!! JAY AMBE !!

9. NERVOUS SYSTEM

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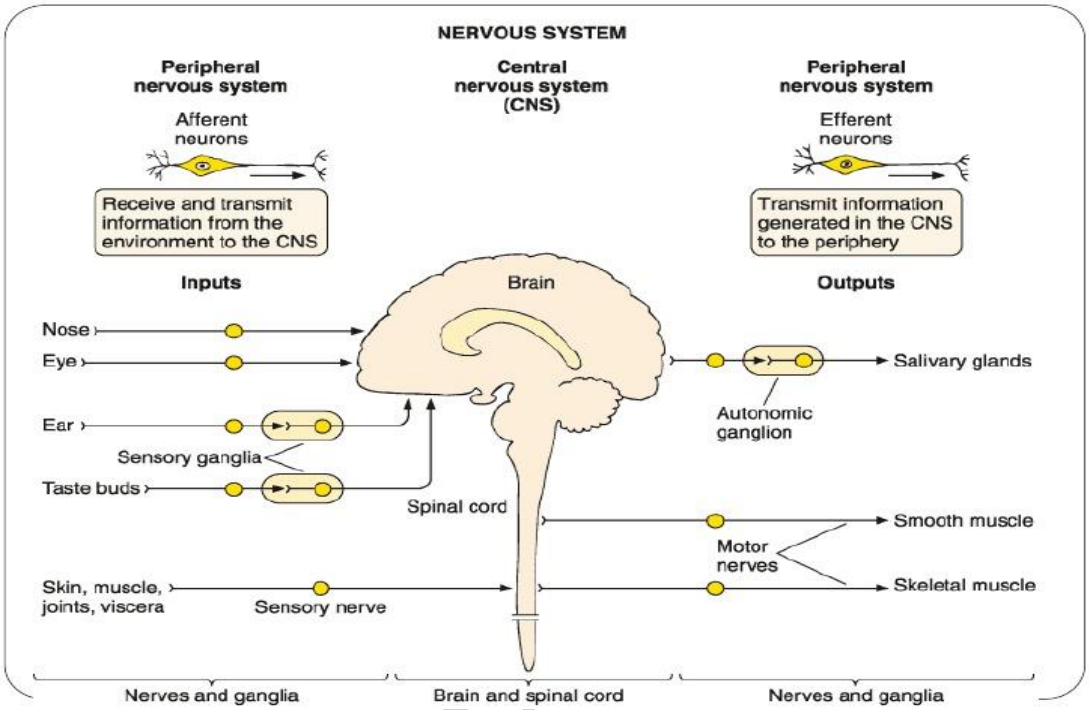

9. NERVOUS SYSTEM

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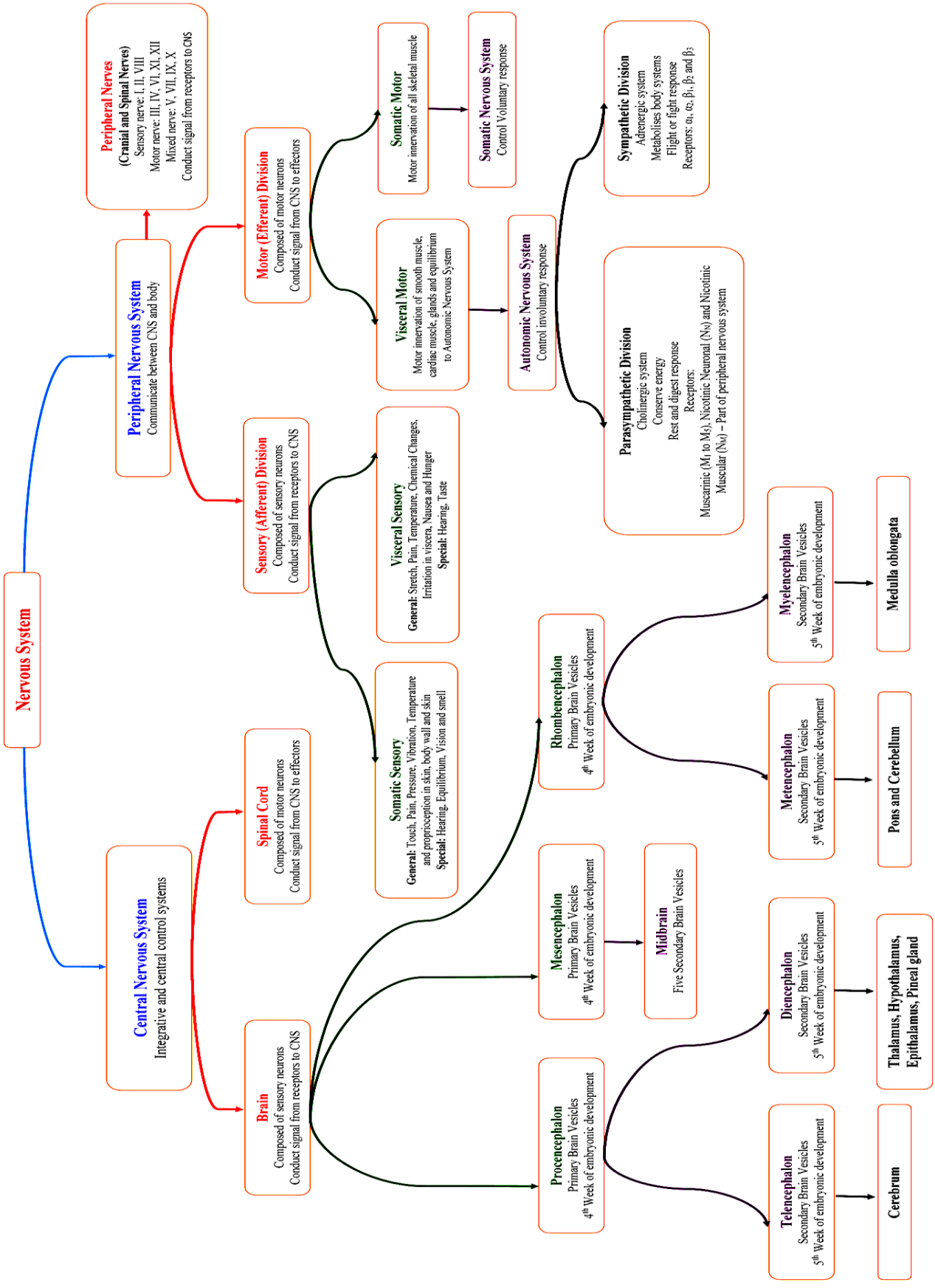
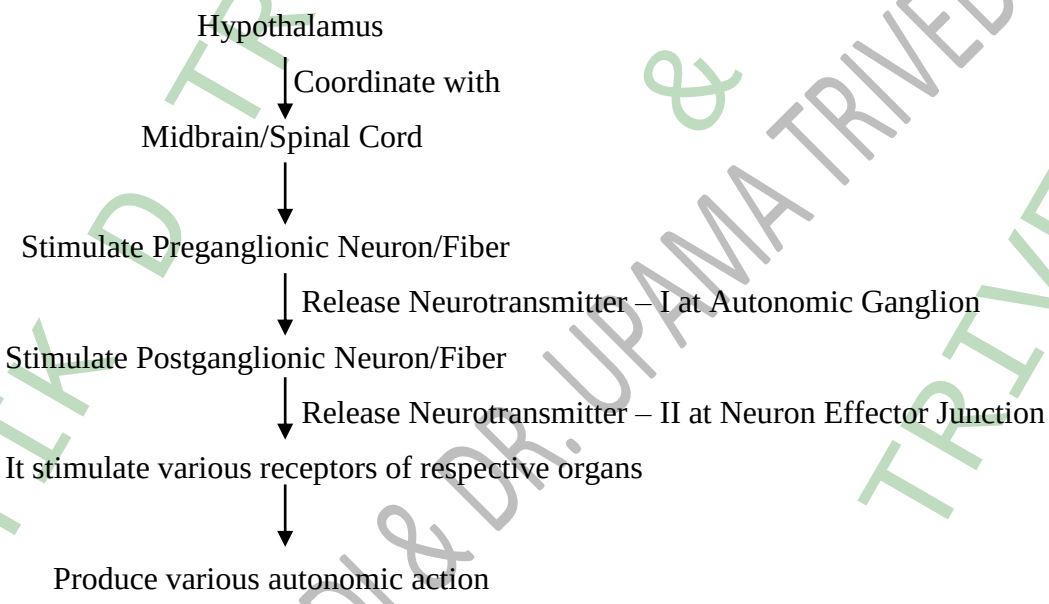


AUTONOMIC NERVOUS SYSTEM

INTRODUCTION OF AUTONOMIC NERVOUS SYSTEM (ANS):

It is the part of nervous system that deals with the involuntary movements. It is also known as visceral nervous systems. It works under the conscious and unconscious conditions and maintain the involuntary functions. It control automatically, pumping of blood, beating of heart, contraction of blood vessel, lungs and GI tract, secretion of saliva, lacrimal fluid etc….

Anatomy of Autonomic Nervous System (ANS):



- In the brain, hypothalamus mainly regulate the autonomic functions of the body. Hypothalamus coordinate with the midbrain and spinal cord for autonomic function.
- From the midbrain and spinal cord, some nerves fibers are emerge out which is called as preganglionic neurons or preganglionic fibers.
- At the end of preganglionic neuron/fiber, post ganglionic neurons/fibers start.
- The gap between the end of preganglionic neurons and starting portion of post ganglionic neurons is known as junction-I, which is known as autonomic ganglion/autonomic junction.
- Post ganglionic neurons end near to the different organ/tissue/cell, and the end portion of post ganglionic neurons near to the different organ/tissue/cell form junction-II which is known as neuron effector junctions.
- Autonomic ganglion (Junction-I) and neuron effector junction (Junction-II), in their gap consist neurotransmitter that stimulate the various respective receptors and gives different kind of autonomic functions.

Autonomic nervous system is subdivided into the two portion:

1. Parasympathetic Nervous System (Cholinergic Nervous System)
2. Sympathetic Nervous Systems (Adrenergic Nervous System)

1. PARASYMPATHETIC NERVOUS SYSTEM (CHOLINERGIC NERVOUS SYSTEM):

Anatomy of Parasympathetic Nervous System (Cholinergic Nervous System)

Superior control by anterior and middle part of hypothalamus

↓

Centre of III, VII, IX and X cranial nerve and sacral part of spinal cord

↓

Activate preganglionic neuron/fiber (Long)

↓

Release neurotransmitter-I (Ach) in Autonomic Ganglion/Junction (Junction-I)

↓ Stimulate (N_N) or (M_1) receptor

Activate postganglionic neuron/fiber (Short) after that Ach is destruct by Acetylcholine Esterase

↓ Stimulate (M_1), (M_2), (M_3) or (N_N) receptor

Release neurotransmitter-II (Ach) in Neuron Effector Junction (Junction-II)

↓

Produce various action after that Ach is destruct by Acetylcholine Esterase (AchE)

- Anterior and middle part of the hypothalamus have the superior control on parasympathetic nervous system.
- It coordinate with the midbrain and spinal cord. Preganglionic fiber of the parasympathetic nervous system originate from the midbrain and sacral part of the spinal cord. Mainly cranial nerve III, VIII, IX, X and gray matter of sacral part of spinal cord emerge out or rise to preganglionic fiber. It is also known as craniosacral outflow.
- Preganglionic fibers travel some distance and end in to the junction-I that is autonomic ganglion from which post ganglionic fibers emerge out. (Usually from 1 preganglionic neuron/fiber, 1 or 2 post ganglionic neuron/fiber are originated except Auorbach's plexus). Here, autonomic ganglion (Jun in their gap consist neurotransmitter-I that is acetylcholine. Which helps to stimulate various receptors like Nicotinic Neuronal (N_N) or Muscarinic (M_1) in autonomic ganglion/junction. Stimulation of N_N and M_1 receptors activate the of post ganglionic neurons/fibers.
- Post ganglionic neuron/fiber end into the neuron effector junction near the various organ/tissue/cell. Neuron effector junction (Junction-II) consist neurotransmitter II that is

also the acetylcholine (Ach) means parasympathetic systems consist neurotransmitter acetylcholine (Ach) in both the junction.

- These neurotransmitter (Ach) stimulate the various muscarinic and nicotinic receptors like M_1, M_2, M_3 and N_N. Here the nicotinic muscular receptor (N_M) is not included because it is the part of somatic nervous systems.
- Stimulation of various parasympathetic receptors gives various kind of autonomic functions. To know these functions it is essential to identify the location of various receptors.

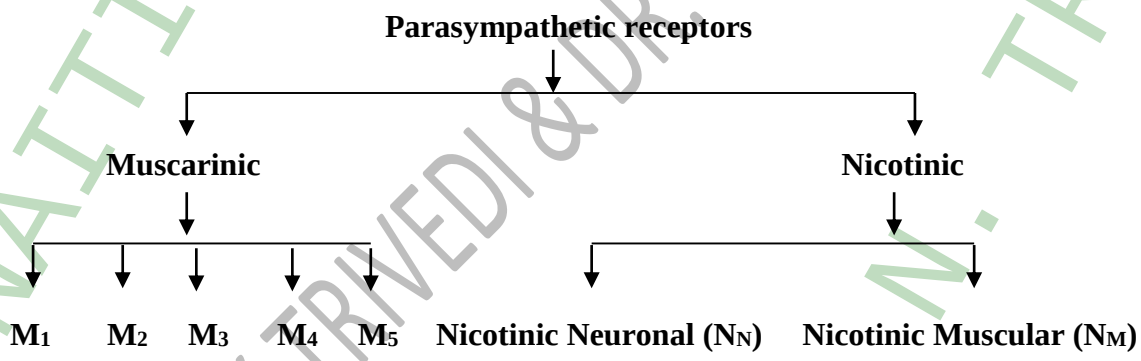
*Preganglionic neuron/fibers are long and post ganglionic neuron/fibers are short in parasympathetic nervous system.

* One preganglionic neuron/fiber, one or two post ganglionic neuron/fiber are originated except Auorbach's plexus - inner circular and outer longitudinal layers of the muscularis externa).

* Acetylcholine esterase (AchE) is the enzyme which destruct the Acetyl Choline (Ach) after their action.

* Parasympathetic system consist two types of receptors: 1) Muscarinic (M_1, M_2, M_3, M_4, M_5) and Nicotinic (N_N – Nicotinic Neuronal, N_M – Nicotinic Muscular).

Location of parasympathetic receptors and their functions:



- **M_1 receptors:** These are G-protein coupled receptors, it activate phospholipase C and stimulate Inositol Triphosphate (IP_3) and Diacylglycerol (DAG) and increase intracellular calcium level and produce below autonomic functions according to their location.

Location	Function
Autonomic ganglion/junction (Junction – I)	Activation of post ganglionic neuron/fiber

- **M_2 receptors:** These are G-protein coupled receptors, it act by opening K^+ channels which reduce cyclic AMP (cAMP) level and produce below autonomic functions according to their location.

Location	Function
Heart	Decrease force of contraction (Negative Inotropic) Decrease heart rate (Negative Chronotropic) Decrease conduction (Negative dromotropic)

- **M_3 receptors:** These are G-protein coupled receptors, it activate phospholipase C and stimulate Inositol Triphosphate (IP_3) and Diacylglycerol (DAG) and increase intracellular calcium level and produce below autonomic functions according to their location.

Location	**Function**
GI smooth muscle	Contraction of GI smooth muscle
Bronchial smooth muscle	Contraction of bronchial smooth muscle (Lungs contraction)
Urinary tract	Contract detrusor – urinary bladder muscle which relax trigon of urinary bladder and produce micturition.
Salivary secretion	Increase secretion of saliva
Lacrimal secretion	Increase secretion of tear/lachrymal fluid
Gastric secretion	Increase secretion of HCl in GI tract
Eye	Produce meiosis (Contraction of pupils) Iris consist two types of smooth muscles 1) Sphincter pupillae 2) Dilator pupillae (Radial Muscle). Contraction of sphincter pupillae constrict pupil known as meiosis and contraction of dilator pupillae produce dilation of pupil known as mydriasis.

N_N receptors: These are the intrinsic ion channel receptors, it act by opening various ion channels like Na^+, K^+ and Ca^+ and produce below autonomic functions according to their location.

Location	**Function**
Autonomic ganglion/junction (Junction – I)	Activation of post ganglionic neuron/fiber
Adrenal medulla	Release of adrenalin and some nor adrenalin
CNS	Complex undefined action but inhibitory

N_M receptors: These are the intrinsic ion channel receptors, it act by opening various ion channels like Na^+, K^+ and Ca^+. It is the part of somatic systems.

Location	**Function**
Neuromuscular Junction	Contraction of skeletal muscle

Synthesis, storage, release and hydrolysis of Ach

Choline + Acetyl Co-A
↓ Choline acetylase
Ach (Store in vesicle)
↓ Release of Ach when needed
Ach produce various action through receptors
↓ Acetylcholine Esterase (AchE) destruct Ach
Ach convert in acetate and choline

Choline and Acetyl Co-A by the help of Choline acetylase produce acetyl choline which can store in to the vesicles, when Ach release it produce various action and after it metabolite by the help of AchE and produce acetate and choline.

