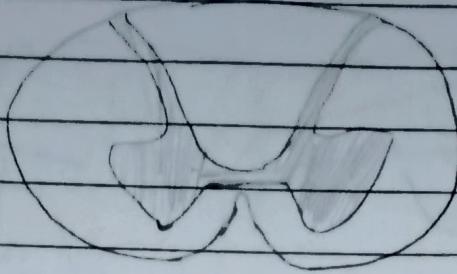
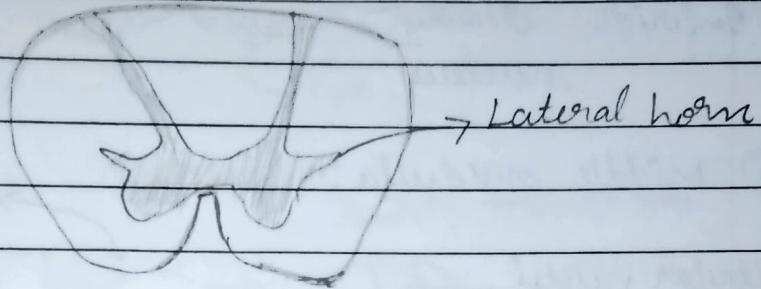


* Internal structure of the spinal cord:

① Cervical



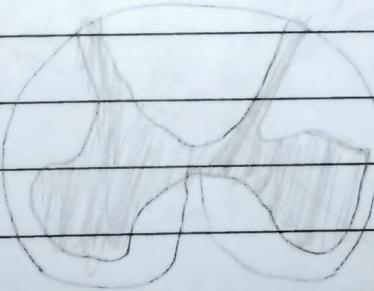
② Thoracic



③ Lumbar



④ Sacral

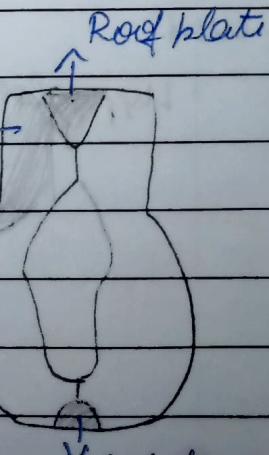


- Embryonic derivation of internal structure in the brainstem.

A larplatia
dorsal horn
(sensory)

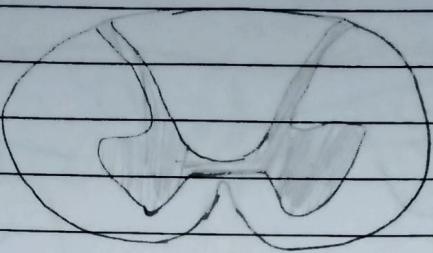
Basal plate.

Ventral horn
(motor)

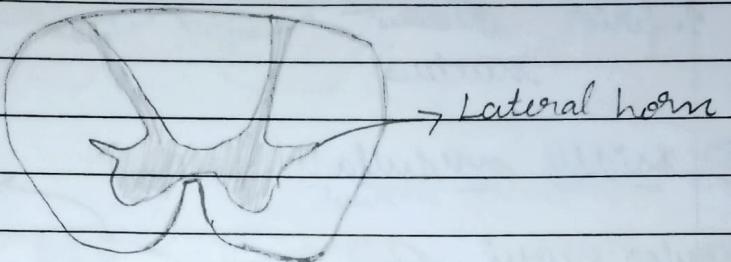


* Internal structure of the spinal cord:

① Cervical



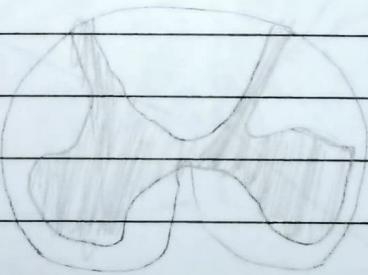
② Thoracic



③ Lumbar



④ Sacral



- Embryonic derivation of internal structure in the brainstem.

A larplatī
dorsal horn
(sensory)

Basal plate.

Ventral horn
(motor)

Roof plate



Footplate

Cerebral aqueduct = Sylvian aqueduct = mesencephalic duct.

1/11/2020

choroid plexus produces it (present in each ventricle)

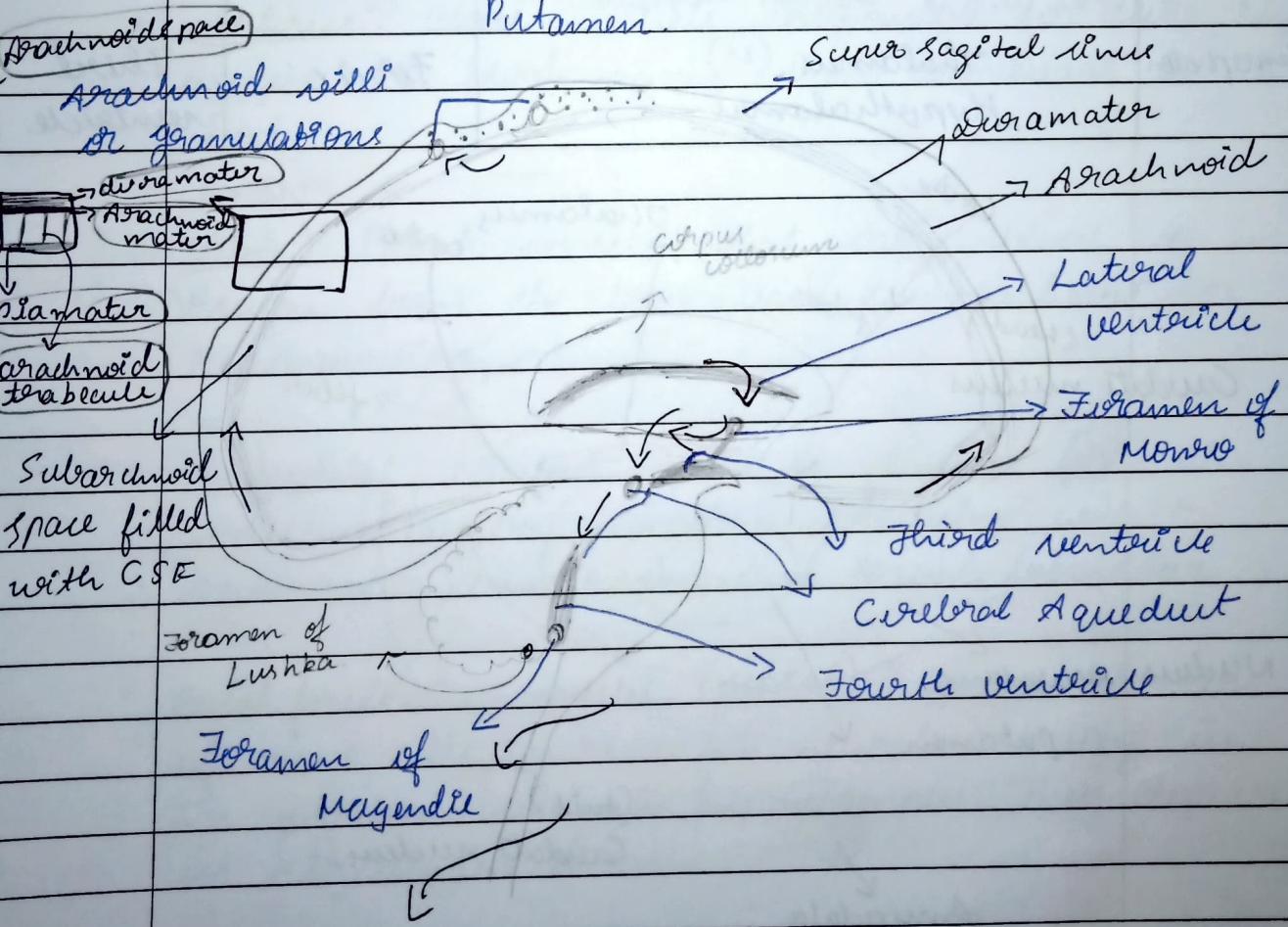
Ventricle

→ CSF exits ^{choroid plexus} inferior part of the 4th ventricle (a space b/w cerebellum and medulla) and it is called "Foramen of Magendie".

