

# **The Nervous system**

# Functions of the Nervous System

The nervous system can be functionally divided into 3 actions:

## **1. Sensation:**

- Receiving information about the environment known as a stimulus.
  - Taste and smell: chemical substances (molecules, compounds, ions, etc.)
  - Touch and hearing: physical or mechanical stimuli.
  - Sight: light stimuli.
  - Those five are all senses that receive stimuli of which there is conscious perception.
- Register the presence of a change from homeostasis
  - Additional sensory stimuli might be from the internal environment (inside the body), such as the stretch of an organ wall or the concentration of certain ions in the blood.

# Functions of the Nervous System

The nervous system can be functionally divided into 3 actions:

**2. Integration:** Combination of sensory perception with high cognitive function such as memories, learning, and emotion to produce a response . Information is processed which leads to the specific response that will be generated.

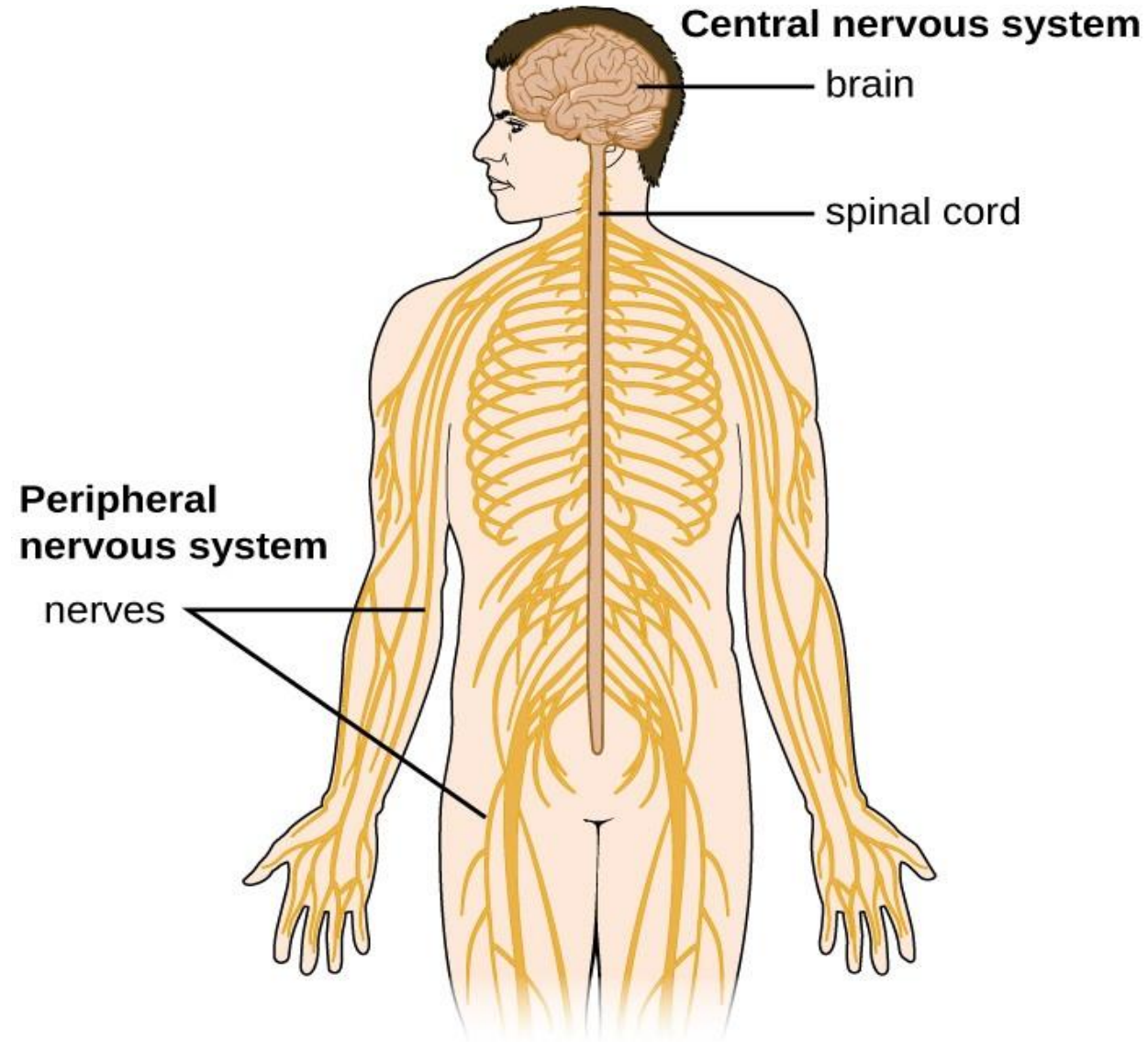
**3. Response:** motor functions resulting from the integration of the sensory information. The nervous system can cause the contraction of all three types of muscle tissue. Responses can be divided into voluntary or conscious (contraction of skeletal muscle) and those that are involuntary (contraction of smooth muscles, regulation of cardiac muscle, activation of glands).

Voluntary responses are governed by the somatic nervous system.

Involuntary responses are governed by the autonomic nervous system.

The nervous system can be divided into regions that are responsible for **sensation** (sensory functions) and for the **response** (motor functions) the **integration** or association areas.

# Structural Divisions of the Nervous System



Central nervous system

brain

spinal cord

Peripheral nervous system

nerves

# Structural Divisions of the Nervous System

The ***central nervous system (CNS)***:

- The brain contained within the cranial cavity of the skull.
- The spinal cord contained within the vertebral cavity of the vertebral column.

The ***peripheral nervous system (PNS)*** is everything else beyond the brain and spinal cord.

- The **sensory** or **afferent division**: Nerves having sensory function and carry impulses to the CNS for integration (interoceptors & exteroceptors).
- The **motor** or **efferent division** include nerve carrying impulses away from the CNS.
  - The ***somatic nervous system (SNS)*** responsible for voluntary motor responses.
    - Contraction of skeletal muscle except in reflexes.
    - Physiological response to an emotional state.
  - The ***autonomic nervous system (ANS)*** responsible for involuntary motor responses.
    - Some somatic motor responses are reflexes.
    - Habit learning” or “procedural memory”.
    - Homeostasis (regulation of the body organ systems (the internal environment)).
    - The motor output to smooth and cardiac muscle as well as glandular tissue.

# Divisions of the Autonomic Nervous System

Regulates many of the internal organs through the balanced action of:

- **The *sympathetic division***

*Fight-or-flight response:*

*Many different effector organs are activated together for a common purpose.*

- *More oxygen needs to be inhaled and delivered to skeletal muscle.*
- *The respiratory, cardiovascular, and musculoskeletal systems are all activated together.*
- *Additionally, sweating removes the excess heat that from muscle contraction*
- *The digestive system shuts down so that blood is not absorbing nutrients when it should be delivering oxygen to skeletal muscles.*

- **The *parasympathetic division*.**

*Rest and digest response:* Dominant under the normal, non-stressful everyday life.

- *Actions focus on conserving energy, resting and digesting activities.*
- *Decrease in heart rate, decrease blood supply to skeletal muscles*
- *Increase blood supply to digestive and urinary organs.*
- *Decrease in blood sugar, and constriction of bronchioles.*

# Homeostasis is the balance between the two systems.

At each target effector, dual innervation determines activity. For example, the heart receives connections from both the sympathetic and parasympathetic divisions.

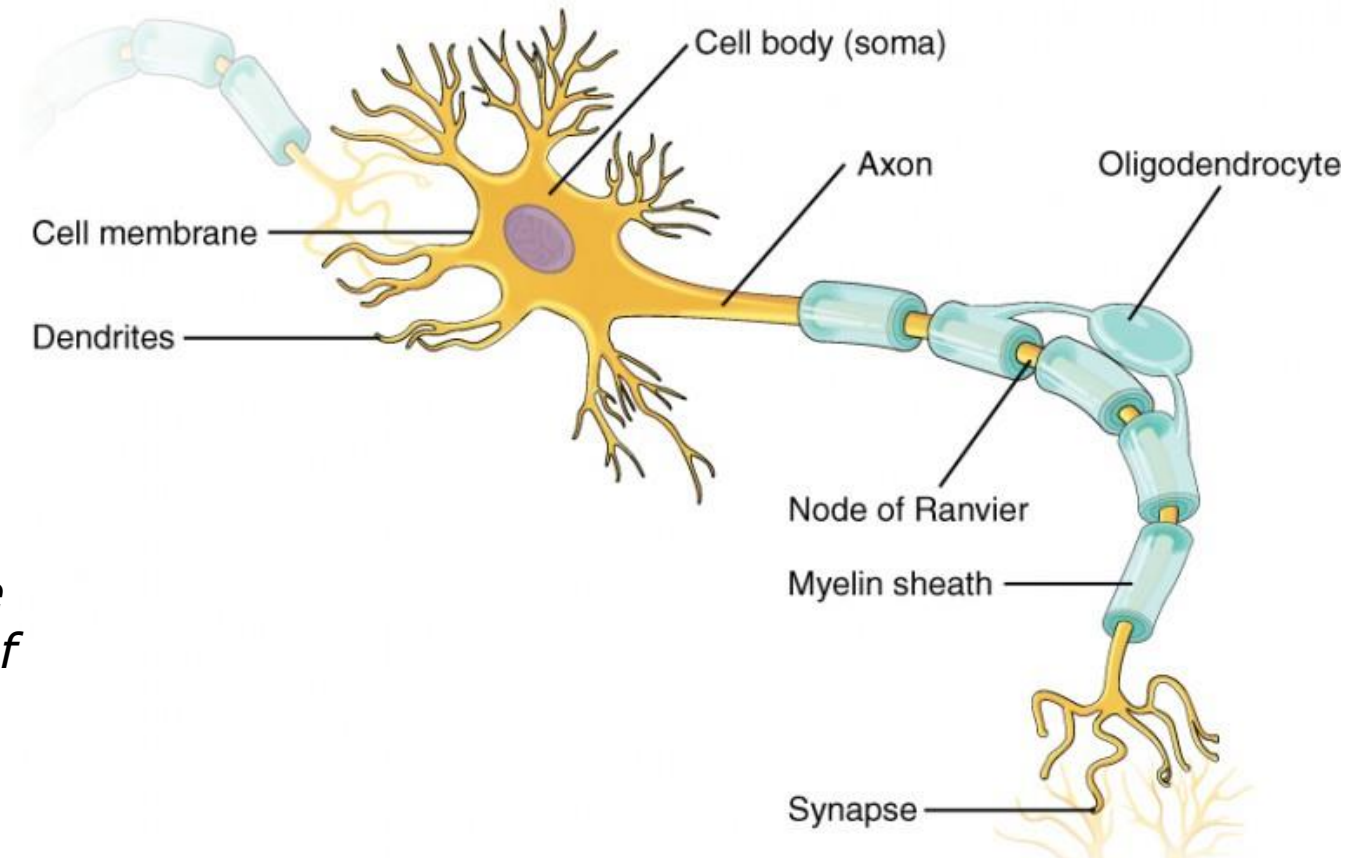
- ***Sympathetic PNS*** causes heart rate to increase.
- ***Parasympathetic PNS*** causes heart rate to decrease.

# Nervous Tissue: Two types of cells

## 1. Neurons:

They are responsible for the sensory, integrative, and motor functions of the nervous system. They are electrically active and release chemical signals to target cells. Neurons are important, but without glial support they would not be able to perform their function.

- Impulse to leap from node to node on the axon by **saltatory conduction**.
- At the *axon terminal* several branches extend each with an enlargement called a *synaptic end bulb* or *synaptic knob* where the electrical impulses trigger the release of neurotransmitters to communicate with the target cells.





Structurally there are three type of neurons depending on the number of processes at the cell body:

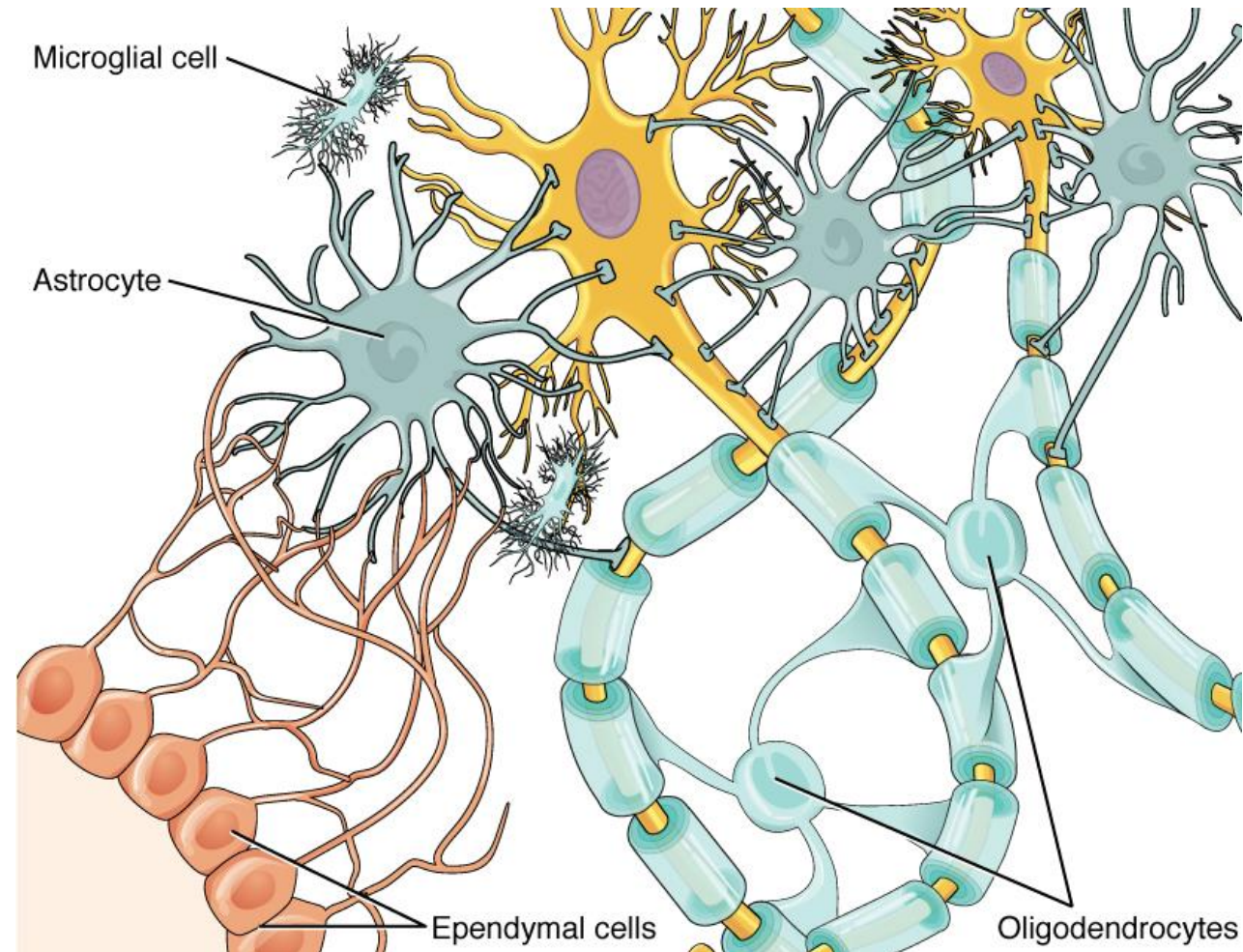
- **Multipolar** - most neurons of the CNS, PNS motor efferent
- **Bipolar** - sensory
- **unipolar** - sensory

Functionally, neurons are classified into three categories:

- **Sensory neurons**, also called afferent neurons, carry impulses from sensory receptors to the CNS.
- **Interneurons** are located completely within the CNS and function to process and interpret impulses received from the sensory neurons.
- **Motor neurons**, also called efferent neurons, carry impulses from the CNS out to the effectors (muscles or glands). They function in the responsive function of the nervous system.

# Nervous Tissue: Two types of cells

- 2. Glial cells:** Many of their functions are directed at helping neurons complete their functions in communication. There are six types of glial cells. Four of them are found in the CNS and two others are found in the PNS.



