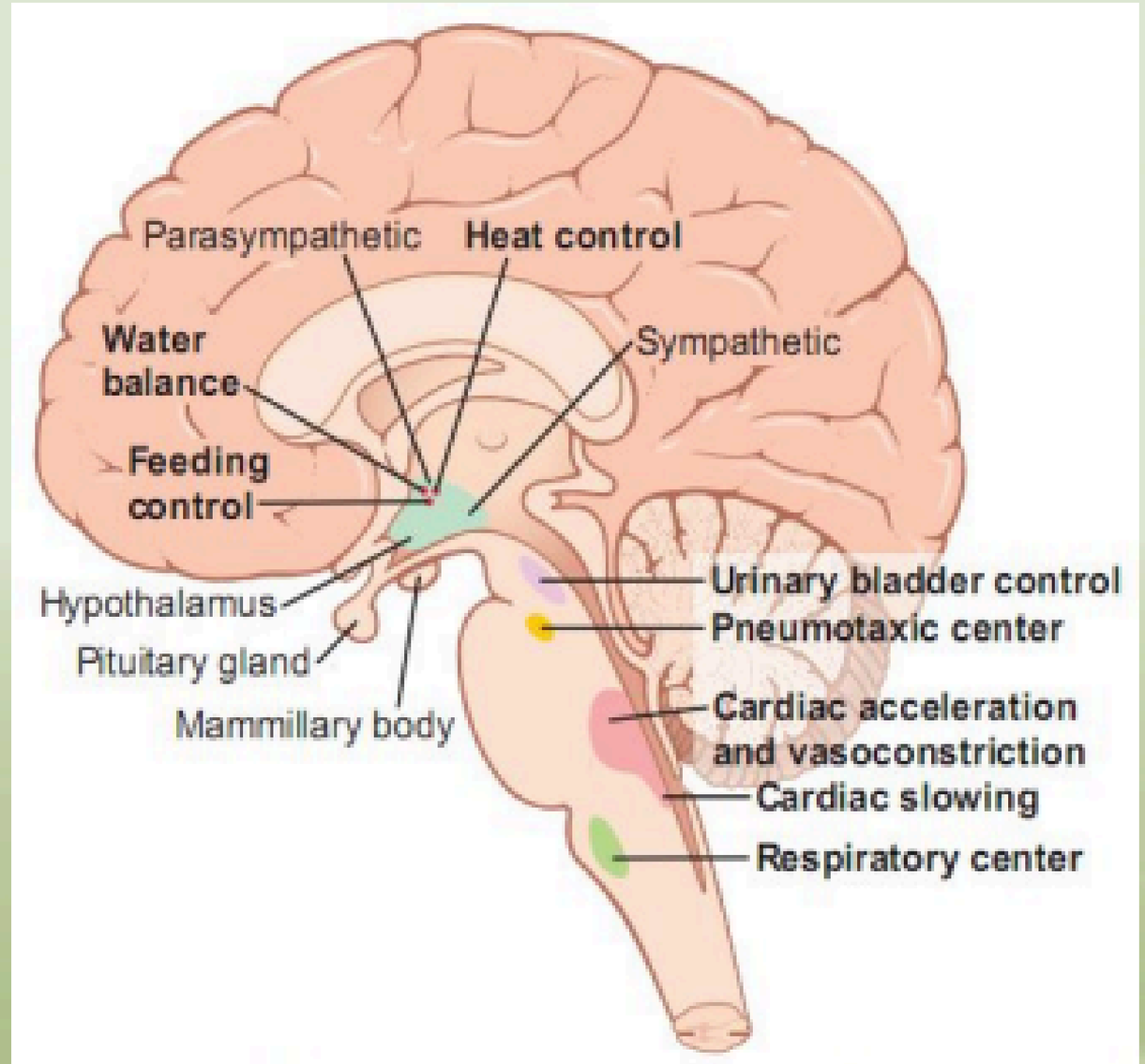


Figure 61-5. Autonomic control areas in the brain stem and hypothalamus.

Control of Brain Stem by Hypothalamus

* Stimulation of posterior hypothalamus can activate medullary cardiovascular control centers strongly enough to increase arterial pressure to more than twice normal.

Pharmacology of Autonomic Nervous System

Drugs that act on adrenergic effector organs—Sympathomimetic Drugs

A. Drugs that cause release of norepinephrine from its storage vesicles in sympathetic nerve endings

- include ephedrine, tyramine and amphetamine.

B. Drugs that block adrenergic activity

1. Reserpine which prevents synthesis and storage of norepinephrine in sympathetic nerve endings.
2. Guanethidine blocks release of norepinephrine from sympathetic endings.
3. Phenoxybenzamine and phentolamine block sympathetic alpha receptors.
4. Propranolol blocks sympathetic beta receptors.

Drugs That Act on Cholinergic Effector Organs—Parasympathomimetic Drugs (Cholinergic Drugs)

A. Drugs that have a parasympathetic potentiating effect—Anticholinesterase drugs

* Eostigmine, pyridostigmine and ambenonium which inhibit acetylcholinesterase and thus preventing rapid destruction of acetylcholine liberated at parasympathetic nerve endings resulting in potentiating parasympathetic effect.

B. Drugs that block cholinergic activity at effector organs—Antimuscarinic drugs

* Atropine and similar drugs such as homatropine and scopolamine block the action of acetylcholine on muscarinic type of cholinergic effector organs.

Drugs that stimulate or block sympathetic and parasympathetic postganglionic neurons

* Nicotine in small dose excites both sympathetic and parasympathetic postganglionic neurons at the same time, resulting in strong sympathetic vasoconstriction in abdominal organs and limbs but at the same time resulting in parasympathetic effects such as increased gastrointestinal activity.

* Tetraethyl ammonium ion, hexamethonium ion and pentolinium block acetylcholine stimulation of postganglionic neurons in both sympathetic and the parasympathetic ganglia simultaneously.

Chapter 8

,Red Blood Cells, Anemia and Polycythemia

Red Blood Cells (Erythrocytes)

Shape of RBCs

* Normal RBCs are biconcave disks and can change remarkably as they squeeze through capillaries.

Concentration of RBCs in blood

* In healthy men, the average number of RBCs per cubic mm is 5,200,000±300,000; in women, it is 4,700,000±300,000.

* Persons living at high altitudes have greater numbers of RBCs.

Quantity of hemoglobin in RBCs

* The whole blood of men contains an average of 15 gm hemoglobin/100 ml; for women, it contains an average of 14 gm/100 ml.

* Each gram of hemoglobin can combine with 1.34 ml of oxygen. Therefore, in a normal man a maximum of about 20 ml of oxygen can be carried in combination with hemoglobin in each 100 ml of blood, and in a normal woman 19 ml of oxygen can be carried.

Areas of the body that produce RBCs

* In early weeks of embryonic life, primitive, nucleated RBCs are produced in yolk sac.

* During the middle trimester of gestation, liver is the main organ for production of RBCs, but reasonable numbers are also produced in spleen and lymph nodes.

* During the last month of gestation and after birth, RBCs are produced exclusively in bone marrow.

- Bone marrow of all bones produces RBCs until a person is 5 years old.

- The marrow of long bones, except for proximal portions of humeri and tibiae, becomes quite fatty and produces no more RBCs after about age 20 years.

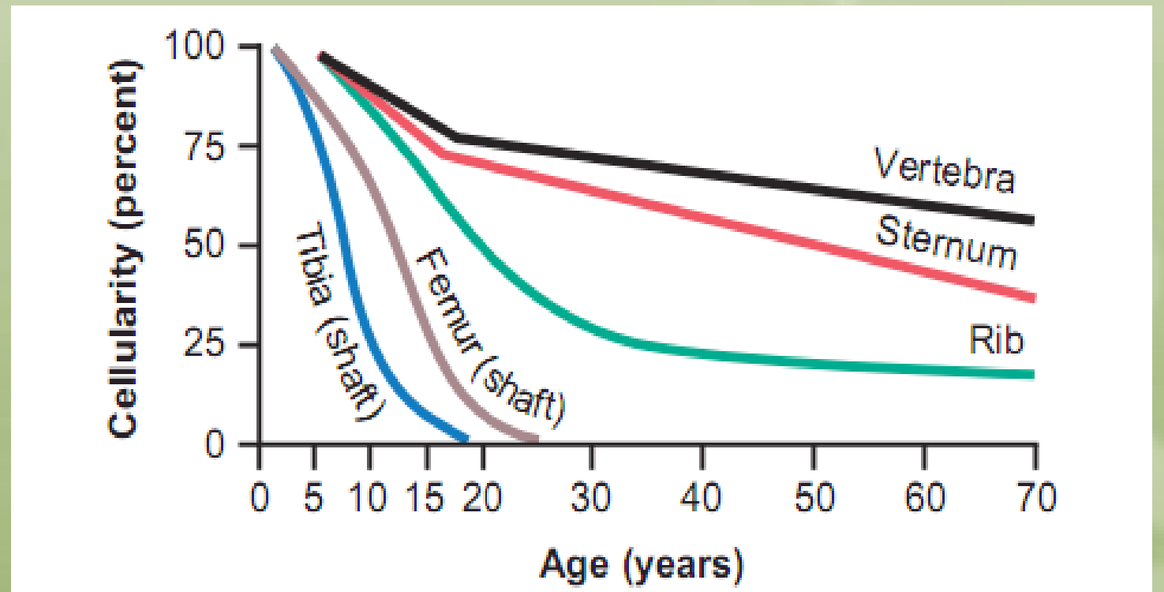


Figure 33-1. Relative rates of red blood cell production in the bone marrow of different bones at different ages.