→ Drainage of CSF is through dural midline - Arachnoid tissue → Arachnoid granulation → Superior Sagittal Sinus → Venous blood.

→ Space b/w folia in cerebellum ⇒ pathology is chronic alcohol abuse.

* Stereatum: Caudate nucleus, Nucleus accumbens, Putamen.



→ Axons descending from (ascending to) the cerebral cortex assemble into large fiber bundle tract called

— / —

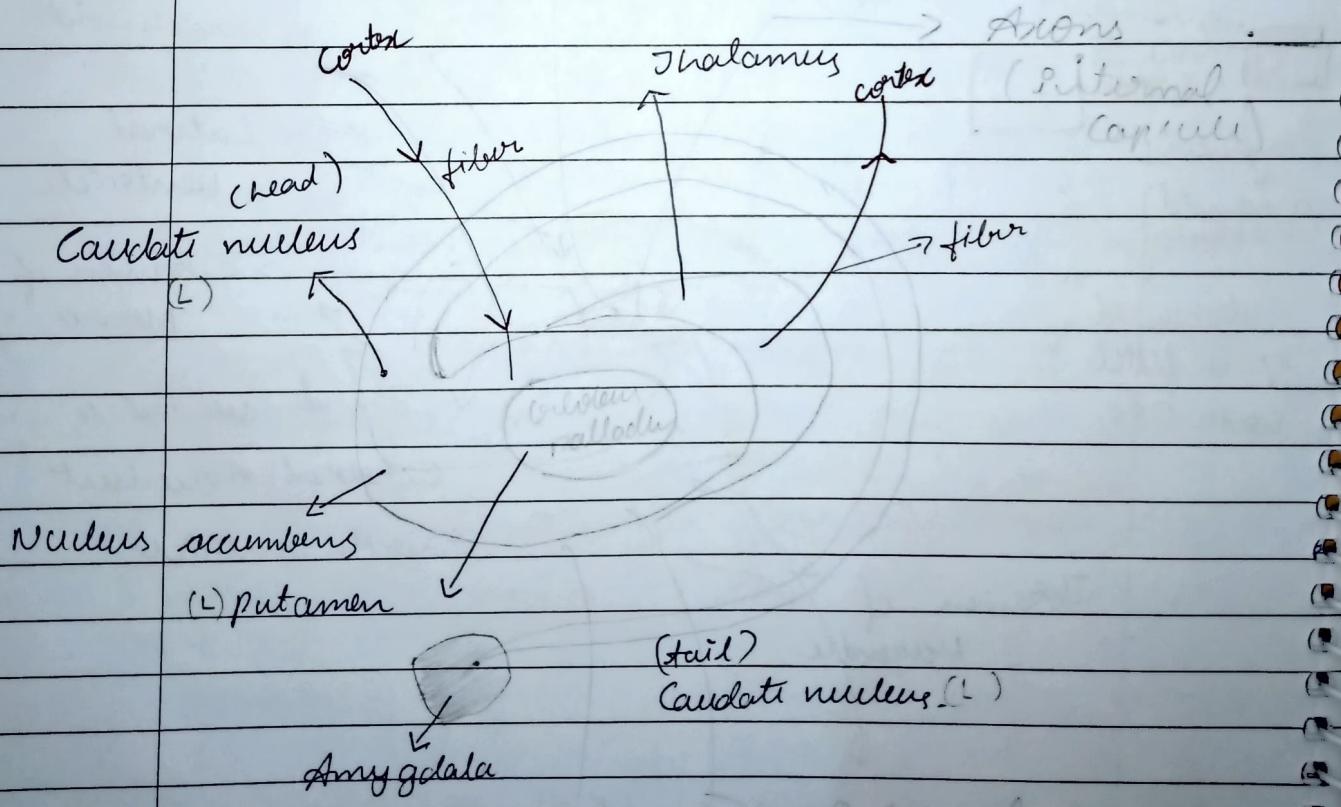
white matter

the internal capsule

- cortex to downwards
- Thalamus to cortex

* Internal anatomy of the forebrain:

	Gray matter	white Matter	Ventricles
Telencephalon (cerebral hemisphere)	Cortical / corticed structures: Cerebral cortex; hippocampus; Amygdala	Corpus callosum, Anterior commissure, Fornix, Internal capsule	Lateral ventricle
	Basal ganglia (deep structures): ^(M) Caudate nucleus, Putamen, ^(I) Nucleus accumbens, ^(L) Globus pallidus.		Ventricles
	(M), (L), (I) core w.r.t inferior capsule.		
Diencephalon	Thalamus, (M) Hypothalamus	Fornix	Third ventricle



(L) - Laterally viewed.

- ⇒ Caudate nucleus forms the later wall of the lateral ventricle
 - ⇒ Putamen, nucleus accumbens, Caudate Nucleus are all about regulating movements
 - Putamen: movement of body
 - Caudate Nucleus: movement of eyes, mind (thought)
 - Nucleus Accumbens: movement of emotion (mood)
 - ⇒ Globus pallidus is seen in middle of basal ganglia.
- Types of blood vessels
- Arteries: Blood vessels responsible for carrying oxygen rich blood away from the heart to the body.
 - Vein: Blood vessels that carry blood low in oxygen from the body back to the heart for reoxygenation.
 - Amygdala: Nucleus part of limbic forebrain concerned with implicit processing w.r.t autonomic, emotional, and sexual behaviour.
 - Basal forebrain nuclei (ventral): Small clusters of nerve cells that modulate neural activity in the cerebral cortex & hippocampus. They degenerate in Alzheimer's disease.

flux (bio) - movement of substance b/w compartments

Particular strength of a stimulus may be encoded by the number of action potentials. 11/20/20

Generating and Propagating Electrical Signals
Electrical signalling underlies all aspects of Brain function.

- Neurons have means of generating steady state electrical potential across their plasma membrane called a "resting membrane potential" (-60 to -90mV)
 - Hyperpolarized = more -ve, depolarized = less negative
 - Action potential = explosive depolarizing event → membrane potential becomes +ve for brief period of time.
 - Threshold = Membrane potential at which an action potential is triggered.
- * 2 molecular mechanisms account for the generation of electrical signals,
- a. Pumps establish concentration gradients that provide the driving force for the diffusion of the ions through channels.
 - b. Nerve cell membrane selective permeable to certain ions, the passage of ion channels across the membrane is due to opening of ion channels.
- Lipid bilayer of plasma membrane has hydrophobic interior.
 - Amplitude of action potential is independent of current used to evoke it. Just after the threshold there spike: "All or none"

Amplitude or duration ↑ ⇒ more spike but no change in amplitude

2/11/2020

* Predicting membrane potential:

$$E_x = \left(\frac{58}{z}\right) \log \frac{[x]_o}{[x]_i}$$

E_x - Equilibrium potential for any ion

z - Valence of the permeant ion

$[x]_o$ = Out ion concentration

$[x]_i$ = Inside ion concentration

* Goldman equation: (multi ion - environment)

$$E_m = 58 \log \left[\frac{P_K [K]_o + P_{Na} [Na]_o + P_{Cl} [Cl]_i}{P_K [K]_i + P_{Na} [Na]_i + P_{Cl} [Cl]_o} \right]$$

P = permeability.