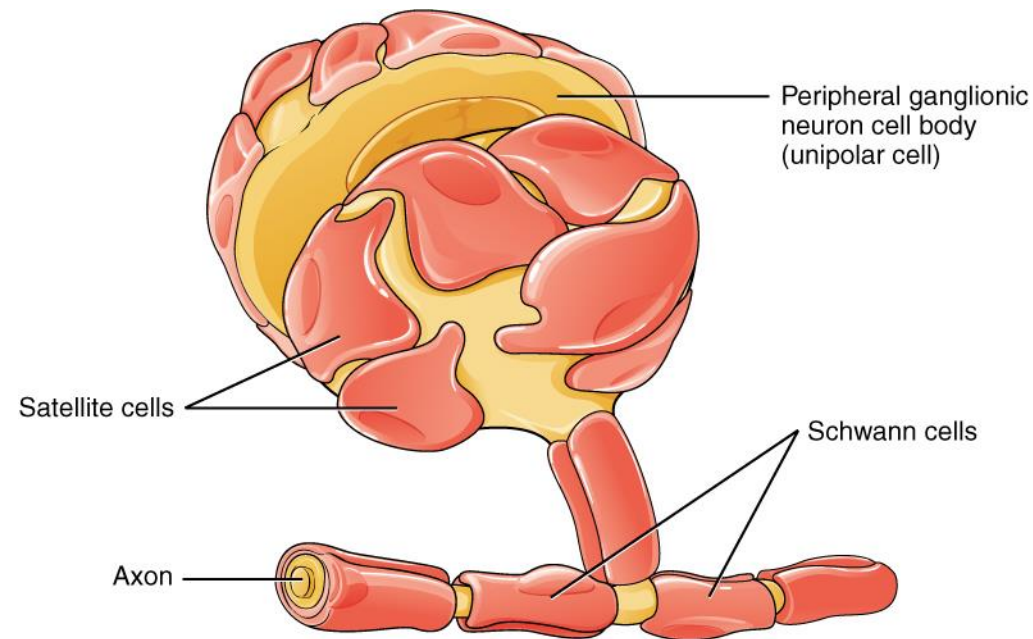
**Glial cells of the CNS**

## A. Glial Cells of the CNS

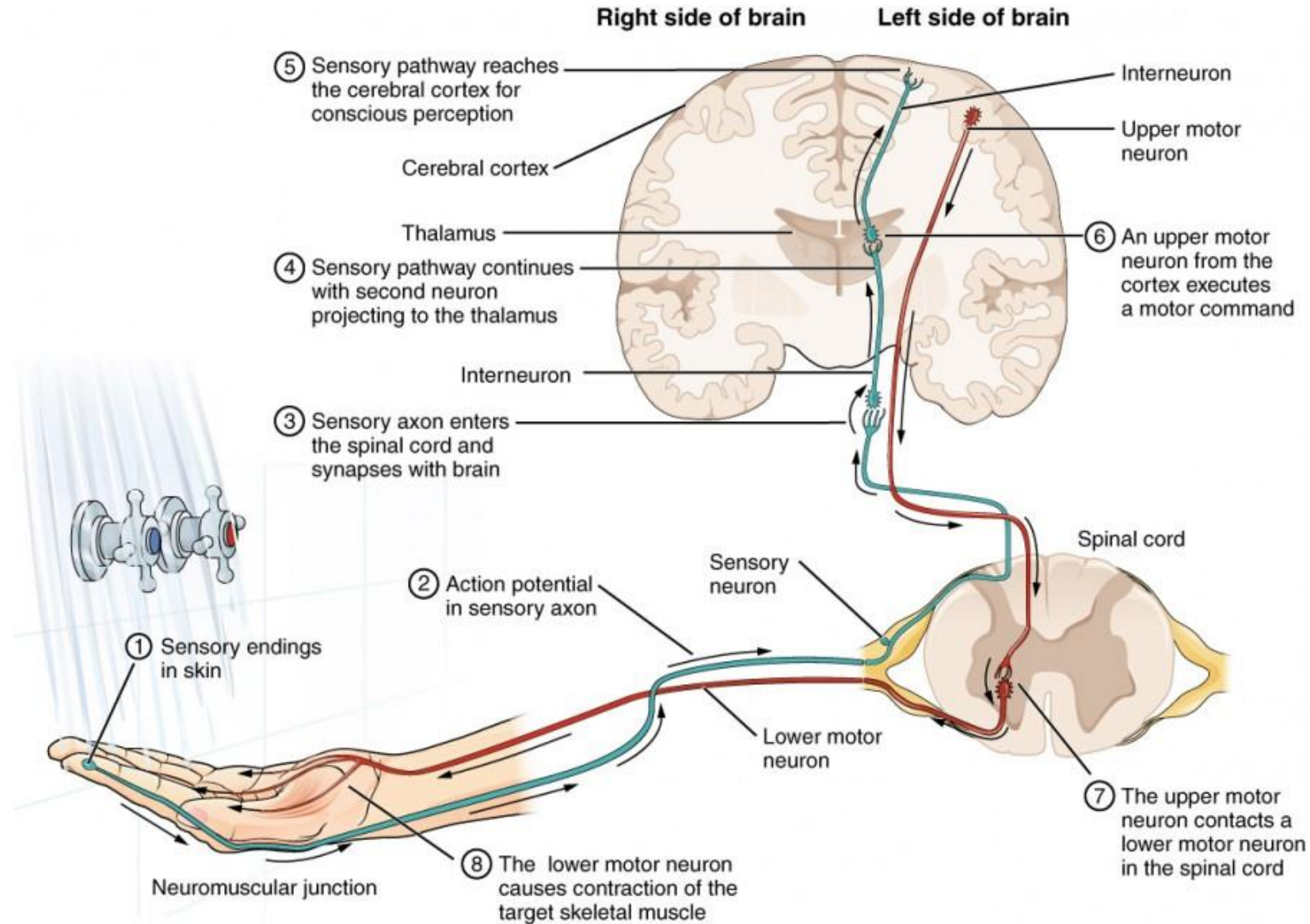
- 1. Astrocyte**, star-shaped with many processes to interact with neurons, blood vessels, or the connective tissue covering the CNS. Maintain the concentration of chemicals in the extracellular space, remove excess signalling molecules, react to tissue damage, and contribute to the **blood-brain barrier (BBB)**.
- 2. Oligodendrocyte** insulates axons in the CNS. They have few processes that extend from the cell body. Each one reaches out and surrounds an axon to insulate it in myelin. One oligodendrocyte can provide the myelin for multiple axon segments, either for the same axon or for separate axons.
- 3. Microglia** similar to macrophages. When they encounter diseased or damaged cells in the CNS, they ingest and digest those cells or the pathogens that cause disease.
- 4. Ependymal cell** filters blood to make cerebrospinal fluid (CSF) that circulates through the CNS. Ependymal cells line each ventricle (cavities). The choroid plexus is where ependymal cells come in contact with blood vessels and filter and absorb components of the blood to produce cerebrospinal fluid. These glial cells appear similar to ciliated epithelial cells, making a single layer of cells with little intracellular space and tight connections between adjacent cells. They are constituent of the **BBB**.

## B. Glial Cells of the PNS

- 1. *Satellite cells*** surround the cell body of neurone in sensory and autonomic ganglia. They provide support, performing similar functions in the periphery as astrocytes do in the CNS—except, of course, for establishing the BBB.
- 2. *Schwann cell***, insulate axons with myelin in the periphery. Schwann cells are different from oligodendrocytes, in that they wrap around a portion of only one axon segment and no others.

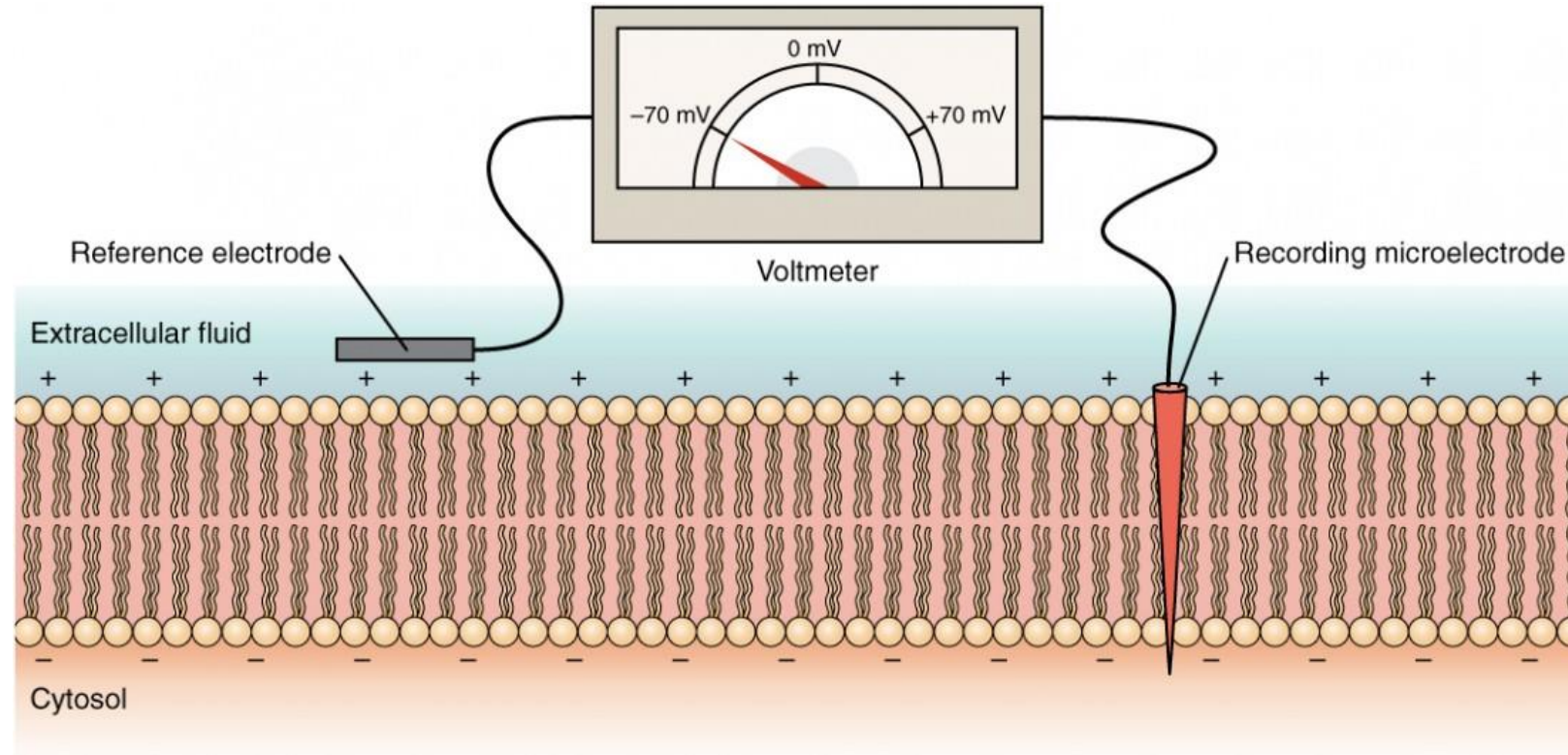


# Sensation, integration, and response



**120 m/s (432 km/h or 275 mph)**

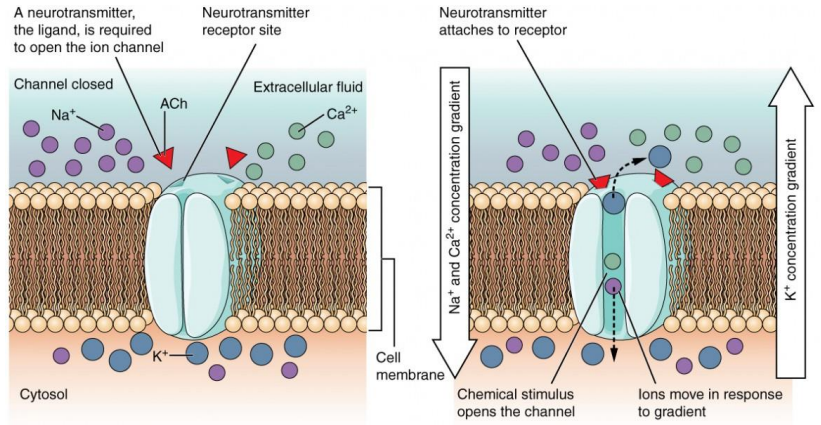
# ***Polarized membrane: Resting membrane potential -70 mV.***



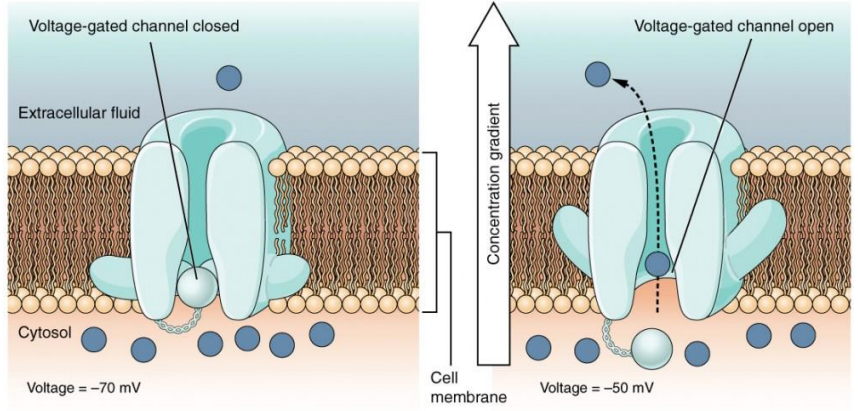
- Concentration of ions in extra- and intra-cellular fluids is largely balanced: Net neutral charge.
- Sodium/potassium pump uses ATP to maintain  $[Na^+]$  higher outside and  $[K^+]$  higher inside the cell. Leakage channel does the opposite. **The resultant generate the resting membrane potential**, a slight difference in charge right at the membrane surface.
- This enabling neurons (and muscle cells) to generate electrical signals such as action potentials.

# Excitable membrane: Action potential

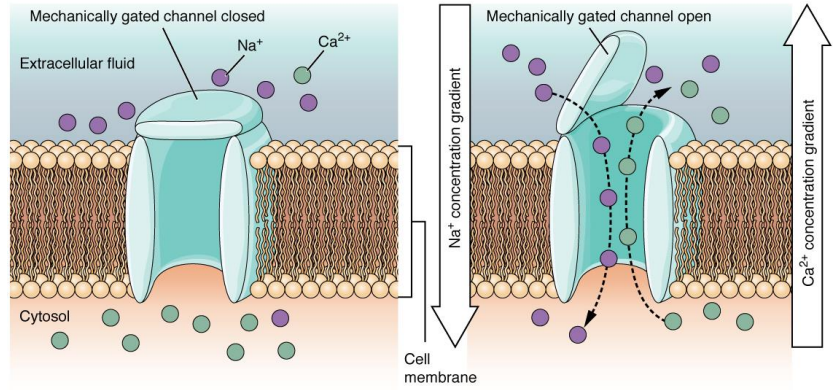
## ligand-gated channel



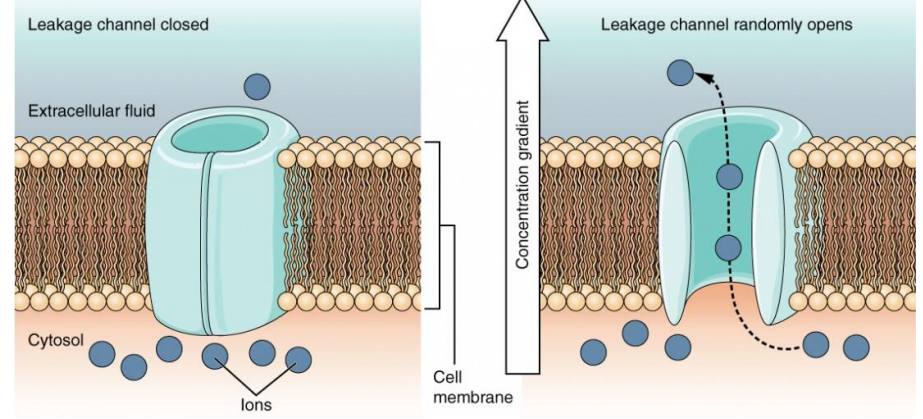
## Voltage-gated channel



## Mechanically gated channel



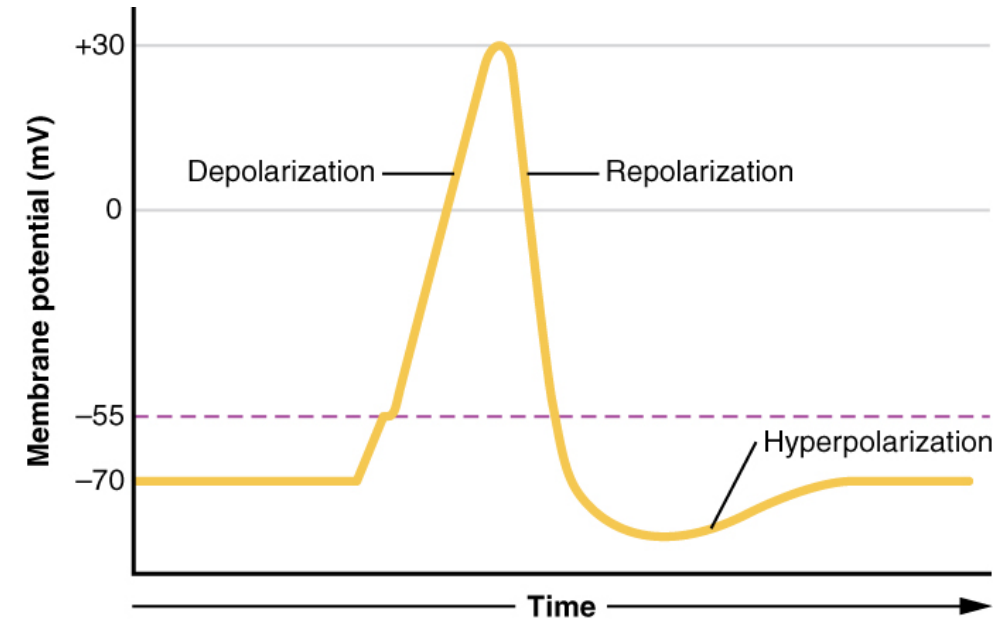
## Leakage Channels



Ligand binding, mechanical change or electrical changes of the membrane trigger the opening of the channel to trigger the **membrane depolarization**.

# ***Excitable membrane: Action potential***

1. Stimuli trigger  $\text{Na}^+$  channels opening,  $\text{Na}^+$  entry and change on voltage inside relatively to outside the cells to **-55mV or higher**.
2. At this **threshold**, voltage-gated  $\text{Na}^+$  channel opens and depolarization reaches **+30mV**.
3. Initial depolarization not reaching this threshold do not result in an action potential.
4. At +30mV voltage-gated  $\text{K}^+$  channels open, and  $\text{K}^+$  leaving the cells triggering the Repolarization.
5. Hyperpolarization due to delayed  $\text{K}^+$  channels closing and  $\text{K}^+$  equilibrium is below -70 mV. Repolarization returns to the resting potential-70 mV.
6. Action potentials are all or none and always peak at +30 mV. Stronger stimuli initiate multiple action potentials more quickly.





# Propagation of the Action Potential

The action potential is initiated at the initial segment of the axon (high density of voltage-gated  $\text{Na}^+$  channels).

**During *continuous conduction*** (unmyelinated axon):

Going downstream along the axon, more voltage-gated  $\text{Na}^+$  channels are opened as the depolarization spreads (because of the diffusion of  $\text{Na}^+$  inside that activate next  $\text{Na}^+$  voltage dependent channel).

Because voltage-gated  $\text{Na}^+$  channels are inactivated at the peak of the depolarization, they cannot be re-opened for a short time, preventing depolarization spreading back upstream the axon.

Continuous conduction is slow because there are always voltage-gated  $\text{Na}^+$  channels opening, and more and more  $\text{Na}^+$  is rushing into the cell.

**During *saltatory conduction*** (myelinated axon) action potential propagates differently.  $\text{Na}^+$  that enters the cell at the initial segment of axon spread until the first node of Ranvier to open another  $\text{Na}^+$  channel. The distance between nodes is the optimal distance to keep the membrane still depolarized above threshold at the next node providing an optimal speed of propagation.

Saltatory conduction is faster because the action potential basically jumps from one node to the next and the new influx of  $\text{Na}^+$  renews the depolarized membrane.

The diameter of the axon also influence the speed of conduction.  $\text{Na}^+$ -based depolarization spreads faster down a wide axon than down a narrow one.