- Beyond this age, most RBCs continue to be produced in the marrow of membranous bones, such as vertebrae, sternum, ribs, and ilia.

Genesis of RBCs

* RBCs begin their lives in bone marrow from a single type of cell called pluripotential hematopoietic stem cell, from which all blood cells are eventually derived.

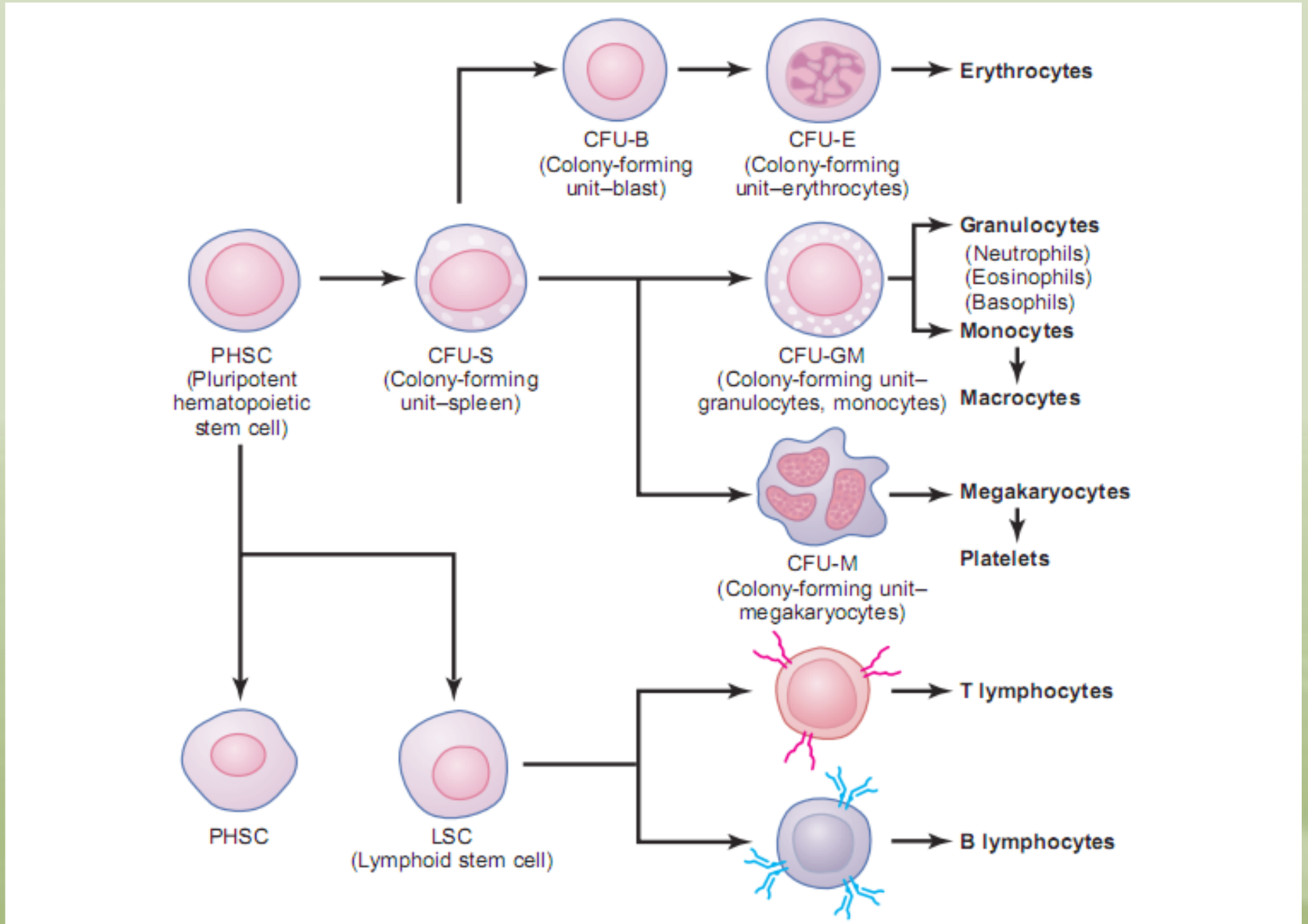


Figure 33-2. Formation of the multiple different blood cells from the original pluripotent hematopoietic stem cell in the bone marrow.

* Pluripotential stem cells become committed stem cells to a particular line of cells. A committed stem cell that produces erythrocytes is called a colony-forming unit–erythrocyte (CFU-E).

Stages of differentiation of RBCs

* The first cell that can be identified as belonging to RBC series is the proerythroblast formed from CFUE stem cells.

* The proerythroblast divides to form basophil erythroblasts (stain with basic dyes) which accumulate very little hemoglobin.

* The cells become filled with hemoglobin and called Polychromatophil erythroblast.

* The nucleus condenses to a small size and the cell called orthochromatic erythroblast, which extrudes its nucleus to from a reticulocyte.

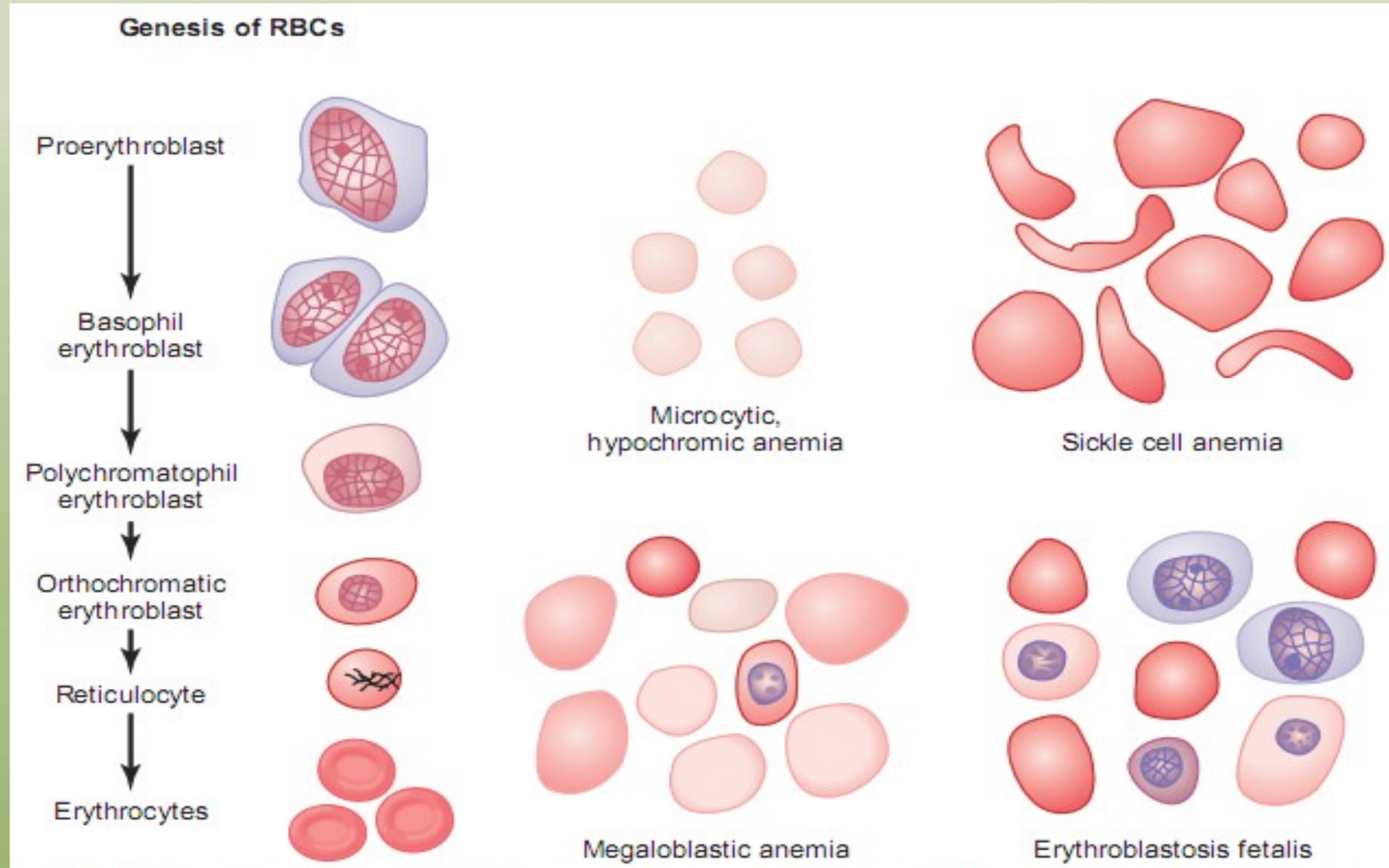


Figure 33-3. Genesis of normal red blood cells *(RBCs)* and characteristics of RBCs in different types of anemias.