→ Early current is carried by Na^+ , Late current is carried by K^+ .

→ g = conductance = $\frac{I}{V_R}$.

$$I_{ion} = g_{ion} (V_m - E_{ion})$$

Driving force

E_{ion} = Normal equilibrium potential.

* Subthreshold depolarization: Membrane potential when $I_{Na^+} = I_{K^+}$.

(+ve phase)

(-ve phase)

* Fast rising phase, slow falling phase

* Well above threshold potential to generate action potential = Supra threshold.

* Sodium channel - Integral membrane protein.

→ At least 10 sodium channel genes.

* It integral protein & gated ion channel

- Kv and HERG
- Inward rectifier
- Ca^{+2} activated
- $\text{I}-\text{P}_4$

→ Sodium / Potassium ATPase consume lot of energy
 ② Ion exchangers.
 ③ Co-transporters.

→ Slower negative feedback loop helps to push action potential downward (forward).

→ diameter \propto Resistance (axial)

Velocity of action potential

→ Fewer ion channels are needed in myelinated axon near nodes of Ranvier for generation of action potential.

But in case of unmyelinated axon action potential needs to be regenerated every adjacent along the segment of axon.

- Amplitude of action potential is independent of magnitude of current used to evoke it.
- More current (duration / amplitude) implies more number of action potentials.
- Above 2 points are opposite to what happens in receptor cells. Synaptic potential \propto no. of synapses, magnitude of stimulus, previous synaptic activity.
- The amplitude of action potential is constant along the length of the axon. Time of appearance of action potential along distance is delayed.

* Protein in plasma membrane:

- ① Active transporters: Actively move ions in and out of cells against their concentration gradients. Against each other = Resting membrane potential, action potential, synaptic & muscle potential.
- ② Ion channels: Allow only certain kinds of ions to cross the membrane in the direction of their concentration gradients.

* At electrochemical equilibrium there is balance between 2 opposing forces,

- ① Concentration gradient: Causes K^+ to move from inside to outside.
- ② Electrical gradient: Increasingly tends to stop K^+ from moving across the membrane.

* Membrane potential: Difference in electrical potential b/w interior and exterior of a biological cell.

* Resting membrane potential: Relatively static membrane potential.

- Resting membrane potential is maintained by constant work of "ion pumps".

IN	OUT		
K^+	K^+		
Cone ⁿ ← 10	1	diffusion	K^+ K^+ 6 5

Charge dif: 0 0

charge: +4 -4

diffusion

+ve charge is built up inside and -ve charge is built up outside and there is attraction.

* Equilibrium potential: when "diffusion force" and "electrostatic force" is equal there ^{net} no flow of ions/charges and the ^{membrane} potential at which this happens is called Equilibrium potential.

* Calculating resting membrane potential using "Hodgkin equation"

$$E_m = \frac{RT}{F} \log \left[\frac{P_{Na^+} [Na^+]_0 + P_{K^+} [K^+]_0 + P_{Cl^-} [Cl^-]_0}{P_{Na^+} [Na^+]_I + P_{K^+} [K^+]_I + P_{Cl^-} [Cl^-]_0} \right]$$

* Calculating Equilibrium potential using Nernst equation.

$$E_{eq, K^+} = \frac{RT}{ZF} \ln \frac{[K^+]_0}{[K^+]_I}$$

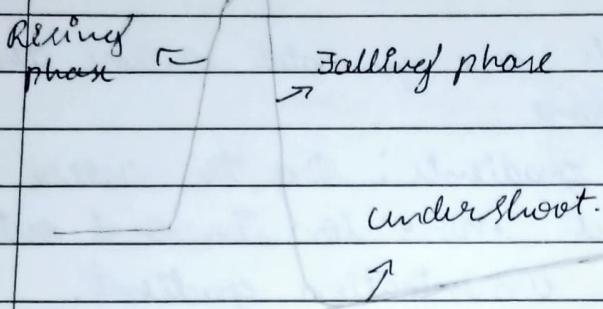
- Depolarization causes increase in conductance of Na^+ channel and also depolarization causes it to decrease over time

-/-

* Ionic Basis of action potential:

- Resting neuronal membrane is slightly permeable to Na^+ , the membrane becomes largely permeable to Na^+ during resting phase and overshoot phase of an action potential. (only short lived).

→ overshoot



→ In some neurons this undershoot can last even longer (plateau). This is because of presence of ion channels permeable to Ca^{2+}

→ The membrane proteins that create and maintain ion gradients are called active transporters.

→ The protein 'ion channels' give rise to selective ion permeability. Types of channels.

① Voltage sensors: Detect electrical potential across the membrane.

② Chemical signals:

③ Mechanical stimuli.

4/11/2020

→ For both K^+ and Na^+ voltage gated channel, depolarization increases the probability of channel opening.
• Hyperpolarization closes them all.

→ Depolarization also "inactivates" Na^+ channel, but not K^+ channel.

Relative refractory period
absolute refractory period

— / —

→ "Cytosol" = "Intracellular fluid"

* Electrical signals:

- ① Ion flux : Selective permeability (ion channels)
- ② Non uniform distribution of ions : Active transporters.

* Electrical potentials are generated across the membranes of neurons

- ① Ion concentration gradients : Due to active transporter protein which move ion in and out of cells against their concentration gradient.
- ② Selective permeability : Ion channel protein that allow only certain kinds of ions to cross the membrane in the direction of their concentration gradient.

* Negative resting potential:

- ① Membrane of resting neuron is more permeable to K^+ than any other ion.
- ② There is more K^+ inside than outside.

→ "Reversal potential for any given ionic species is the membrane potential at which ionic species is in equilibrium"

* Removing Na^+ outside : Early current reverses its polarity and becomes an outward current at a membrane potential that gave rise to an inward current when Na^+ was present.
(Permeability increase - Na^+ , direction is not a question here).

Human brain contains 86 billion neurons.

In electrical synapse current passes by direct diffusion of ion from one cell to other. 4/11/2020

Synaptic Transmission

- • Electrical synapse are rapid. These connection exist b/w neurons
 - There won't be any synaptic cleft/gap.
 - Communication are bidirectional (ion movements)
 - Present in embryological
- • Chemical synapse have cleft
 - Common in human CNS.
 - Slower comparatively (4-5 times slower)
 - Unidirectional
 - Synaptic transmission very unreliable ($5\text{-}10\%$ success)
- Some vesicles are attached to the presynaptic membrane - "docked" - localized near active zone.
- Ca^{+2} is necessary and sufficient to trigger vesicle fusion and release of neurotransmitter.
- Synaptotagmin is a molecule in the vesicular membrane that binds to Ca^{+2} .
- SNARE complex facilitate the formation of a fusion pore b/w the vesicle membrane and the presynaptic terminal membrane.

* Sequence of events involved in chemical neurotransmission

① Presynaptic terminal:

② Neurotransmitter is stored and synthesized in synaptic vesicles.

③ Some vesicles are docked along an active zone in the presynaptic membrane, poised to fuse with the plasma membrane.