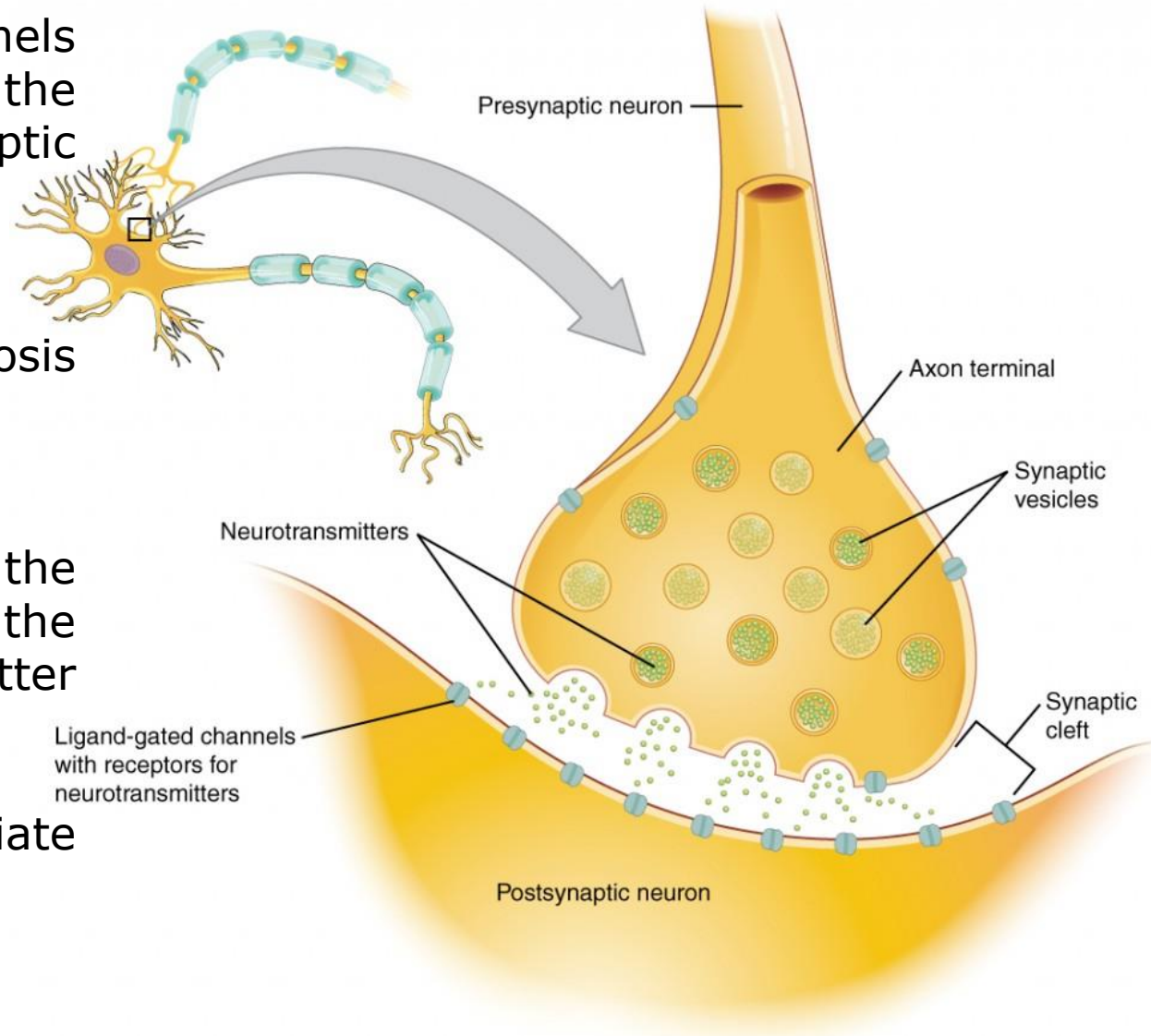
# Neurotransmitter Release

At the axon terminals, voltage-gated  $\text{Ca}^{2+}$  channels open. Intracellular  $[\text{Ca}^{2+}]$  increases to trigger the merging of the vesicle with the presynaptic membrane.

The neurotransmitter is released through exocytosis into the ***synaptic cleft***.

In the synaptic cleft, the neurotransmitter diffuses the short distance to the postsynaptic membrane of the next neuron and interacts with neurotransmitter receptors on the dendrites or cell body.

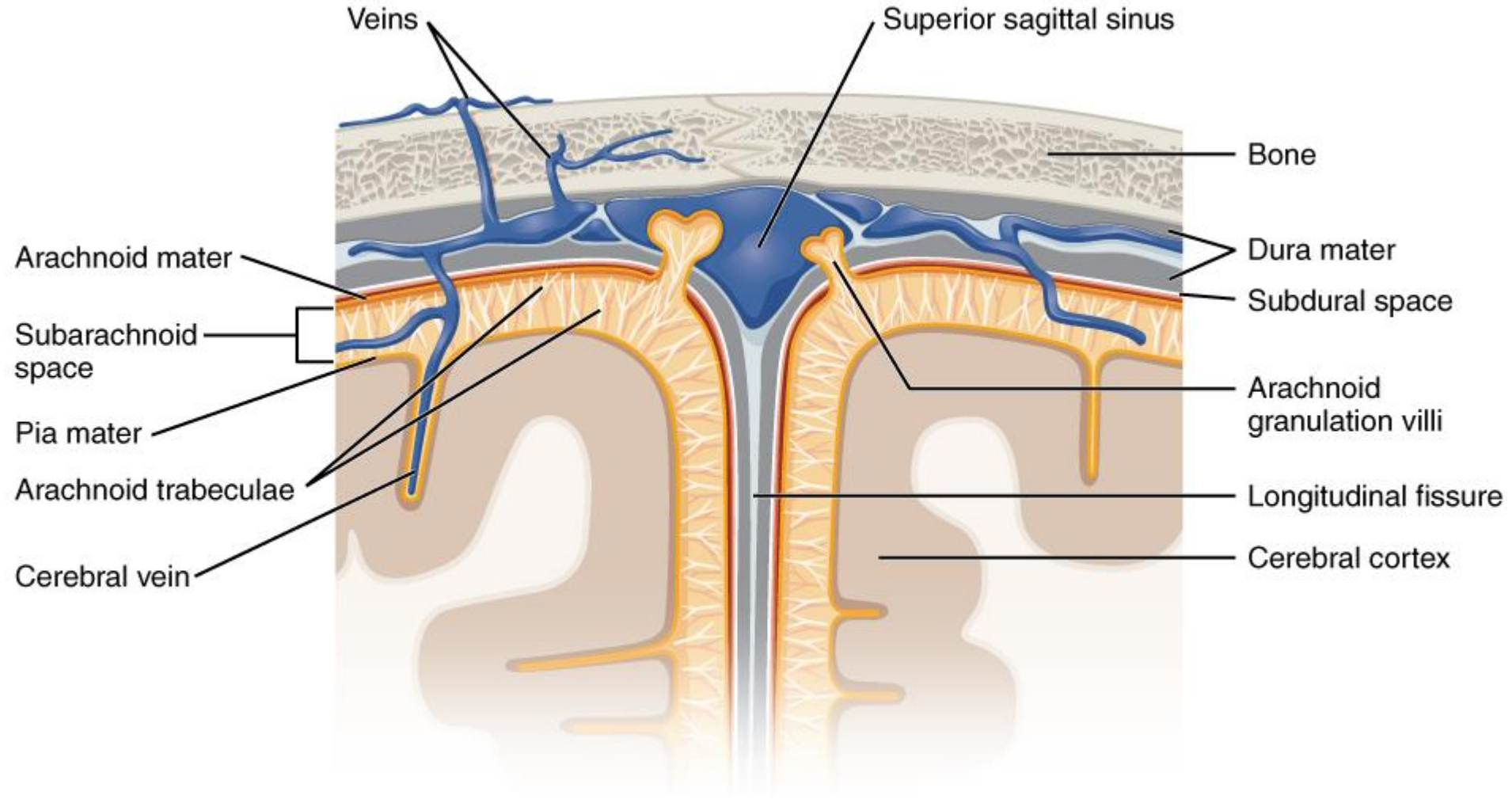
Binding of neurotransmitter to its receptor initiate action potential on the next neuron.



# The Central Nervous System

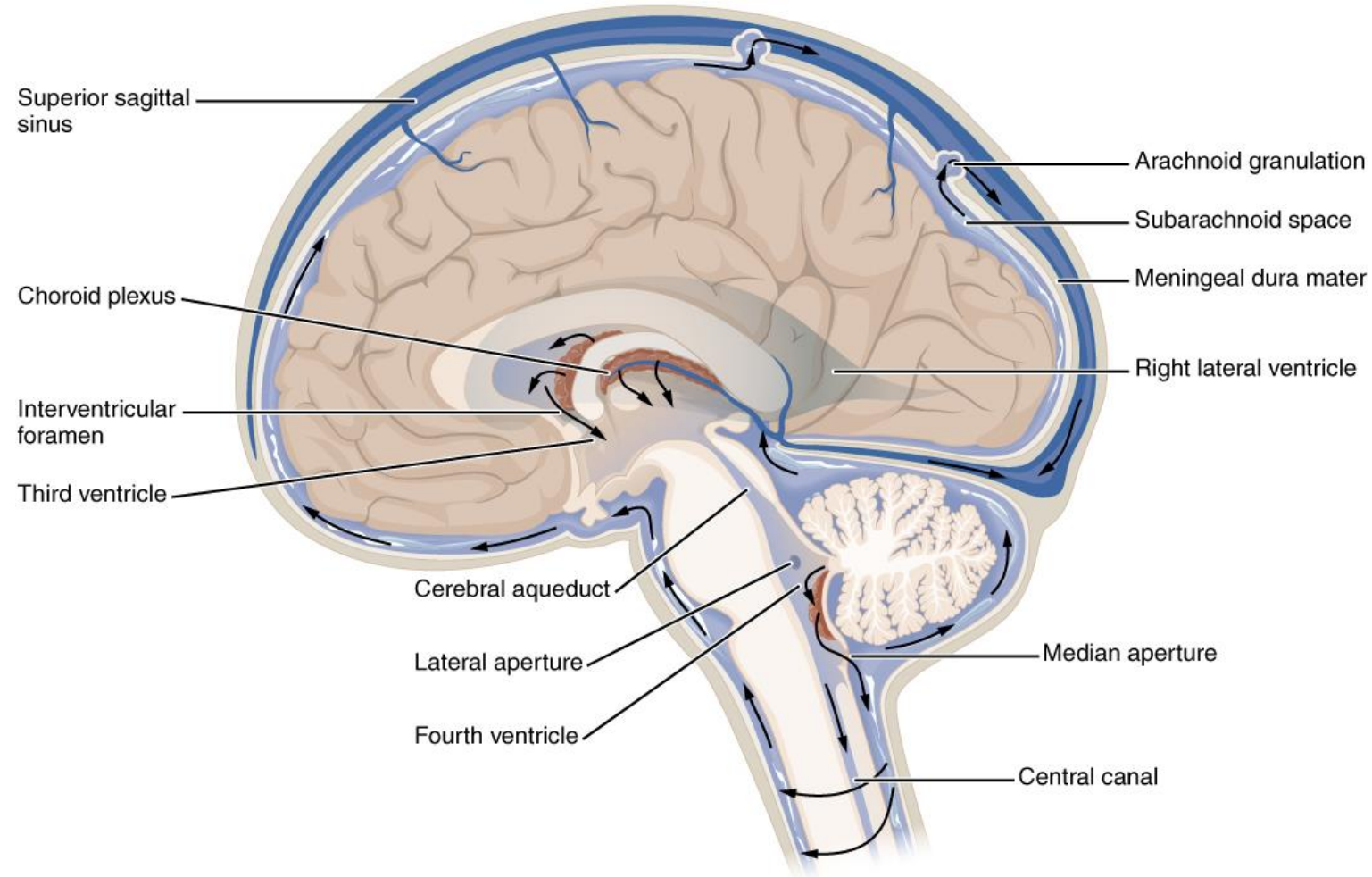
The CNS is composed of brain and spinal.

The function of the tissue in the CNS is crucial to the survival of the organism.



# Cerebrospinal Fluid(CSF)

- circulates throughout and around the CNS.
- Contains a limited amount of the constituents of blood, water, small molecules, and electrolytes, O<sub>2</sub> and CO<sub>2</sub>.
- Is produced by special capillaries called the **choroid plexus** and flows through the nervous tissue of the CNS.
- CSF circulates to remove metabolic wastes from the interstitial fluids of nervous tissues and return them to the blood stream.
- The CSF circulates through all ventricles to emerge into the subarachnoid space where it will be reabsorbed into the blood. There are four ventricles within the brain. The first two are named the **lateral ventricles** and are deep.



Various protective structures surrounding the brain and spinal cord.

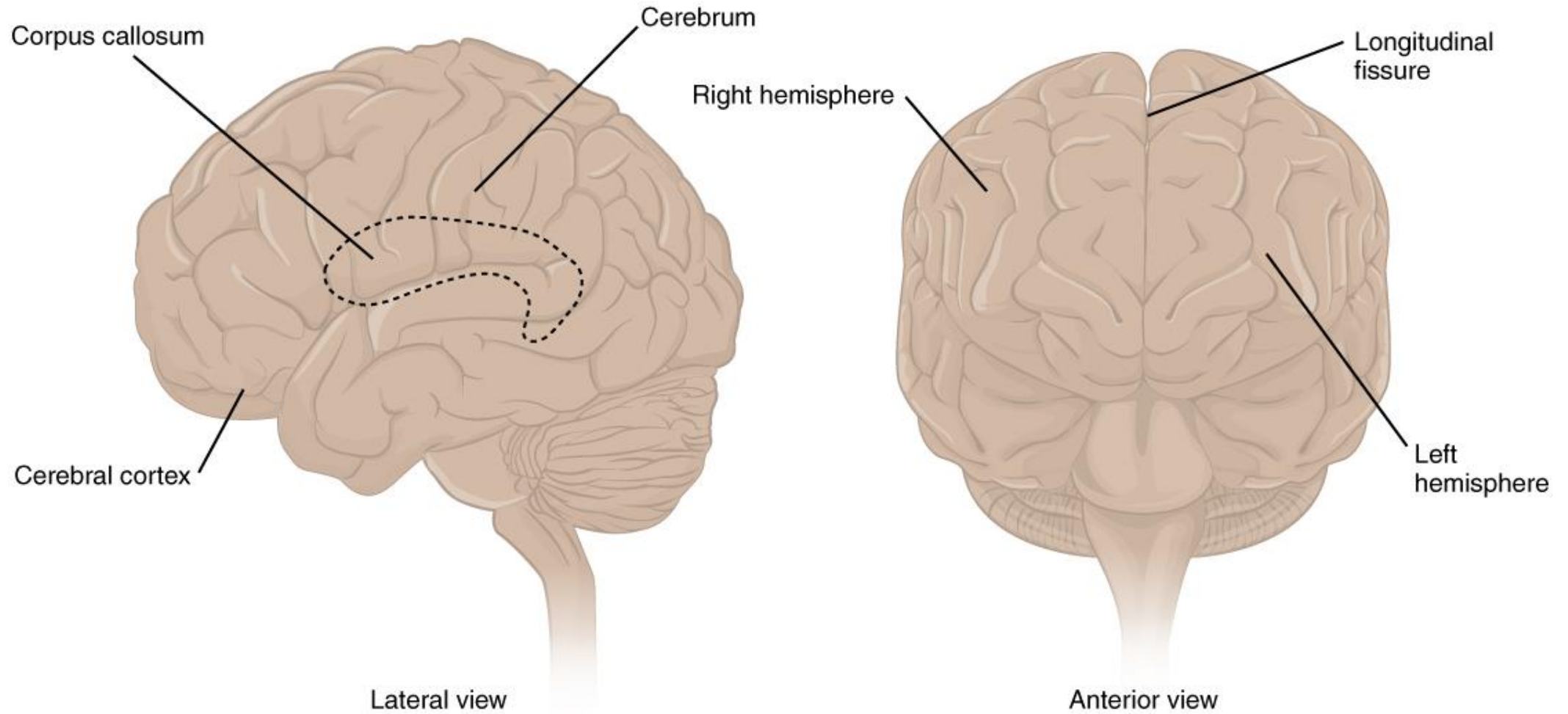
- **The cranial bones and vertebrae** protect from physical trauma.
- **Blood-brain Barrier**, maintains a privileged blood supply to the brain. Protect from toxins and pathogens in the blood stream. Astrocytes form a barrier between capillaries and neurons within the brain. Brain capillaries are the most impermeable capillaries within the body, allowing the most essential nutrients and minerals to enter the tissue. These capillaries and the astrocytes form the blood-brain barrier.
- **The meninges**: membranes composed of connective tissue covering the outer surface of the CNS.
- **The dura mater** a thick fibrous layer and strong protective sheath over the entire brain and spinal cord. It is anchored to the inner surface of the cranium and vertebral cavity.
- **The arachnoid mater** a membrane of thin fibrous tissue that forms a loose sac around the CNS.
- **The arachnoid trabeculae** a thin, filamentous mesh like a spider web, giving this layer its name.
- **Cerebrospinal fluid** circulates below the arachnoid mater in the subarachnoid space.
- **The pia mater**, a thin fibrous membrane that follows the convolutions of gyri and sulci in the cerebral cortex and fits into other grooves and indentations.

# The Cerebrum

The gray mantle of the human brain making up most of the mass of the brain.

The ***longitudinal fissure*** make a large separation between the two hemispheres.

The ***cerebral cortex***, a wrinkled outer portion covers the ***corpus callosum*** the white matter providing the major pathway for communication between the two hemispheres of the cerebral cortex.