* During this reticulocyte stage, the cells pass from bone marrow into blood capillaries by diapedesis to become mature erythrocytes.

* **Growth inducers** control growth and reproduction of different stem cells e.g. interleukin-3.

* **Differentiation inducers** causes one type of committed stem cell to differentiate one or more steps toward a final adult blood cell.

* Formation of growth and differentiation inducers is controlled by factors outside bone marrow e.g. in case of RBCs, exposure of blood to low oxygen for a long time causes growth induction, differentiation and production of greatly increased numbers of RBCs.

Regulation of RBCs Production

I. Tissue oxygenation

Conditions that decrease tissue oxygenation (hypoxia) increase the rate of RBC production. These conditions include low blood volume, anemia, low hemoglobin, poor blood flow and pulmonary disease.

II. Erythropoietin

* The principal stimulus for RBC production in hypoxia is a circulating hormone called erythropoietin, a glycoprotein with a molecular weight of about 34,000.

* In the absence of erythropoietin, hypoxia has little or no effect to stimulate RBC production. However, when erythropoietin system is functional, hypoxia causes a marked increase in erythropoietin production and erythropoietin, in turn, enhances RBC production until hypoxia is relieved.

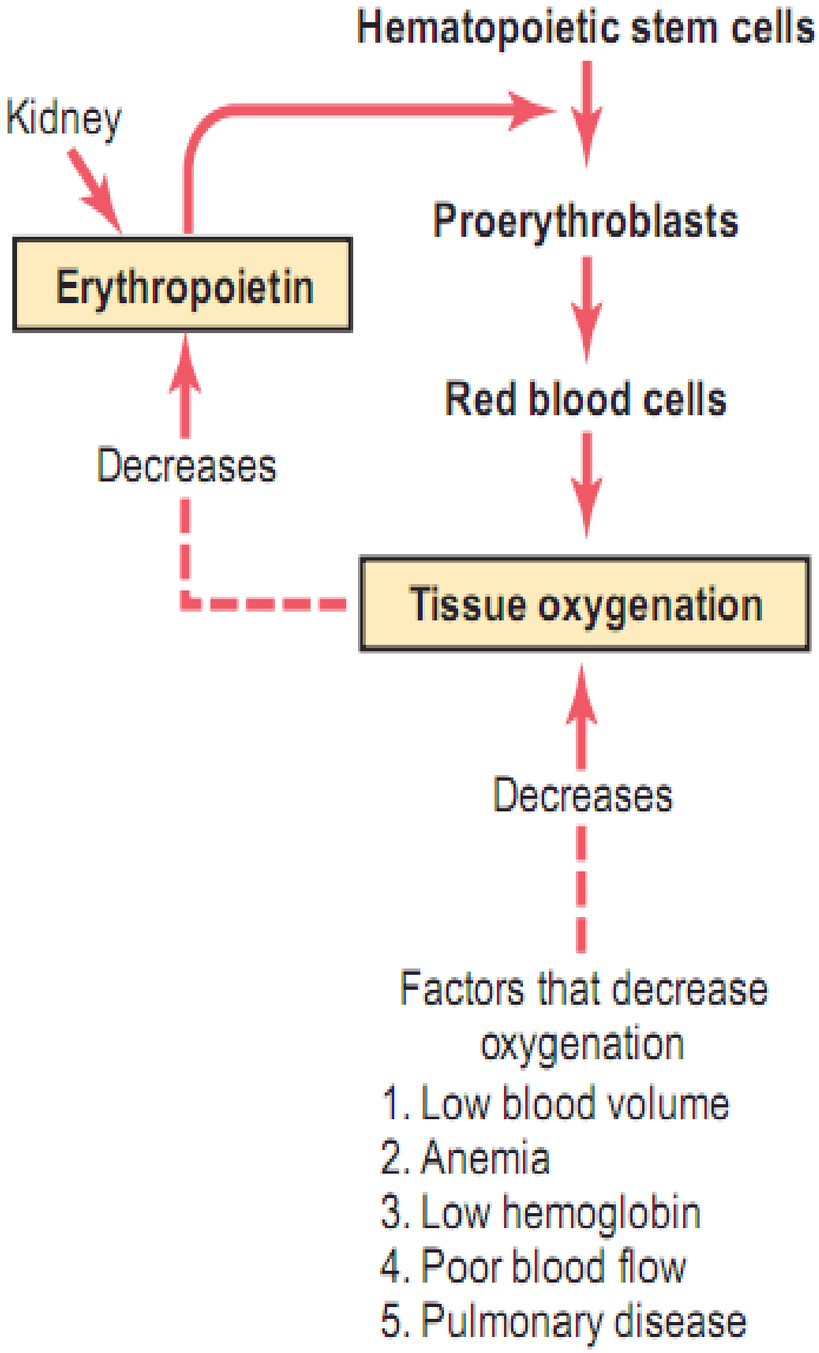


Figure 33-4. Function of the erythropoietin mechanism to increase production of red blood cells when tissue oxygenation decreases.

Erythropoietin is formed mainly in the kidneys

* Normally, about 90% of erythropoietin is formed in the kidneys, and the remainder 10% is formed mainly in the liver.

* Erythropoietin is suggested to be secreted by fibroblast-like interstitial cells surrounding renal tubules and also by renal epithelial cells.

* Renal tissue hypoxia leads to increased tissue levels of hypoxia-inducible factor–1 (HIF1), which binds to a hypoxia response element in erythropoietin gene, inducing transcription of mRNA and, ultimately, increased erythropoietin synthesis.

* When both kidneys are removed from a person or when kidneys are destroyed by renal disease e.g. renal failure, the person becomes anemic because the 10 % of normal erythropoietin formed in liver is sufficient to cause only one third to one half the RBC formation needed by the body.

Erythropoietin Stimulates Production of Proerythroblasts from Hematopoietic Stem Cells

* When a person is placed in an atmosphere of low oxygen, erythropoietin begins to be formed within minutes to hours, and it reaches maximum production within 24 hours.

* New RBCs appear in the circulating blood about 5 days later.

* Erythropoietin stimulates production of proerythroblasts from hematopoietic stem cells in the bone marrow.

* Then, erythropoietin causes proerythroblasts to pass rapidly through different erythroblastic stages to produce new RBCs which continues as long as the person remains in a low oxygen state or until enough RBCs have been produced to carry adequate amounts of oxygen to tissues; at this time, the rate of erythropoietin production decreases to its basal level.

Maturation of RBCs Requires Vitamin B12 and Folic Acid

* Vitamin B12 and folic acid are required for formation of thymidine triphosphate, one of the essential building blocks of DNA. Therefore, lack of either vitamin B12 or folic acid causes abnormal and diminished DNA and, consequently, failure of nuclear maturation and erythroblastic cell division.

* Instead, erythroblastic cell produce larger oval cells than normal RBCs called macrocytes which are capable of carrying oxygen normally, but their fragility causes them to have a short life, one half to one-third normal.

Maturation Failure of RBCs caused by:

1. Poor Absorption of Vitamin B12 from GIT—Pernicious Anemia

* Parietal cells of stomach secrete a glycoprotein called intrinsic factor (IF), which combines with vitamin B12 in food and protects it from digestion by gastric secretion.

* IF with vitamin B12 leave stomach and IF binds to its receptor on mucosal cells in the ileum and then vitamin B12 is transported into blood by pinocytosis and stored in liver to be released slowly as needed by bone marrow.

* Lack of IF, therefore, decreases availability of vitamin B12 resulting in maturation failure of RBCs and pernicious Anemia.

* The minimum amount of vitamin B12 required each day to maintain normal RBC maturation is only 1 to 3 micrograms.

2. Maturation Failure Caused by Folic Acid Deficiency

* Folic acid is a normal constituent of green vegetables, some fruits, and meats (especially liver). However, it is easily destroyed during cooking.

* People with gastrointestinal absorption abnormalities such as a small intestinal disease called sprue, have serious difficulty in absorbing both folic acid and vitamin B12, resulting in maturation failure of RBCs.

Hemoglobin

* Synthesis of Hb begins in proerythroblasts and continues to reticulocyte stage of RBCs.