- / —
- (1) Action potential reaches presynaptic terminal
 - (2) Due to change in membrane potential Ca^{+2} voltage-gated ion channels open.
 - (3) Due to concentration gradient for Ca^{+2} across the plasma membrane, Ca^{+2} rushes into the presynaptic terminal
 - (4) Through cascade of molecular events, Ca^{+2} causes the fusion of docked vesicles with the presynaptic plasma membrane along the synaptic cleft
 - (5) This vesicle fusion releases neurotransmitters into the synaptic cleft. = "Exocytosis"
 - (6) Neurotransmitters diffuse across the synaptic cleft and bind specific receptors in the post-synaptic membrane
 - (7) The binding of neurotransmitters opening/closing of certain ion channels in post-synaptic membrane
 - (8) Current flows through the open channels. The post-synaptic membrane becomes either depolarized or hyperpolarized.
 - +ve current flow membrane is depolarized
 - -ve current flow then the membrane is hyperpolarized.
 - (9) Neurotransmitter is removed by glia or presynaptic uptake or by enzymatic degradation
 - (10) Vesicular membrane is retrieved from presynaptic membrane
- Fusion requires the co-ordinated interaction of dozen of molecules in the vesicular membrane, presynaptic cytosol and presynaptic terminal membrane.

- • Ca^{+2} influx : "Synaptotagmin" binds to vesicular membrane.
- "SNARE" complex are then activated to accomplish the fusion of docked vesicles.
- "Botox" is a commercial formulation of the botulinum toxin that is especially useful clinically to treat spasticity and other forms of involuntary muscle fasciculation and twitching.

* Passive current:

- ① Stimulus: Receptor potential or injected current.
- ② Local depolarization: Action potential is generated at this site.
- ③ Some of the local current generated by the action potential will then flow passively down the axon. This flow of passive current does not require movement of Na^+ along the axon. This current flow is due to shuffling of charge (similar to wires).
- ④ This passive current depolarizes the membrane potential in the adjacent region of the axon.

- * Small molecule neurotransmitter:
- Synthesis occurs within pre-synaptic terminal.
 - Vesicles packing small molecules - 40 to 60 nm dia

- * Neuropeptides:
- Synthesized in the cell body of a neuron.
 - Brought down to synaptic cleft via axonal transport
 - Vesicles packing neuropeptides - 90 to 250 nm diameter.

* Synaptic transmission:

→ 2 classes of neurotransmitters

① Small molecule neurotransmitters

② Peptide neurotransmitters

→ 2 classes of receptors.

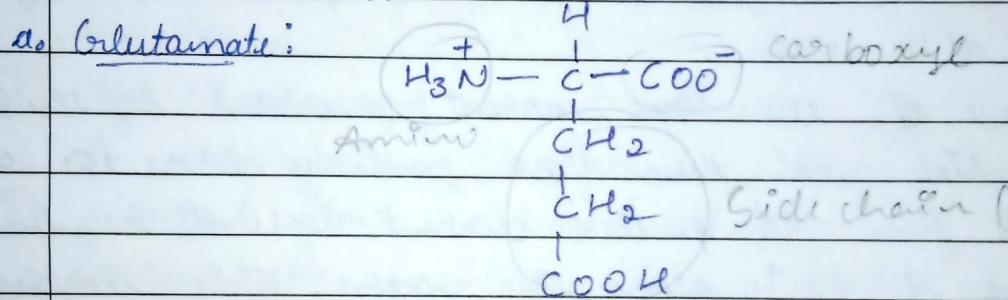
① Ionotropic receptors - Receptors on ligand gated ion channels. (faster)

② Metabotropic receptors: Receptors that activate second messenger system (slowly and longer lasting)

not attached to neurotransmitters

① * Small - molecule neurotransmitter:

• Amino acids.

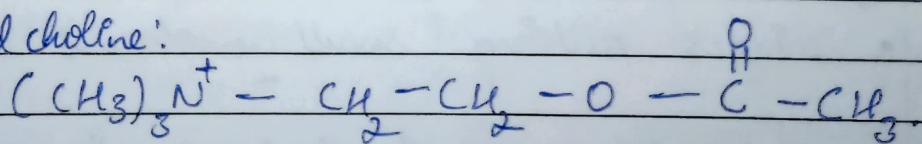


Cellular metabolism, concentrated in synaptic vesicles.

$\frac{1}{2}$ of all brain synapses release glutamate.

Glutamate receptors: NMDA, AMPA, Kainate.

• Acetylcholine:



→ Relaxed on muscle fibres - leading to contraction of muscle fibres

→ Excitatory neuromuscular transmission, post-ganglionic parasympathetic fibres.

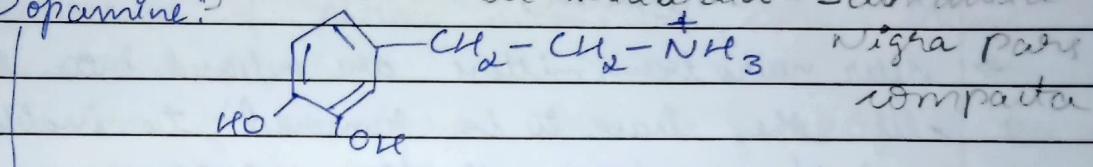
- GABA - (gamma amino buteric acid) - It is a metabolite.
 - Synaptic inhibition.

- Biogenic Amines:

→ Modulate neural circuits

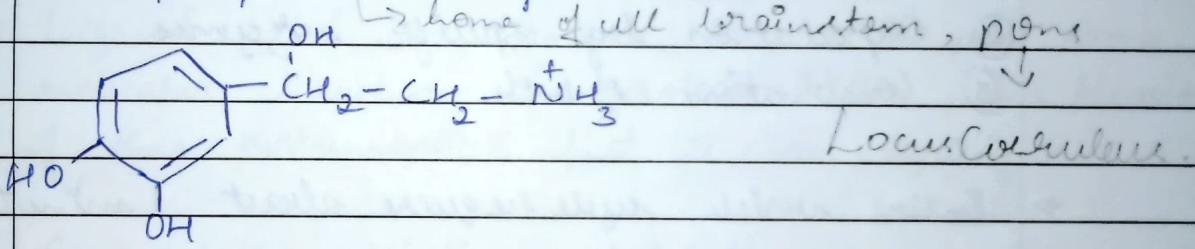
→ Motivation and reward system.

(a) Dopamine: → cell bodies in midbrain - Substantia nigra pars compacta

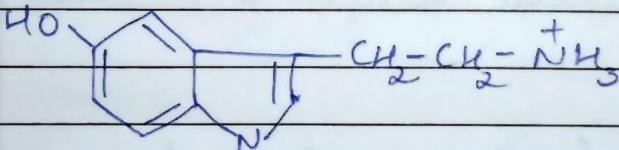


→ modulating movements as well.

(b) Norepinephrine: Heightened attention



(c) Serotonin: Drug prescribed Psychiatrist



Cell body is found in brainstem: Raphe nuclei.

(d) Neuropeptides (large molecules):

→ react with metabotropic receptors

→ slower and long lasting synaptic effect.

→ "Endocannabinoids" play a role in the plasticity of the inhibitory circuits in the brain.

→ Current flows through connexons in electrical synapse which are specialized membrane channels that connect 2 cells at gap junctions.

Connexon → 6 connexins.
Connexin → Connexine = 4 transmembrane domains.
(ion channel protein)

→ After neurotransmitters are released into synaptic cleft they have to be removed to enable next cycle of postsynaptic transmission.

- ① Reuptake into nerve terminals or surrounding glial cells (small molecules protein)
- ② Degradation by specific enzymes
- ③ Combination of both.

→ Entire vesicle cycle requires about 1 minute

→ Reducing the concentration of Ca^{+2} outside a presynaptic nerve terminal reduces EPP (End plate potential).

→ ATPase NSF (NEM-sensitive fusion protein) and SNAPs (soluble NSF-attachment protein), are important for vesicle fusion with membrane and are also involved in priming synaptic vesicles for fusion.