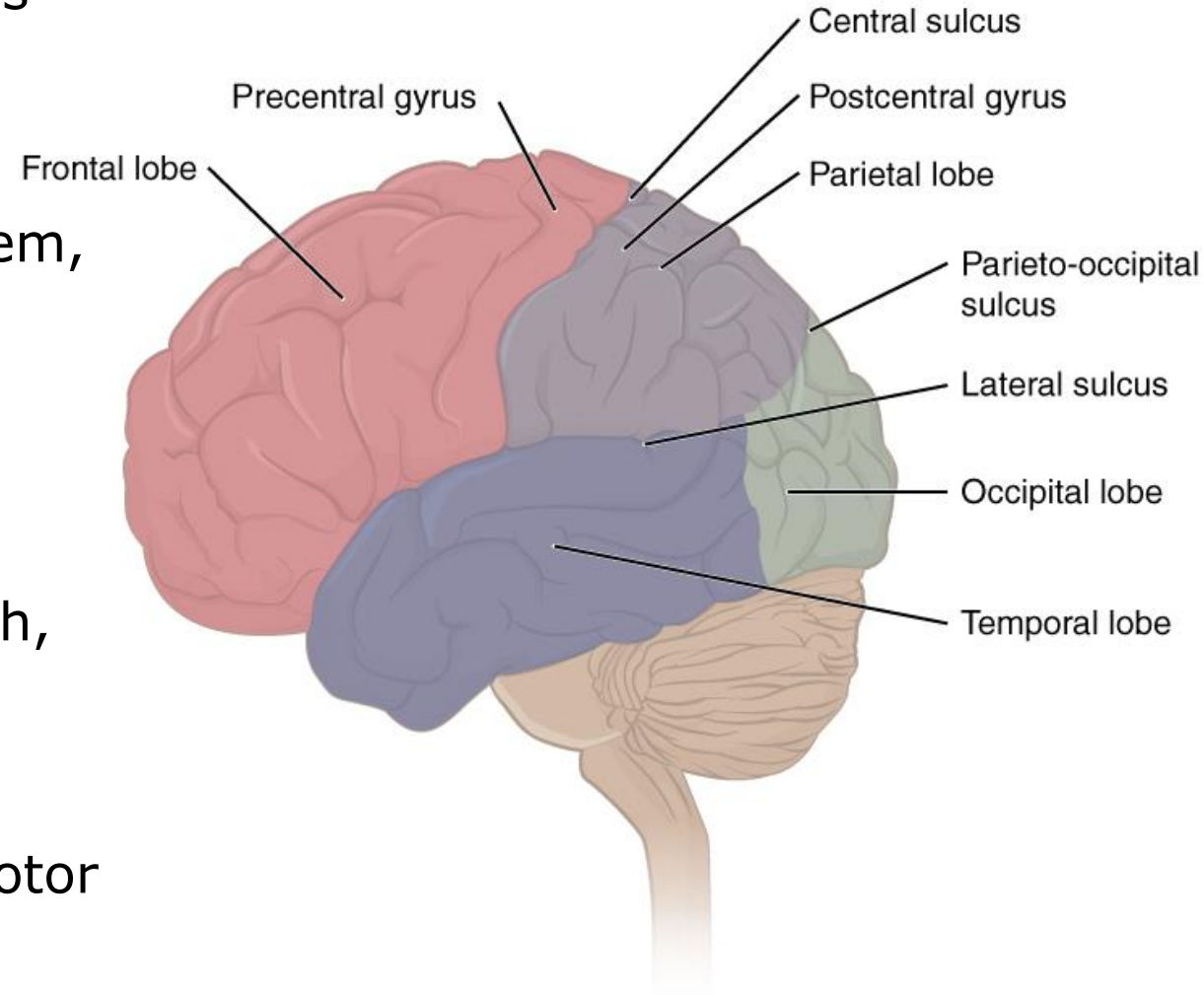
**The occipital lobe** is responsible for primary visual perception. Since visual information is complex, so it is processed in the temporal and parietal lobes as well.

**The temporal lobe** is associated with primary auditory sensation. Being part of the limbic system, play role in memory and long-term memory (hippocampus).

**The parietal lobe** is associated with the main sensation (***somatosensorial***), all of the tactile senses are processed in this area, including touch, pressure, tickle, pain, itch, and vibration, proprioception and kinaesthesia.

**The frontal lobe** is primarily associated with motor functions, language, or controlling movements responsible for speech.

**The prefrontal lobe**, serves cognitive functions basis of personality, short-term memory, and consciousness.



# The Diencephalon

Connection between the cerebrum and the rest of the nervous system.

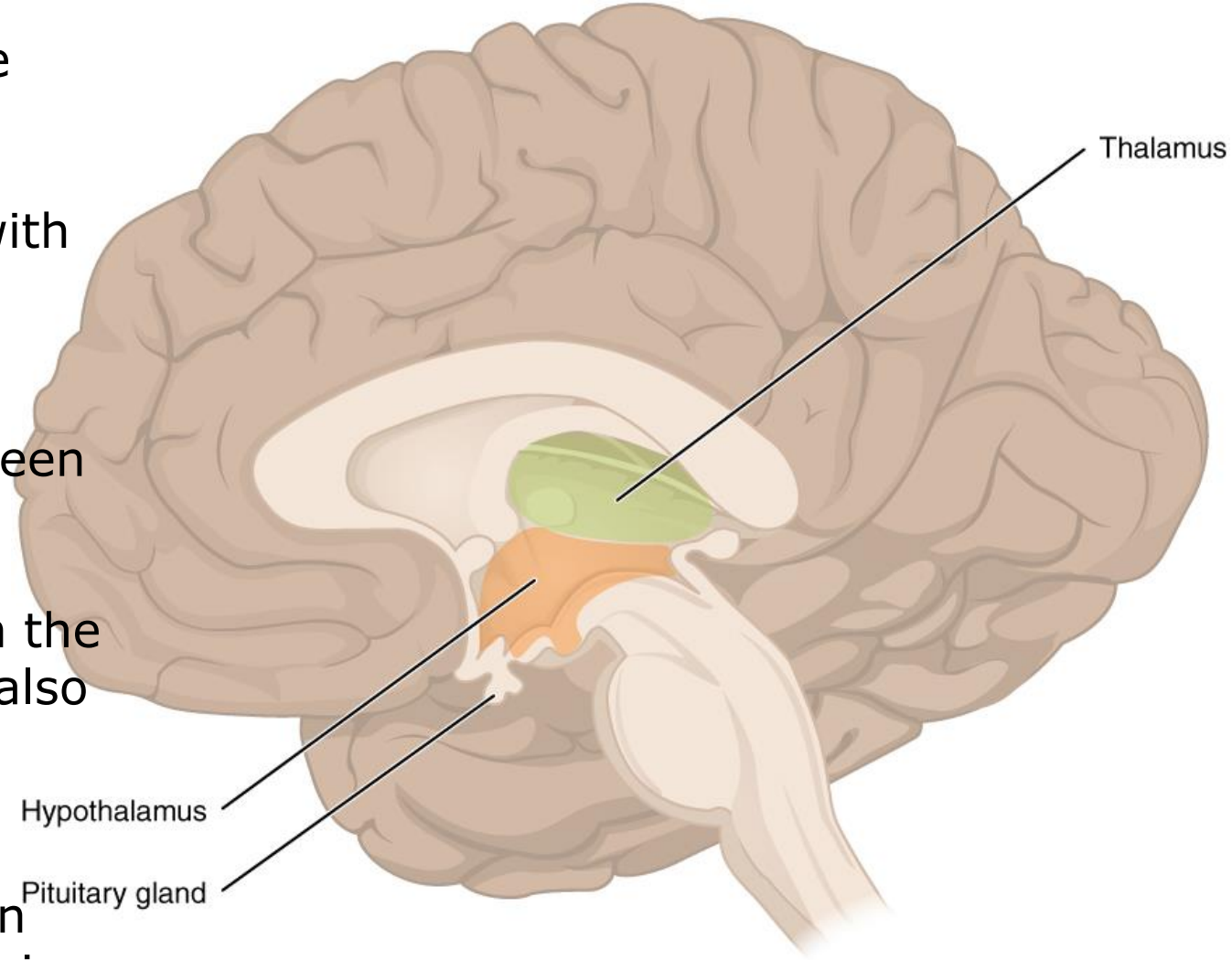
The rest of the brain, the spinal cord, and the PNS all send information to the cerebrum through the diencephalon. Only the system associated with **olfaction** connects directly with the cerebrum.

## Thalamus

Collection of nuclei relaying information between the cerebral cortex and the periphery, spinal cord, or brain stem. All sensory information, except for the sense of smell, passes through the thalamus before processing by the cortex. It also processes that information.

## Hypothalamus

Collection of nuclei that are largely involved in regulating homeostasis. The executive region in charge of the autonomic nervous and endocrine system (regulates anterior pituitary gland).

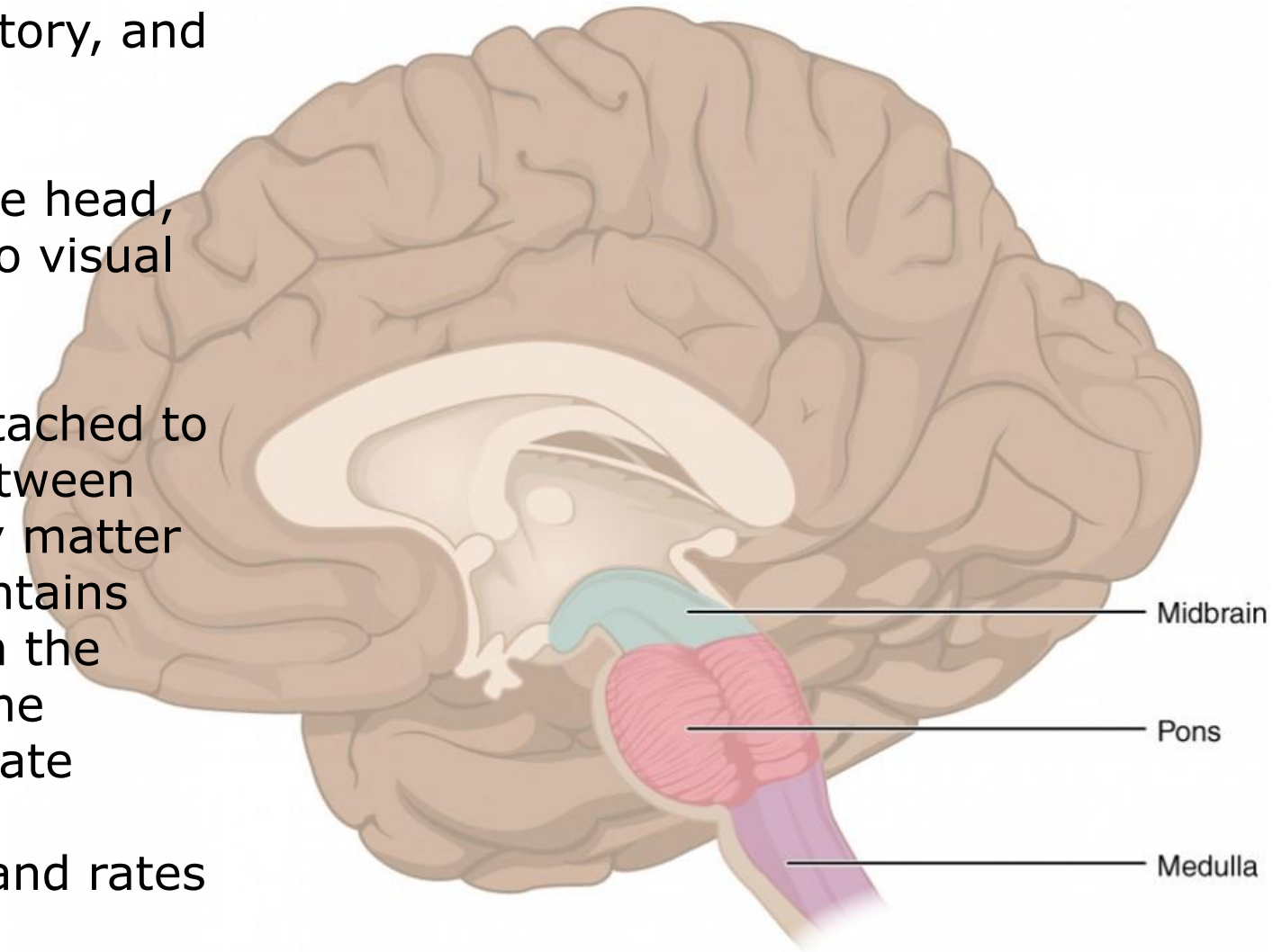




# Brain Stem

Connects the brain to the spinal cord, coordinates sensory representations of the visual, auditory, and somatosensory perceptual spaces.

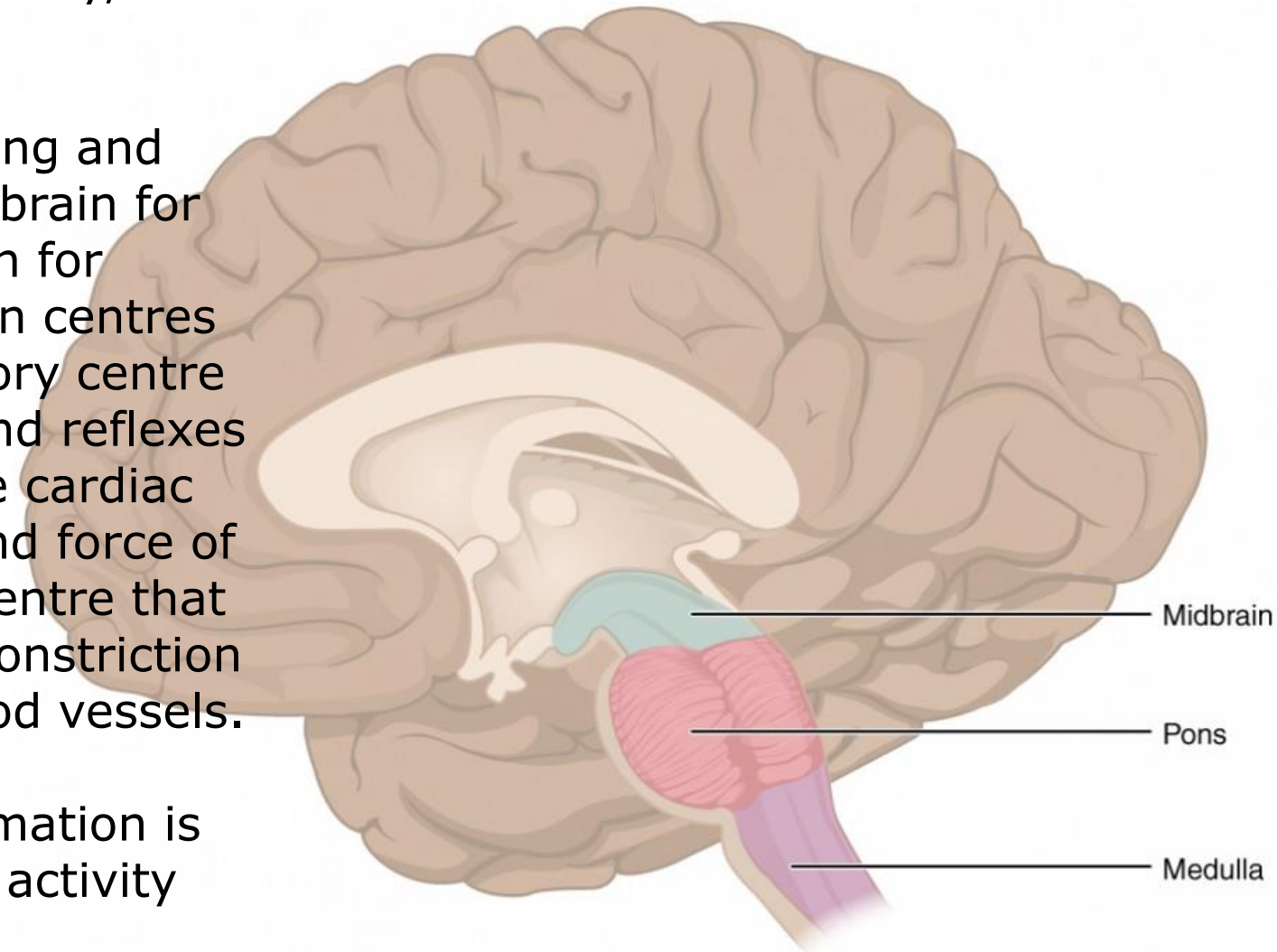
- **Midbrain:** Contains reflex centers for the head, eye, and body movements in response to visual and auditory stimuli.
- **Pons:** A thick bundle of white matter attached to the cerebellum. The main connection between the cerebellum and the brain stem. Gray matter in the tegmentum region of the pons contains neurons receiving descending input from the cerebrum and thalamus that is sent to the cerebellum. Together with medulla regulate several crucial functions, including the cardiovascular and respiratory systems and rates



# Brain Stem

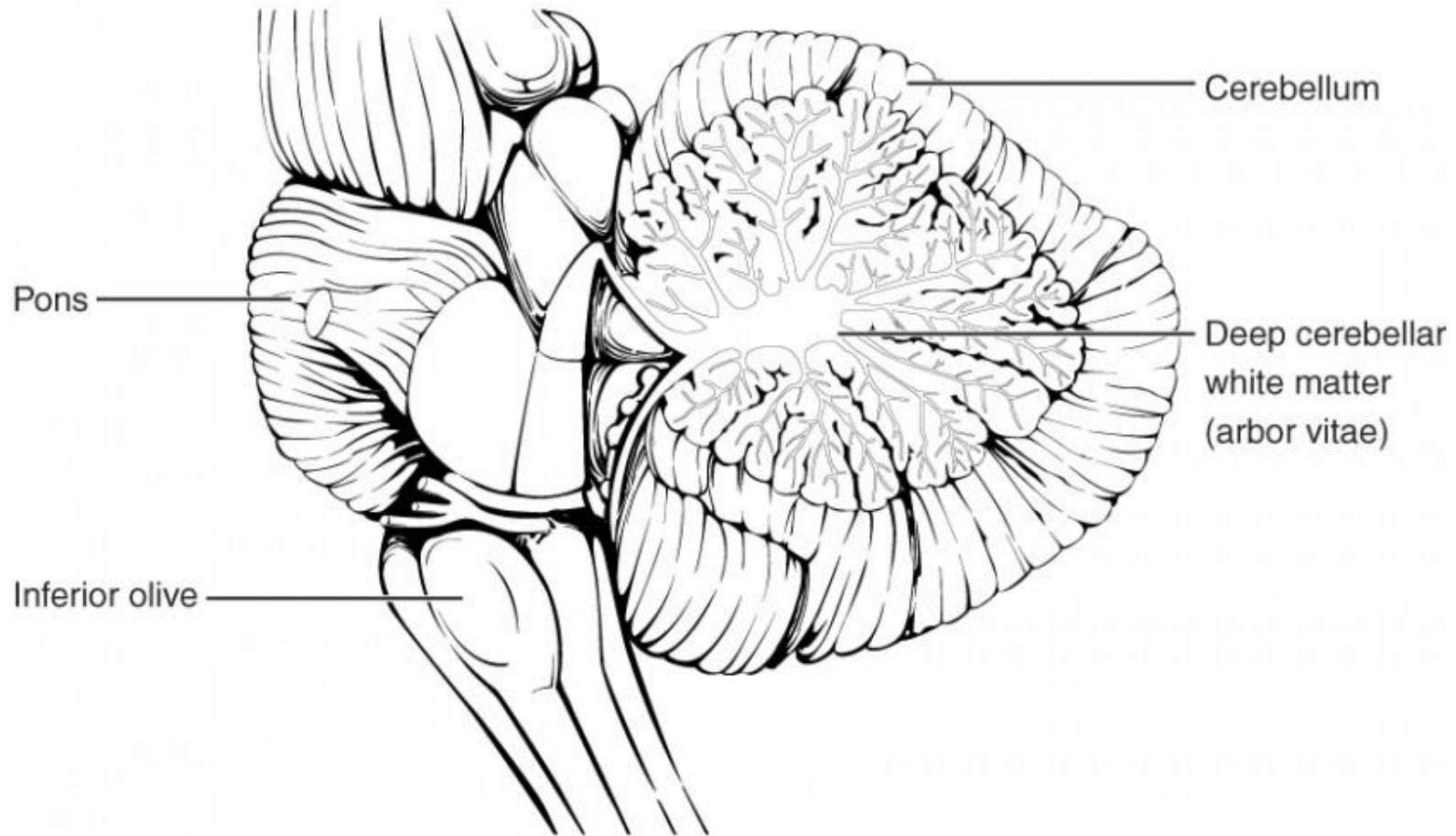
Connects the brain to the spinal cord, coordinates sensory representations of the visual, auditory, and somatosensory perceptual spaces.