2. SYMPATHETIC NERVOUS SYSTEMS (ADRENERGIC NERVOUS SYSTEM)

Anatomy of sympathetic nervous system (Adrenergic System)

Superior control by posterior and lateral part of hypothalamus

↓

Preganglionic fibers origenate from Thoracic 1 to Lumber 3 segments

↓

Activate preganglionic neuron/fiber (Short)

↓

Release neurotransmitter-I (Ach) in Autonomic Ganglion/Junction (Junction-I)

↓ Stimulate (N_N) or (M_1) receptor

Activate postganglionic neuron/fiber (Long) after that Ach is destruct by Acetylcholine Esterase

↓ Stimulate (α_1), (α_2), (β_1), (β_2) or (β_3) receptor

Release neurotransmitter-II (Adr) in Neuron Effector Junction (Junction-II)

↓

Produce various action

- Posterior and lateral part of the hypothalamus have the superior control on sympathetic nervous system.
- Preganglionic neuron/fiber of sympathetic nervous systems originate from the thoracic 1 to lumber 3 segment of spinal cord spinal cord. Preganglionic fiber of sympathetic nervous systems are usually short and it emerge out 20 to 100 post ganglionic fiber which is longer than the preganglionic fiber. Here, autonomic ganglion – Junction-I consist neurotransmitter-I that is acetylcholine. Which helps to stimulate various receptors like Nicotinic Neuronal (N_N) or Muscarinic (M_1) in autonomic ganglion/junction. Stimulation of N_N and M_1 receptors activate the of post ganglionic neurons/fibers.
- Post ganglionic neuron/fiber end into the neuron effector junction near the various organ/tissue/cell. Neuron effector junction (Junction-II) consist neurotransmitter II that is noradrenalin (NA) means sympathetic systems consist neurotransmitter-I is acetylcholine (Ach) in autonomic ganglion (Junction-I) and neurotransmitter – II that is adrenalin in neuron effector junction (Junction-II).
- These neurotransmitter (Noradrenalin - NA) stimulate the various α and β receptors like α_1, α_2, β_1, β_2 and β_3.
- Stimulation of various sympathetic receptors gives various kind of autonomic functions. To know these functions it is essential to identify the location of various receptors.

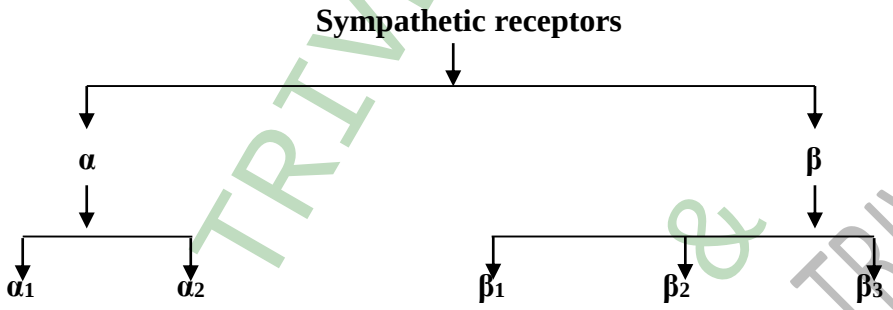
*Preganglionic neuron/fibers are short and post ganglionic neuron/fibers are long in sympathetic nervous system.

* One preganglionic neuron/fiber emerge out 20 to 100 post ganglionic neuron/fiber.

* Sympathetic nervous system consist both the neurotransmitter that is acetylcholine in autonomic ganglion/junction and noradrenalin in neuron effector junction.

* Parasympathetic system consist two types of receptors: α (α_1, α_2) and β (β_1, $\beta 2$, β_3)

Location of sympathetic receptors and their functions:



- **α_1 receptors:** These are G-protein coupled receptors, it activate phospholipase C and stimulate Inositol Triphosphate (IP_3) and Diacylglycerol (DAG) and increase intracellular calcium level and produce below autonomic functions according to their location.

Location	Function
Blood vessels	Produce vasoconstriction
Iris	It contract radial muscles and dilate the pupil known as mydriasis
GI tract	Contract the GI sphincter and relax the the GI muscle
Urinary bladder	Contract the trigon and relax the urinary bladder
Glands	Increase the secretion of glands
Uterus	It produce contraction in nonpregnant uterus
Heart	Weak action on heart
Male sex organ	Penile erection and ejaculation
Skin	Contraction of pilomotor muscles.

α_2 receptors: These receptors alter the K^+ or Ca^+ channel conduction and decrease the cAMP level.

Location	Function
Presynaptic nerve ending	It reduce release of noradrenalin
Blood vessels	Produce constriction of blood vessels
CNS	Reduction in central sympathetic flow due to decrease of Noradrenalin level
Pancreas	Reduce insulin level so increase blood sugar level
Platelets	Aggregate platelets
GI muscle	Relaxation of GI muscle

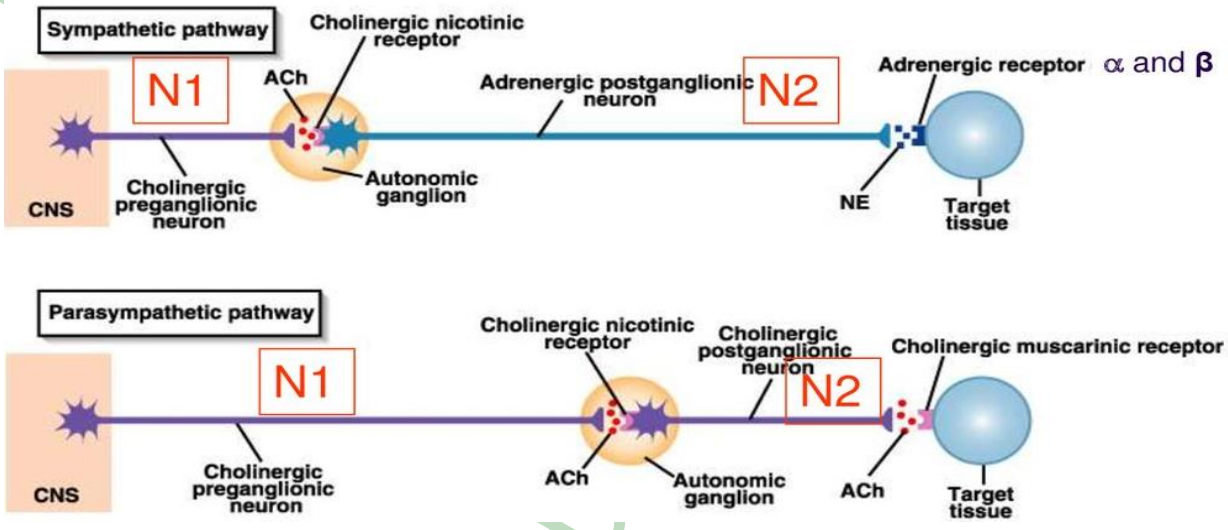
- **β_1 receptors:** These are G-protein coupled receptors, it act by activation of adenylyl cyclase which increase cyclic AMP (cAMP) level and produce below autonomic functions according to their location.

Location	Function
Heart	Increase force of contraction (Positive Inotropic) Increase heart rate (Positive Chronotropic) Increase conduction (Positive dromotropic)
Kidney	Release of renin, so renin activate angiotensinogen I which convert in angiotensinogen II by the help of angiotensinogen converting enzyme (ACE) and activate the aldosterone. Which retain the Na^+ and water and increase the blood volume as well as angiotensinogen act on AT-I and AT-II receptor and contract the blood vessels.

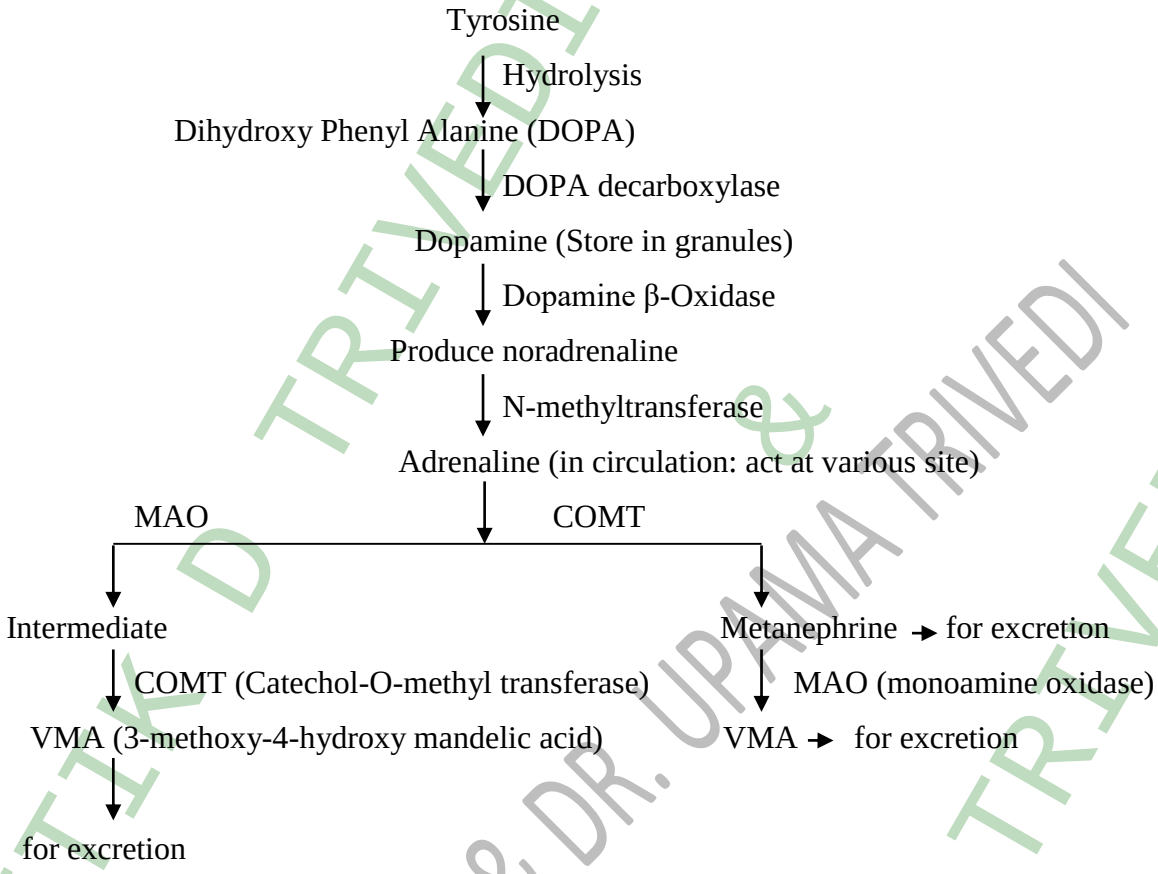
- **β_2 receptors:** These are G-protein coupled receptors, it act by activation of adenylyl cyclase which increase cyclic AMP (cAMP) level and produce below autonomic functions according to their location.

Location	Function
Blood vessels	Dilation of blood vessels
Lungs	Dilation of bronchial smooth muscles and lungs
GI muscle	Relaxation of GI muscle
Bladder	Relaxation of detrusor produce relaxation in urinary bladder (contract the trigon)
Liver	Produce glycogenolysis means conversion of glycogen to glucose and increase blood sugar level
Pancreas	Increase glucagon secretion which increase blood sugar level
Adipose tissue	Lipolysis (Break down of fats)
Uterus	Produce relaxation in pregnant uterus

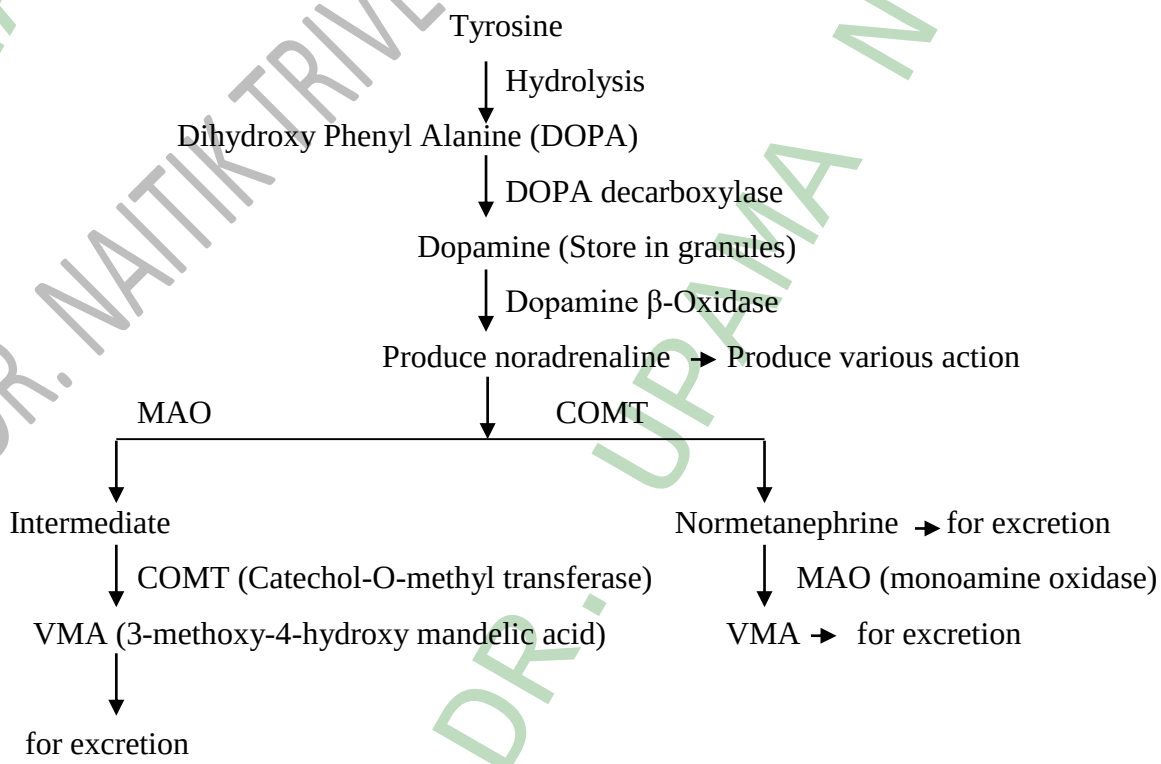
- **β_3 receptors:** Role and functions of β_3 receptors are not clearly defined.