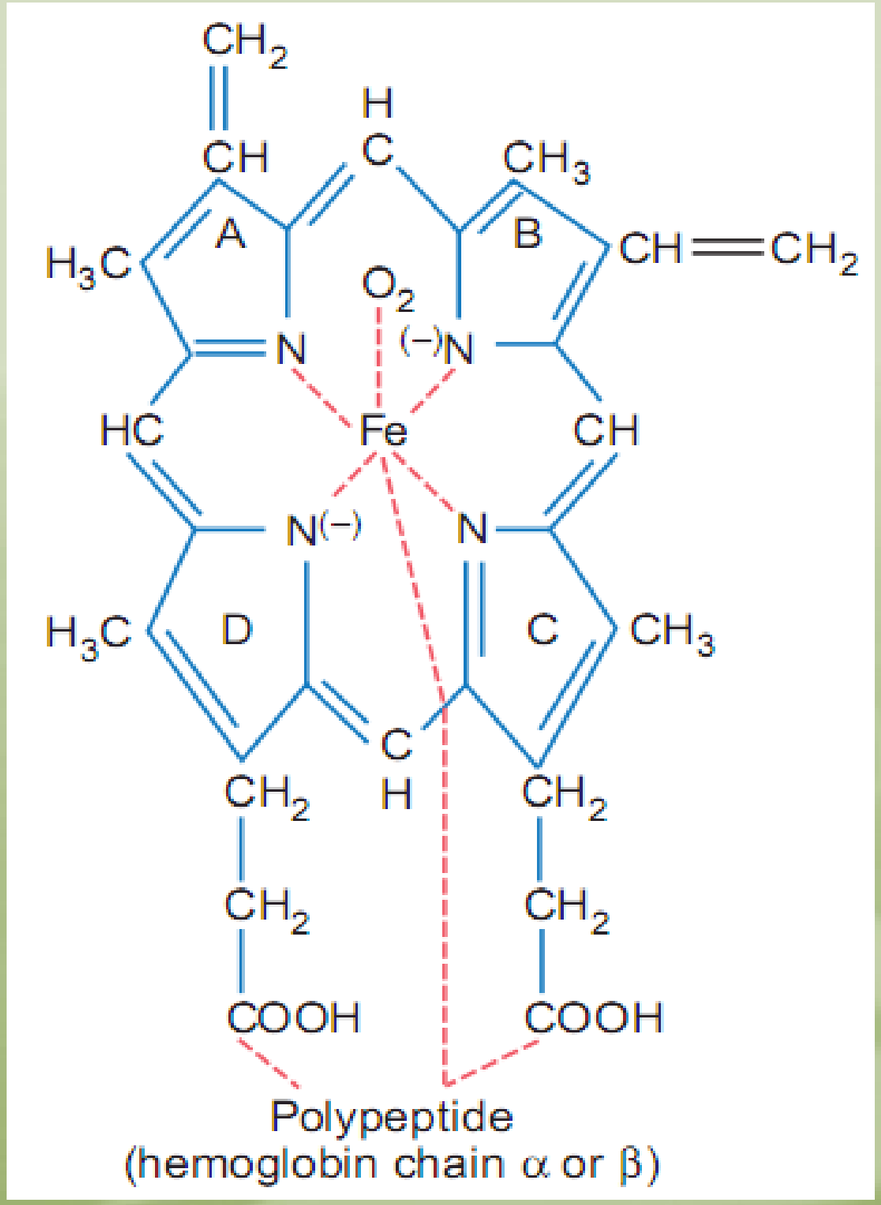
* Each Hb molecule consists of 4 heme chains and 4 globin polypeptides.

* Each heme chain consists of protoporphyrin IX (4 pyrrole molecules) combines with iron.

* Each globin polypeptide is synthesized by ribosomes forming a subunit of Hb (Hb chain).

* The different types of chains are designated as alpha, beta, gamma and delta chains.

* **Adult Hb A** is a combination of two alpha chains and two beta chains whereas **Fetal Hb** is a combination of two alpha chains and two gamma chains.



* The type of Hb chains determine the binding affinity of Hb for oxygen. Fetal Hb has a higher affinity for oxygen than adult Hb.

* Abnormalities of the chains can alter the physical characteristics of Hb molecule. For instance, in sickle cell anemia, the amino acid valine is substituted for glutamic acid in each of the two beta chains. When this type of Hb is exposed to low oxygen, it forms elongated crystals inside RBCs which make it impossible for RBCs to pass through small capillaries, and spiked ends of crystals rupture cell membranes.

Hemoglobin Combines Loosely And Reversibly With Oxygen

* Oxygen binds loosely with one of the so-called coordination bonds of iron atom. This bond is extremely loose, so the com bination is easily reversible.

* Oxygen is carried as molecular oxygen to tissues, where, because of the loose and reversible combination, it is released into tissue fluids still in the form of molecular oxygen rather than ionic oxygen.

Iron Metabolism

***The total quantity of iron in the body averages 4-5 grams:**

- About 65 % in the form of Hb

- About 4 % in the form of myoglobin

- 1 % in the form of various heme compounds that promote intracellular oxidation

- 0.1 % is combined with the protein transferrin in plasma

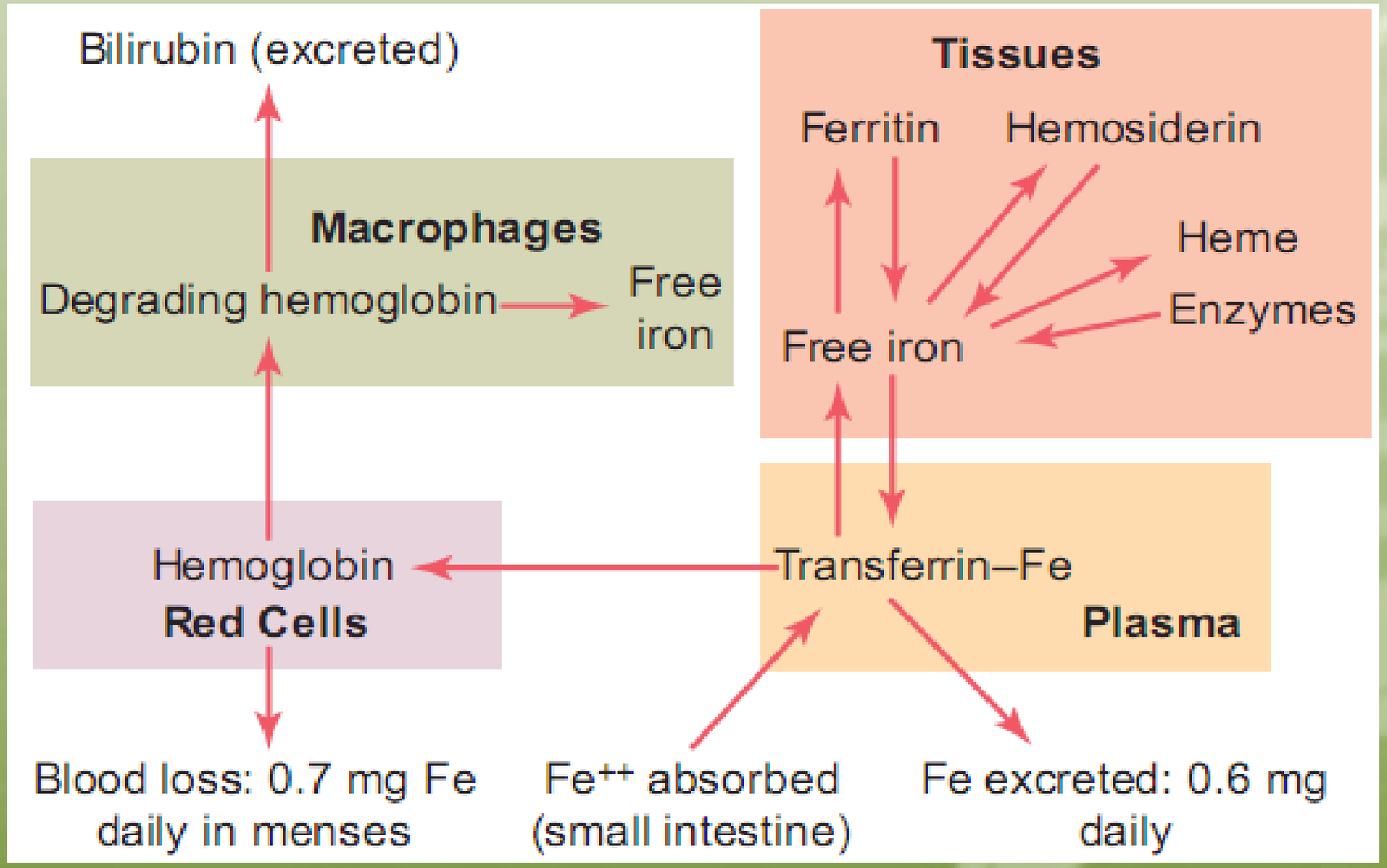
- 15-30 % is stored for later use, mainly in RES and liver parenchymal cells, principally in the form of ferritin.