SNARE's are proteins which are SNAP receptors.

* "Exocytosis": The transport of material out of a cell.

* Mechanisms of exocytosis during neurotransmitter release.

- ① Four SNARES are present in vesicle and plasma membranes.
- ② SNARE complex forms as vesicle docks.
- ③ Synaptotagmin binds to SNARE complex.
- ④ Entering Ca^{+2} binds to synaptotagmin, leading to curvature of plasma membrane, which brings membrane together.
- ⑤ Fusion of membranes leads to exocytic release of neurotransmitter.

Somotropic Neurotransmitters Receptors

* Ligand-gated ion channels: Receptor is part same molecular structure of neurotransmitter and because of this postsynaptic effect is very rapidly.

→ Acetylcholine - Nicotine acetylcholine receptors

↳ 5 subunit come together ($\alpha, \beta, \gamma, \delta, \epsilon$) .

It allows many ion pass through them.

* GABA receptors.

→ Current through ligand gated ion channels:

$$\text{Post synaptic current (PSC)} = g_{\text{ligand}} (V_m - E_{\text{rev}})$$

driving force

- The main excitatory nerve transmitter in the brain is "amino acid glutamate".
- The main inhibitory nerve transmitter is γ -aminobutyric acid (GABA).
- Neuropeptides: 3 to 36 amino acid.
- GABA, glutamate, acetylcholine, serotonin are smaller than neuropeptides.

6-11-2020

- * Most important small molecule neurotransmitters
- ① Glutamate: Major excitatory N.T in CNS
↳ more than $\frac{1}{2}$ brain synapses release this neurotransmitter
- ② GABA: Major inhibitory nerve transmitter in the mature brain.
- ③ Glycine: Major inhibitory neurotransmitter in the spinal cord.
- ④ Acetylcholine: Excitatory neurotransmitter of somatic motor neurons, autonomic ganglia, post-ganglionic parasympathetic fibres, special modulatory system.
(Serotonin, histamine)
- ⑤ Biogenic amines: Involved in motivation and reward. Linked to neuropsychiatric disorders and movement disorders. Dopamine, norepinephrine, epinephrine, serotonin, histamine.
- * most important neuropeptides neurotransmitter:
- ① S substance P: Neurotransmitter of pain and temperature fibres that synapse in the spinal cord.
- ② Opioids: Have analgesic effects in brain, Inhibit release of substance P in spinal cord.

③ Hypothalamic releasing hormones and posterior pituitary hormones

* Unconventional nerve transmitter

① ATP and purines: It is released with other small molecule nerve transmitter.

→ when these are in extracellular space, ATP is metabolized into adenosine.

→ Adenosine: Modulates wakefulness by promoting sleepiness.

→ "Xanthine" (including caffeine) block adenosine receptor. which is why caffeine fights sleepiness.

② Endocannabinoids: It is produced by membrane lipids and bind to receptors that bind the psychoactive component of marijuana.

→ Hydrophobic

→ Play a role in the plasticity of inhibitory circuits in the brain

③ Nitric oxide (NO): NO is produced from the metabolism of the amino acid, arginine (a process regulated by calcium).

→ Viagra and related drugs work by affecting NO-mediated signalling.

→

many peptide known to be hormones also act as neural transmitters

→ 5 categories of peptide nerve transmitter: Brain/but peptide, spinal peptides, pituitary peptides, hypothalamic releasing hormones, catch all category.

Neurotransmitter receptors are proteins that are embedded in the plasma membrane of post-synaptic cells and hence are extracellular neurotransmitter binding site they detect the presence of neurotransmitter in the synaptic cleft

Neurotransmitter Receptors

① Ionotropic receptor:

- Composed of 4 to 5 subunits
- Different subunits may be combined to produce functional diversity for any type of channel.

a. Nicotine Acetylcholine receptor: (neuromuscular junction)

- Channel pore is non-selective. Univalent cation can pass (Na^+ , K^+).

$$\rightarrow E_{\text{rev}} = 0 \text{ mV}$$

- Channel is gated by acetylcholine

b. NMDA receptor:

- Channel pore is gated by glutamate, but also requires 'co-agonist' amino acid glycine.

- Channel pore contains binding site for Mg^{+2}

- When post-synaptic neuron is at resting potential extracellular Mg^{+2} is attracted to the channel pore and effectively blocks the pore.

- When post-synaptic neuron is depolarized, extracellular Mg^{+2} is repelled from the channel pore and pore is unblocked. Now the channel is gated by glutamate.

- Non-selective for Cations (Na^+ , K^+ , Ca^{+2}).

② Metabotropic receptor: Passage of ions require one or more metabolic steps.

- Receptors interact with ion channels via set of G-proteins.

Types of ACh receptors: Nicotinic ACh receptor ($nAChR$)
muscarinic ACh receptors ($mAChR$ s).

Types of ionotropic Glutamate receptors: AMPA receptors /
NMDA receptors, kainate receptors. } ionotropic
} glutamatergic
} well.

E_{exc} > threshold = excitatory.

E_{exc} < threshold = inhibitory.

\rightarrow Some neurotransmitter can induce EPSP's and IPSP's.

* Reversal potential: Is the membrane voltage at which there is no net flow of a particular ion from one side of the membrane to the other.

$$\text{End plate current (EPIC)} = g_{ACh}(V_m - E_{\text{ion}}).$$

\rightarrow A change in concentration gradients could shift E_{exc} to one side of the threshold or the other.

\rightarrow GABA is inhibitory for most immature neurons in the brain because Cl^- concentration is high inside cell and low outside cells.

\rightarrow GABA is inhibitory for most if not all mature neurons because chloride pumps develop that reverse the gradient: Cl^- concentration becomes low inside of cells and high in extracellular space.

\rightarrow In the core of NMDA receptor there is binding site for Mg^{+2} ion. If there is sufficient depolarization (inside becomes more +ve and Mg is $+2$) Mg^{+2} is repelled out of binding site.

* EPPs and MEPP's: observed in synapse b/n spinal motor neurons and skeletal muscle cells.

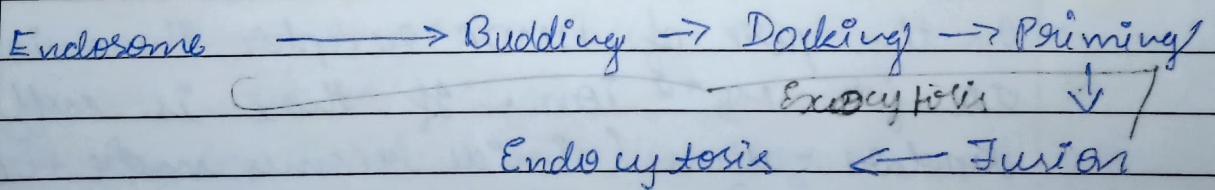
① EPP: action potential in the presynaptic motor neuron can be seen to elicit a transient depolarization of postsynaptic muscle fibre. This membrane potential is called "End plate potential" (EPP). This EPP is large enough to produce postsynaptic action potential.

② MEPP (miniature end plate potentials): are small depolarizations of the postsynaptic terminals caused by the release of small number of vesicles into the synaptic cleft. These depolarizations happen without pre-synaptic action potential.

→ Exocytosis can increase the surface area of presynaptic terminals (for short duration).

* "Endocytosis": process of capturing a substance or particle from outside the cell by engulfing it with the cell membrane, and bringing it into the cell.

* Vesicle fusion process:



→ Lowering the concentration of Ca^{+2} decreases the size of the EPP.

Hippocampus is important for formation and retrieval of some forms of memory.