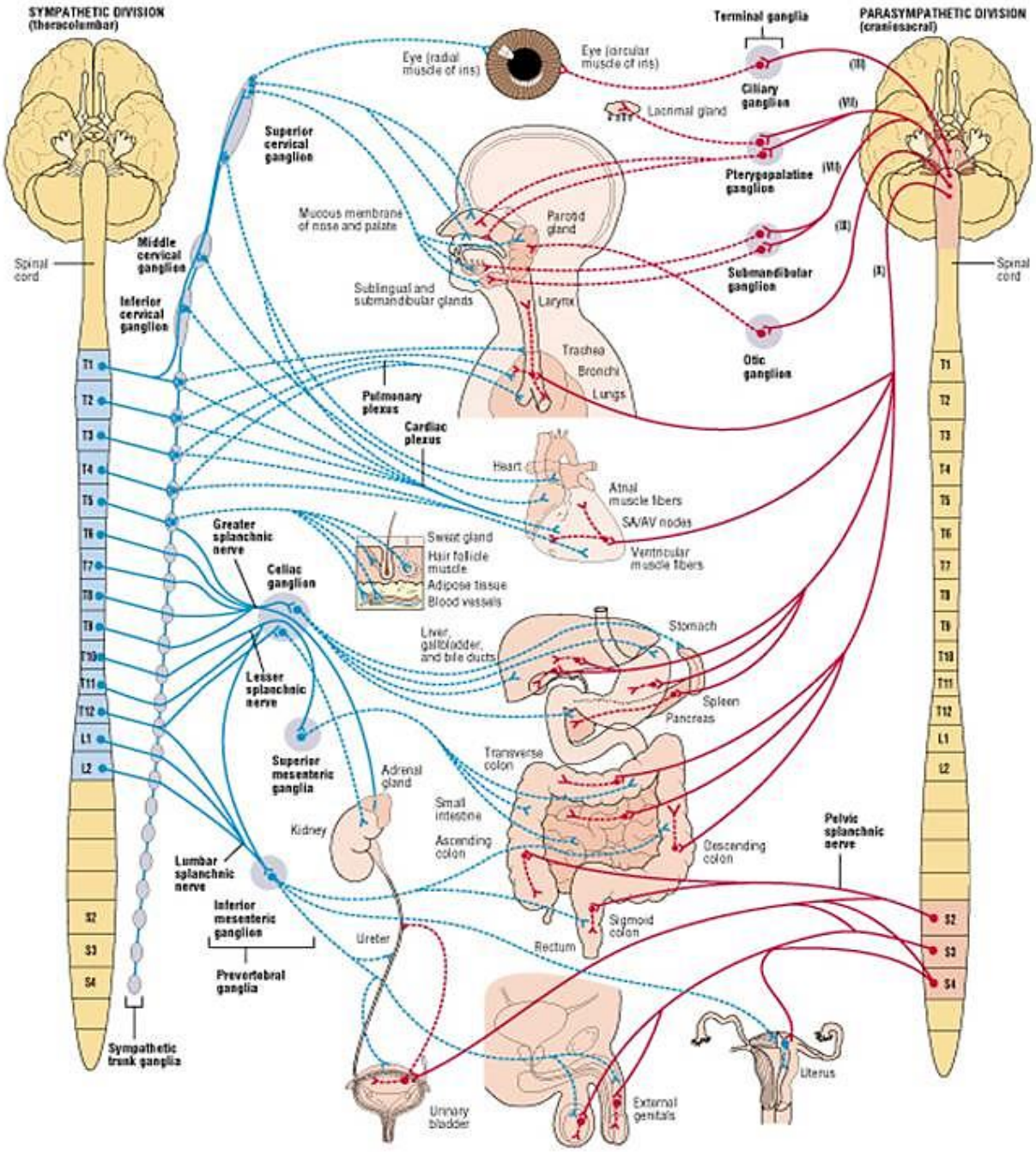


Synthesis, storage, release and hydrolysis of adrenaline



Synthesis, storage, release and hydrolysis of noradrenaline

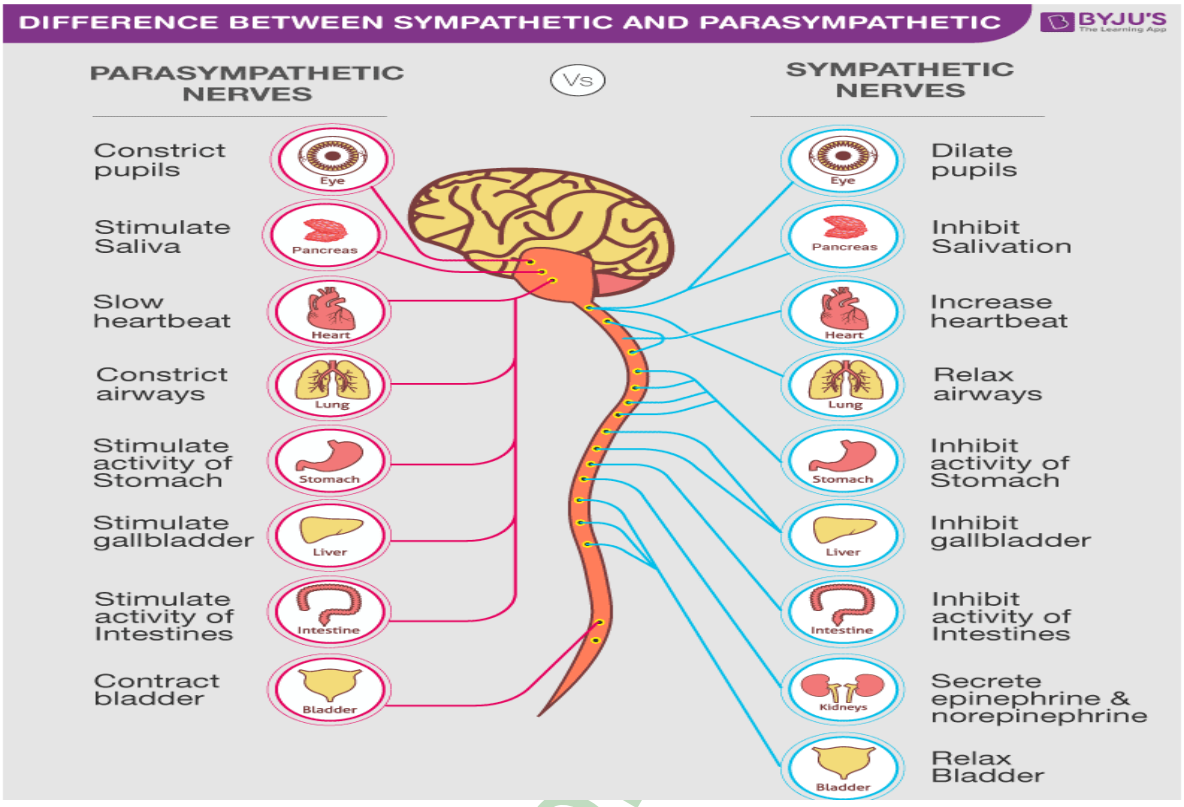




Sympathetic and parasympathetic nervous system (Ref: Tortora)

Sympathetic and Parasympathetic Effects		
Structure	**Sympathetic**	**Parasympathetic**
Eye (pupil)	Dilation	Constriction
Nasal Mucosa	Mucus reduction	Mucus increased
Salivary Gland	Saliva reduction	Saliva increased
Heart	Rate increased	Rate decreased
Arteries	Constriction	Dilation
Lung	Bronchial muscle relaxation	Bronchial muscle contraction
Gastrointestinal Tract	Decreased motility	Increased motility
Liver	Conversion of glycogen to glucose increased	Glycogen synthesis
Kidney	Decreased urine	Increased urine
Bladder	Contraction of sphincter	Relaxation of sphincter
Sweat Glands	↑Sweating	No change

Neurotransmitter	Neurotransmitter – I is acetylcholine and Neurotransmitter – II is Adrenalin	Neurotransmitter – I and II both are acetylcholine
Preganglionic fiber	Short	Long
Postganglionic fiber	Long	Short



CENTRAL NERVOUS SYSTEM

THE BRAIN

ANATOMY OF BRAIN:

Adult brain consist average 100 billion neurons and 1000 billion neuroglia. Weight of the adult brain is approximately 1.3-1.5 kg in human. Brain mainly divided into four parts:

1. Brain Stem: It is the superior portion and continuous with the spinal cord consist medulla oblongata, pons and midbrain.
2. Cerebellum: It located posterior to the brain stem.
3. Diencephalon: It is located superior to the brain stem. It consist thalamus, epithalamus, subthalamus, hypothalamus and pineal gland.
4. Cerebrum: It look like cap of mushroom. It occupies the most of the part of cranium and it is divided into right and left halves known as cerebral hemispheres.

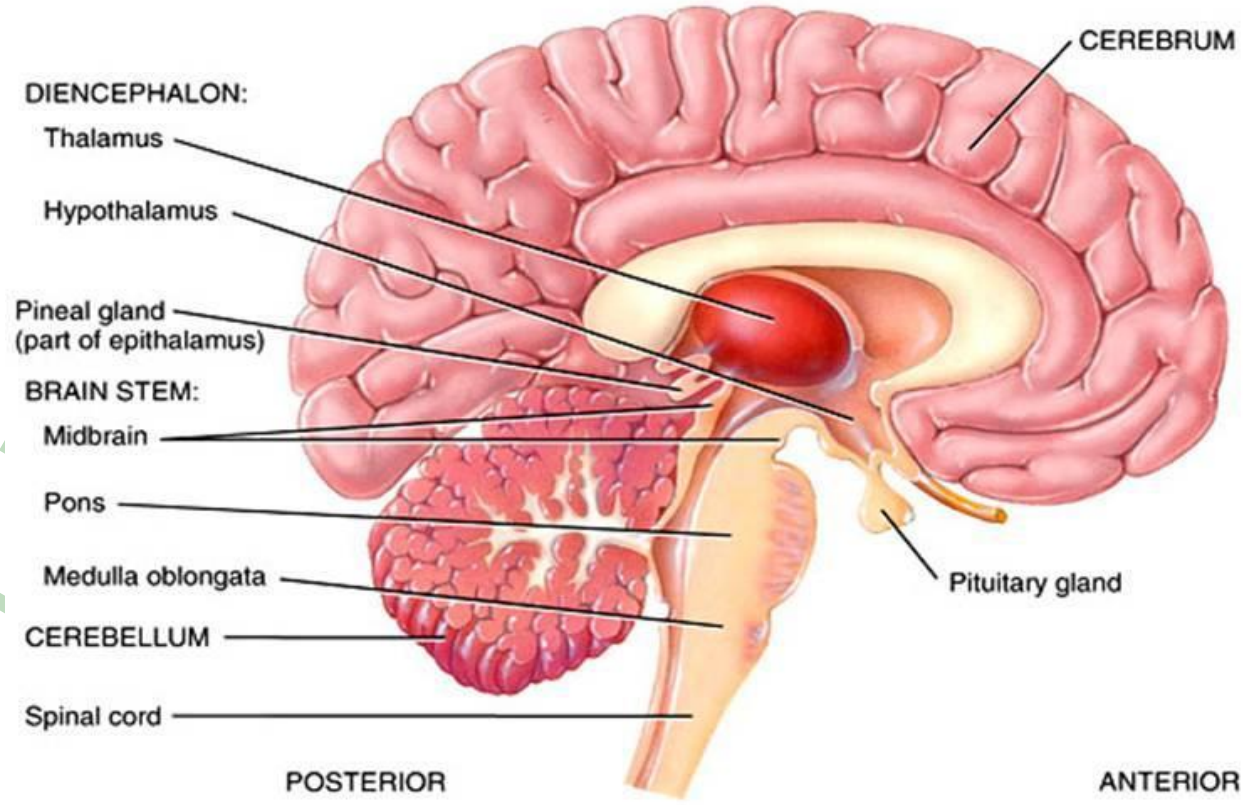


Diagram of brain

According to the embryonic development brain is divided mainly into the three parts at the third weeks of embryonic development which is also known as primary brain vesicles:

1. Prosencephalon – Forebrain
2. Mesencephalon – Midbrain
3. Rhombencephalon – Hindbrain

During the further development of the embryo primary vesicles is divided and form secondary vesicles at the 5th weeks of embryonic development.

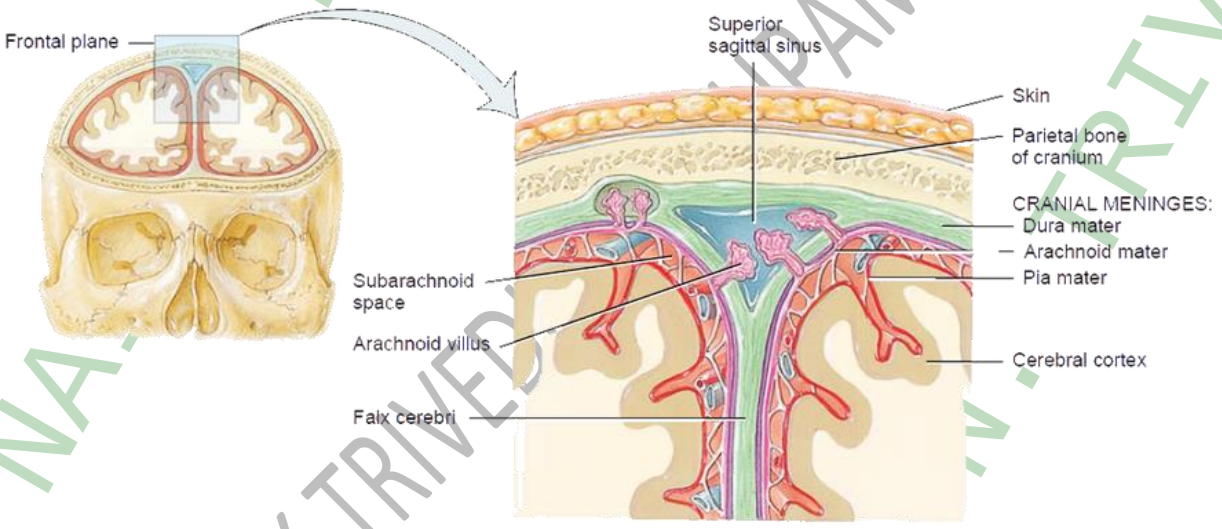
- Procencephalon develop telencephalon and diencephalon
- Mesencephalon develop midbrain
- Rhombencephalon develop metencephalon and myelencephalon

At the final stage of embryonic development:

- Telencephalon forms cerebrum
- Diencephalon forms epithalamus, hypothalamus, subthalamus, thalamus and pineal gland
- Metencephalon forms pons and cerebellum
- Myelencephalon forms medulla oblongata

The brain grow rapidly during the first few years of life (between the ages of 1-12 years).

PROTECTION AND COVERING OF THE BRAIN:



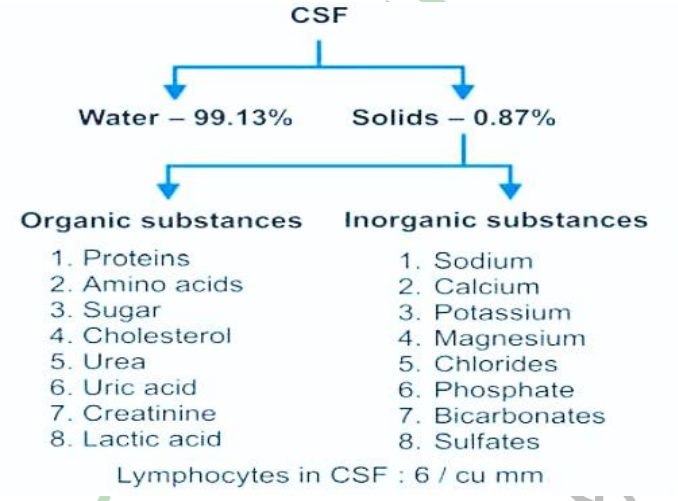
- Cranial bones and cranial meninges mainly protect the brain.
- Cranial bones produce the superficial layer of the brain.
- Cranial meninges surrounds the brain and continuous towards the spinal cord and known as spinal meninges.
- In the brain, outer portion of the cranial manages known as dura meter, middle portion known as arachnoid and inner portion is known pia meter.
- Extension portion of the dura meter separates two hemisphere of the brain which is known as flax cerebri. Same as extension portion of the dura meter separates the hemisphere of cerebellum which is known as falx cerebelli. Dural extension also separates the cerebrum from cerebellum is known as tentorium cerebelli.

CEREBROSPINAL FLUID (CSF):

Cerebrospinal fluid protect the brain and spinal cord from chemical, mechanical and some extent biological injury.

It is a clear, colorless body fluid found in the brain and spinal cord. It is produced by the specialized ependymal cells in the choroid plexuses of the ventricles of the brain, and absorbed in the arachnoid granulations. The entire central nervous system contains between 80 – 150 mL of CSF, and about 500 mL is generated every day.

Compositions of cerebrospinal fluid:

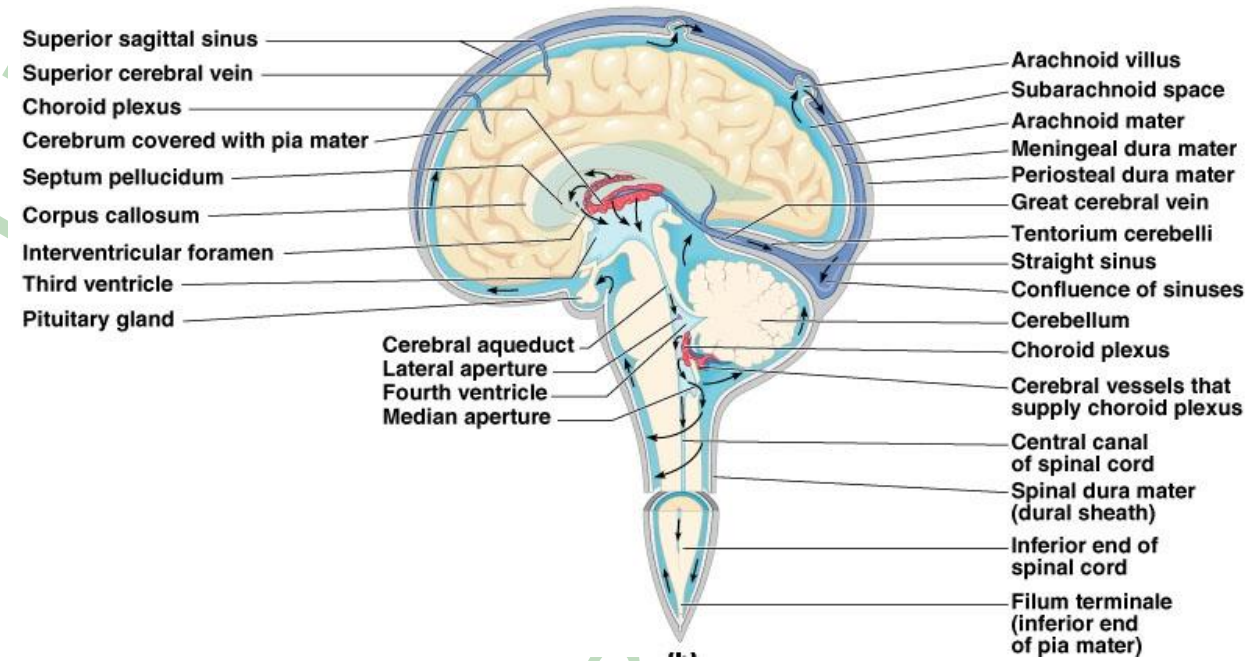


Composition of CSF

Substance	Plasma	CSF
Na^+ (mEq/l)	145.0	150.0
K^+	4.8	2.9
Ca^{++}	5.2	2.3
Mg^{++}	1.7	2.3
Cl^-	108.0	130.0
HCO_3^-	27.4	21.0
Lactate	7.9	2.6
PO_4^{---}	1.8	0.5
Protein	7000.0	20.0
Glucose	95.0	60.0