Transport and Storage of Iron

*** When iron is absorbed from small intestine, it immediately combines in plasma with a beta globulin, apotransferrin, to form transferrin, which is then transported in plasma and released iron to any cell.**

* In the cell cytoplasm, iron combines mainly with a protein, apoferritin, to form ferritin which is stored for later use.

* Small quantities of iron are in an insoluble form called hemosiderin which is stored in the form of large clusters that can be observed microscopically. In contrast, ferritin particles are so small and dispersed that can be seen only with electron microscope.



* When iron in plasma falls, some of iron in ferritin storage pool is removed and transported in the form of transferrin to needed organs.

* Transferrin molecule binds strongly with receptors in cell membranes of erythroblasts in bone marrow. Then, it is ingested into erythroblasts by endocytosis and transferrin delivers iron directly to mitochondria, where heme is synthesized. In people who do not have adequate quantities of transferrin, failure to transport iron to erythroblasts can cause hypochromic anemia.

Daily Loss of Iron

* A man excretes about 0.6 mg of iron daily, mainly into feces. For a woman, additional menstrual loss of blood brings long-term iron loss to an average of 1.3 mg/day.

Absorption of Iron from Intestinal Tract

* Iron absorption from intestines is extremely slow, at a maximum rate of a few milligrams per day. This means that when large amounts of iron are present in food, only small proportions can be absorbed.

Regulation of Total Body Iron by Controlling Rate of Absorption

When the body has become saturated with iron (all apoferritin combined with iron), the rate of additional iron absorption from GIT decreased. Conversely, when iron stores depleted, the rate of absorption can accelerate five or more times normal.

Life Span OF RBCs Is About 120 Days

* Mature RBCs do not have a nucleus, mitochondria or ER, they do have cytoplasmic enzymes that are capable of metabolizing glucose and forming ATP. These enzymes also (1) maintain pliability of cell membrane, (2) maintain membrane transport of ions, (3) and keep iron of Hb in ferrous form rather than ferric form.

Destruction of Hemoglobin by Macrophages

* When RBCs burst, Hb is phagocytized by macrophages and iron released into blood to be used for synthesis of new Hb. The porphyrin portion is converted by macrophages to bile pigment bilirubin, which is removed by secretion through liver into bile.

Anemias

Anemia means deficiency of Hb in blood, which can be caused by either few RBCs or little Hb in cells.

Types of anemia

1. Blood Loss Anemia: Caused by hemorrhage and chronic blood loss in which a person cannot absorb enough iron to form Hb as rapidly as it is lost. RBCs are smaller than normal and have little Hb, giving rise to microcytic hypochromic anemia.

2. Aplastic Anemia: Due to bone marrow dysfunction caused by exposure to radiation or chemotherapy, toxic chemicals e.g. insecticides or benzene and autoimmune disorders such as lupus erythematosus. In about half of aplastic anemia cases the cause is unknown (idiopathic aplastic Anemia). People with severe aplastic anemia usually die unless they are treated with blood transfusions or by bone marrow transplantation.

3. Megaloblastic Anemia: caused by lack of vitamin B12, folic acid or IF. RBCs grow large, with odd shapes, and are called megaloblasts. Atrophy of stomach mucosa, gastrectomy or intestinal sprue can lead to megaloblastic anemia. RBCs are capable of carrying oxygen normally, but their fragility causes them to have a short life, one-half to one-third normal.

4. Hemolytic Anemia:

A. Hereditary spherocytosis in which RBCs are small and spherical rather than biconcave disks. Upon passing through splenic pulp and tight vascular beds, they are easily ruptured.

B. Sickle cell anemia which is present in 0.3-1.0 % of West African and American blacks, RBCs have an abnormal type of Hb called Hb S, containing faulty beta chains (valine is substituted for glutamic acid). When this type of Hb is exposed to low oxygen, it forms elongated crystals inside RBCs which make it impossible for RBCs to pass through small capillaries, and spiked ends of crystals rupture cell membranes.

C. Erythroblastosis fetalis in which Rh+ RBCs in fetus are attacked by antibodies from an Rh- mother. These antibodies make the Rh+ RBCs fragile, leading to rapid rupture and causing the child to be born with a serious case of anemia.

Polycythemia

1. Secondary Polycythemia: occurs upon hypoxia in which bone marrow produces extra RBCs reaching an count of 6-7 million/mm3, about 30 % above normal. This physiological polycythemia occurs in natives who live at altitudes.

2. Polycythemia Vera (Erythremia): a pathological condition in which RBC count may be 7-8 million/mm3 and hematocrit may be 60-70 % instead of the normal 40-45 %. Polycythemia vera is caused by a genetic aberration in hemocytoblastic cells that no longer stop producing RBCs causing excess RBCs production and total blood volume increases, sometimes twice normal. As a result, vascular system becomes engorged and blood viscosity may increase from the normal of 3 times the viscosity of water to 10 times that of water.

Chapter 9

Leukocytes, Granulocytes, the Monocyte-Macrophage System, and Inflammation

Leukocytes (white blood cells)

* Leukocytes are formed partially in bone marrow (granulocytes and monocytes and a few lymphocytes) and partially in lymph tissue (lymphocytes).
* The real value of leukocytes is that most of them are specifically transported to areas of serious infection and inflammation, thereby providing a rapid and potent defense against infectious agents.

Types of White Blood Cells

1. Polymorphonuclear cells: neutrophils, eosinophils and basophils
2. Monocytes
3. Lymphocytes

* Polymorphonuclear cells have a granular appearance (Granulocytes) with multiple nuclei.

* **Granulocytes and monocytes** protect the body against invading organisms by phagocytosis or by releasing antimicrobial or inflammatory substances that have multiple effects that aid in destroying the offending organism.
* **Lymphocytes** function mainly in connection with the immune system.

Concentrations of White Blood Cells

The adult human being has about 7000 WBCs per microliter. The normal percentages of the different types are approximately the following:

62.0%	Neutrophils
2.3%	Eosinophils
0.4%	Basophils
5.3%	Monocytes
30.0%	Lymphocytes

Genesis of White Blood Cells

* Pluripotential hematopoietic stem cell differentiates into cells committed to form WBCs. Two lineages of WBCs are formed:

1. Myelocytic lineage which begins with myeloblast.
2. Lymphocytic lineage which begins with lymphoblast.

* Granulocytes and monocytes are formed only in bone marrow.
* Lymphocytes are produced mainly in lymphogenous tissues e.g. lymph glands, spleen, thymus, tonsils, and various pockets of lymphoid tissue in the body e.g. bone marrow and Peyer's patches.
* The WBCs formed in bone marrow are stored within the marrow until they are needed in the circulatory system.
* Normally, about 3 times as many WBCs are stored in bone marrow as circulate in the entire blood. This quantity represents about a 6-day supply of these cells.
* Lymphocytes are mostly stored in lymphoid tissues, except for a small number that are temporarily being transported in blood.

Life Span of White Blood Cells

* The life of granulocytes after being released from bone marrow is normally 4 to 8 hours circulating in blood and another 4 to 5 days in tissues. In times of serious tissue infection, this total life span is often shortened to only a few hours.

* Monocytes also have a short transit time, 10 to 20 hours in blood, before wandering through capillary membranes into tissues. Once in tissues, they swell to much larger sizes to become tissue macrophages, and, in this form, they can live for months unless destroyed while performing phagocytic functions.

* Lymphocytes enter the circulatory system continually, along with drainage of lymph from lymph nodes and other lymphoid tissue. After a few hours, they pass out of the blood back into tissues by diapedesis. Then they re-enter the lymph and return to blood again and again; thus, there is continual circulation of lymphocytes through the body. The lymphocytes have life spans of weeks or months, depending on the body's need for these cells.

Neutrophils and Macrophages

Defend against infections

* Neutrophils and tissue macrophages are the main cells that attack and destroy invading bacteria, viruses, and other injurious agents.
* Neutrophils are mature cells that can attack and destroy bacteria even in the circulating blood.
* Conversely, tissue macrophages begin life as blood monocytes, which are immature cells and have little ability to fight infectious agents. However, once they enter the tissues, they begin to swell and are now called macrophages, and they are extremely capable of combating disease agents in tissues.