6/11/2020

Synaptic Plasticity

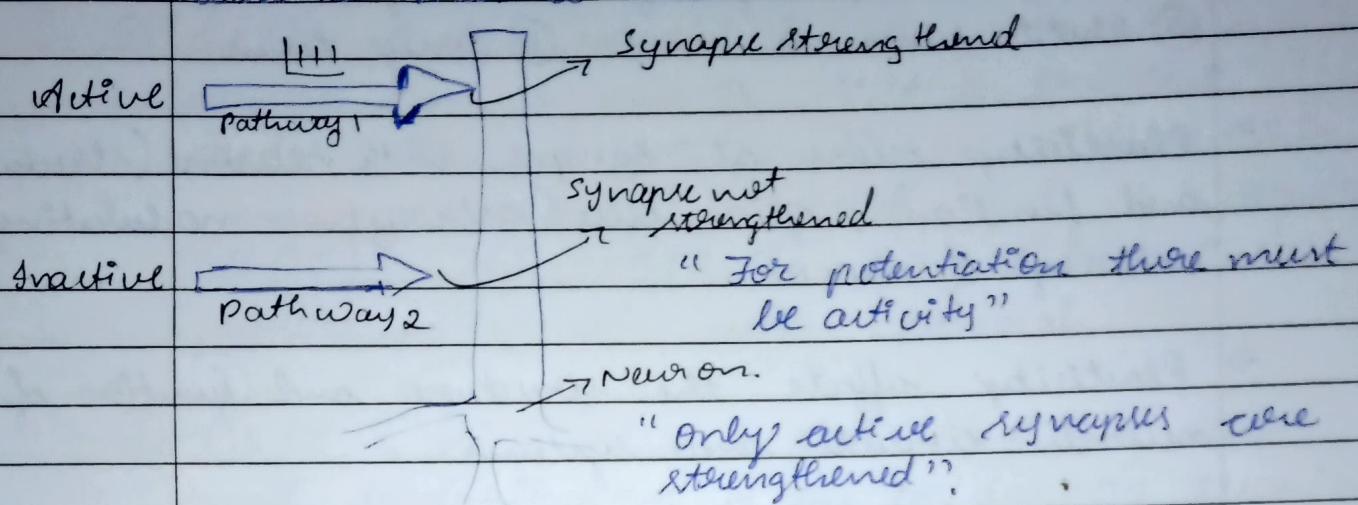
Plasticity = "Capacity of nervous system to change"

- (a) Short term.
- (b) Long term.

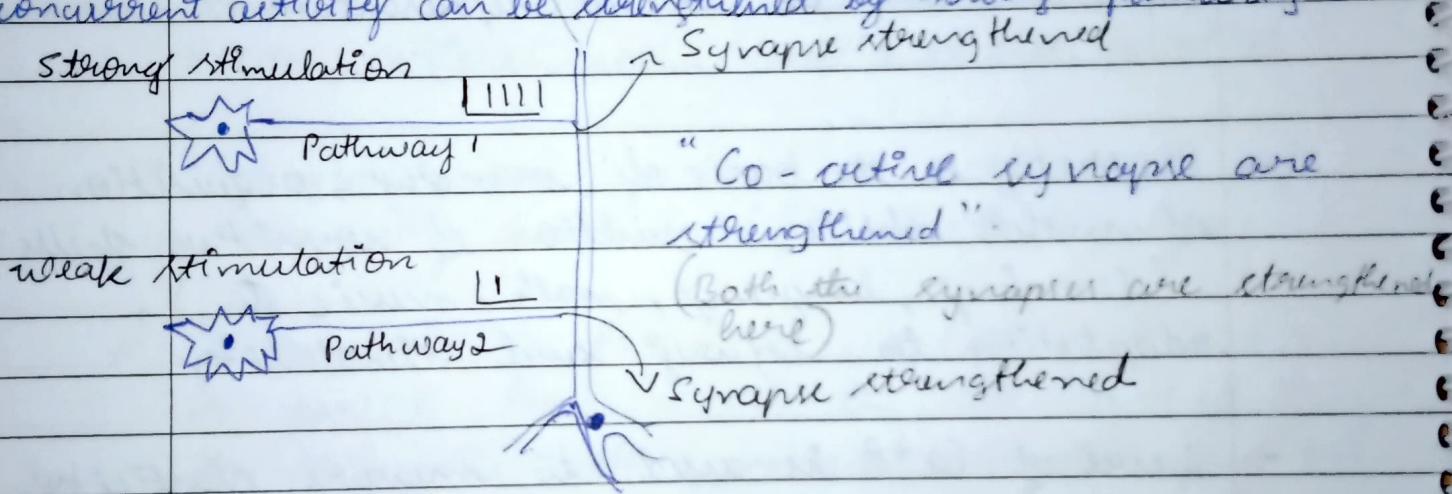
- Plasticity occurs at synapse, with neurons (structure and function), glia cells (astrocytes - modulating activity of neurons).
- Plasticity affects the structure and function of neural circuits and systems.
- Plasticity affects the organization of functional representation (e.g. Cortical representation (Learning and representation refinement))
- Plasticity is the basis of: memory, acquisition of motor skills, acquisition of cognitive skills (learning, language, math, music etc.), adaptation to injury and disability
- Level of Ca^{+2} is used to measure plasticity.
- Long lasting changes in synaptic strength are brought about by alterations in gene transcription.
- Tetanus - (high freq electrical pulses) is used to stimulate the pathway and induce long term potentiation.
- LTP: long lasting increase in synaptic strength.
- LTD: " decrease "

Long term potentiation (LTP) :

- * Specificity: "In order for a pathway to be potentiated it must be active".



- * Associativity: "The pathway that has weak but has concurrent activity can be strengthened by strong pathway".



→ Iono tropic receptor: Site for binding neurotransmitter is part of ion channels.