- **Medulla oblongata** consists of ascending and descending tracts that are entering the brain for sensory integration and exiting the brain for motor responses. Contains 3 integration centres vital for homeostasis: (1) the respiratory centre that controls the rhythm of breathing and reflexes such as coughing and sneezing, (2) the cardiac control centre that regulates the rate and force of heart contractions, (3) the vasomotor centre that regulates blood pressure through vasoconstriction of blood vessels and vasodilation of blood vessels.
- **Reticular formation.** The reticular formation is responsible for regulating general brain activity and attention. It is related to sleep and wakefulness



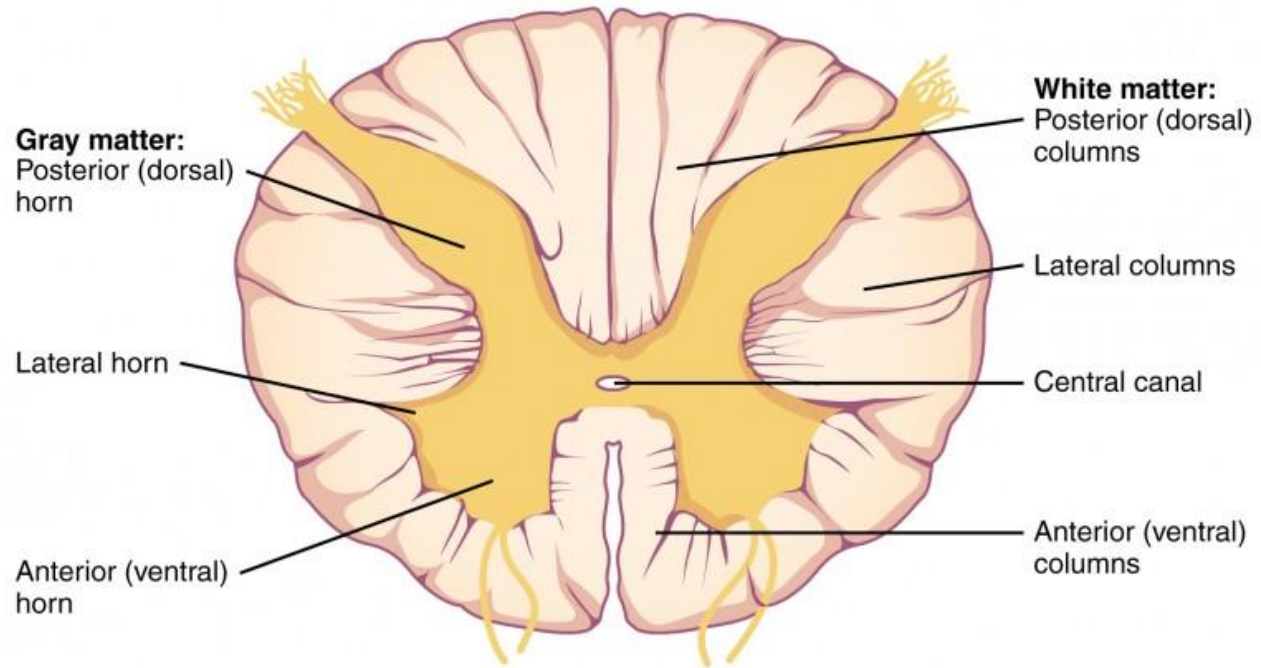
# The Cerebellum

Responsible for coordinating the interactions of skeletal muscles. It controls posture, balance, and muscle coordination during movement.



# The Spinal Cord

Continuous with the brain, it descends from the medulla through the foramen magnum of the occipital bone and extends to the lumbar vertebrae. A centred butterfly shaped of gray matter with outstretched wings. Two basic functions, transmits nerve impulses to and from the brain, and serves as a reflex centre for spinal reflexes.



# The Peripheral Nervous System

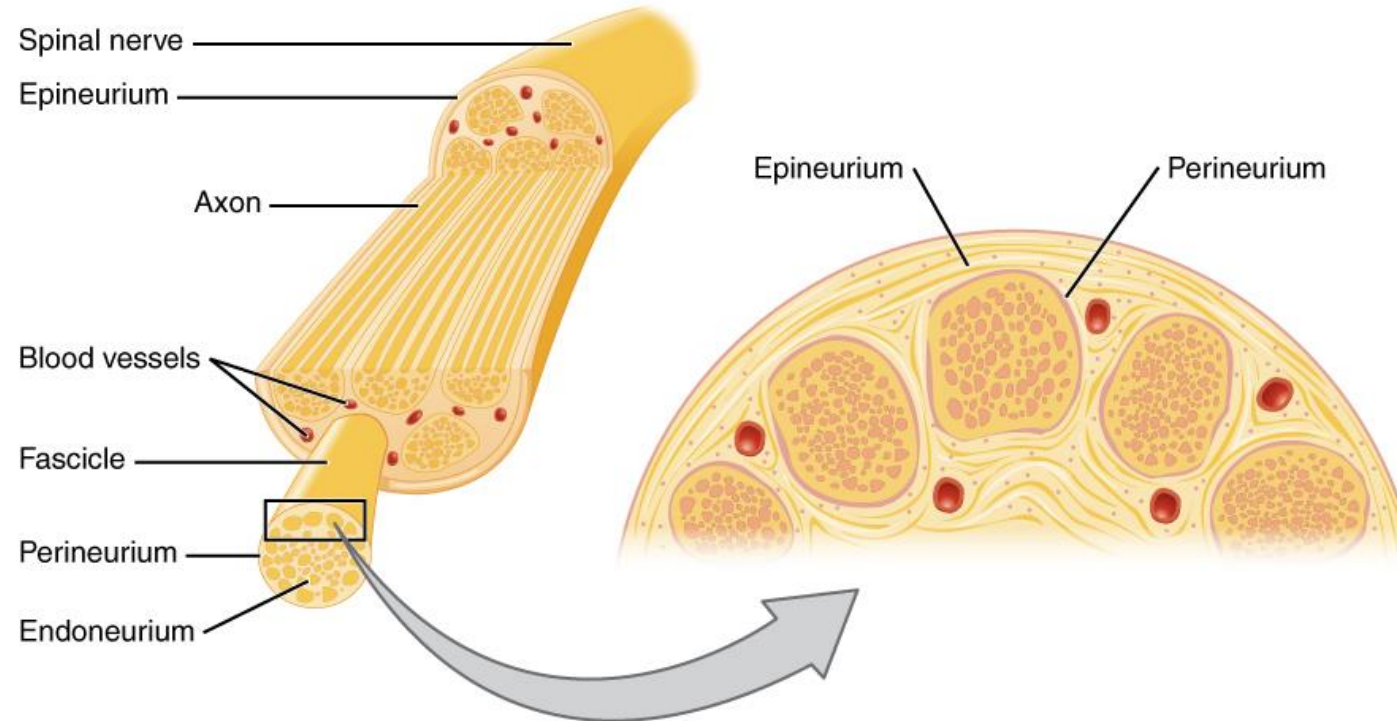
## Nerves

Bundles of axons. Nerves are composed of more than just nervous tissue. They have connective tissues invested in their structure, as well as blood vessels supplying the tissues with nourishment.

**Epineurium:** surrounding layer of fibrous connective tissue **on the** outer surface of a nerve.

**Perineurium** layer of fibrous connective tissue surrounding **fascicles of axons** within the nerve.

**Endoneurium** loose connective tissue surrounding individual axons.



# **Cell Injury and cell adaptation**

# Injury and Death:

Pathology is the study of structural and functional abnormality that manifest as disease of organs and systems. It starts with the study of injury to the cells and organs and their capacity to adapt to such injury.

Disease is manifest as the result of injury to cells, the smallest living units of the body.

This concept can be further develop at the molecular level.

Normal cell function / dysfonctionnement of the cells

# Multicellular organism advantage

- Controlled extracellular environment.
  - Temperature
  - Oxygen availability
  - Ionic content
  - Nutrient Supply
- Possibility of cell specialization in different function
  - Energy storage (hepatocytes and adipocytes)
  - Communication (neurons)
  - Contractile activity (muscle cells)
  - Absorption (intestinal cells)
  - Defense (immune cells)



## Cellular stress:

- Perturbations resulting in the changes in organism's internal and external environment.

## Cell injury:

- Limited responses to persistent sublethal state lead to a state of cell injury.

## Reaction to stress and injury:

- Pattern of response to the stress is the cellular basis of Disease.

## Cell death:

- When injuries exceed the cellular adaptive capacity cell dies.

# Reversible cell injury:

Acute: Environmental changes exceed the cell's capacity to maintain homeostasis.

- Damages will be reversible with complete restoration of structure and function:
  - If the stress is removed in time.
  - If cell can withstand the assault.
    - Interruption of circulation to the heart lasting less than 30 minutes.  
All the structural and functional alterations are reversible.

Chronic: Exposure to persistent sublethal stress.

- Cells have time to adapt to reversible injuries in a number of ways.
  - Each with a morphologic counterpart.

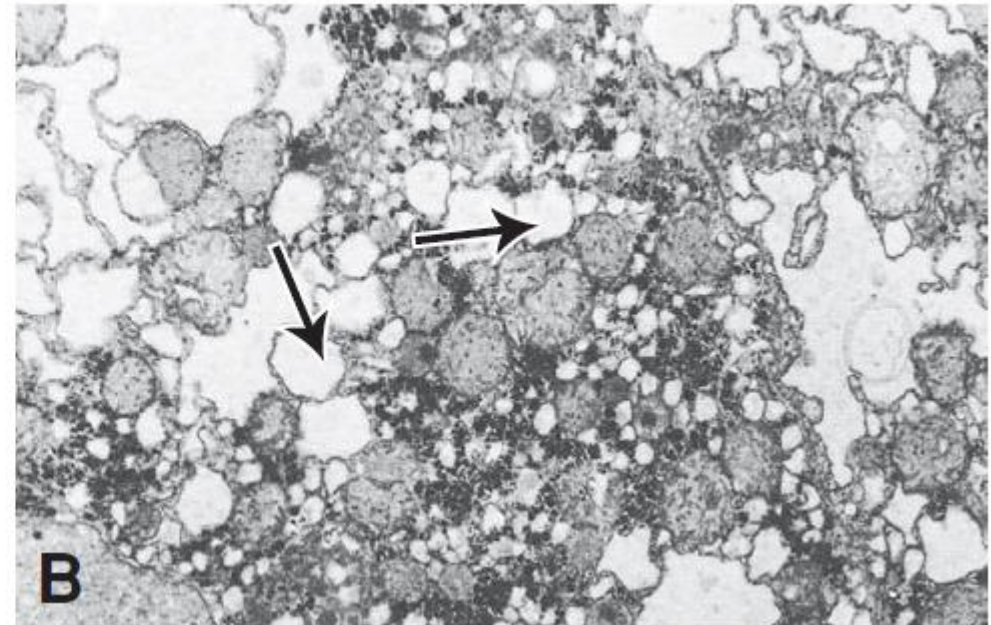
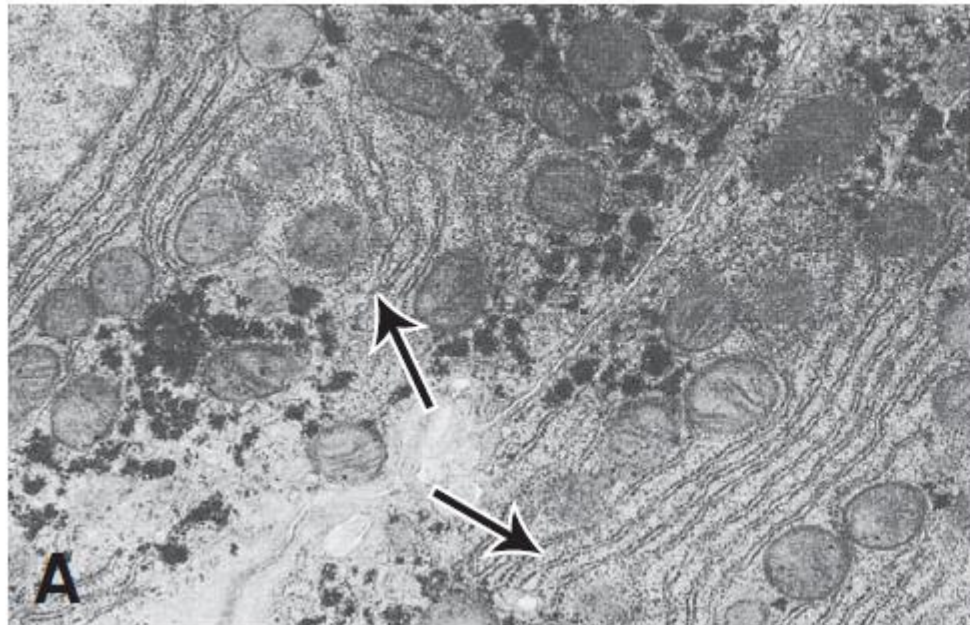
# Irreversible cell injury:

Stress is sufficiently severe irreversible injury leads to cell death.

# Hydropic Swelling Is a Reversible Increase in Cell Volume

Caused by increased water content following acute, reversible cell injury.

- Chemical toxins
- Biological toxins,
- Viral or bacterial infections
- Ischemia,
- Excessive heat or cold exposure



# Hydropic swelling:

Impairment of cellular volume regulation that controls cytoplasmic ionic concentrations

This regulation, particularly for sodium, involves three components:

## 1) The plasma membrane

- Play a critical role in maintaining cell viability.
- Structural and functional barrier between internal milieu and outside.
- Structural envelope to contain the cell's informational, synthetic and catabolic constituents (segregation of the biochemistry of life).
- Maintains constant internal ionic composition beside large gradient differences.
- Semi-permeability.
- Prevents two gradient-driven ion flows:
  - The flow of  $\text{Na}^+$  into the cell.  
The barrier to  $\text{Na}^+$  is leaky and permits some passive entry of sodium into the cell.
  - The flow of  $\text{K}^+$  out of the cell.

2) The  $\text{Na}^+/\text{K}^+$ -ATPase pump: Uses ATP to extrudes  $\text{Na}^+$  from the cell.

3) Adenosine triphosphate (ATP).

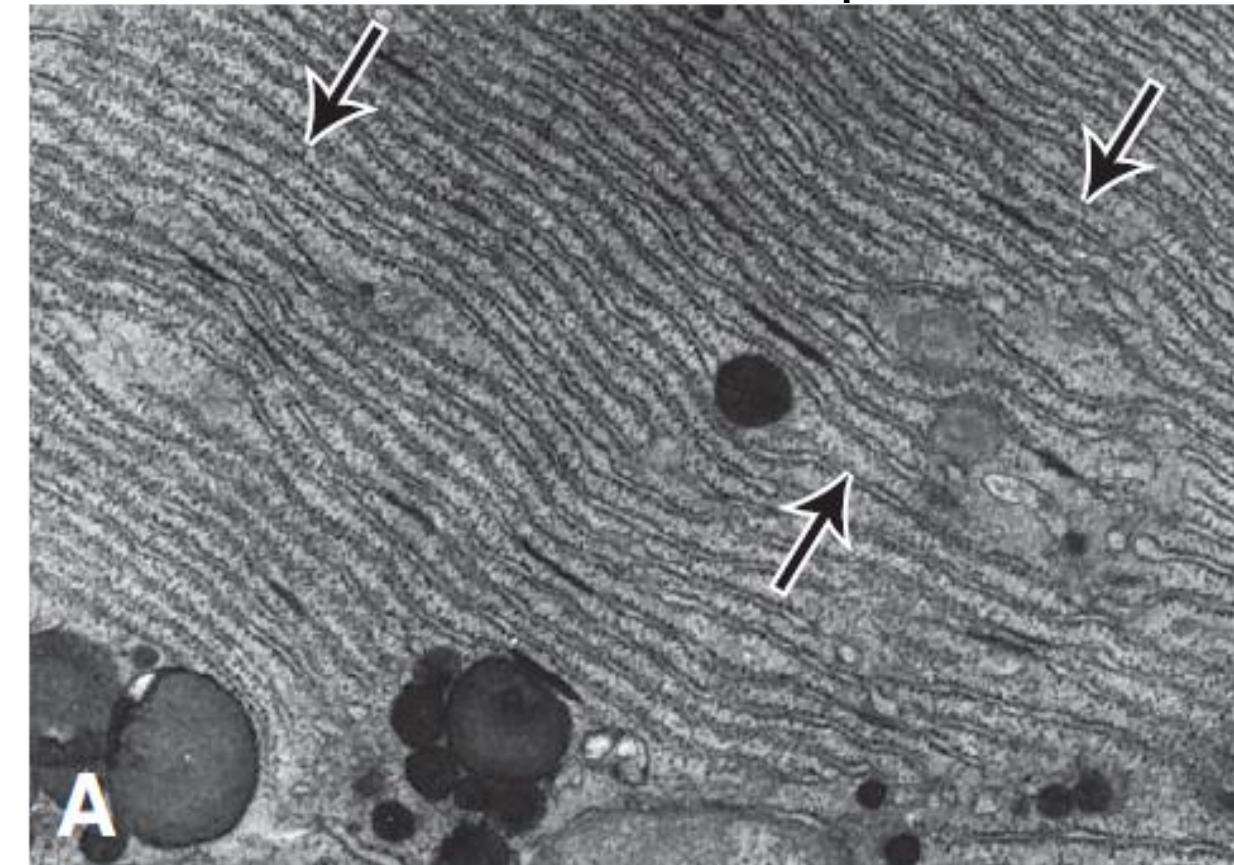
Noxious agents may interfere with this membrane-regulated process by:

- (1) increasing plasma membrane permeability to  $\text{Na}^+$ , exceeding the capacity of the pump to extrude the ion;
- (2) Damaging the pump directly
- (3) Interfering with ATP synthesis

Accumulation of  $\text{Na}^+$  in the cell leads to increased intracellular water to maintain isosmotic conditions. The cell then swells.