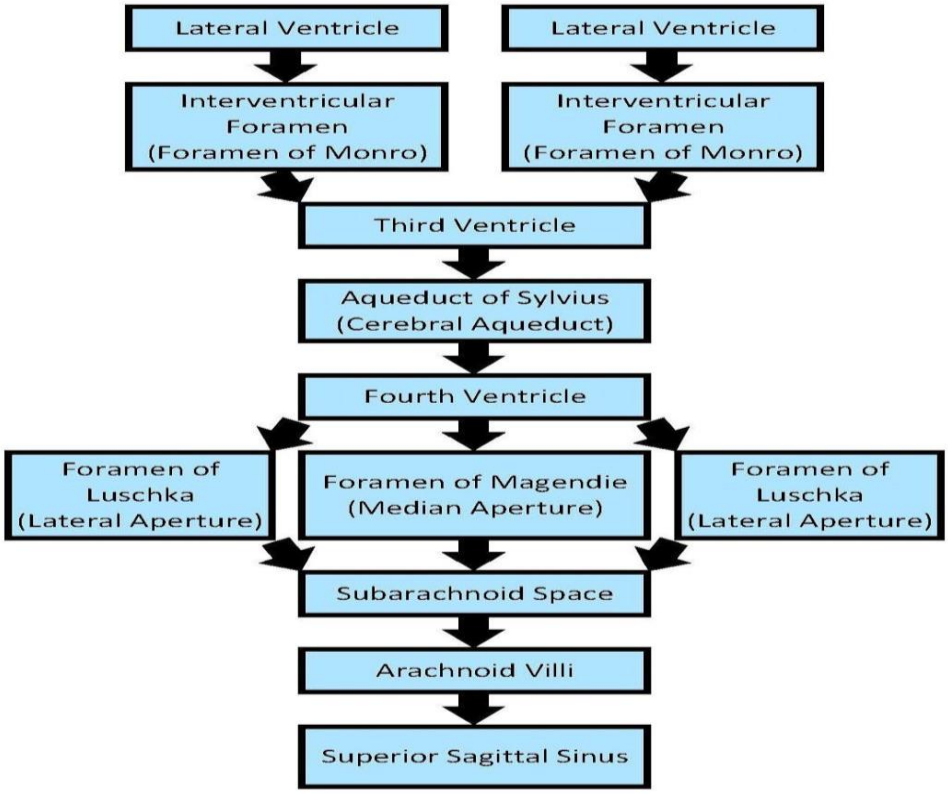
(protein and glucose expressed as mg/100 ml)

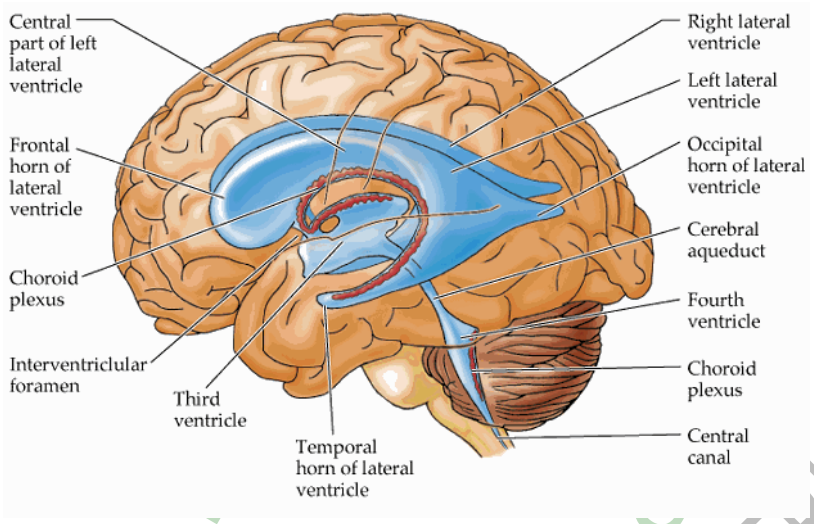
Flow/circulation of cerebrospinal fluid:

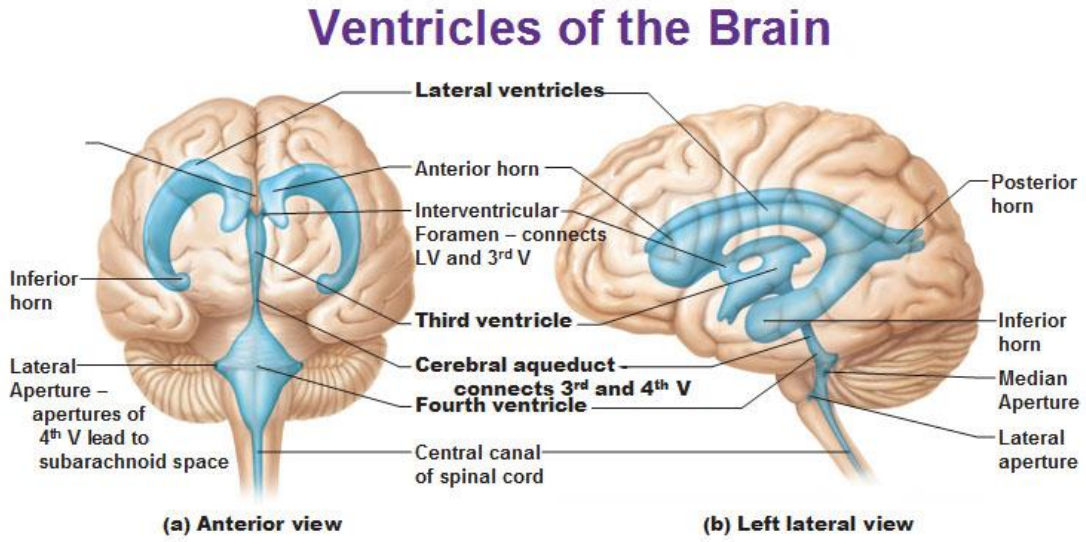


- Choroid plexuses are network of blood capillary in the wall of ventricles of brain. The capillaries are covered by ependymal cells that form the cerebrospinal fluids which can filtrate and secret from the blood plasma of capillaries.

- Choroid plexuses form the tight junction of the cell so filtered CSF cannot leaked out.
- From the each lateral ventricles formed CSF flow into the third ventricle through the intraventricular foramina as well as choroid plexus directly add some amount of CSF into the third ventricles.
- From the third ventricle fluid goes into cerebral adequate duct to fourth ventricle of midbrain.
- From the fourth ventricle to fluid goes into the subarachnoid space through three opening at the top of the fourth ventricle, a median aperture and paired lateral apertures (one of each side). Then it circulate in the central canal of the spinal cord and subarachnoid space around the surface of brain and spinal cord.
- Subarachnoid villi the finger like extension of arachnoid portion reabsorb CSF back into blood.
- Normally, CSF is reabsorbed as rapidly as it formed by the choroid plexuses at the rate about 20mL/hr. Means the formation and the reabsorption rates are same which maintain the CSF pressure in normal range.



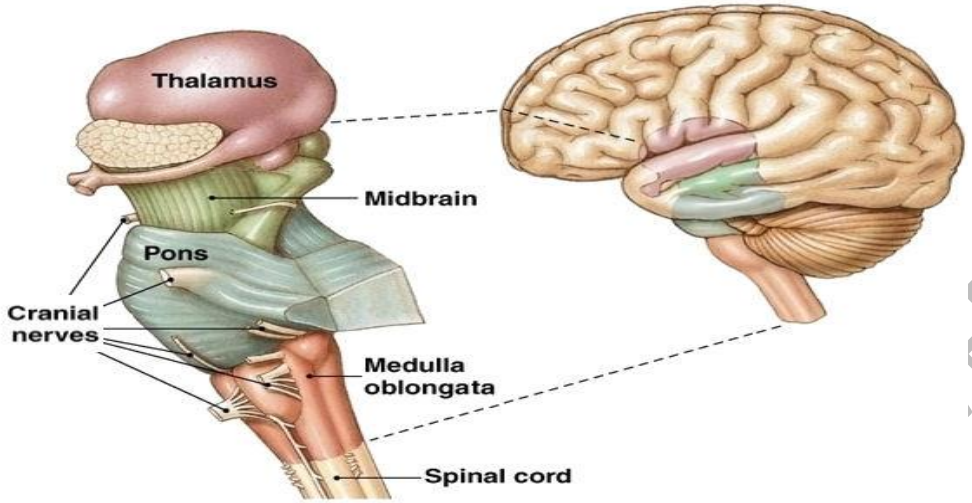




Functions of cerebrospinal fluid (CSF):

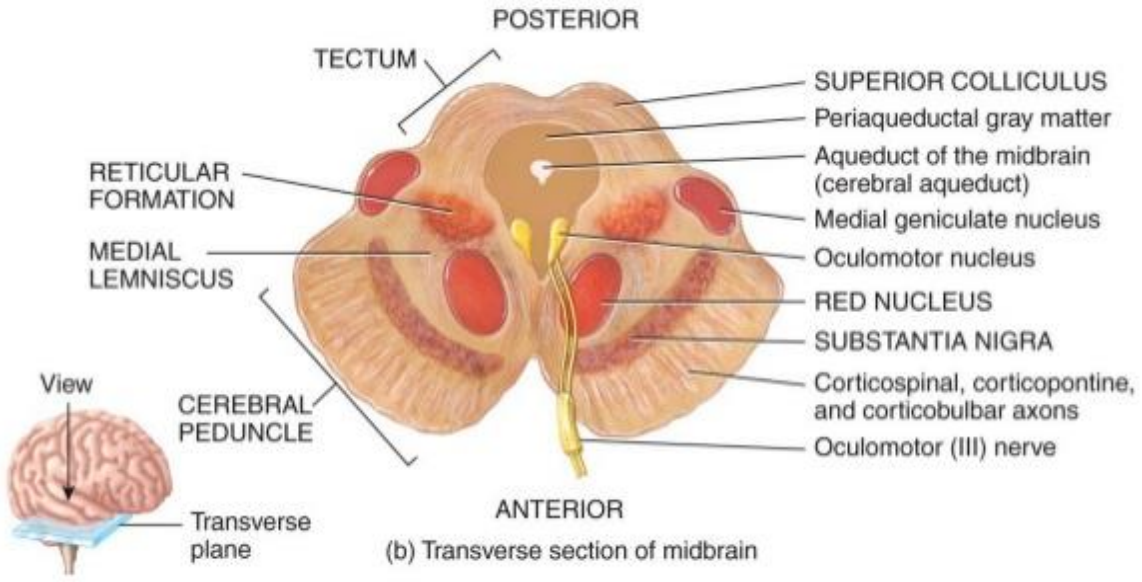
1. Mechanical Protection:
   - Cerebrospinal fluid absorb the shock and protect the delicate tissue of the brain and spinal cord.
   - It also act as a lubricating fluid and reduce the friction during the movement.
2. Chemical Protection:
   - It maintain the electrolytes and chemical balance which is required for regulation of post synaptic potential and action potential.
3. Provide nutrients:
   - It provide the essential nutrient through the circulation in brain and spinal cord.
4. Provide immunity:
   - It consist some amount of the WBCs which can fight against the harmful bacteria and virus.
5. Remove the toxin:
   - CSFs remove the metabolites, waste products and toxin from the brain and spinal cord through the circulation.

BRAIN STEM:



- The midbrain, pons and medulla oblongata of the hindbrain are collectively referred to as the "brain stem". These structures connects brain to the spinal cord.
- The midbrain coordinates sensory representations of the visual, auditory and somatosensory perceptual spaces.
- The pons is the main connection with the cerebellum. The pons and the medulla regulate several crucial functions, including the cardiovascular and respiratory systems.
- The cranial nerves connect through the brain stem and provide the brain with the sensory input and motor output associated with the head and neck, including most of the special senses.
- The major ascending and descending pathways between the spinal cord and brain, specifically the cerebrum, pass through the brain stem.

1. Midbrain:



- The midbrain is a small region between the thalamus and pons. It develop from the mesencephalon.
- It is about 2-3 cm in length.
- The adequate duct passes through the centre of midbrain and it connect third ventricle above and fourth ventricle below.
- Midbrain consist white and gray matter tract.
- Anterior side it consist two tract known as cerebral peduncles, it connect the midbrain with the cerebellum.
- Posterior portion of the midbrain is called the tectum, it consist four rounded elevated projection like structure which is known as corpora quadrigemina, out of which two superior elevated portion is known as superior colliculi. These region serve as reflex centre for movement of eyes, head and neck.
- Midbrain consist substantia nigra which is the dark pigmented nuclei and it controls subconscious muscle activity.
- Midbrain consist red nuclei at right and left side. It consist rich amount of blood supply and iron so it produce red pigmented portion.
- Two nuclei of the midbrain are associated with the cranial nerves: 1. Oculomotor (III) nerve, responsible for movement of eye ball and changes in pupil size and shapes. 2. Trochlear (IV) nerves coordinates the eyeball movement.
- A band of white matter known as medial lemniscus in the midbrain, pass the impulse medulla oblongata to thalamus for discriminative touch, pressure and vibration.

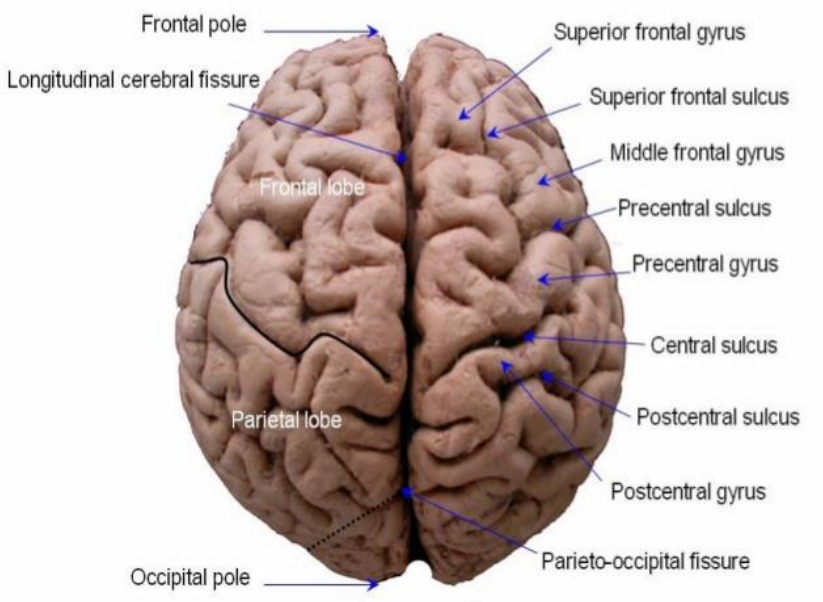
2. Pons:

- The word pons comes from the Latin word for bridge. It is visible on the anterior surface of the brain stem as the thick bundle of white matter attached to the cerebellum. The pons is the main connection between the cerebellum and the brain stem. It is about 2-3 cm long.
- Like medulla, it also consist sensory tract and motor tract.
- It contains nuclei that deals with respiration, swallowing, bladder control, hearing, equilibrium, eye ball movements, facial expressions etc.
- The nuclei contain four kind of cranial nerves:
    i. Trigeminal nerve (V): coordinate chewing and sensation of head and neck.
    ii. Abducens nerve (VI): regulate eyeball movement
    iii. Facial nerve (VII): coordinate taste, salivation and facial expression
    iv. Vestibulocochlear (VIII): for auditory equilibrium