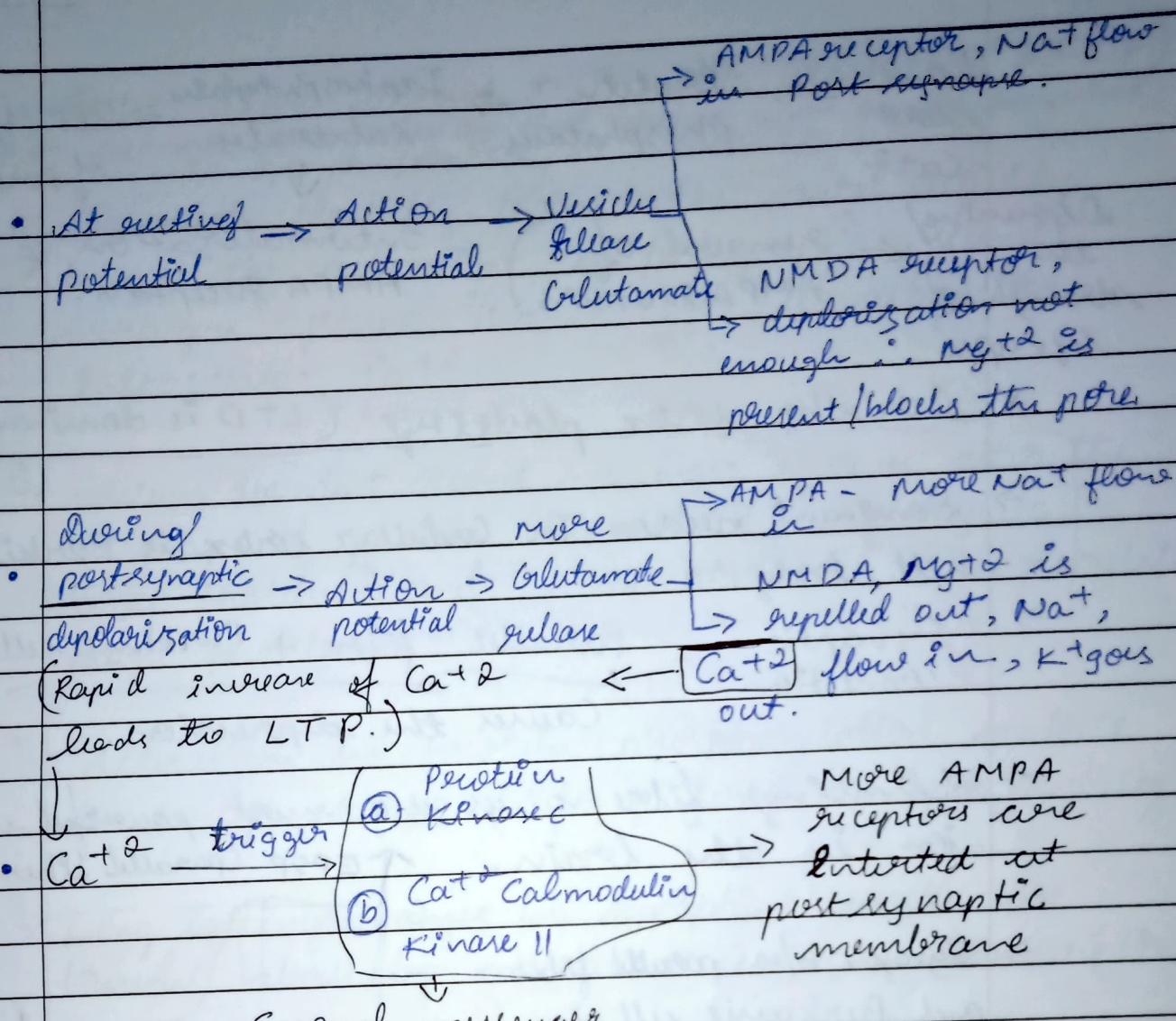
→ LTP is dependent upon 2 glutamate receptors

① AMPA receptor:

ionotropic

↓
Rapid conductance

② NMDA receptor:



This can also happen due to cocaine use

* Silent synapse: NMDA - receptors only.
Growing/developing brain

* Functional synapse AMPA - P + NMDA - R : Can be seen in mature brain.

Long term Depression (LTD)

- Low frequency stimulation
- Activity is necessary here also but nature of the activity differs from that of LTP (low freq)
enough to release glutamate and also sufficient to repel Mg²⁺.
- Rise of Ca²⁺ is慢 (slower + lower)

Long slow Ca^{+2} → Protein phosphatase → Dephosphorylates substrates \rightarrow opp effect of AMPA-R

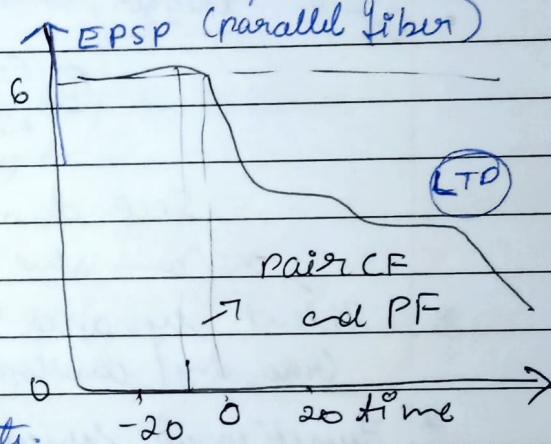
Depressing the strength of synapse \leftarrow (removal of AMPA receptors) \leftarrow Internalization of AMPA receptors.

* Cerebellar cortex plasticity (LTD is dominant)

→ Dominant neuron in cerebellar cortex is Purkinje cell body.

Synaptic connection - Parallel fibre + Purkinje cell body
Causes the depression.

→ Climbing fibre gives one most powerful connection in the brain.



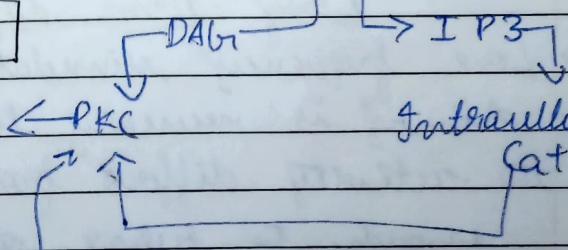
→ Synapse b/w parallel fiber and Purkinje cell is glutameric synapse.

→ Metabotropic receptors are present for glutamate.

* mGluR \rightarrow Phospholipase C \rightarrow PI P₂

Internalization of AMPA receptor

LTD \leftarrow Phosphorylated substrate protein



Climbing fiber depolarizer V

LTP - Protein kinases.

LTD - protein phosphatases.

-/-

Spike Time dependent Synaptic Plasticity (STDP)

Changes in synaptic transmission that depend upon temporal relationships b/w presynaptic & postsynaptic responses

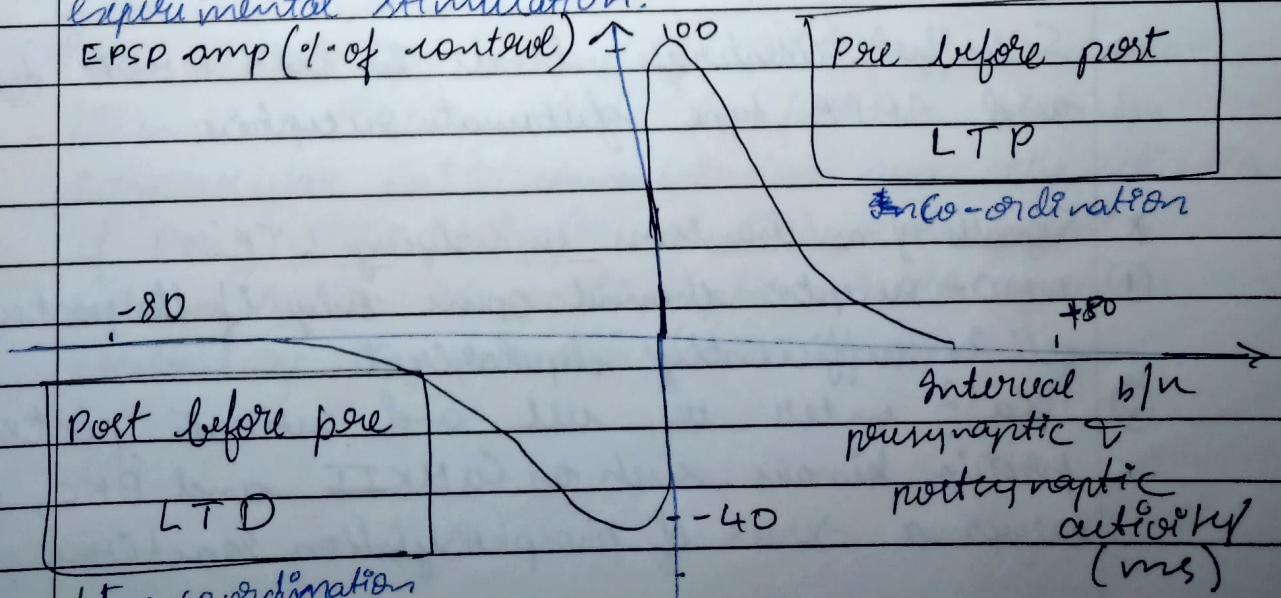
→ Synaptic plasticity begins when neural activity triggers the activation of postsynaptic, second messenger systems. This trigger is alteration intracellular Ca^{+2} .