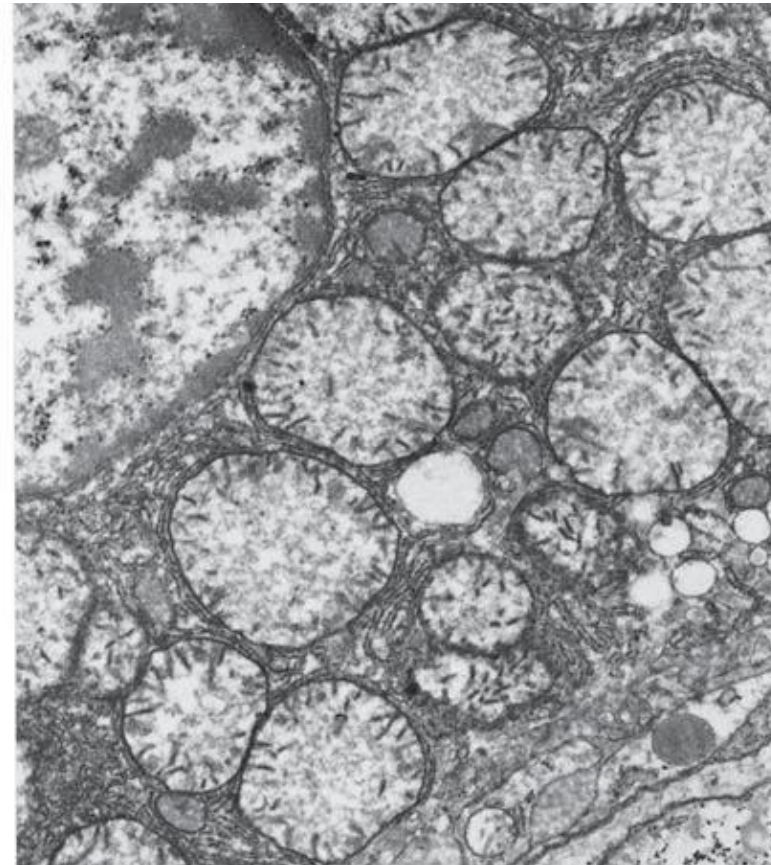
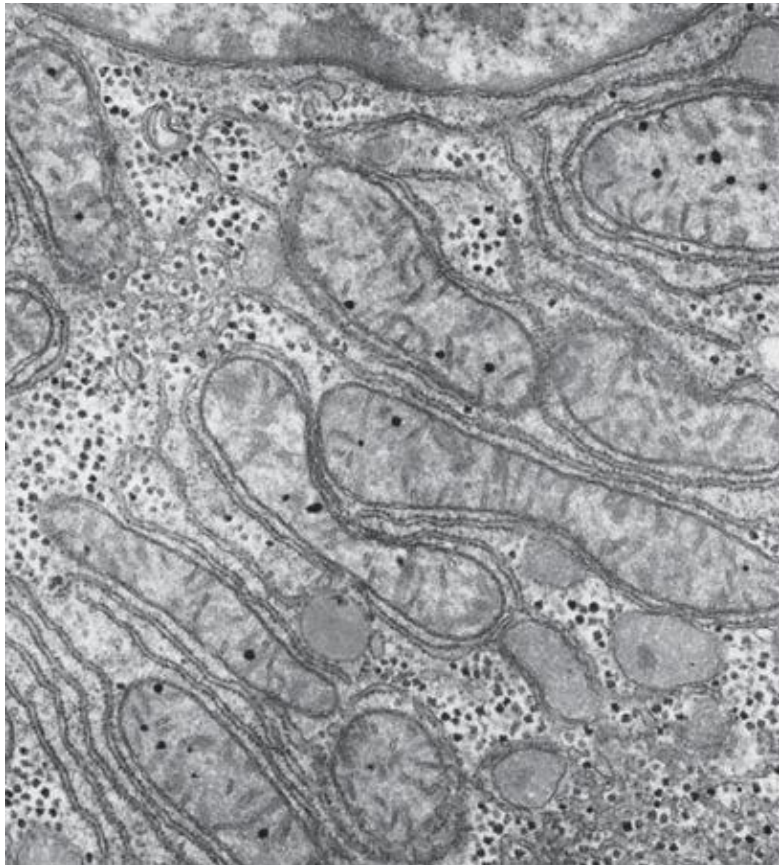
# Subcellular Changes in Reversibly Injured Cells.

**Endoplasmic reticulum (ER):** The cisternae of the ER are distended by fluid in hydropic swelling. Membrane-bound polysomes may disaggregate and detach from the surface of the endoplasmic reticulum.



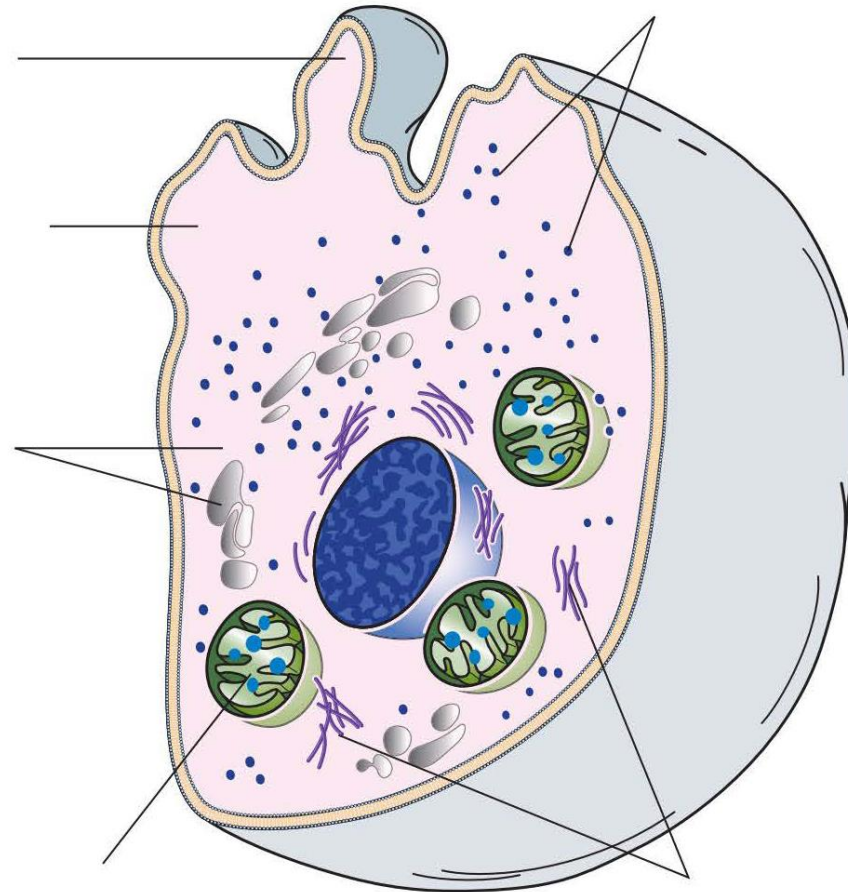
# Subcellular Changes in Reversibly Injured Cells.

**Mitochondria:** In some forms of acute injury, particularly ischemia (lack of adequate blood flow; see below) mitochondria swell. This enlargement is due to dissipation of the mitochondrial energy gradient (membrane potential), impairing volume control.



# Subcellular Changes in Reversibly Injured Cells.

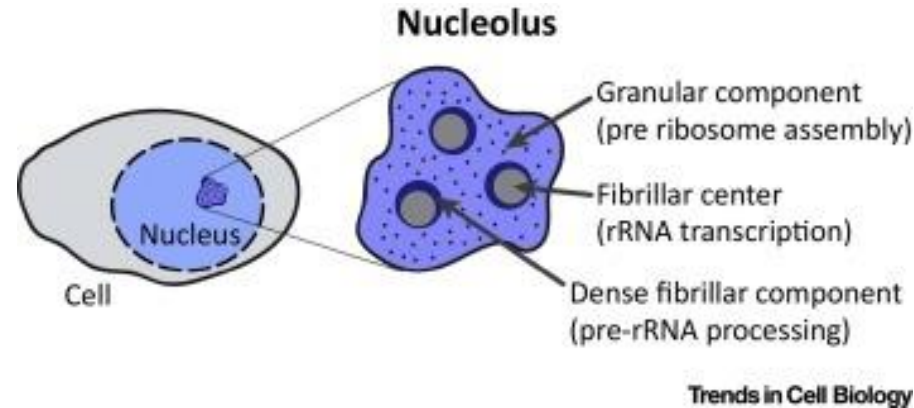
**Plasma membrane:** Blebs of plasma membrane resulting from focal extrusions of the cytoplasm. These can detach from the membrane into the external environment without loss of cell viability.





# Subcellular Changes in Reversibly Injured Cells.

**Nucleus:** Reversible injury of the nucleus is reflected mainly by segregation of the fibrillar and granular components of the nucleolus. Alternatively, the granular component may be diminished, leaving only a fibrillar core.



These morphological changes in cell organelles are reflected in dysfunctions.

- Reduced protein synthesis.
- Impaired energy production.

**After withdrawal of the stress causing the reversible cell injury, by definition, the cell returns to its normal state.**

# Ischemic Cell Injury: Results from Obstruction to blood Flow.

During the resulting oxygen deprivation, ATP cannot be produced by aerobic metabolism. Therefore inefficiently ATP production by anaerobic metabolism take place.

Ischemia initiates a series of chemical and pH imbalances.

Increased generation of injurious free radical species (ROS).

The damage produced by short periods of ischemia tends to be reversible if circulation is restored.

However, long periods of ischemia lead to irreversible cell injury and death.

# Oxidative Stress Is a Key Trigger for Cell and Tissue Injury and Adaptive Responses.

**Reactive Oxygen Species (ROS):** Are the causes of many cell and tissue injury.

Oxygen ( $O_2$ ) the terminal electron acceptor in mitochondria is reduced to form  $H_2O$ . During this process energy is harnessed as an electrochemical potential across the mitochondrial inner membrane.

Three partially reduced species intermediate between  $O_2$  and  $H_2O$

- $O_2^{\cdot-}$ , Superoxide (one electron);
- $H_2O_2$ , hydrogen peroxide (two electrons)
- $OH^{\cdot}$ , the hydroxyl radical (three electrons).

Physiologic sources of these ROS:

- Leaks from mitochondrial electron transport
- Leaks from mixed-function oxygenases (P450).
- NADPH oxidases .....

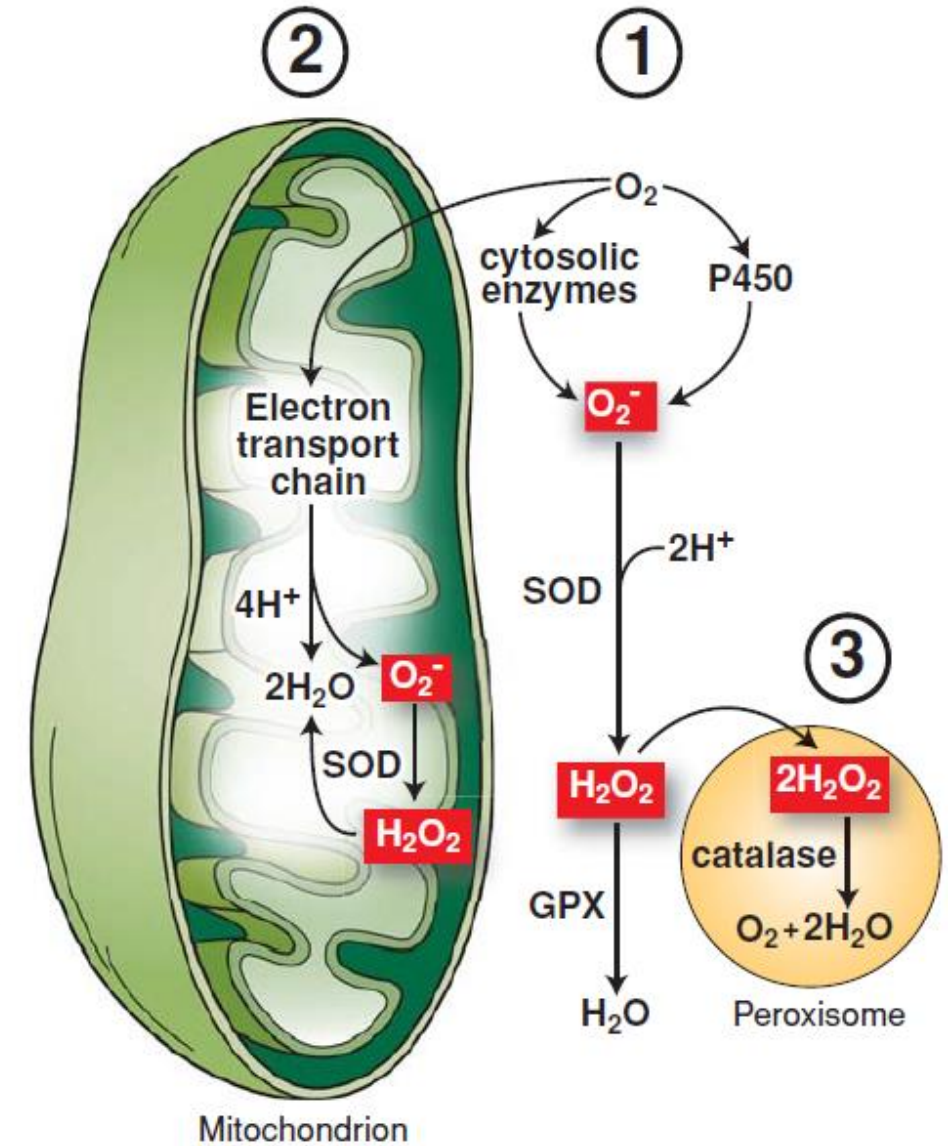
ROS are also important cellular signalling intermediates.

Importantly, excessive ROS levels both cause and aggravate many disorders.

**Superoxide** anion ( $O_2^{\cdot-}$ ) is produced mainly by leaks from mitochondrial electron transport or as part of inflammatory responses.

Coenzyme Q (CoQ) and other imperfections in the electron transport chain allow transfer of electrons to  $O_2$  yielding  $O_2^{\cdot-}$ .

In phagocytic inflammatory cells, activation of a plasma membrane oxidase produces  $O_2^{\cdot-}$  which is then converted to  $H_2O_2$  and eventually to other ROS.



## Hydrogen Peroxide ( $\text{H}_2\text{O}_2$ ):

$\text{O}_2^{\cdot-}$  anions are converted by superoxide dismutase (SOD) to  $\text{H}_2\text{O}_2$ .

$\text{H}_2\text{O}_2$  is also produced directly by a number of oxidases.

However, in excess,  $\text{H}_2\text{O}_2$  is converted to highly reactive  $\text{OH}\cdot$ .

In neutrophils, myeloperoxidase transforms  $\text{H}_2\text{O}_2$  to hypochlorite ( $\text{OCl}^-$ ) to kill microorganisms. If released extracellularly, can kill cells.

Most cells have efficient mechanisms for removing  $\text{H}_2\text{O}_2$ .

Catalase within peroxisomes

Glutathione peroxidase (GPX) in both the cytosol and mitochondria using glutathione (GSH) as a cofactor.

$\text{H}_2\text{O}_2$  is membrane permeable, affects the oxidant balance in all the cell (can diffuse).

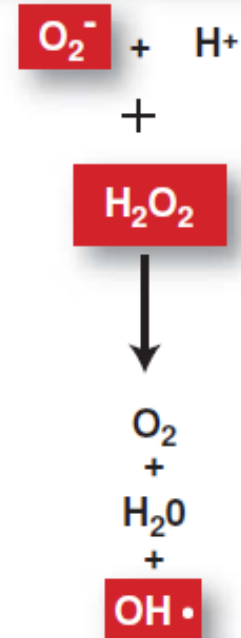
# Hydroxyl Radical (OH•):

- Radiolysis of water.
- Reaction of H<sub>2</sub>O<sub>2</sub> with ferrous iron (Fe<sup>2+</sup>) or cuprous ion (Cu<sup>+</sup>) (Fenton reaction).
- Conversion of O<sub>2</sub><sup>-•</sup> with H<sub>2</sub>O<sub>2</sub> (Haber-Weiss reaction).

## Fenton Reaction



## Haber-Weiss Reaction



***OH<sup>•</sup> is the most reactive ROS can virtually react with all type of macromolecule in the cell.***

**■ Lipid peroxidation:**

- OH<sup>•</sup> removes a hydrogen atom from unsaturated fatty acids in membrane phospholipids to generate a lipid radical.
- The lipid radical then reacts with molecular O<sub>2</sub> to generate a lipid peroxide radical.
- Lipid peroxides act as initiators to initiate a new cycle.
- Lipid peroxides are unstable and break down into smaller molecules.
- Destruction of unsaturated fatty acids of phospholipids results in a loss of membrane integrity.



***OH<sup>•</sup> is the most reactive ROS can virtually react with all type of macromolecule in the cell.***

**■ Protein interactions:**

OH<sup>•</sup> attack proteins by targeting

- The sulfur-containing amino acids cysteine and methionine.
- The nitrogen-containing moieties arginine, histidine and proline, are especially vulnerable.