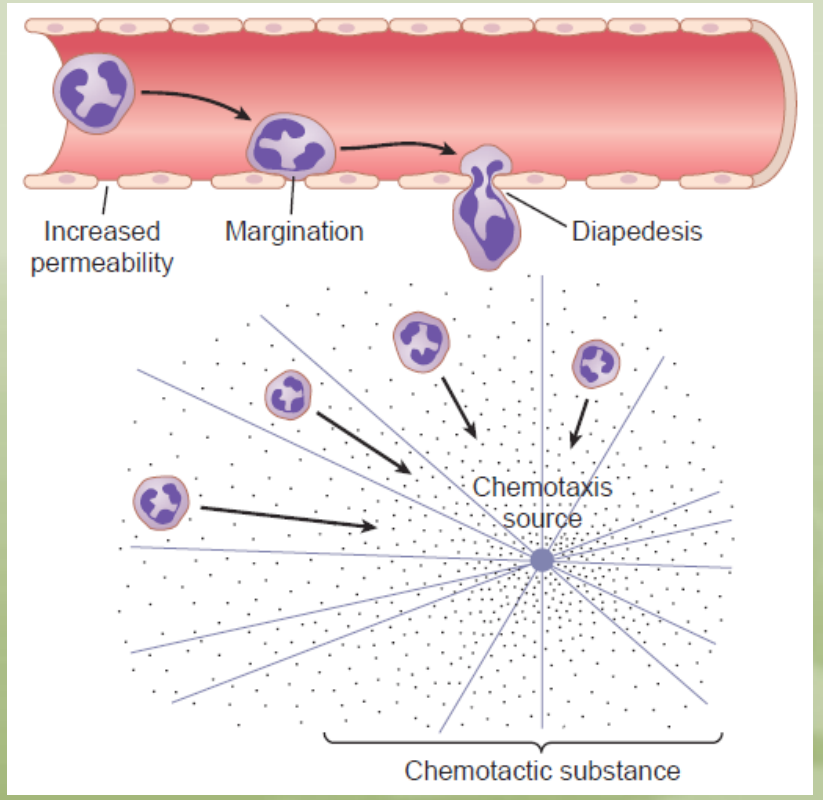
White Blood Cells Enter the Tissue Spaces by Diapedesis

* Neutrophils and monocytes can squeeze through the pores of the blood capillaries by diapedesis.

White Blood Cells Move Through Tissue Spaces by Ameboid Motion

* Both neutrophils and macrophages can move through the tissues by ameboid motion.

White Blood Cells Are Attracted to Inflamed Tissue by Chemotaxis



* Many different chemical substances in tissues cause both neutrophils and macrophages to move toward the source of the chemical (Chemotaxis).
* When a tissue becomes inflamed at least a dozen different products that can cause chemotaxis toward the inflamed area are formed. They include 1) some of bacterial or viral toxins, 2) degenerative products of inflamed tissues, (3) several reaction products of "complement complex" activated in inflamed tissues, and (4) several reaction products caused by plasma clotting in inflamed area.

* Chemotaxis depends on the concentration gradient of the chemotactic substance. The concentration is greatest near the source, which directs the unidirectional movement of the WBCs.

* Chemotaxis is effective up to 100 micrometers away from an inflamed tissue. Therefore, because almost no tissue area is more than 50 micrometers away from a capillary, the chemotactic signal can easily move hordes of WBCs from capillaries into inflamed area.

Phagocytosis

* Phagocytosis means cellular ingestion of offending agents and it is performed mostly by neutrophils and macrophages.

* Phagocytosis depends on 3 selective procedures:

1. Smooth surfaces of tissues resist phagocytosis while rough surfaces increased phagocytosis .
2. Most natural substances of the body have protective protein coats that repel phagocytes while most dead tissues and foreign particles have no protective coats, which makes them subject to phagocytosis.

3. The immune system develops antibodies against bacteria. The antibodies then adhere to the bacterial membranes and thereby make bacteria tasty for phagocytosis (Opsonization).

Phagocytosis by Neutrophils

*** The neutrophil first attaches to the particle and then projects pseudopodia in all directions around the particle.**

*** The pseudopodia meet one another on the opposite side and fuse, creating an enclosed chamber that contains the phagocytized particle.**

*** Then the chamber invaginates to the inside and breaks away from the outer cell membrane to form a phagocytic vesicle inside the cytoplasm.**

*** A single neutrophil can usually phagocytize 3 to 20 bacteria before the neutrophil becomes inactivated and dies.**

Phagocytosis by Macrophages

* Macrophages are much more powerful phagocytes than neutrophils, often capable of phagocytizing as many as 100 bacteria.
* Macrophages have the ability to engulf much larger particles, even whole RBCs, whereas neutrophils are not capable of phagocytizing particles much larger than bacteria.
* After digesting particles, macrophages can extrude residual products and often survive and function for many more months.

Once Phagocytized, Most Particles Are Digested by Intracellular Enzymes

* Once a foreign particle has been phagocytized, lysosomes in neutrophils or macrophages immediately come in contact with the phagocytic vesicle, and their membranes fuse, thereby dumping their digestive enzymes and bactericidal agents into the vesicle to become now a digestive vesicle where digestion occurs.

* Lysosomes of both neutrophils and macrophages contain proteolytic enzymes which digest bacteria.
* Lysosomes of macrophages (but not of neutrophils) contain lipases which digest thick lipid membranes of some bacteria such as tuberculosis bacillus.

Neutrophils and Macrophages Can Kill Bacteria

* In addition to digestion of bacteria, neutrophils and macrophages contain bactericidal agents that kill most bacteria even when lysosomal enzymes fail to digest them.
* Bactericidal agents are powerful oxidizing agents and include superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl ions (OH^-), which are lethal to most bacteria.
* The lysosomal enzyme myeloperoxidase catalyzes the reaction between H_2O_2 and chloride ions to form hypochlorite, which is exceedingly bactericidal.
* Some bacteria have coats that are resistant to lysosomal digestion making them responsible for chronic diseases e.g. tuberculosis.

Monocyte-macrophage Cell System (RES)

* After entering tissues and becoming tissue macrophages, another large portion of monocytes remains attached to tissues for months or even years until they are called on to perform specific local phagocytic functions or they can break away from their attachments and once again become mobile macrophages that respond to chemotaxis.

* The total combination of monocytes, mobile macrophages, fixed tissue macrophages, and a few specialized endothelial cells in bone marrow, spleen, and lymph nodes is called RES system or monocyte-macrophage cell system.

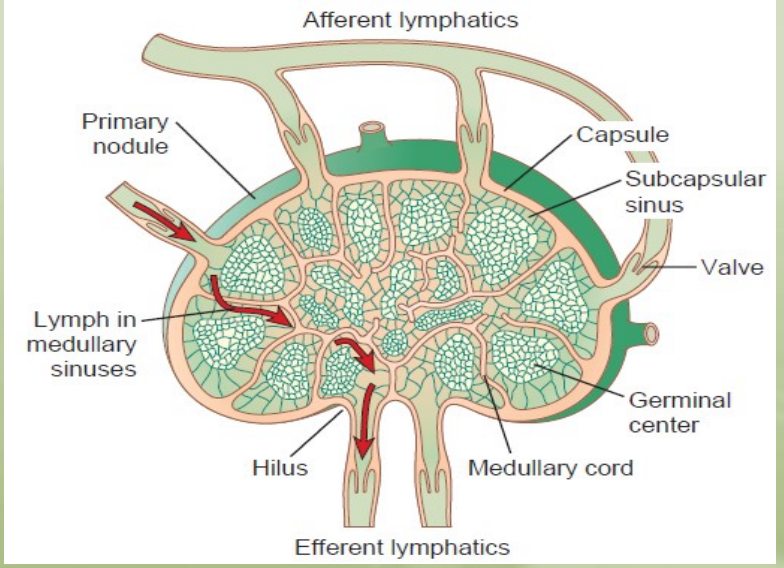
Macrophages in Skin and Subcutaneous Tissues (Histiocytes)

When infection begins in a subcutaneous tissue and local inflammation ensues, local tissue macrophages (histiocytes) divide in situ and form more macrophages to combat infectious agents.

Macrophages in Lymph Nodes

* The foreign particles enter the lymph and flow to lymph nodes through afferent lymphatics, then through nodal medullary sinuses, and finally passing out the hilus into efferent lymphatics that eventually empty into venous blood.

* Large numbers of tissue macrophages line lymph sinuses, and if any particles enter the sinuses, macrophages phagocytize them and prevent general dissemination throughout the body.

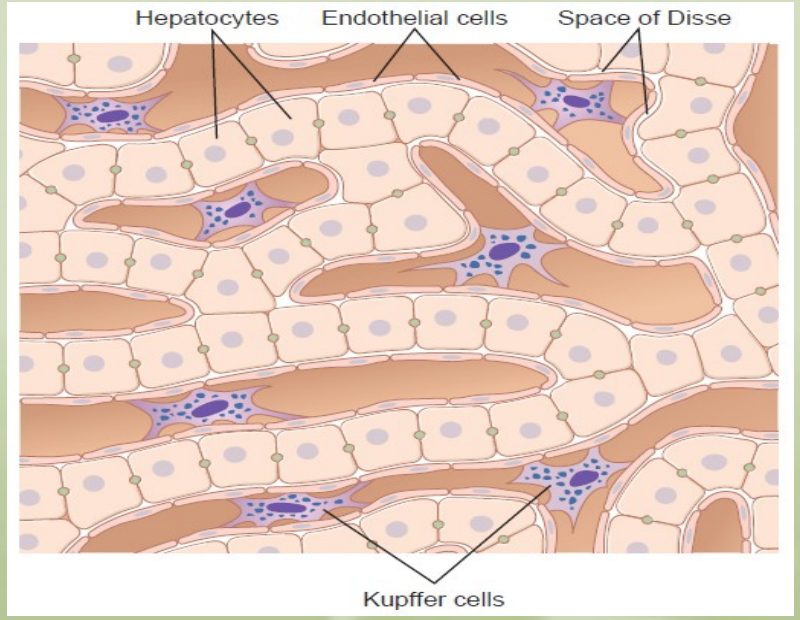


Alveolar Macrophages in Lungs

* Large numbers of tissue macrophages are present in alveolar walls to phagocytize particles 1) If the particles are digestible, the macrophages Digest, 2) If the particle is not digestible, the macrophages form a “giant cell” capsule around the particle to be slowly dissolved e.g. capsules are formed around tuberculosis bacilli and silica dust particles.