3. Medulla oblongata:

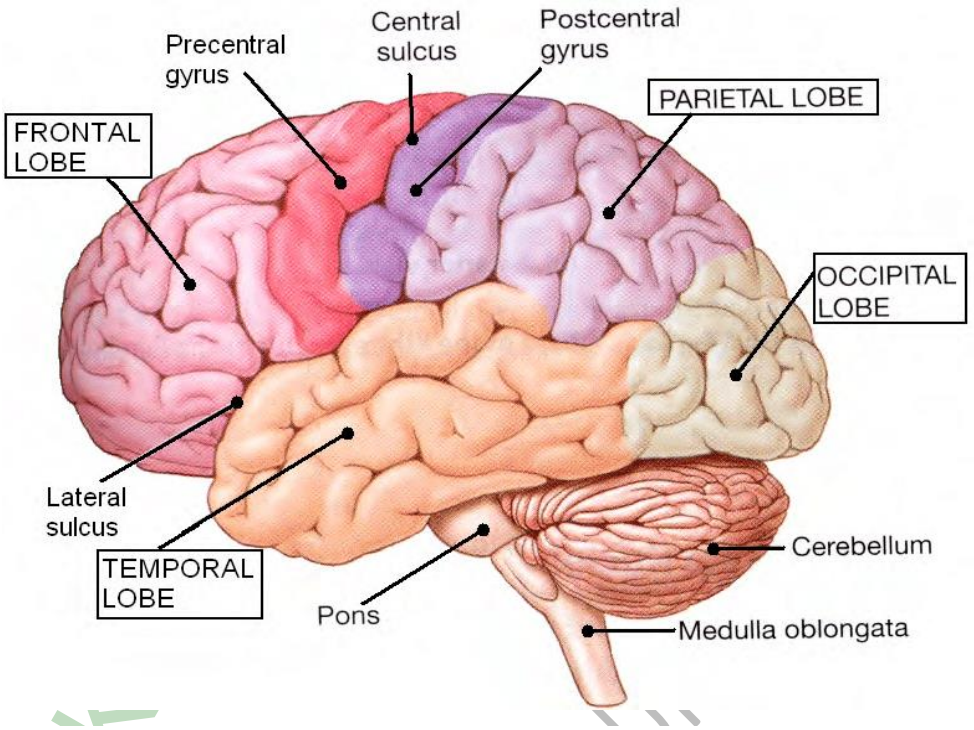
- It is lowermost part of the brain stem & continuation of the superior portion of spinal cord. It is developed from mylencephalon from the embryonic development.
- Situated at the base of the skull/ starts from foramen magnum & extends to the inferior border of the pons, a distance of about 3 cm.
- The ascending & descending sensory & motor white mater tracts (nerves) that connect brain to spinal cord pass through medulla oblongata.
- Anterior side of medulla oblongata consist two bulge known as pyramid. They contains the large motor tracts that pass from cerebrum to the spinal cord.
- Superior to the junction of the medulla with the spinal cord, most of the axons in the left pyramid cross to the right side and axon in the right side pyramid cross to the left side.
- So neurons in the left cerebral cortex control the muscle movement of right side and right cerebral cortex control muscle movement of left side.
- Medulla oblongata consist cardiovascular centre that regulates rate and force of the heart beats and diameter of blood vessels.
- It also consist medullary rhythmic area which regulate rhythm of breathing.
- Other centre of medulla oblongata regulate and coordinate swallowing, vomiting, coughing, sneezing and hiccupping.
- From the medulla oblongata five pairs of cranial nerves:
    i. Vestibulocochlear (VIII): coordinate auditory equilibrium.
    ii. Glossopharyngeal (IX): Coordinate swallowing, salivation and taste
    iii. Vegus (X): Which relay impulses to and from many thoracic and viscera.
    iv. Accessory (XI): Coordinate the head and shoulder movement.
    v. Hypoglossal (XII): Responsible for tongue movement

CEREBRUM:



- Cerebrum support diencephalon and brainstem. It develop from the telencephalon.
- The superficial layer of the cerebrum is gray matter which is known as cerebral cortex.
- Cerebral cortex is 2-4 mm thick and consists billion of neurons.
- Deep to the cerebral cortex consist white matter.
- During the embryonic development when brain size increase rapidly the gray matter of the cortex enlarge much faster than the white matter so cortical region rolls and folds itself. The folds are known as gyri.
- The deepest grooves between folds are known as fissures and the narrower grooves between folds are known as sulci.
- The most prominent fissure is longitudinal fissure which separates cerebral in right and left hemispheres. These hemispheres are joined internally by the white matters.
- Each hemisphere controls the opposite side of the body. If a stroke occurs on the right side of the brain, your left arm or leg may be weak or paralyzed.
- Not all functions of the hemispheres are shared. In general, the left hemisphere controls speech, comprehension, arithmetic, and writing. The right hemisphere controls creativity, spatial ability, artistic, and musical skills. The left hemisphere is dominant in hand use and language in about 92% of people.

Lobes:



- The cerebral hemispheres have distinct fissures, which divide the brain into lobes. Each hemisphere has 4 lobes: frontal, temporal, parietal, and occipital.
- Each lobe may be divided, once again, into areas that serve very specific functions. It's important to understand that each lobe of the brain does not function alone. There are very complex relationships between the lobes of the brain and between the right and left hemispheres.

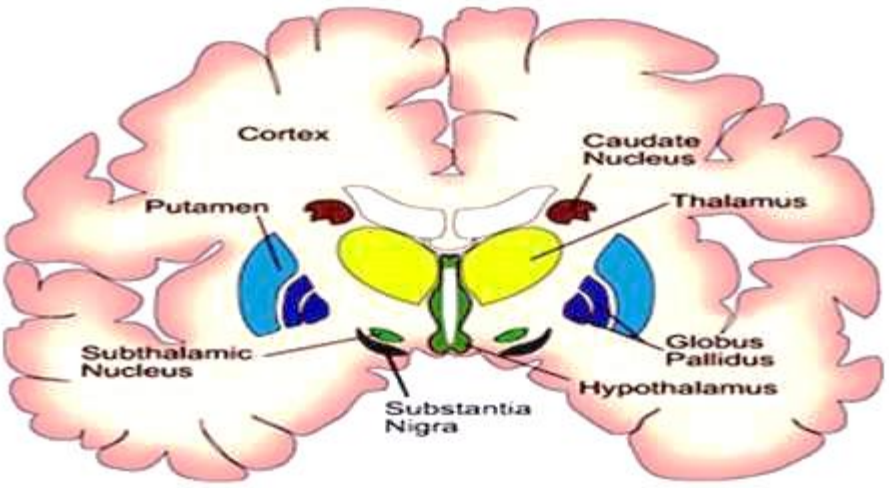
i. Frontal lobe
   - Personality, behavior, emotions
   - Judgment, planning, problem solving
   - Speech: speaking and writing (Broca's area)
   - Body movement (motor strip)
   - Intelligence, concentration, self awareness

ii. Parietal lobe
   - Interprets language, words
   - Sense of touch, pain, temperature (sensory strip)
   - Interprets signals from vision, hearing, motor, sensory and memory
   - Spatial and visual perception

iii. Occipital lobe
   - Interprets vision (color, light, movement)

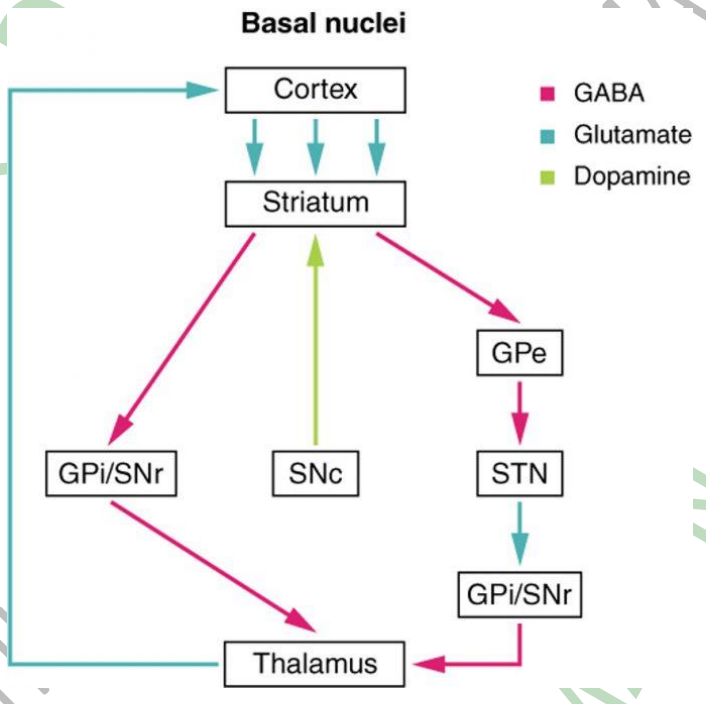
iv. Temporal lobe
- Understanding language (Wernicke's area)
- Memory
- Hearing
- Sequencing and organization

Basal ganglia:



- The basal ganglia are the several groups of nuclei in each hemispheres.
- The major structures of the basal nuclei that control movement are the caudate, putamen, and globus pallidus, which are located deep in the cerebrum.
- The caudate is a long nucleus that follows the basic C-shape of the cerebrum from the frontal lobe, through the parietal and occipital lobes, into the temporal lobe.
- The putamen is mostly deep in the anterior regions of the frontal and parietal lobes. Together, the caudate and putamen are called the striatum.
- The globus pallidus is a layered nucleus that lies just medial to the putamen; they are called the lenticular nuclei because they look like curved pieces fitting together like lenses. The globus pallidus has two subdivisions, the external and internal segments, which are lateral and medial, respectively.
- The basal nuclei in the cerebrum are connected with a few more nuclei in the brain stem that together act as a functional group that forms a motor pathway.
- Two streams of information processing take place in the basal nuclei.
- All input to the basal nuclei is from the cortex into the striatum.

- The direct pathway is the projection of axons from the striatum to the globus pallidus internal segment (GPi) and the substantia nigra pars reticulata (SNr). The GPi/SNr then projects to the thalamus, which projects back to the cortex.
- The indirect pathway is the projection of axons from the striatum to the globus pallidus external segment (GPe), then to the subthalamic nucleus (STN), and finally to GPi/SNr. The two streams both target the GPi/SNr, but one has a direct projection and the other goes through a few intervening nuclei. The direct pathway causes the disinhibition of the thalamus (inhibition of one cell on a target cell that then inhibits the first cell), whereas the indirect pathway causes, or reinforces, the normal inhibition of the thalamus. The thalamus then can either excite the cortex (as a result of the direct pathway) or fail to excite the cortex (as a result of the indirect pathway).



[Connections of Basal Nuclei: Input to the basal nuclei is from the cerebral cortex, which is an excitatory connection releasing glutamate as a neurotransmitter. This input is to the striatum, or the caudate and putamen. In the direct pathway, the striatum projects to the internal segment of the globus pallidus and the substantia nigra pars reticulata (GPi/SNr). This is an inhibitory pathway, in which GABA is released at the synapse, and the target cells are hyperpolarized and less likely to fire. The output from the basal nuclei is to the thalamus, which is an inhibitory projection using GABA.]

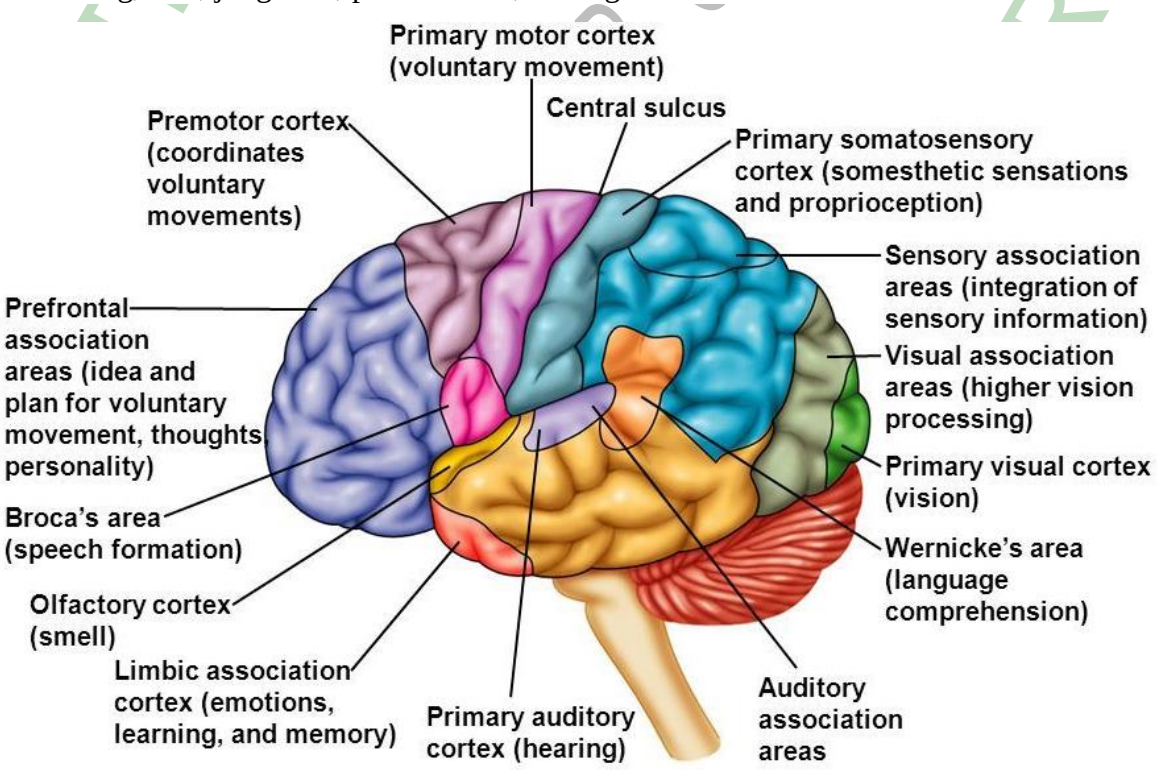
- The switch between the two pathways is the substantia nigra pars compacta, which projects to the striatum and releases the neurotransmitter dopamine. Dopamine receptors are either excitatory (D1-type receptors) or inhibitory (D2-type receptors).

- The direct pathway is activated by dopamine, and the indirect pathway is inhibited by dopamine. When the substantia nigra pars compacta is firing, it signals to the basal nuclei that the body is in an active state, and movement will be more likely.
- When the substantia nigra pars compacta is silent, the body is in a passive state, and movement is inhibited. To illustrate this situation, while a student is sitting listening to a lecture, the substantia nigra pars compacta would be silent and the student less likely to get up and walk around. Likewise, while the professor is lecturing, and walking around at the front of the classroom, the professor's substantia nigra pars compacta would be active, in keeping with his or her activity level.

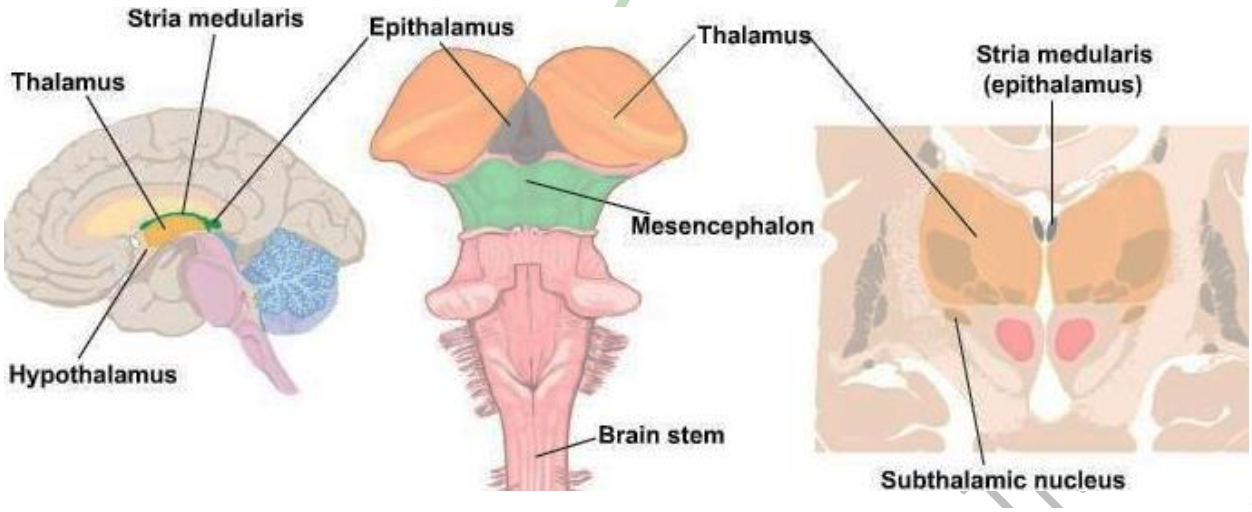
Functional area of the cerebral cortex:

Cerebral cortex consist mainly three kinds of functional areas.

1. Sensory areas: receives and interpret sensory impulses.
2. Motor areas: control muscular movements
3. Association areas: deals with more complex integrative functions such as memory, emotion, reasoning, will, judgment, personalities, intelligence etc.



DIENCEPHALON:



- The diencephalon is the connection between the cerebrum and the rest of the nervous system, with one exception.
- The rest of the brain, the spinal cord, and the PNS all send information to the cerebrum through the diencephalon.
- Output from the cerebrum passes through the diencephalon. The single exception is the system associated with olfaction, or the sense of smell, which connects directly with the cerebrum.
- The diencephalon is deep beneath the cerebrum and constitutes the walls of the third ventricle. The diencephalon consists thalamus, hypothalamus, epithalamus, subthalamus and pineal gland.

Thalamus:

- It is 3 cm in length and occupy 80 % part of the diencephalon.
- It consist paired oval shaped gray matter.
- The thalamus is a collection of nuclei that relay 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. Axons from the peripheral sensory organs, or intermediate nuclei, synapse in the thalamus, and thalamic neurons project directly to the cerebrum. It is a requisite synapse in any sensory pathway, except for olfaction.
- The thalamus does not just pass the information on, it also processes that information. For example, the portion of the thalamus that receives visual information will influence what visual stimuli are important, or what receives attention.

- The cerebrum also sends information down to the thalamus, which usually communicates motor commands. This involves interactions with the cerebellum and other nuclei in the brain stem. The cerebrum interacts with the basal nuclei, which involves connections with the thalamus. The primary output of the basal nuclei is to the thalamus, which relays that output to the cerebral cortex. The cortex also sends information to the thalamus that will then influence the effects of the basal nuclei. Median geniculate nucleus—related to hearing, lateral geniculate nucleus—related to vision, Ventral posterior nucleus—related to taste & somatic sensations like touch, pain, pressure, cold, heat, vibrations etc.