As a result of oxidative damage, proteins undergo fragmentation, cross-linking, aggregation and eventually degradation.

***OH• is the most reactive ROS can virtually react with all type of macromolecule in the cell.***

**■ Sugars:**

OH• can attack a variety of sugars and other carbohydrates to generate reactive intermediates that alter proteins and lipids to form toxic modification called advanced glycation end-products (AGEs).

- The presence and accumulation of AGEs in many different cell types affect extracellular and intracellular structure and function.
- AGEs contribute to a variety of microvascular and macrovascular complications.
  - Contribute to the development of atherosclerosis.

***OH• is the most reactive ROS can virtually react with all type of macromolecule in the cell.***

**■ DNA damage:**

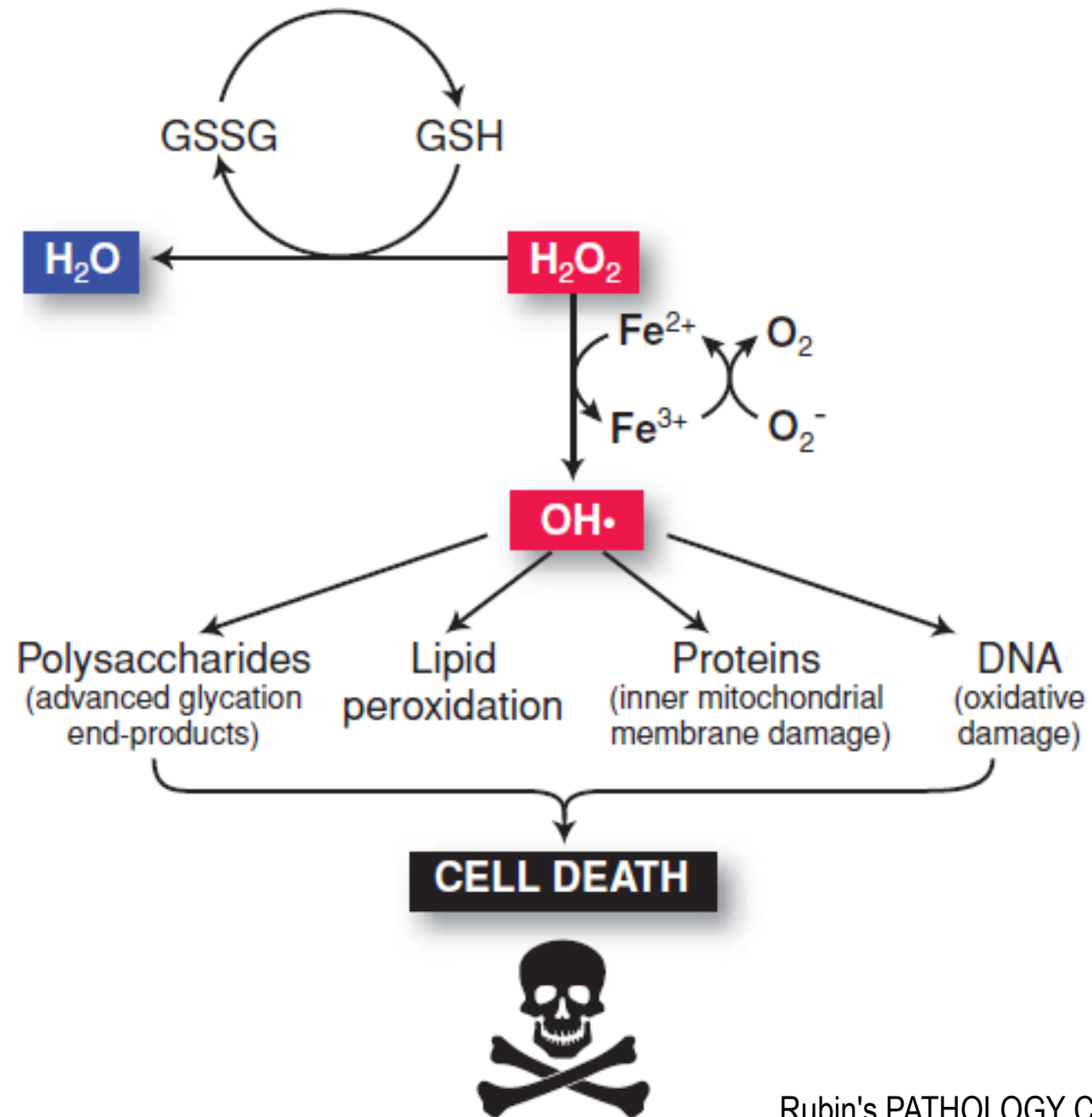
OH• causes diverse structural alterations in DNA.

- Strand breaks.
- Modified bases.
- Cross-links between strands.

When oxidative damage to DNA is sufficiently extensive

The DNA repair pathways are not able to maintain the integrity of the genome.

- Permanent DNA mutations
- Cell death may result as



## **Nitric Oxide ( $\bullet\text{NO}$ ) and Peroxynitrite ( $\text{ONOO}^-$ )**

NO is a reactive nitrogen molecule found in many cells (half-life in seconds).

Nitric oxide synthase (NOS),

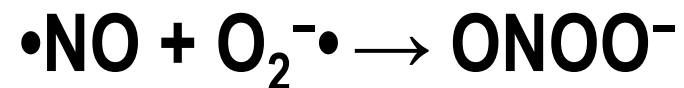
Inducible NOS (iNOS)

Constitutive NOSs found in several tissues.

- NO has diverse signaling properties: Vasodilation.

May be harmful or protective depending on the circumstances.

- Nitrosylation of amines or sulfurs in some amino acids



Peroxynitrite attacks lipids, proteins and DNA.

# Cellular antioxidant machinery determine the outcome of ROS-mediated Injury.

## Detoxifying Enzymes

- SOD is the first line of defense against  $O_2^{\cdot-}$  converting it to  $H_2O_2$  and  $O_2$  ( $2O_2^{\cdot-} + 2H^+ + O_2 \rightarrow H_2O_2 + O_2$ ).
- Catalase located in peroxisomes, converts  $H_2O_2$  to water, ( $2H_2O_2 \rightarrow 2H_2O + O_2$ ), preventing its conversion to  $OH^{\cdot}$ .
- Glutathione peroxidase (GPX) catalyzes the reduction of  $H_2O_2$  and lipid peroxides in mitochondria and the cytosol ( $H_2O_2 + 2GSH \rightarrow 2H_2O + GSSG$ ).

## Scavengers of ROS

- **Vitamin E ( $\alpha$ -tocopherol)** a fat soluble terminal electron acceptor that aborts free radical chain reactions. Protects the membranes from lipid peroxidation.
- **Vitamin C (ascorbate)** is water soluble and reacts directly with  $O_2^{\cdot-}$ ,  $OH\cdot$  and some products of lipid peroxidation. Regenerate the reduced form of vitamin E.
- **Retinoids**, the precursors of vitamin A, are lipid soluble and act as chain-breaking antioxidants.
- **$\cdot NO$**  may scavenge ROS, principally by chelation of iron and combination with other free radicals.

Extracellular molecules that act as antioxidants include albumin.

# REACTIONS TO PERSISTENT STRESS AND CELL INJURY

Persistent stress often requires that a cell either adapt or die.

At the cell level, there is chronic adaptation rather than chronic injury.

The major adaptive responses are:

- Atrophy
- Hypertrophy
- Hyperplasia
- Metaplasia
- Dysplasia
- Intracellular storage

In some settings, as noted, neoplasia may follow adaptive responses.

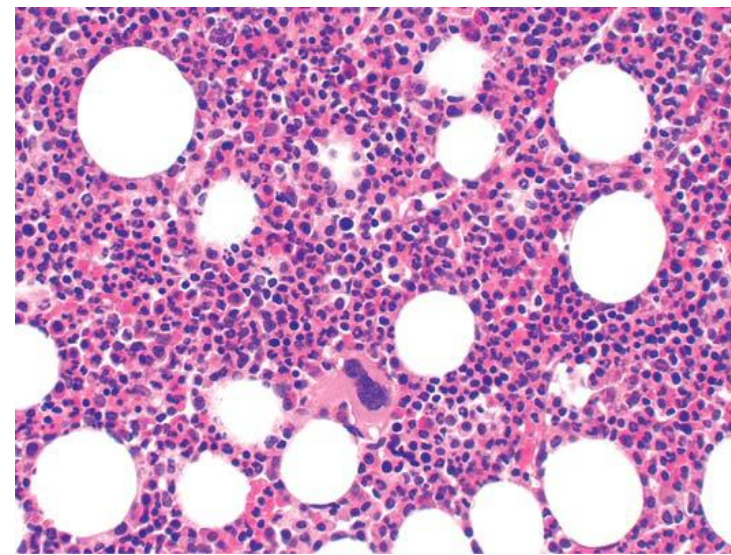
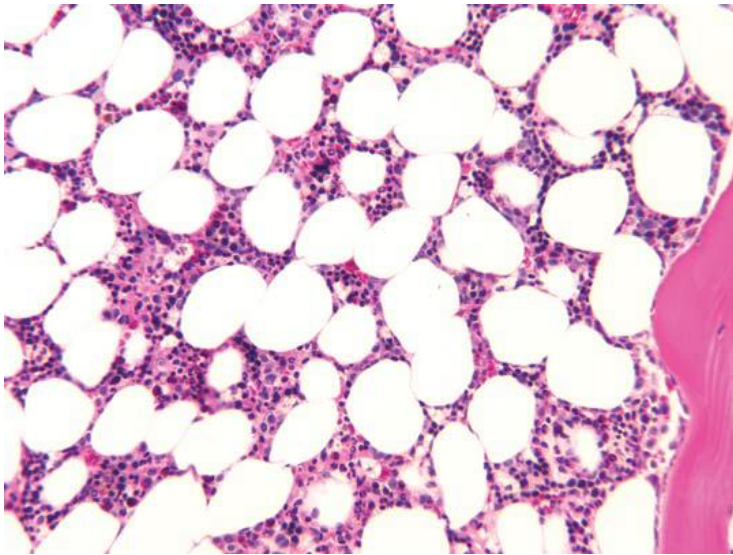


# Hyperplasia: an increase in cell numbers in an organ or tissue.

Stimuli causing hyperplasia and the mechanisms involved depend on the tissue and cell type.

Cells divide to generate an organ or tissue that contains more cells (hypercellular).

- From cells that are already cycling.
- From resting progenitors.



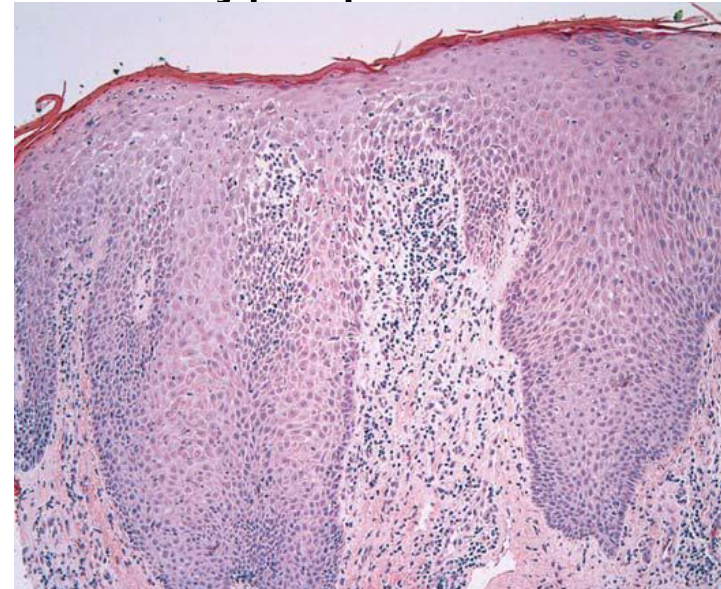
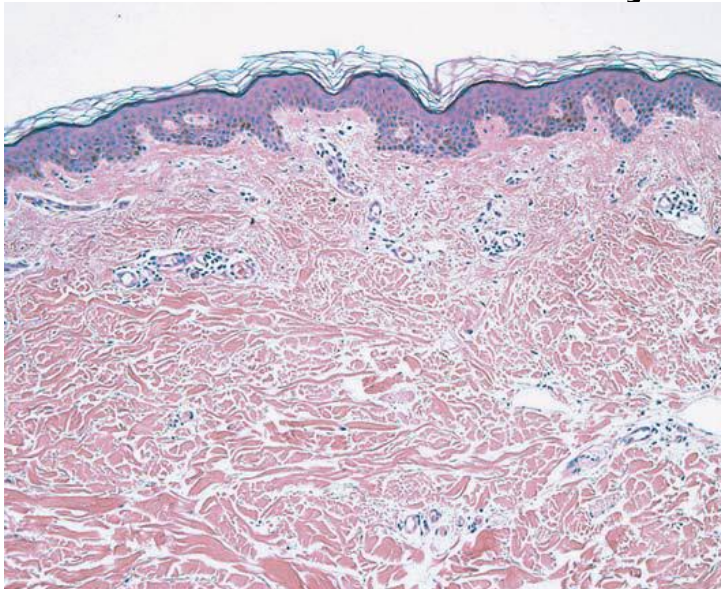
**Hyperplasia** may occur as a response to:

- Altered endocrine milieu.
  - Increase in estrogens at puberty or early in the menstrual cycle leads to increased numbers of endometrial and uterine stromal cells.
  - Erythropoietin secretion by renal tumors leads to hyperplasia of erythrocytes in the bone marrow.
- Increased functional demand.
  - Hyperplasia bone marrow.
    - High altitudes, low O<sub>2</sub> tension
    - Chronic blood loss, as in excessive menstrual bleeding.
  - Immune response to antigens may lead to lymphoid hyperplasia.

## Chronic Injury: persistent injury may result in hyperplasia.

- *Unresolved* inflammation.
- Chronic physical or chemical injury.
  - Compensatory hyperplastic response.
    - Corns or calluses
      - Hyperplasia of the skin to protect from continued pressure.

Inappropriate hyperplasia can itself be harmful  
psoriasis, which is characterized by conspicuous hyperplasia of the skin.



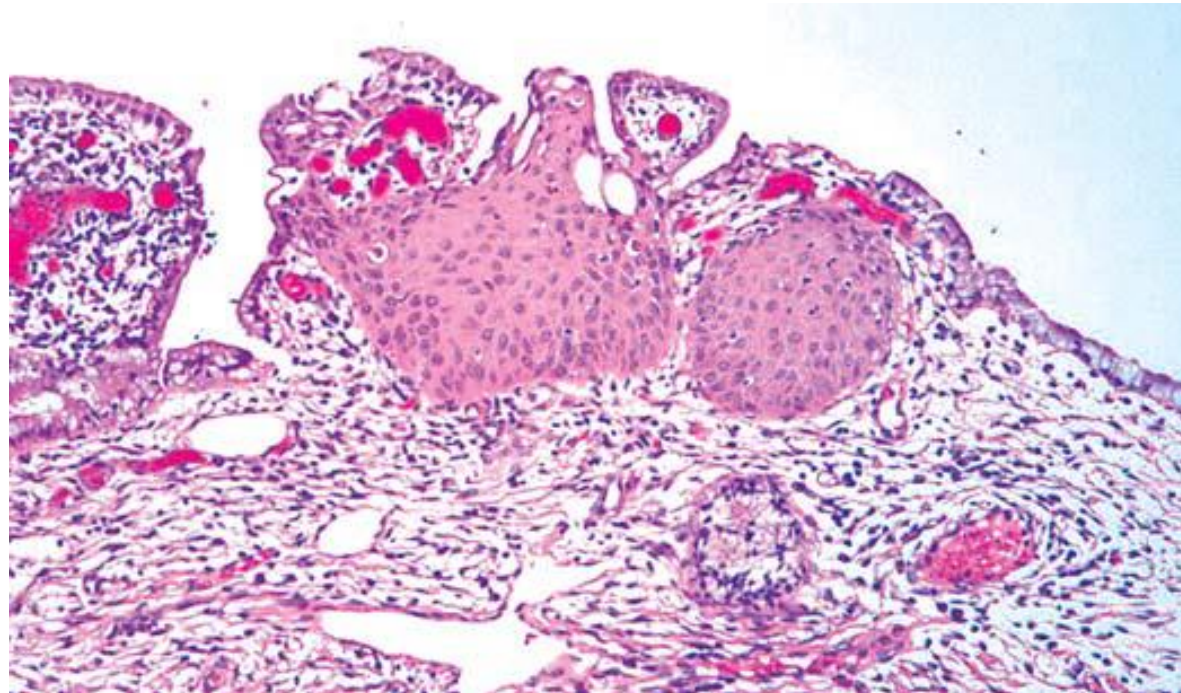
## Hyperplastic responses:

- Cellular and molecular mechanisms responsible for the increased mitotic activity. Relates to altered control of cell proliferation.
- **Hypertrophy may occur simultaneously with hyperplasia.**

# Metaplasia: Conversion of one differentiated cell type to another.

Allow tissue to assume a phenotype that protects it best from the insults.

- Glandular epithelium is replaced by squamous epithelium.
- Replacement of one glandular epithelium by another.
  - Altered differentiation of maturing cells.
  - Change in the commitment of tissue stem cells from one lineage to another.



Endocervix normal columnar epithelium and a focus of squamous metaplasia in the center

## **Metaplasia: Conversion of one differentiated cell type to another.**

Although metaplasia is an adaptive response it is not necessarily innocuous.