Macrophages (Kupffer Cells) in the Liver Sinusoids

Liver sinusoids are lined with tissue macrophages called Kupffer cells which form an effective particulate filtration system that almost none of bacteria from GIT pass from portal blood into general systemic circulation.



Macrophages of Spleen and Bone Marrow

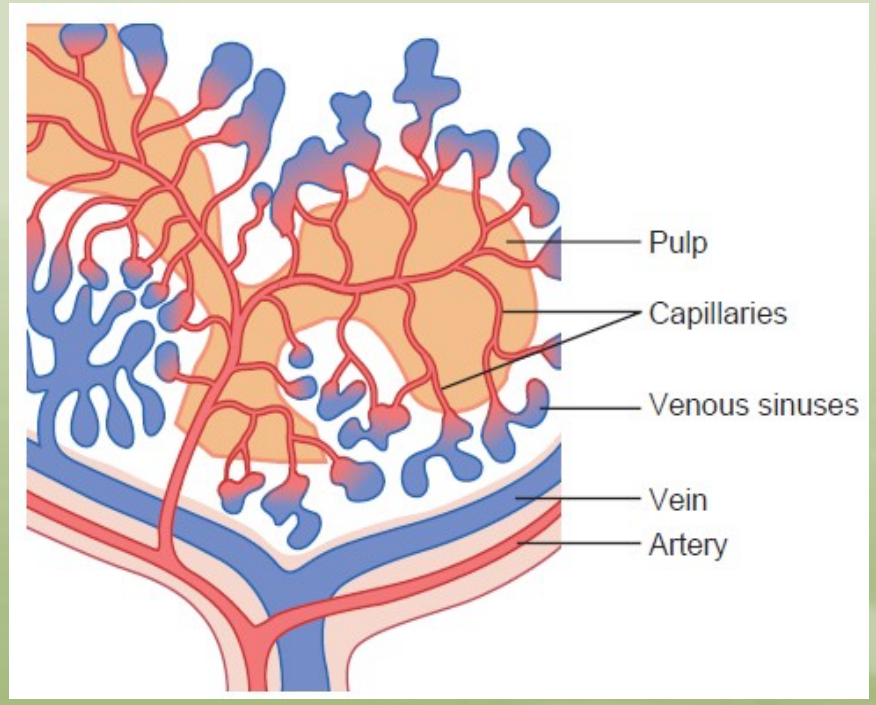
*** In spleen and bone marrow, macrophages are entrapped by reticular meshwork of the two organs and when foreign particles come in contact with these macrophages, they are phagocytized.**

*** The spleen is similar to lymph nodes, except that blood, instead of lymph, flows through the tissue spaces of the spleen.**

* The figure shows that a small artery penetrates from splenic capsule into splenic pulp and terminates in small capillaries.

* The capillaries are highly porous, allowing whole blood to pass out of capillaries into cords of red pulp.

* The blood then gradually squeezes through the trabecular meshwork of these cords and eventually returns to circulation through endothelial walls of venous sinuses.



* The trabeculae of red pulp and venous sinuses are lined with vast numbers of macrophages.

* This peculiar passage of blood through cords of red pulp of the spleen provides an exceptional means of phagocytizing unwanted debris in blood, including old and abnormal RBCs.

Inflammation

* When tissue injury occurs, multiple substances are released by the injured tissue and cause dramatic secondary changes in the surrounding uninjured tissues. This entire complex of tissue changes is called inflammation.

* Inflammation is characterized by (1) vasodilation of local blood vessels, with excess local blood flow; (2) increased permeability of capillaries, allowing leakage of fluid into interstitial spaces; (3) clotting of fluid in interstitial spaces because of increased amounts of fibrinogen leaking from capillaries; (4) migration of large numbers of granulocytes and monocytes into tissue; and (5) swelling of tissue cells.

* Some of tissue products that cause these reactions are histamine, bradykinin, serotonin, prostaglandins, reaction products of complement system, reaction products of blood clotting system, and lymphokines that are released by sensitized T cells.

* Several of these substances strongly activate macrophage system, and within a few hours, macrophages begin to phagocytize destroyed tissues.

“Walling-Off” Effect of Inflammation

* One of the first results of inflammation is to “wall off” the area of injury from the remaining tissues.

* Tissue spaces and lymphatics in the inflamed area are blocked by fibrinogen clots which delays spread of bacteria or toxic products.

* The intensity of the inflammatory process is proportional to the degree of tissue injury. For instance, when staphylococci invade tissues, they release extremely lethal cellular toxins. As a result, inflammation develops rapidly and the walling-off process also develops rapidly, preventing staphylococcal infection from spreading through the body.

* Streptococci, in contrast, do not cause such intense local tissue destruction. Therefore, the walling-off process develops slowly, allowing streptococcal infection to spread through the body and cause death than do staphylococci, even though staphylococci are far more destructive to tissues.

Tissue macrophages provide a first line of defense

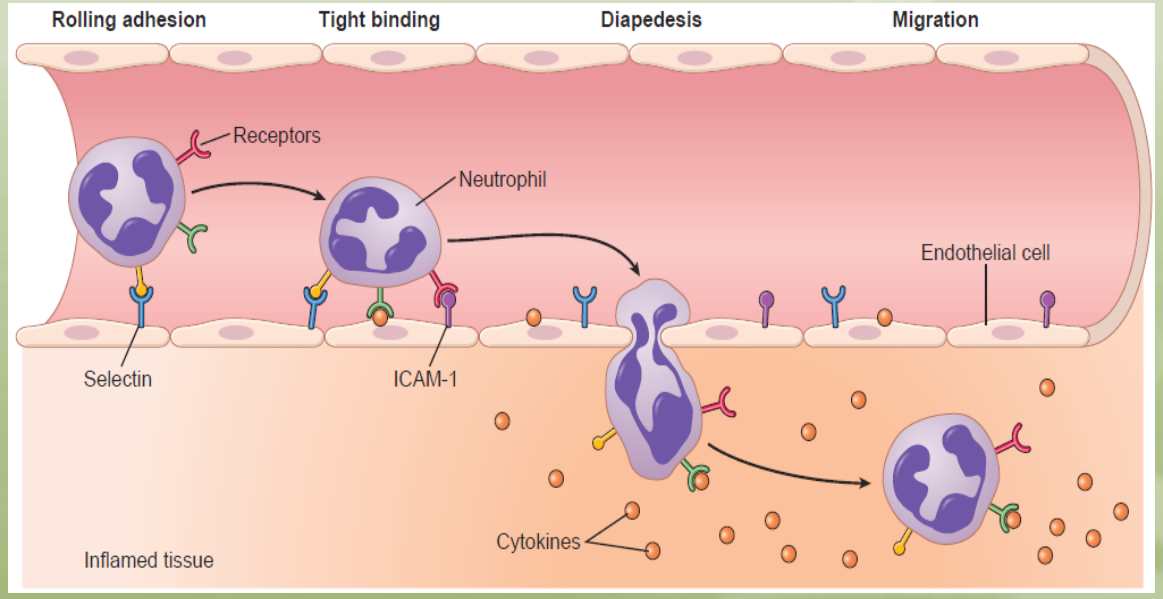
* Within minutes after inflammation begins, macrophages already present in tissues immediately begin their phagocytic actions.
* When activated by tissue products of infection and inflammation, tissue macrophages undergo rapid enlargement and many of the sessile macrophages break loose from their attachments and become mobile, forming the first line of defense against infection during the first hour or so.
* The numbers of these early mobilized macrophages often are not great, but they are lifesaving.

Neutrophil invasion of inflamed area is a second line of defense

* Within the first hour after inflammation begins, large numbers of neutrophils begin to invade the inflamed area from the blood. This invasion is caused by inflammatory cytokines (e.g., tumor necrosis factor and interleukin-1) produced by inflamed tissues that initiate the following reactions:

1. They cause increased expression of adhesion molecules e.g. selectins and intercellular adhesion molecule–1 (ICAM-1) on the surface of endothelial cells in capillaries and venules. These adhesion molecules, reacting with complementary integrin molecules on the neutrophils, cause neutrophils to stick to capillary and venule walls in inflamed area. This effect is called **margination**.