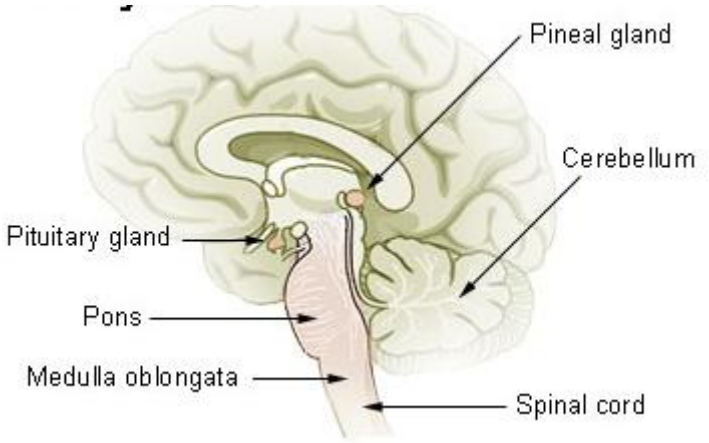
Hypothalamus:

- Inferior and slightly anterior to the thalamus is the hypothalamus, the other major region of the diencephalon. The hypothalamus is a collection of nuclei that are largely involved in regulating homeostasis. The hypothalamus is the executive region in charge of the autonomic nervous system and the endocrine system through its regulation of the anterior pituitary gland. Other parts of the hypothalamus are involved in memory and emotion as part of the limbic system.
- Other functions regulated by the hypothalamus are:
  - ✓ Controls autonomic nervous system
  - ✓ Center for emotional response and behavior
  - ✓ Regulates body temperature
  - ✓ Regulates food intake (appetite)
  - ✓ Regulates water balance and thirst
  - ✓ Controls sleep-wake cycles
  - ✓ Controls endocrine system
  - ✓ Controls CVS regulation- Heart rate & BP
- The hypothalamus is shaded blue. The pituitary gland extends from the hypothalamus.

Epithalamus:

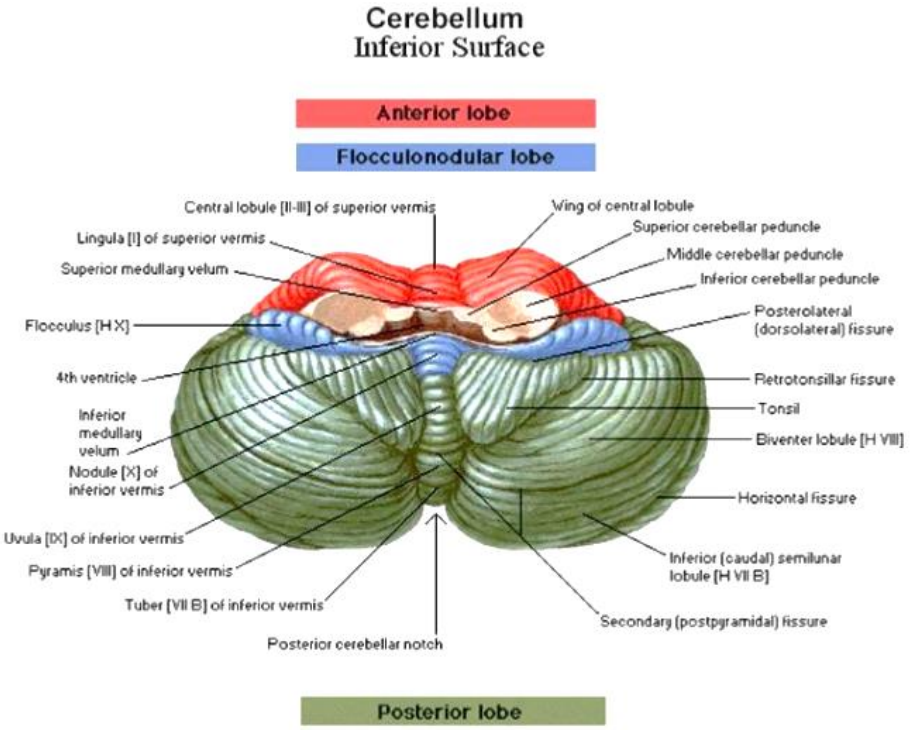
- The epithalamus is a posterior segment of the diencephalon.
- The diencephalon is a part of the forebrain that also contains the thalamus, the hypothalamus and pituitary gland.
- The function of the epithalamus is to connect the limbic system to other parts of the brain. Some functions of its components include the secretion of melatonin by the pineal gland (involved in circadian rhythms), and regulation of motor pathways and emotions.

Pineal gland:



- It is the endocrine gland of the brain.
- The pineal gland produces melatonin, a serotonin-derived hormone which modulates sleep patterns in both circadian and seasonal cycles.
- The shape of the gland resembles a pine cone from which it derived its name.
- The pineal gland is located in the epithalamus, near the center of the brain, between the two hemispheres.

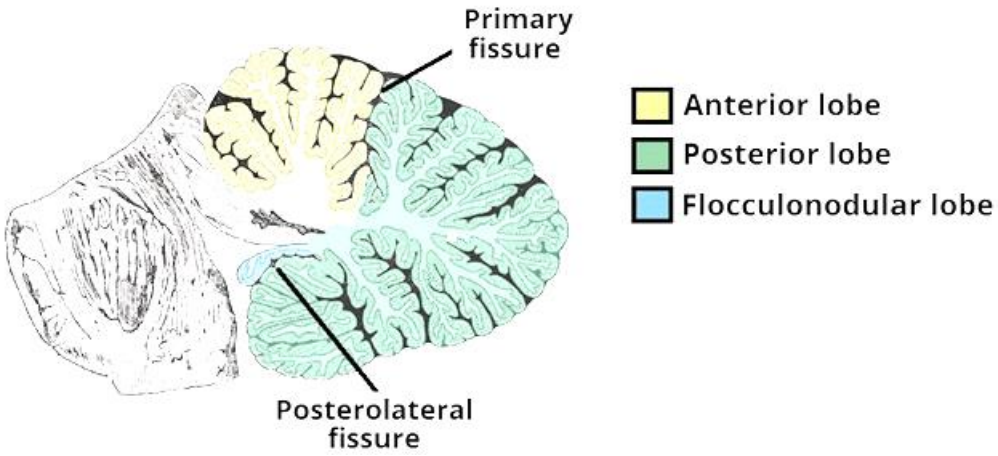
CEREBELLUM:



Anatomy of Cerebellum:

- The cerebellum, which stands for “little brain”, is a structure of the central nervous system. It has an important role in motor control.
- In particular, it is active in the coordination, precision and timing of movements, as well as in motor learning.
- The cerebellum is located at the back of the brain, immediately inferior to the occipital and temporal lobes, and within the posterior cranial fossa. It is separated from these lobes by the tentorium cerebelli, a tough layer of dura mater.
- It lies at the same level of and posterior to the pons, from which it is separated by the fourth ventricle.
- The cerebellum consists of two hemispheres which are connected by the vermis, a narrow midline area. Like other structures in the central nervous system, the cerebellum consists of grey matter and white matter:
- Grey matter – located on the surface of the cerebellum. It is tightly folded, forming the cerebellar cortex.
- White matter – located underneath the cerebellar cortex. Embedded in the white matter are the four cerebellar nuclei (the dentate, emboliform, globose, and fastigi nuclei).

- There are three ways that the cerebellum can be subdivided – anatomical lobes, zones and functional divisions
- There are three cerebellar zones. In the midline of the cerebellum is the vermis. Either side of the vermis is the intermediate zone. Lateral to the intermediate zone are the lateral hemispheres. There is no difference in gross structure between the lateral hemispheres and intermediate zones



There are three anatomical lobes that can be distinguished in the cerebellum; the anterior lobe, the posterior lobe and the flocculonodular lobe. These lobes are divided by two fissures – the primary fissure and posterolateral fissure.

Functional division of cerebellum:

The cerebellum can also be divided by function. There are three functional areas of the cerebellum – the cerebrocerebellum, the spinocerebellum and the vestibulocerebellum.

i. **Cerebrocerebellum** – the largest division, formed by the lateral hemispheres. It is involved in planning movements and motor learning. It receives inputs from the cerebral cortex and pontine nuclei, and sends outputs to the thalamus and red nucleus. This area also regulates coordination of muscle activation and is important in visually guided movements.

ii. **Spinocerebellum** – comprised of the vermis and intermediate zone of the cerebellar hemispheres. It is involved in regulating body movements by allowing for error correction. It also receives proprioceptive information.

iii. **Vestibulocerebellum** – the functional equivalent to the flocculonodular lobe. It is involved in controlling balance and ocular reflexes, mainly fixation on a target. It receives inputs from the vestibular system, and sends outputs back to the vestibular nuclei.

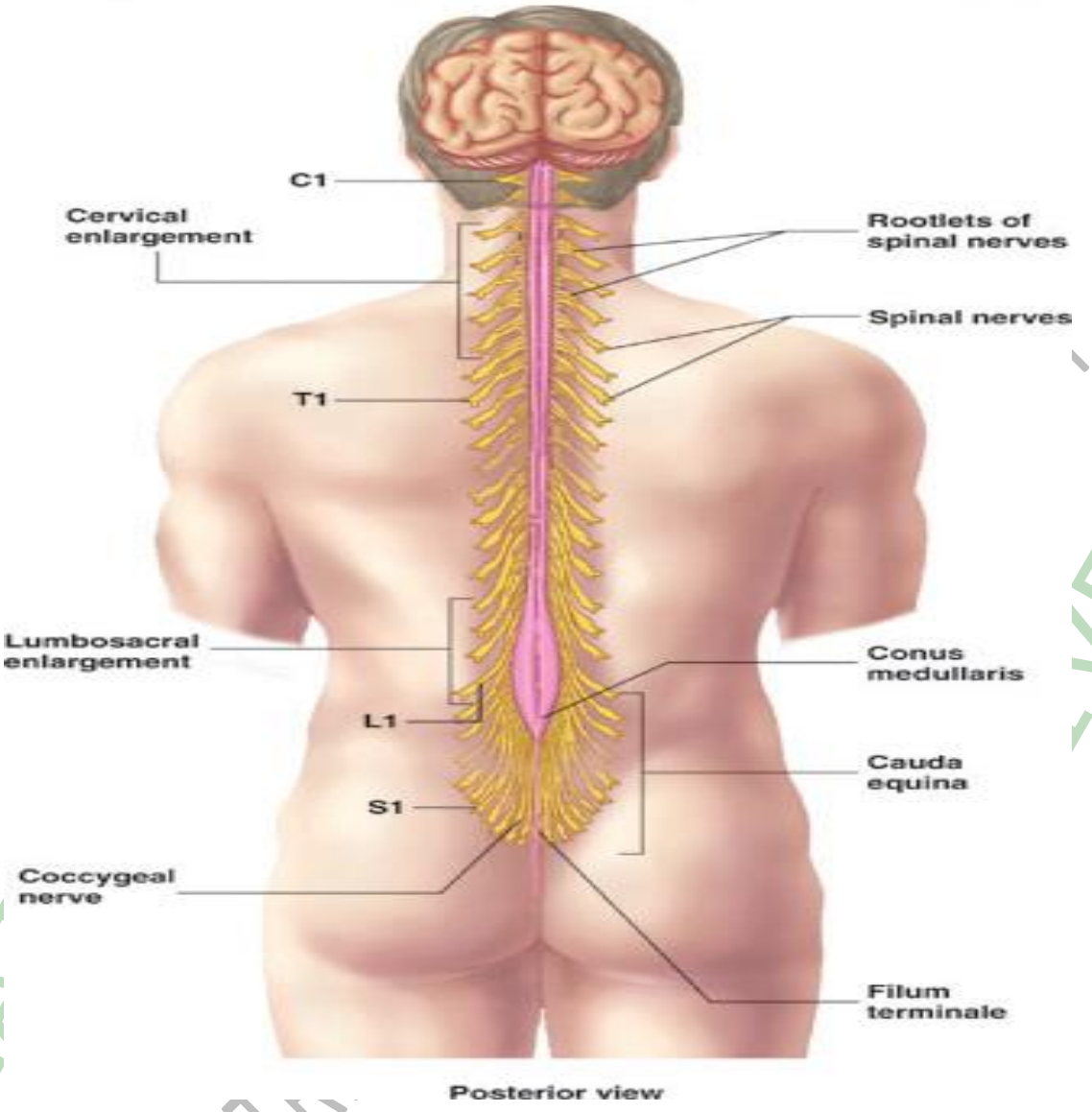
THE SPINAL CORD

FUNCTIONS:

- The spinal cord with its 31 pairs of *spinal nerves* serves two important functions.
- It is the connecting link between the brain and most of the body.
- It is involved in spinal reflex actions, both somatic and visceral.

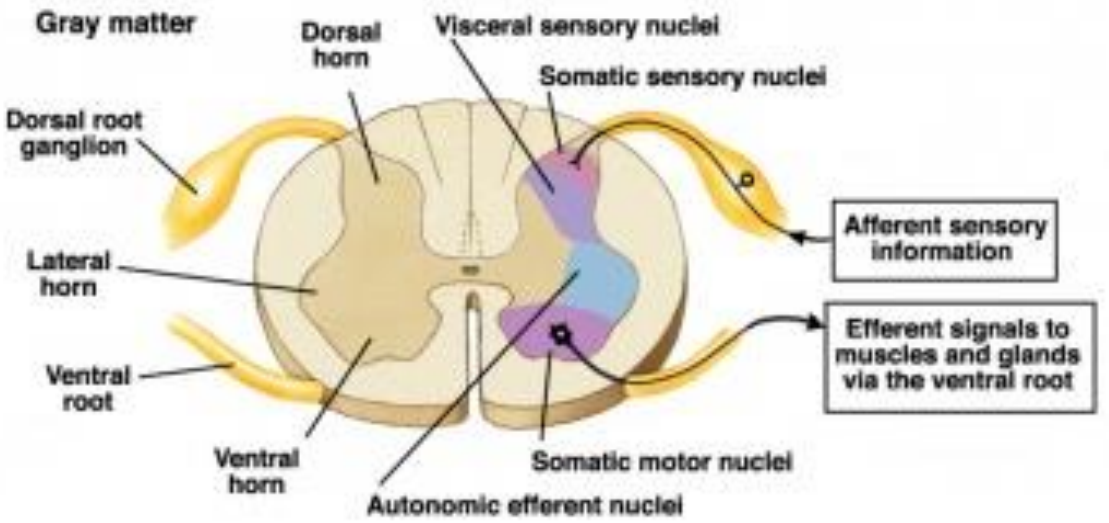
BASIC EXTERNAL ANATOMY OF THE SPINAL CORD:

- The spinal cord extends caudally from the brain for about 45 cm and has a width of ~14 mm. Its upper end is continuous with the brain (medulla oblongata). The cord is slightly thicker than a pencil.
- There are 31 pairs of spinal nerves:8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and coccygeal. The roots of the lumbar and sacral are called *cauda equina*.
- Surrounding and protecting the spinal cord is the vertebral column.
- The spinal cord is slightly flattened dorsally and ventrally, with two enlargements-cervical and lumbosacral from which the spinal nerves emerge that innervate the upper and lower limbs.
- The cervical enlargement supplies nerves to the pectoral girdle and upper limbs.
- The lumbar enlargement supplies nerves to the pelvis and lower limbs.
- Inferior to the lumbar enlargement, the spinal cord becomes tapered and conical-conus medullaris.
- Filum terminale-slender strand of fibrous tissue that extends from conus medullaris.



Basic Internal Anatomy of Spinal Cord:

- If the spinal cord is cut in X.S., a tiny central canal is observed, which contains CSF.
- There is a dark portion of H-shaped or butterfly shaped "gray matter", surrounded by a larger area of "white matter".
- The spinal cord is divided into more or less symmetrical halves by a deep groove called the anterior (ventral) median fissure and a median septum called posterior (dorsal) median sulcus.
- Extending from the spinal cord are the ventral and dorsal roots of the spinal nerves.



GRAY MATTER:

- The gray matter of the spinal cord consists of nerve cell bodies, dendrites and axon terminals (unmyelinated) and neuroglia. It is pinkish-gray color because of a rich network of blood vessels.
- The gray matter forms an H shape and is composed of three columns of neurons-posterior, anterior and lateral horns. The projections of gray matter toward the outer surface of spinal cord are called horns.
- The two that run dorsally-posterior horns which function in afferent input. The two that run ventrally-anterior horns which function in efferent somatic output. The two that extend laterally-lateral horns.
- The nerve fibers that form the cross of the H are known as gray commisure-functions in cross reflexes.