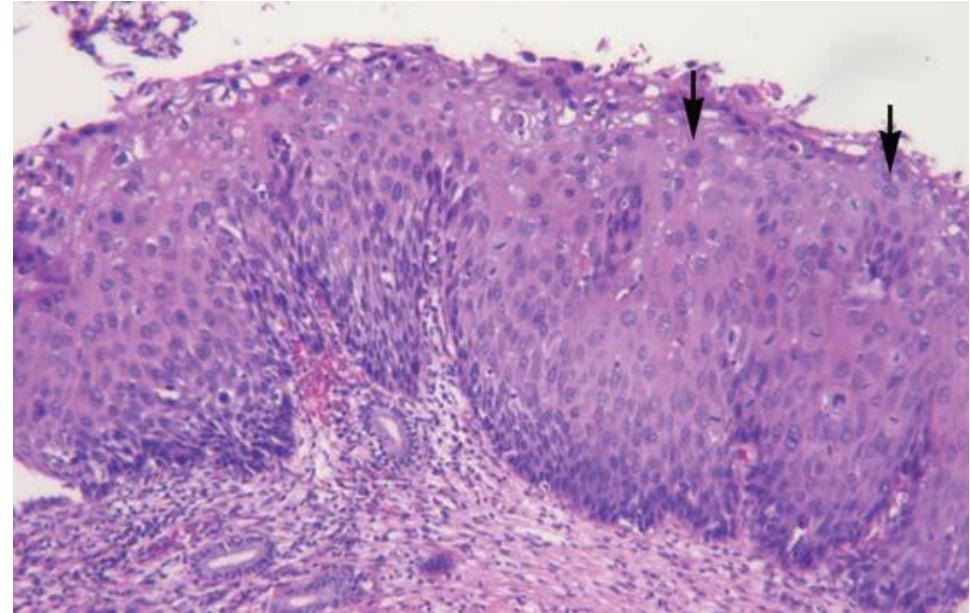
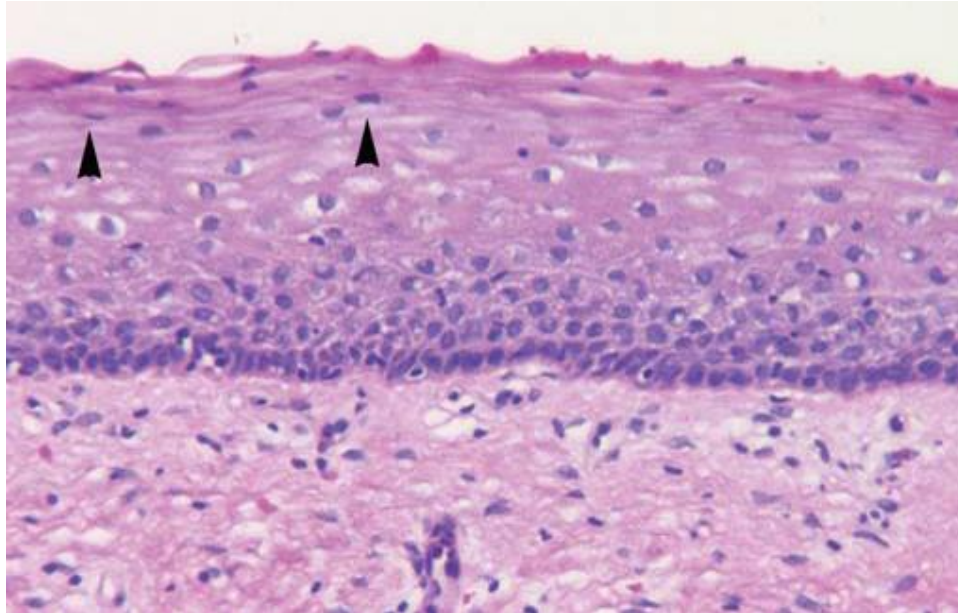
- Squamous metaplasia protects bronchus from tobacco smoke, but it also impairs mucus production and ciliary clearance.
- Cancers may develop in metaplastic epithelium of the lung, cervix, stomach and bladder often arise in such areas.

Metaplasia is usually fully reversible if the noxious stimulus is removed.

# Dysplasia is disordered cellular growth and maturation

Epithelium lining normally exhibit cells with uniform size, shape and nuclei. Cells are arranged in a regular fashion; e.g. squamous epithelium progresses from plump basal cells to flat superficial cells. In dysplasia, this pattern is disturbed.

Dysplasia occurs most often in hyperplastic squamous epithelium and in areas of squamous metaplasia, such as in the bronchus or the cervix.



***Dysplasia is a preneoplastic lesion, in that it is a necessary stage in the multistep cellular evolution to cancer.***

- Dysplasia is included in morphologic classifications of the stages of intraepithelial neoplasia in several organs (e.g., cervix, prostate, bladder).
- Severe dysplasia is an indication for aggressive preventive therapy to
  1. Cure the underlying cause.
  2. Eliminate a noxious agent.
  3. Surgically remove the offending tissue.

Dysplasia results from sequential mutations in a proliferating cell population.

Dysplasia is the morphologic expression of a disturbance in growth regulation.

However, unlike cancer cells, dysplastic cells are not entirely autonomous, and with intervention the tissue may still revert to normal.



# **Atrophy and Hypertrophy are two sides of the same coin**

Atrophy is the decreased size or function of cells or organs.

- Pathologic: processes involved in some chronic diseases and aging.
- Physiologic settings:           Disuse of skeletal muscle.  
  Loss of hormonal signals following menopause.  
  To accommodate changes in its environment.

## **Atrophy of an organ differs from cellular atrophy.**

Reduction in an organ's size:

- Either by reversible cell shrinkage.

Disused limb cause muscle cells to shrink. Reversed with physical activity.

- Either by irreversible loss of cells.

Atrophy of the brain in Alzheimer disease due to excessive cell death is irreversible.

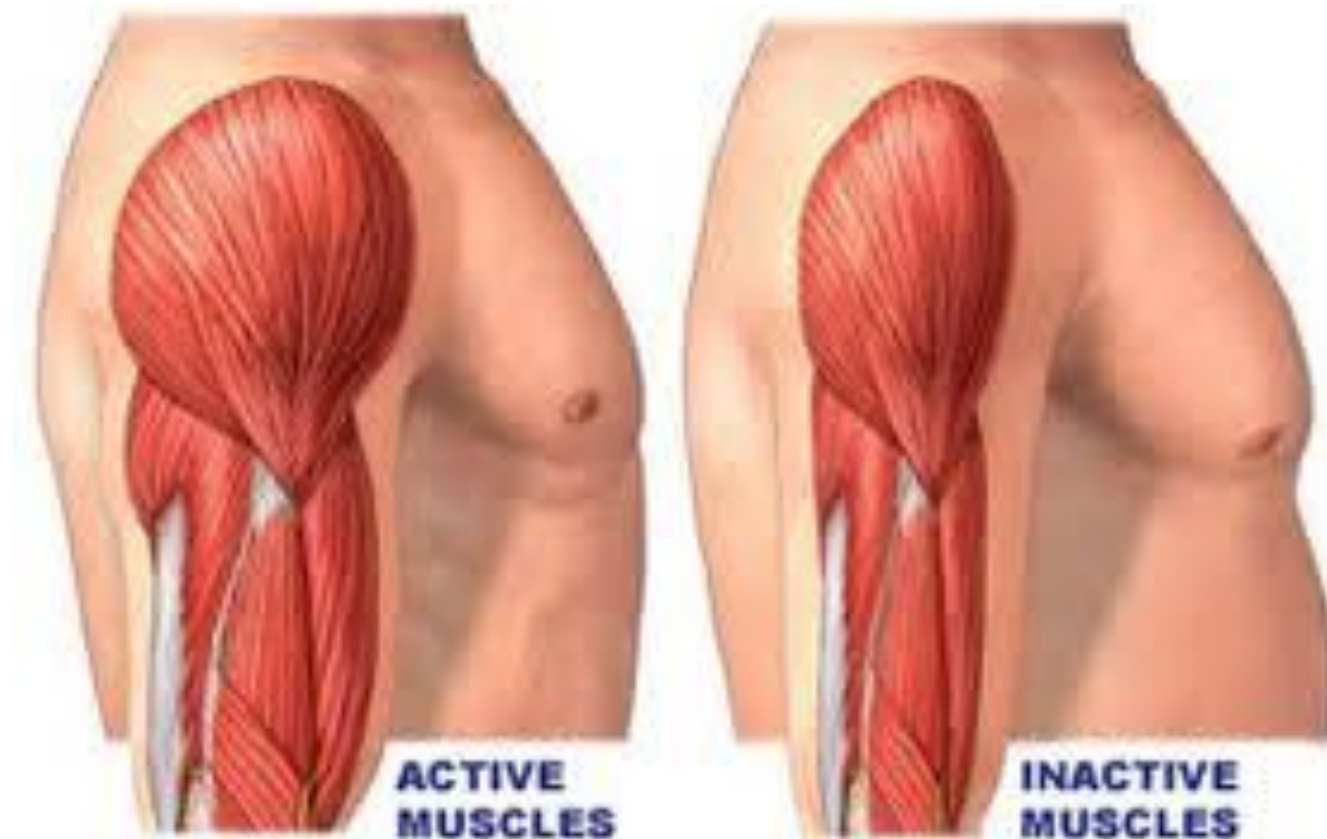
# Atrophy of the brain



Marked atrophy of the frontal lobe is characterized by thinned gyri and widened sulci.

# Cell Atrophy

- Shrinkage in cell size due to the loss of the cells content (molecules and organelles)
- The entire tissue or organs diminishes in size and functional capacity.



## **Normal homeostasis determines individual cell mass**

Cell size reflects an equilibrium between anabolic and catabolic processes. Skeletal muscle is the best studied model.

Myocytes can adapt to increased functional demand:

- Increasing synthesis of muscle proteins.
- Downregulating their degradation.

Muscle atrophy (wasting) may have many causes:

- Reduced synthesis.
- Increased degradation of contractile proteins.

# Conditions leading to atrophy

## Reduced functional demand

After immobilization the limb's muscle cells lose mass, and strength is correspondingly reduced.

## Inadequate supply of oxygen

***Interference with blood supply to tissues, called ischemia*** causes O<sub>2</sub> deprivation. If the ischemia is not sufficient to kill cells, affected cells may be viable but functionally impaired.

## Insufficient nutrients

Starvation or malnutrition leads to wasting (decreased mass) of skeletal muscle and adipose tissue. Decreased size is prominent in cells that are not vital to the survival of the organism.

## **Interruption of trophic signals**

The activities of many cells depend on signals placing functional demands on them:

- Hormonal
- Neuromuscular transmission.

If the source of the signal is removed cells depending on that stimulus will atrophy.

- Ablation of an endocrine gland.
- Denervation.

Resection of the anterior pituitary leads to deficiency:

- Thyroid-stimulating hormone (TSH),
- Adrenocorticotrophic hormone (ACTH, also called corticotropin)
- Follicle-stimulating hormone (FSH)

Results in atrophy of the thyroid, adrenal cortex and ovaries respectively.

## **Persistent Cell Injury**

Persistent cell injury during:

- Prolonged viral or bacterial infections
- Inflammation in immunologic and granulomatous disorders.
  - Atrophy of the gastric mucosa during chronic gastritis.
  - Small intestinal villous atrophy during celiac disease.

## **Increased Pressure**

Prolonged pressure in inappropriate locations, produces atrophy.

Prolonged bed rest may create sustained pressure on the skin, causing decubitus ulcers (bed sores).

# Aging

In addition to conspicuous loss of skeletal muscle and adipose tissue one hallmark of aging is decreased size and/or number of nonreplicating cells.

- Brain size is invariably diminished.
- Heart: **senile atrophy** of the heart.
- The mass of all parenchymal organs decreases with age.

## Chronic Diseases

Cancer.

Congestive heart failure.

AIDS.

Are associated with generalized atrophy of many tissues.

Tissue loss exceeds what can be attributed to decreased caloric intake and reflects alterations in cytokines and other mediators.



**Conditions that cause atrophy are often the inverse of those that stimulate hypertrophy:** the signalling pathways controlling hypertrophy and atrophy are closely interconnected.

**Hypertrophy** is an increase in cell or organ size and functional capacity. In condition of increased trophic signals or functional demands.

- Larger cells (hypertrophy)
- Increased cell number (hyperplasia) in some cases.

Heart

Skeletal muscle.

Such adaptive responses are achieved mainly by increased cell size, which leads to increased organ mass.

In kidney cell numbers and cell size may both increase.

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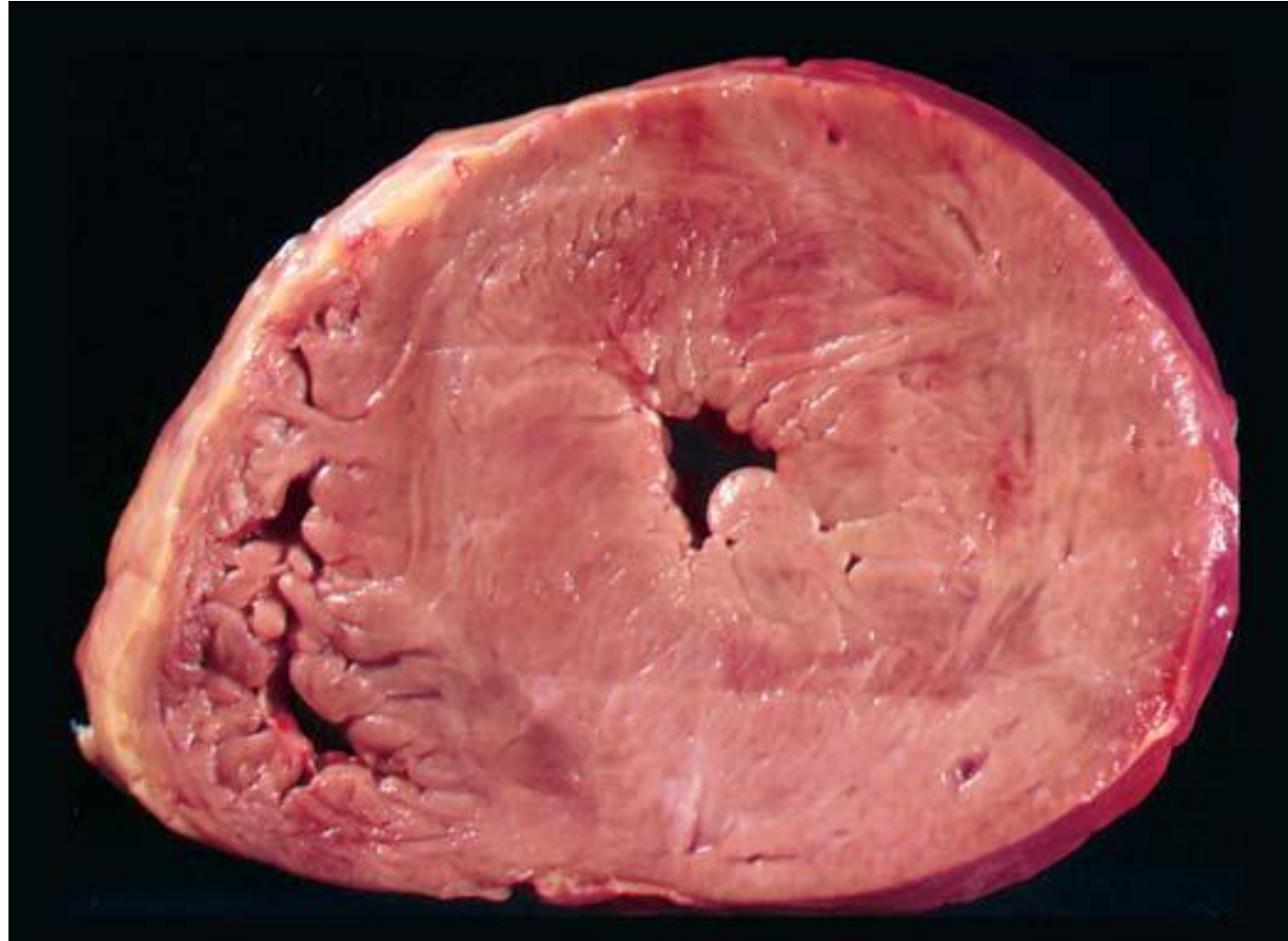
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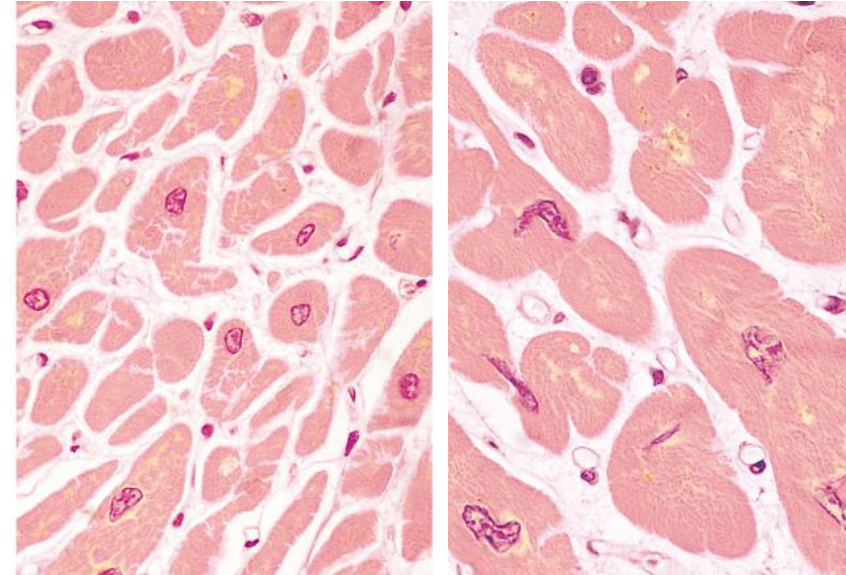
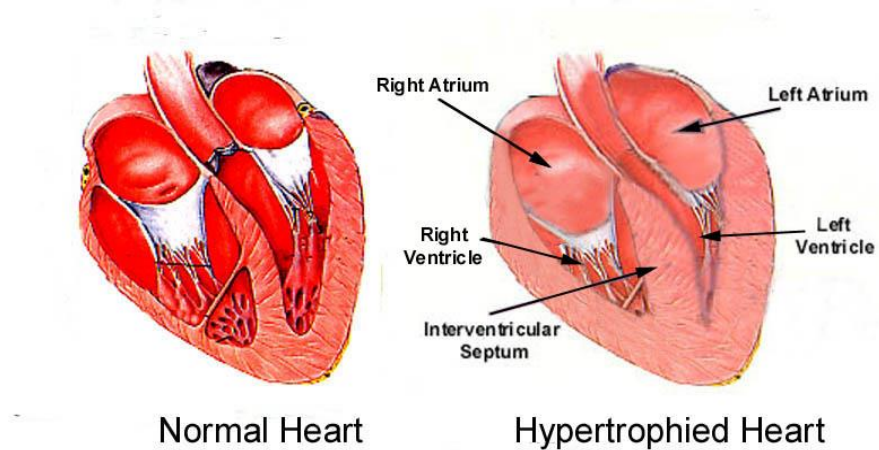
# Myocardial hypertrophy.



# Hypertrophy

- Can be pathologic (hypertrophy of myocardium – hypertension/aortic valve disease)

## Hypertrophic Cardiomyopathy



Normal heart

Hypertrophic heart