2. They also cause intercellular attachments between endothelial cells of capillaries and small venules to loosen, allowing openings large enough for neutrophils to crawl from blood into tissues by **diapedesis**.



3. They then cause **chemotaxis** of neutrophils toward injured tissues. Then neutrophils immediately begin their scavenger functions of killing bacteria and removing foreign matter.

Neutrophilia

* Within a few hours after the onset of acute, severe inflammation, the number of neutrophils in the blood sometimes increases fourfold to fivefold—from a normal of 4000-5000 to 15,000-25,000 neutrophils per microliter. Such acute increase in the number of neutrophils in the blood is called **neutrophilia**.

Second Macrophage Invasion into Inflamed Tissue Is a Third Line of Defense

* **At the beginning of inflammation**, the number of monocytes in blood and bone marrow stores is much less than neutrophils. Therefore, the buildup of macrophages in the inflamed tissue area is slower than that of neutrophils.
* **After several days of inflammation**, macrophages finally come to dominate neutrophils because of greatly increased bone marrow production of new monocytes. This is the second macrophage invasion into inflamed tissue (Third line of defense).

Increased Production of Granulocytes and Monocytes by Bone Marrow Is a Fourth Line of Defense

* The fourth line of defense is greatly increased production of granulocytes and monocytes by bone marrow. This action results from stimulation of granulocytic and monocytic progenitor cells of the marrow. It takes 3 to 4 days before newly formed granulocytes and monocytes reach the stage of leaving bone marrow.
* If the stimulus from inflamed tissue continues, bone marrow can continue to produce these cells in tremendous quantities for months and even years, sometimes at a rate 20 to 50 times normal.

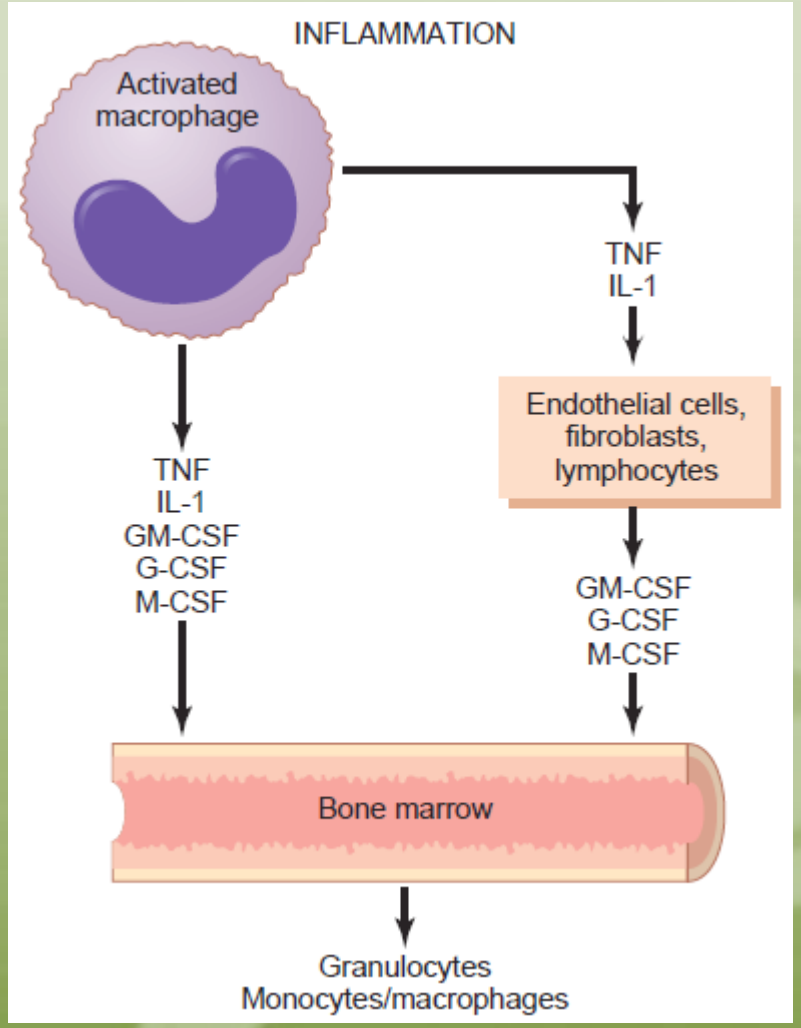
Feedback Control of the Macrophage and Neutrophil Responses

* Five factors are believed to play dominant role in control of macrophage response to inflammation:

1. Tumor necrosis factor (TNF)
2. Interleukin-1 (IL-1)

3. Granulocyte-monocyte colony-stimulating factor (GM-CSF)
4. Granulocyte colony-stimulating factor (G-CSF) and
5 Monocyte colony-stimulating factor (M-CSF).

* These factors are formed by activated macrophages in inflamed tissues.
* These factors increased production of granulocytes and monocytes by bone marrow.
* The combination of TNF, IL-1, and colony-stimulating factors provides a powerful feedback mechanism that begins with tissue inflammation and proceeds to formation of large numbers of defensive WBCs that help remove the cause of the inflammation.



Formation of Pus

* When neutrophils and macrophages engulf large numbers of bacteria and necrotic tissue, all neutrophils and most of macrophages eventually die.

* After several days, the cavity in the inflamed tissue contains varying portions of necrotic tissue, dead neutrophils, dead macrophages, and tissue fluid. This mixture is called pus.

* After the infection has been suppressed, dead cells and necrotic tissue in the pus gradually autolyze over a period of days, and the end products are eventually absorbed into surrounding tissues and lymph.

Eosinophils

* Eosinophils are weak phagocytes and they exhibit chemotaxis.
* Eosinophils are produced in large numbers in people with parasitic infections.
* Eosinophils attach themselves to parasites by special surface molecules and release substances that kill many parasites. For instance, eosinophils attach themselves to juvenile forms of schistosomiasis parasite and kill many of them by:

1. releasing hydrolytic enzymes from their granules, which are modified lysosomes
2. releasing highly reactive forms of oxygen
3. releasing a highly larvacidal polypeptide called major basic protein.

* Trichinosis is another parasitic disease that causes eosinophilia, resulting from invasion of body's muscles by Trichinella parasite ("pork worm") after a person eats undercooked infested pork.

Basophils

* Basophils in the circulating blood are similar to the large tissue mast cells.

* Both mast cells and basophils liberate heparin (anticoagulant), histamine, bradykinin and serotonin.

* The mast cells and basophils play an important role in allergic reactions How?

- Immunoglobulin E (IgE) attached to mast cells and basophils.
- Then, the specific antigen reacts with IgE, causing mast cell or basophil to rupture and release large quantities of histamine, bradykinin, serotonin, heparin, slow-reacting substance of anaphylaxis (a mixture of three leukotrienes), and a number of lysosomal enzymes.
- These substances cause local vascular and tissue reactions that cause most of allergic manifestations.

Leukopenia

* Leukopenia is a clinical condition in which bone marrow produces few WBCs which leaves the body unprotected against many bacteria and other invaders.

* Normally, human body lives in symbiosis with bacteria:

- The mouth and respiratory tract contains various spirochetal, pneumococcal, and streptococcal bacteria.
- The distal GIT is loaded with colon bacilli.
- Surfaces of eyes, urethra and vagina have bacteria.

* Leukopenia allows invasion of adjacent tissues by these bacteria and ulcers may appear in the mouth and colon, or some form of severe respiratory infection might develop, and death may occur within a week.

* Exposure to x- or gamma rays, or to drugs and chemicals that contain benzene or anthracene nuclei, is likely to cause bone marrow aplasia. Indeed, chloramphenicol (an antibiotic), thiouracil (treat thyrotoxicosis) may cause leukopenia.

Leukemias

* Leukemias are uncontrolled production of abnormal WBCs that can be caused by cancerous mutation of a myelogenous or lymphogenous cell.

* Types of leukemia

1. Lymphocytic leukemia: caused by cancerous production of lymphoid cells, usually beginning in a lymph node or other lymphocytic tissue and spreading to other areas of the body.
2. Myelogenous leukemia: begins by cancerous production of young myelogenous cells in bone marrow and then spreads throughout the body.

* Leukemia cells are bizarre and undifferentiated and not identical to normal WBCs. Usually, the more undifferentiated the cell, the more acute is the leukemia, often leading to death within a few months if untreated.

Effects of leukemia on the body

1. Metastatic growth of leukemic cells in abnormal areas of the body.

2. Leukemic cells from bone marrow may reproduce so greatly that they invade the surrounding bone, causing pain and, eventually, a tendency for bones to fracture easily.

3. Development of infection, severe anemia, and a bleeding tendency caused by thrombocytopenia.

4. Excessive use of metabolic substrates by the growing cancerous cells. Consequently, energy of the patient is greatly depleted, and excessive utilization of amino acids by leukemic cells causes rapid deterioration of normal protein tissues. Thus, while leukemic tissues grow, other tissues become debilitated. After metabolic starvation has continued long enough, this factor alone is sufficient to cause death.