WHITE MATTER:

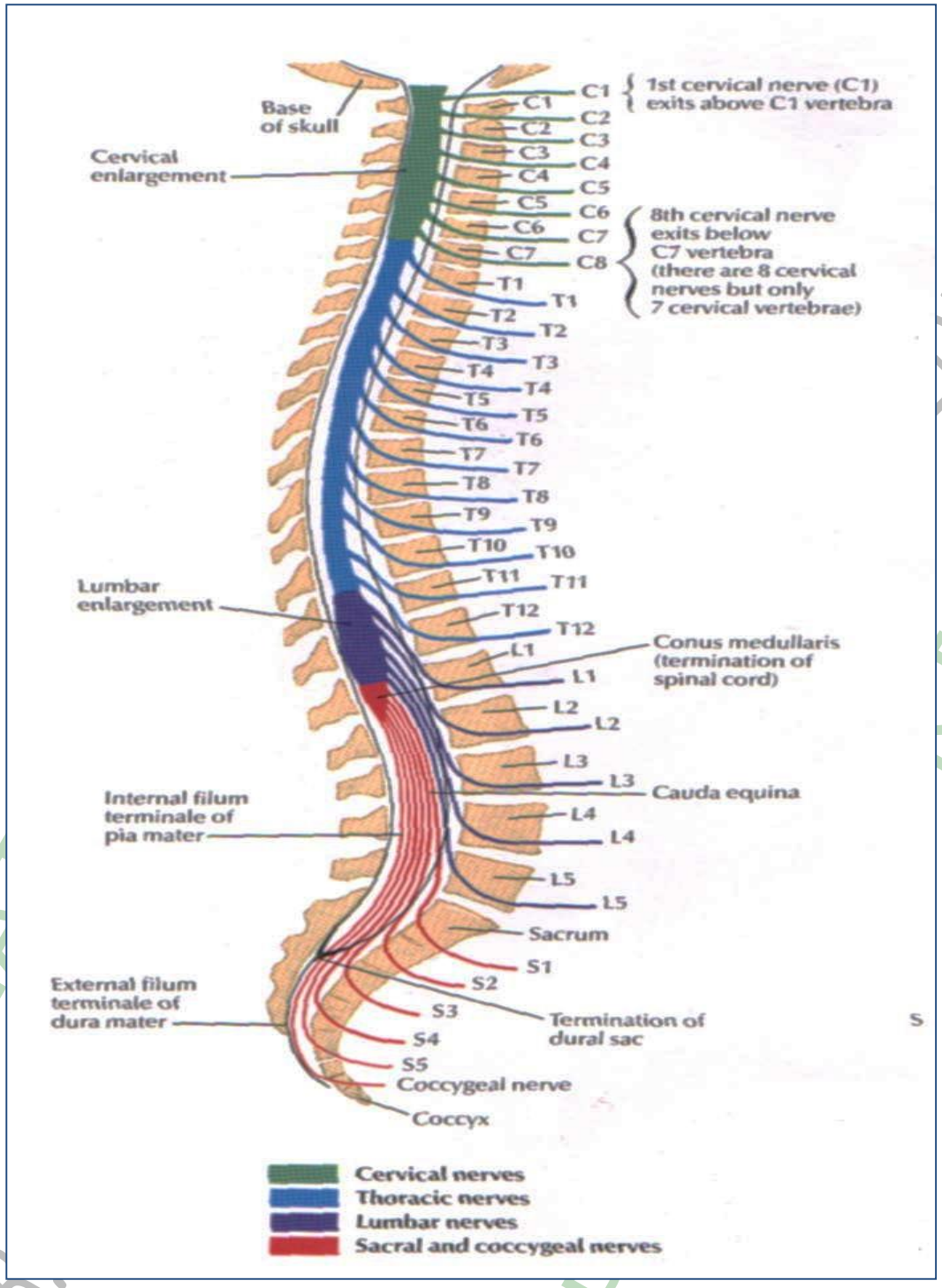
- The white matter gets its name because it is mainly composed of myelinated nerve fibers, and myelin has a whitish color.
- The white matter is divided into three pairs of columns or funiculi of myelinated fibers-anterior, posterior, lateral and a commisure area.
- The bundles of fibers within each funiculus are divided into tracts called fasciculi.
- Ascending tracts-sensory fibers carry impulse up the spinal cord to the brain.
- Descending tracts-motor neurons transmit impulse from the brain down the spinal cord.

SPINAL MENINGES:

- The outer layer is called dura mater. This is a tough, fibrous memebrane that merges with the filum terminale.
- The middle layer, the arachnoid, runs caudally to the S2 vertebral level. This is delicate and transparent.
- The innermost is called, pia mater. It is highly vascular and tightly attached to the spinal cord and its roots. Meningitis-bacterial or viral infection.
- Between the dura mater and periosteum of the vertebrae is the epidural space that contains many blood vessels and fat.
- Anesthetics can be injected here below the L3 vertebral level, from which it ascends to act upon sensory neurons to help dull pain. This procedure is called caudal block.(epidural block)
- Space between dura mater and archnoid-subdural space-no CSF.
- Space between arachnoid and pia mater-subarchnoid space-CSF, blood vessels, spinal roots.

SPINAL NERVES:

- There are 8 cervical nerves (C), 12 thoracic (T), 5 lumbar (L), 5 sacral (S), and 1 coccygeal (Co).



- Each pair of spinal nerves passes through a pair of intervertebral foramina located between two successive vertebrae. Each spinal nerve caudal to the first thoracic vertebra takes its name from the vertebra immediately preceding it.
- The nerves are then distributed to a specific pair of segments of the body.
- The spinal cord and the roots of its nerves are protected by the vertebral column, its ligaments, spinal meninges and cerebrospinal fluid.
- A series of connective tissue layer surrounds each spinal nerve.

- **Epineurium**-outermost layer, consists of a dense network of collagen fibers.
- **Perineurium**-extend inward from the epineurium, dividing the nerve into a series of compartments.
- **Endoneurium**-delicate connective tissue fibers.

Ventral and Dorsal Roots:

- In the vicinity of the cord, each spinal nerve divides into a ventral (anterior, motor) root and a dorsal (posterior, sensory) root.
- Ventral roots contain mostly efferent nerve fibers and convey motor information.
- Dorsal roots contain afferent nerve fibers and convey sensory information.
- The axons of motor neurons whose cell bodies are located within the CNS in the anterior Horn emerge from the spinal cord to form ventral roots (motor).
- Groups of sensory neurons, whose axons make up the dorsal roots lie outside the cord in the dorsal root ganglia or spinal ganglia of the PNS.

Peripheral distribution of Spinal Nerves:

- A typical spinal nerve has a white ramus (this contains myelinated axons), and a gray ramus (unmyelinated fibers that innervate glands and smooth muscles in the body wall or limbs)
- A dorsal ramus(providing sensory and motor innervation to the skin and muscles of the back), and a ventral ramus (supplying the ventrolateral body surface, structures in the body wall and the limbs).
- Each pair of nerves monitors a region of the body surface called a dermatome.

Nerve Plexuses:

- A complex, interwoven network of nerves is a nerve plexus.
- The three large plexuses are the cervical plexus, the brachial plexus and the lumbosacral plexus. The latter can be further divided into the lumbar plexus and the sacral plexus.

CLASSIFICATION OF REFLEXES:

1. Reflexes are classified according to:
2. Their development: innate and acquired
3. Site of information processing: cranial and spinal reflexes.
4. Nature of resulting motor response: somatic and visceral reflexes.
5. The complexity of the neural circuit: monosynaptic and polysynaptic reflexes.

TYPES OF REFLEXES:

1. Stretch (Myotatic Reflex)- monosynaptic reflex arc.
    - Maintains erect posture. Eg. Knee-jerk or patellar reflex. Ipsilateral-response and stimulus on same side.
2. Gamma Motor Neuron Reflex Arc.
    - This acts to smooth out the movements of muscle contractions or to sustain the contraction of a muscle.
3. Plantar Reflex:
    - This clinically tests the integrity of the spinal cord from L4 to S2. It is tested by drawing a blunt instrument down the lateral aspect of the sole (plantar surface) of the foot. A normal response is a curling or downward flexion of the foot.
4. Withdrawal reflex arc:
    - Involves sensory receptors, afferent neurons, interneurons, alpha motor neurons, skeletal muscles.

CRANIAL NERVES

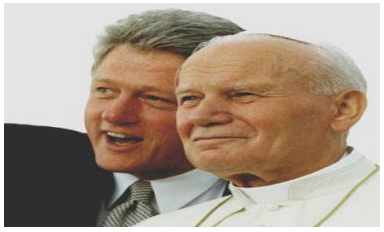
- The brain communicates with the body through the spinal cord and twelve pairs of cranial nerves.
- Ten of the twelve pairs of cranial nerves that control hearing, eye movement, facial sensations, taste, swallowing and movement of the face, neck, shoulder and tongue muscles originate in the brainstem. The cranial nerves for smell and vision originate in the cerebrum.
- The Roman numeral, name, and main function of the twelve cranial nerves:

Number	Name	Function
I	olfactory	smell
II	optic	sight
III	oculomotor	moves eye, pupil
IV	trochlear	moves eye
V	trigeminal	face sensation
VI	abducens	moves eye
VII	facial	moves face, salivate
VIII	vestibulocochlear	hearing, balance
IX	glossopharyngeal	taste, swallow
X	vagus	heart rate, digestion
XI	accessory	moves head
XII	hypoglossal	moves tongue

ALZHEIMER'S DISEASE

INTRODUCTION:

- A condition characterized by a specific group of signs and symptoms
- Alzheimer's Disease is the most common form of Dementia.
- Brain disorder that affects the ability to control thought, memory, and language
- Symptoms are different for each individual.



Pope John Paul II

CAUSES:

- No known single cause
- Involves the malfunction or death of nerve cells
- Strokes increase risk
- Brain damage occurs years before first symptoms appear
- Nerve cells that process, store, and retrieve information have already begun to die when symptoms emerge

TEN WARNING SIGNS:

1. **Memory loss**
    - Forgetting recently learned information
    - Most common early stage sign
2. **Difficulty performing familiar tasks**
    - Failure preparing a meal, placing a telephone call or playing a game
    - Hard to plan or complete everyday tasks
3. **Problems with language**
    - Forget simple words
    - Substitute words ("that thing for my mouth" instead of "toothbrush")
4. **Disorientation to time and place**
    - Become lost in own neighborhood
    - Forget where they are and how they got there
    - Not know how to get back home
5. **Poor or decreased judgment**
    - Inappropriate dress (layers on a warm day or little clothing in cold)
    - Poor judgment (give away large sums of money to telemarketers)
6. **Problems with abstract thinking**
    - Difficulty performing mental tasks (using numbers)

7. **Misplacing things**
    - Put things in unusual places (iron in freezer, wristwatch in sugar bowl)
8. **Changes in mood or behavior**
    - Rapid mood swings (calm to tears to anger for no apparent reason)
9. **Changes in personality**
    - Personality changes dramatically
    - Extremely confused, suspicious, fearful or dependent on family
    - Anxiety, agitation, and delusions or hallucinations are seen
10. **Loss of initiative**
    - May become very passive (sitting in front of the TV for hours, sleeping more than usual, not wanting to do usual activities)

DIAGNOSIS:

Only definite way to diagnose AD is to do an autopsy of the brain (impossible before death).

No specific test can detect Alzheimer's

- Diagnosis involves multiple tests
- 90% accurate

Tests included:

- Physical examination: nutritional status, blood pressure, and pulse
- Test sensation, balance, and other functions of the nervous system
- Brain scan: detects other causes of dementia such as stroke
- Mental status evaluation assessing:
    - ✓ sense of time and place
    - ✓ ability to remember, understand, and communicate
    - ✓ ability to do simple math problems
- Lab tests: blood & urine (determine other causes of dementia)

RISK FACTORS:

Increasing age (Greatest known factor)

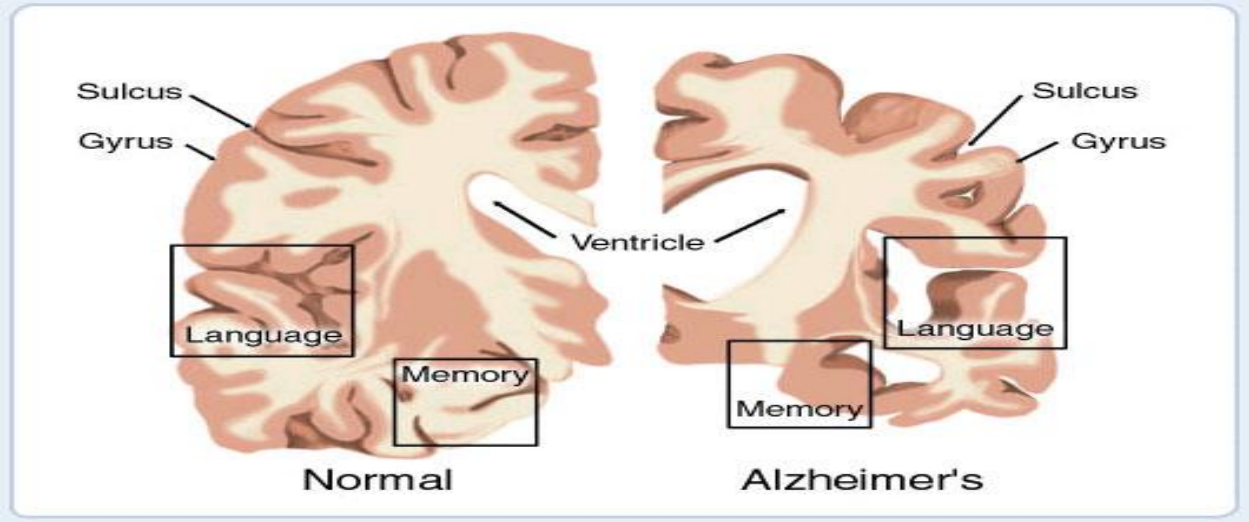
- Risk doubles every five years after age 65
- Risk is nearly 50 % after age 85

Family history/ Genetics

- A gene has been identified that increases the risk of Alzheimer's
- Not guarantee an individual will develop the disorder
- Found in only a few hundred extended families worldwide

PREVENTION:

- Decrease head injuries
- Keep overall good health of your brain
  - ✓ eat a healthy diet
  - ✓ stay socially active
  - ✓ avoid tobacco, excess alcohol, and other drugs
  - ✓ exercise the body & mind
- Monitor heart and blood vessels conditions which increase risk: heart disease, diabetes, stroke, high blood pressure, & cholesterol



TREATMENTS:

Currently, there is no cure.

- Drug and non-drug treatments may help with cognitive (brain) and behavioral symptoms.
- Drug Treatment:
  - ✓ Prevents the breakdown of acetylcholine (a chemical messenger in the brain important for memory and other thinking skills)
  - ✓ Keeps levels of acetylcholine high, even while the cells that produce it continue to become damaged or die
  - ✓ The first Alzheimer medications to be approved were cholinesterase inhibitors.
  - ✓ Memantine and Vitamin E supplements are also used

Stages:

Alzheimer's can be broken up into three stages:

- Early
- Middle
- Late

Early Stage:

*Can last from virtually no time to about five years.

Characteristics:

- Difficulty remembering most recent information
- Difficulty performing familiar tasks
- Decreased or altered judgment
- Language Changes
- Changes in personality, behavior, & mood
- Disoriented with time and place
- Problems with abstract thinking

Middle Stage:

*Lasts anywhere from 2 and 12 years

*Symptoms are usually more obvious in this stage.

Characteristics:

- Remembers less and less (Forgets quicker than in Early Stage)
- Increased difficulty or inability to perform familiar tasks
- Lack of judgment
- Increased changes in behavior, mood, and personality (suspiciousness)
- More confused about time and place
- Loss of ability to think abstractly
- Changes in the five senses
- Changes occur physically (loss of bladder control, less steady while walking, etc.)

Late Stage:

*Lasts about 1 to 3 years

Characteristics:

- Little or no short term memory remains
- Unable to perform tasks
- Lack of judgment
- Unable to communicate effectively
- Doesn't recognize self or family
- Puts things in their mouth or touches & grabs things
- Five senses have little or no function
- Physical activity declines (loss of ability to walk and/or trouble swallowing)

Former US President Ronald Reagan

SYNAPTIC TRANSMISSION

INTRODUCTION

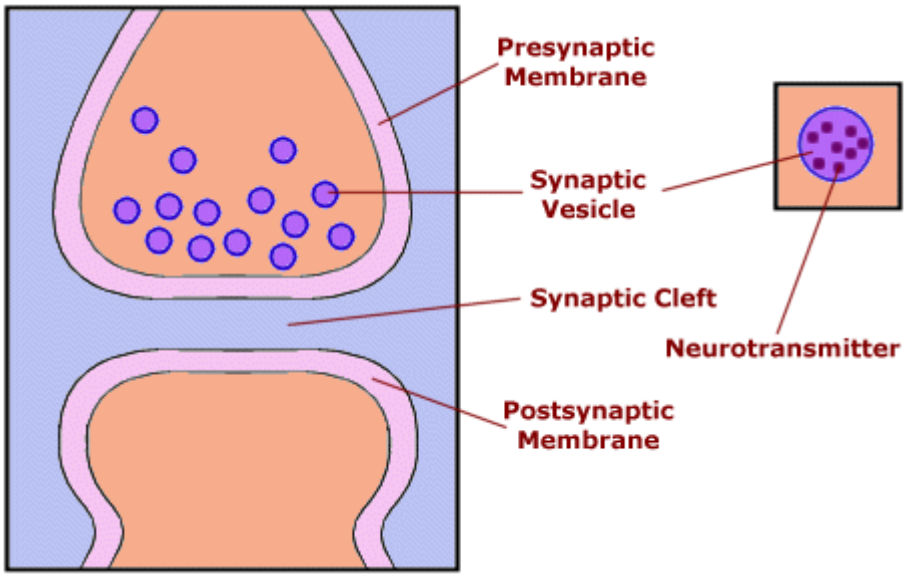
Neurons receive information from sensory organs, send information to motor organs, or share information with other neurons. The process of communicating information is very similar, whether it is to another neuron or to a muscle or gland cell. However, by far the largest number of neuronal connections is with other neurons. The rest of this tutorial therefore focuses on inter-neuronal communication. The transmission of information is accomplished in two ways:

- Electrically: the neuron is directly adjacent to other neurons. Small holes in each cell's membrane, called *gap junctions*, are juxtaposed so that as the action potential reaches the end of the axon (at the terminal boutons), the depolarization continues across the membrane to the postsynaptic neuron directly.
- Chemically: there is a space (the synaptic cleft) between the axon terminus and the adjacent neuron. As the action potential reaches the end of the axon, a chemical is released that travels across the synaptic cleft to the next neuron to alter its electric potential.

With very few exceptions, mammalian organisms use chemical means to transmit information.

SYNAPSE STRUCTURE

- The part of the synapse that belongs to the initiating neuron is called the *presynaptic membrane*.
- The part of the synapse that belongs to the receiving neuron is called the *postsynaptic membrane*.
- The space between the two is called the *synaptic cleft*. It is approximately 20 nm wide (20 x 10^{-9} m).
- Presynaptic terminals contain numerous *synaptic vesicles*
- Synaptic vesicles contain *Neurotransmitters*, chemical substances which ultimately cause postsynaptic changes in the receiving neuron, is contained within the synaptic vesicles. Common neurotransmitters include:
    - Acetylcholine
    - Dopamine
    - Norepinepherine (a.k.a., noradrenaline)
    - Serotonin



TRANSMISSION

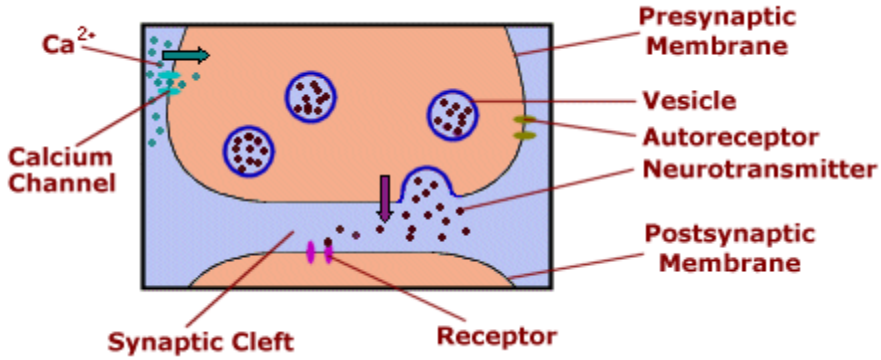
Electrical transmission occurs by virtue of the fact that the cells are in direct contact with each other: depolarization of the presynaptic cell membrane causes a depolarization of the postsynaptic cell membrane, and the action potential is propagated further. Here transmission of information is always excitatory: the conduction of information always causes a depolarization of the adjacent cell's membrane.

Chemical transmission, albeit more complex allows for far more control, including the ability to excite or inhibit the postsynaptic cell. Here the conduction of information can cause either depolarization or hyperpolarization, depending on the nature of the chemical substance.

The sequence of events that lead to postsynaptic changes is as follows:

1. The action potential signal arrives at the axon terminal (the bouton).
2. The local depolarization causes Ca^{2+} channels to open. Ca^{2+} enters the presynaptic cell because its concentration is greater outside the cell than inside.
3. The Ca^{2+}, by binding with calmodulin, causes vesicles filled with neurotransmitter to migrate towards the presynaptic membrane.
4. The vesicle merges with the presynaptic membrane.
5. The presynaptic membrane and vesicle now forms a continuous membrane, so that the neurotransmitter is released into the synaptic cleft. This process is called *exocytosis*.
6. The neurotransmitter diffuses through the synaptic cleft and binds with receptor channel membranes that are located in both presynaptic and postsynaptic membranes.
7. The time period from neurotransmitter release to receptor channel binding is less than a millionth of a second.

The process is depicted in the diagram below:



Direct and Indirect Binding to Postsynaptic Receptor

There are two kinds of receptor channels: direct and indirect

1. Direct: the receptor channel allows ions to pass through the membrane. The neurotransmitter acts like a key which opens the ion channel. This is the fastest kind of channel (about 0.5 ms). This is called an ionotropic receptor.
2. Indirect: the binding of neurotransmitter to the receptor channel causes the release of a molecule, called a secondary messenger, which indirectly activates nearby ion channels. This is called a metabotropic receptor.

- This process is much slower than direct receptor ion channels: from 30 ms up to 1 second.
- However, this is the most common type of postsynaptic receptor channel

Postsynaptic Stimulation

Once the postsynaptic ion channel is opened, whether directly or indirectly, the effect can be either excitatory (depolarizing) or inhibitory (hyperpolarizing).

- Excitatory Postsynaptic Potentials (EPSP)
  - ✓ Excitatory ion channels are permeable to Na^+ and K^+
  - ✓ Because of the electrical and concentration gradient, more Na^+ moves into the cell than K^+
  - ✓ The inside of the cell becomes more positive, hence causing a local depolarization
  - ✓ If enough depolarization occurs (for example, because the neurotransmitter released caused nearby ion channels to open), an action potential is generated
- Inhibitory Postsynaptic Potentials (IPSP)
  - ✓ Inhibitory ion channels are permeable to Cl^- and K^+
  - ✓ Because of the concentration gradient (not electrical), Cl^- moves into the cell and K^+ moves out of the cell

- ✓ The inside of the cell thus becomes more negative, hence causing a local hyperpolarization
- ✓ The hyperpolarization will make it more difficult for the cell membrane potential to reach threshold, thereby making it less likely that an action potential will be generated

Summation

- Depending on the kind of neurotransmitter released, the effect can be either excitatory or inhibitory
- The local excitatory depolarizations or inhibitory hyperpolarizations are graded (passive) potentials and therefore can summate or cause additive changes to the post-synaptic membrane potential. This process is known as *summation*
  - ✓ Spatial summation occurs when multiple synapses in nearby locations are stimulated simultaneously
  - ✓ Temporal summation occurs when the same channel is repeatedly opened (for example, because the presynaptic cell receives many impulses in a row), thereby altering the membrane potential further before it has the time to return to normal
- Although receptor ion channels are all chemically gated, enough depolarization past threshold can cause nearby voltage gated channels to open. An action potential would then be generated

Neurotransmitter Deactivation

If neurotransmitters were continually in the synaptic cleft, the postsynaptic channels would be continually stimulated and the membrane potential would not be able to become stable. There are three ways in which neurotransmitter is deactivated:

1. Degradation: Enzymes located in the synaptic cleft break down the neurotransmitter into a substance which has no effect on the receptor channel
2. Reuptake: The neurotransmitter can reenter the presynaptic cell through channels in the membrane.
3. Autoreceptors: Receptors for a particular neurotransmitter are located on the presynaptic membrane that act like a thermostat. When there is too much neurotransmitter released in the synapse, it decreases the release of further neurotransmitter when the action potential arrives at the presynaptic membrane. It may accomplish this by decreasing the number of Ca^{2+}channels that open when the next action potential arrives at the presynaptic terminal

NEUROTRANSMITTERS

A molecule is considered a neurotransmitter if it meets the following criteria:

- Synthesis of the neurotransmitter occurs in the neuron itself
- It can be found in the presynaptic membrane (because it was carried there from the soma, or because it was synthesized there directly)
- Its release into the synaptic cleft causes a change in the postsynaptic membrane
- Its effect on a neuron is the same whether released exogenously (i.e., from outside the organism as a drug) or endogenously (from the presynaptic terminal)
- Once released, the molecule is specifically removed from the synaptic cleft either by reuse or degradation

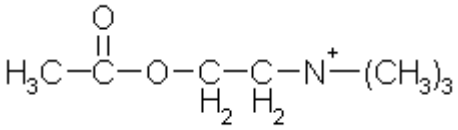
There are two classes of neurotransmitters:

- Small molecules, such as acetylcholine (ACh) or dopamine
  - ✓ Are packaged in small vesicles
  - ✓ Are released by exocytosis at active zones associated with Ca^{2+} channels
- Large molecules made up of chains of amino acids
  - ✓ Are packaged in large vesicles (which can contain small molecules as well)
  - ✓ Are released by exocytosis generally anywhere from the presynaptic membrane

Most neurons contain both types of vesicles, but in different concentrations.

SMALL MOLECULES

Acetylcholine (ACh)



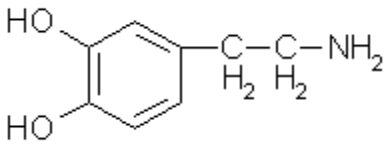
- The only small molecule that is not an amino acid or derived from one
- Uses *choline* as a precursor
- Choline cannot be synthesized by the body and must be obtained from external food sources
- Used by motor neurons as an excitatory neurotransmitter in the spinal cord
- Used at neuromuscular junctions as an excitatory neurotransmitter to influence muscle activation
- Used by the Autonomic Nervous System, such as smooth muscles of the heart, as an inhibitory neurotransmitter in preganglionic neurons and postganglionic parasympathetic neurons

- Used everywhere in the brain. For example, memory systems of the CNS (may be related to Alzheimer's Disease).
- Most receptors for acetylcholine are ionotropic

MONOAMINES

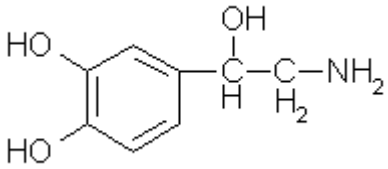
a. Synthesized from tyrosine

1. Dopamine



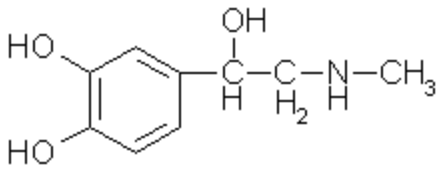
- Is synthesized in three steps from the amino acid tyrosine
- Is the direct precursor to norepinepherine.
- Enzyme converts tyrosine to L-DOPA
- Generally involved in regulatory motor activity
- In the basal ganlgia, involved in mood, sensory perception, and attention
- Schizophrenics have too much dopamine, patients with Parkinson's Disease have too little

2. Norepinepherine



- Synthesized directly from dopamine, and forms the direct precursor to epinepherine. It is synthesized in four steps from tyrosine
- Synthesized within vesicles (the only neurotransmitter synthesized this way)
- Also known as *noradrenaline*
- Used in the CNS by neurons that project in the cortex, cerebellum, and spinal cord; as such has many uses including sleep/wakefulness regulation
- Activates sympathetic and parasympathetic neurons in the Autonomic Nervous System

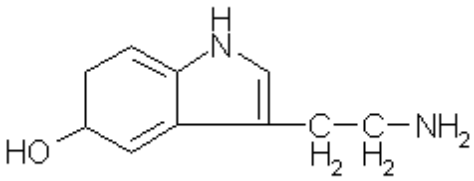
3. Epinepherine



- Synthesized in five steps from tyrosine, and directly from norepinepherine in the biosynthetic pathway
- Also known as adrenaline (from Latin: ad means "above" and renal means "kidney," while in Greek, epi means "above" and nephron means "kidney")
- Produced by the adrenal medulla, a gland above the kidney
- Few neurons in the brain use this neurotransmitter
- Activates sympathetic neurons in the Autonomic Nervous System

b. Synthesized from tryptophan

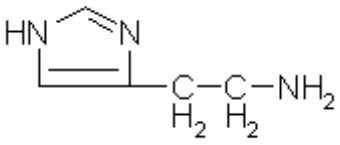
1. Serotonin (5-HT)



- Synthesized in two steps from the amino acid tryptophan
- Actual name: 5-hydroxytryptamine (5-HT)
- Regulates attention and other complex cognitive functions, such as sleep (dreaming), eating, mood, pain regulation
- Neurons which use serotonin are distributed throughout the brain and spinal cord
- Directly implicated in depression (also norepinepherine)
- Used by metabotropic receptors

c. Synthesized from histidine

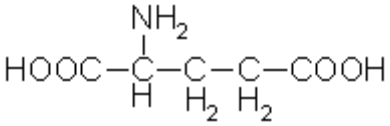
Histamine



- Synthesized from the amino acid histidine
- Used in control of smooth muscle, exocrine glands, and vasculature
- High concentration in the hypothalamus, which regulates the secretion of horomones
- Used during inflammatory reactions

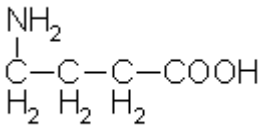
Amino Acids

Glutamate (Glu)



- Most prevalent neurotransmitter in the Central Nervous System. Used by more that 50% of neurons
- Derived from a -ketoglutarate
- Glutamate is the most important excitatory (EPSP) neurotransmitter, exciting about 90% of the postsynaptic terminals to which it contacts
- As an excitatory neutrotransmitter, it binds to with ionotropic receptors, causing depolarization by opening Na^+ ion channels
- At metabotropic receptors, it is modulatory

g-Aminobutyric Acid (GABA)



- Synthesized directly from glutamate
- GABA is the most important inhibitory (IPSP) neurotransmitter
- Present in high concentrations in the CNS, preventing the brain from becoming overexcited
- As an inhibitory neutrotransmitter, it binds to both ionotropic and metabotropic receptors, causing hyperpolarization by opening Cl^- ion channels
- Used by inhibitory interneurons in the spinal cord

LARGE MOLECULES

Neuropeptides

- Derived from secretory proteins formed in the cell body
- They are first processed in the endoplasmic reticulum (ER) and are moved to the Golgi apparatus before being secreted as large vesicles and transported down the axon in preparation for exocytosis
- More than 50 peptides have been isolated in nerve cells. For example,
  - ✓ *Substance P* and *enkephalins*: Active during inflammation and pain transmission in the PNS
  - ✓ *Endorphins*: Endogenous opiates which cause euphoria, suppress pain, or regulate responses to stress
- Are either excitatory or inhibitory, and can also act as neuromodulators, affecting the amount of neurotransmitter released
- Some form part of the neuroendocrine system by functioning both as hormones and neurotransmitters

As neurotransmitters, each one of these molecules undergo a similar life cycle:

1. Synthesis: Neurotransmitters are synthesized by the enzymatic transformation of precursors. The biosythetic pathway can be immediate (as in GABA from glutamate) or in multiple steps (as in epinepherine from norepinepherine from dopamine, etc.). The synthesis occurs either at the terminal boutons of the axon, or in the soma. In the latter case, it is transported to the axon terminals probably by way of microtubular tracks.
2. Storage: They are packaged inside synaptic vesicles. These vesicles vary in size, depending on the size of the neurotransmitter.
3. Release: The neurotransmitters are released from the presynaptic terminal by exocytosis and diffuse across the synaptic cleft to the postsynaptic membrane
4. Binding: The neurotransmitters bind to receptor proteins imbedded in the postsynaptic cell's membrane. There are two kinds of receptors: ionotropic (direct) and metabotropic (indirect).
5. Inactivation: The neurotransmitter is degraded either by being broken down enzymatically, or reused by active reuptake in which case the cycle begins again

DRUGS

Drugs can affect any of the stages in the "life-cycle" of a neurotransmitter.

Drugs that bind with receptors on the post-synaptic (and sometimes pre-synaptic) membrane fall into two groups:

- Agonists: Bind to receptors and simulate or enhance a neurotransmitter's actions (i.e., opening ion channels and causing EPSPs or IPSPs).
- Antagonists: Have the opposite effect of agonists by blocking the receptors and inactivating it (usually by taking up the space but without specifically causing the opening of the channel or the operation of the secondary messenger). The neurotransmitter's effect is nullified or diminished.

The table below lists some common drugs, they action in the brain and their observable behavior:

Drug	**Action (Brain)**	**Behavior**
Nicotine	Acetylcholine receptor agonist	Smokers: relaxation, alertness, reduced desire for food. Non-smokers: Nausea, vomiting, cramps, and diarrhea.
Alcohol	1. Reduces flow of Ca^{2+} into cells 2. GABA agonist 3. Increases number of binding sites for glutamate 4. Interferes with some secondary messenger systems	Low doses effect is excitatory. Moderate to high doses effect is inhibitory.
Cocaine and crack	Blocks reuptake of dopamine and norepinepherine	Feelings of well-being and confidence. Reduced desire for sleep and food.
Opiates (heroin, morphine, codeine)	Endorphin agonist	Pain suppression and euphoria. Suppresses cough and diarrhea
LSD	Serotonin receptor agonist	Visual hallucinations