→ Calcium dependent second messenger systems alter the activity of protein kinases = (phosphorylate target proteins) and phosphatases = (dephosphorylate target proteins).

→ Alterations in protein phosphorylation mediate the early stages of long term synaptic plasticity

→ Long lasting changes in synaptic strength are brought about by alterations in gene transcription

* There are many connections / synapses to a neuron. So it is possible for a postsynaptic neuron to be stimulated before pre-synaptic neuron by some other neuron or through experimental stimulation.



Collateral: the axon typically develops side branches called Schaffer collaterals. This enables neuron to send info to many others.

- Synapse strengthens when presynaptic activity precedes postsynaptic activity by ~20 msec or less.
(co-ordinated activity)
- Synapses weaken when presynaptic activity follows postsynaptic activity by upto ~40 msec un-coordinated activity.

Hibbs Postulate

"Co-ordinated activity of a presynaptic terminal and a postsynaptic cell would strengthen the synaptic connection between them".

"Conversely, uncoordinated activity between synaptic partners would weaken their synaptic connections"

"neurons that fire together, wire together".

LTP, LTD continued:

→ when LTP is induced by activation of one synapse it does not occur in other, inactive synapse that contact the same neuron.

This individual synapse activation results in large information storage capacity.

→ Schaffer collaterals binds to both NMDA type and AMPA type glutamate receptors.

* Signalling mechanisms underlying LTP:

- ① NMDA receptor channel opens only if the postsynaptic cell is sufficiently depolarized.
- ② Ca^{2+} enter the cell and activate postsynaptic protein kinases, such as CAMKII and PKC, that trigger a series of phosphorylation reactions.

LTP - more AMPA due to insertion

LTD - less AMPA due to internalization

— / —

- (3) Trafficking of postsynaptic AMPA receptors through recycling endosomes, leading to insertion of new AMPA receptors into the postsynaptic spine.
- (4) Subsequent diffusion of AMPA receptors to the subsynaptic regions yields an increase in the spine's sensitivity to glutamate, which causes LTP.

continued.

* Long term Depression (LTD)

→ LTD can erase the increase in EPSP size due to LTP. LTP can erase the decrease in EPSP size due to LTD.

→ In cerebellum:

- (1) LTD requires depolarization of Purkinje cells, produced by climbing fiber activation, as well as signals generated by active parallel fiber synapses.
- (2) Glutamate released by parallel fibers activate both AMPA receptors and metabotropic glutamate receptors (mGluR).
- (3) Activated mGluRs produce second messengers, DAGs and IP₃, which interact with Ca²⁺ that enters when climbing fiber activation opens voltage-gated Ca²⁺ channels.
- (4) The resulting release of Ca²⁺ from the endoplasmic reticulum leads to further rise in intracellular Ca²⁺ concentration and the activation of PKC, which triggers clathrin-dependent internalization of postsynaptic AMPA receptors, weakening the parallel fiber synapse.

continued

Ionic basis of action potential:

$$I_{\text{ion}} = g_{\text{ion}} (V_m - E_{\text{ion}})$$

V_m from Goldman's eqn?

$V_m - E_{\text{ion}}$ - Electrochemical driving force

E_{ion} - Equilibrium potential.

① → Na^+ and K^+ conductances change over time and both Na^+ and K^+ conductance require some time to activate. K^+ is delayed.

- Na^+ conductance rises rapidly, it quickly declines (Both activation and Inactivation).
- K^+ only activation (but delayed).

② → Both Na^+ and K^+ conductances are voltage dependent.

→ At relative refractory period it is possible to generate action potential only with greater stimulus.

* Long distance signalling by means of action potentials.

- ① Stimulus
- ② Depolarization opens Na^+ channels locally and produces an action potential.
- ③ The resulting inward current flows passively along the axon, depolarizing the adjacent region of the axon.
- ④ Action potential is generated and steps

decreases the internal resistance to passive current flow.

② Myelination of axons:

- Voltage gated Na^+ channels are localized at nodes of Ranvier.
- Local / passive current in response to action potential flows down the axon. Presence of myelin prevents the local current from leaking across the internodal membrane. An action potential is generated at nodes of Ranvier.

* Ion channels and Transporters:

- Second messenger - Inter cellular signals.

continued: Plasticity:

- ① Synaptic facilitation: A rapid increase in synaptic strength when 2 or more action potentials invade the presynaptic terminal within a few milliseconds gap.
- ② Synaptic depression: Causes neurotransmitter release to decline during sustained synaptic activity.
- ③ Augmentation: Activity dependent form of short term plasticity that enhances synaptic transmission over a time course of few seconds. It is caused by an increase in the amount of neurotransmitter released in response to presynaptic action potential and results from persistent calcium signalling.
- ④ Synaptic potentiation: Enhancement of synaptic transmission resulting from high freq. trains of action potential.

How an increase in presynaptic Ca^{+2} concentration on the trigger vesicle fusion is not fully understood.

13/11/2020

continued

* Synaptic transmission.

→ There is voltage gated Ca^{+2} channels in pre-synaptic terminal.

* Molecular mechanisms of Synaptic Vesicle Cycling

• Syntarin: Reversibly binds to synaptic vesicles keeps these vesicles tethered within the reserve pool by cross-linking vesicle to each other.

Mobilization of reserve pool vesicles: Caused by phosphorylation of syntarin by protein kinases, notably the $\text{Ca}^{+2}/\text{calmodulin}$ -dependent protein kinase, type II (CaMKII) which allows syntarin to dissociate from the vesicles.

• SNARE protein: Responsible for docking of free vesicles to the membrane.

Priming AT Prox NSF (NEM-sensitive fusion protein) and SNAPS (soluble NSF-attachment protein): These 2 proteins are important for the fusion of vesicles with the membrane of endoplasmic reticulum.

These are also involved in priming synaptosomal vesicles for fusion. These 2 proteins work by regulating the assembly of other proteins that are called SNARES (SNAP receptors).

→ Priming is to organize SNARE proteins into the correct conformation for membrane fusion.

- SNARE: Synaptobrevin (membrane of synaptic vesicle), Syntaxin and SNAP-25 (on plasma membrane) : These 3 proteins can form a macromolecular complex that spans the 2 membranes, thus bringing them into close apposition.
- SNARE proteins do not bind Ca^{2+} and thus are not responsible for Ca^{2+} regulation of neurotransmitter release.
- Synaptotagmin (found in membrane of synaptic vesicle) is responsible for Ca^{2+} regulation of neurotransmitter release.
- Ca^{2+} binds Ca^{2+} at concentrations similar to those required to trigger vesicle fusion within the presynaptic terminal, and this property allows synaptotagmin to act as a Ca^{2+} sensor that triggers vesicle fusion by signalling the elevation of Ca^{2+} within the terminal.
- Ca^{2+} binding to synaptotagmin leads to exocytosis by changing the chemical properties of synaptotagmin thereby allowing it to invert into the plasma membrane.
- Thus, SNARE proteins bring the 2 membranes close together, while Ca^{2+} induced change in synaptotagmin then produces the final curvature that enables rapid fusion of these membranes.

* Endocytosis:

- C. latherin: Involved in endocytic budding of vesicles from the plasma membrane. Clathrin has triskelion structure.
Adaptor protein help assemble individual triskelia into dome like structure.
- Dynamin: Forms a singlike coil that encircles the lipid stalk. This coil causes the final pinching-off of membrane that severs the stalk and completes the production of coated vesicle.
- Actin (cytoskeletal protein): Coated vesicles are transported away by this protein. This allows the clathrin coats to be removed by an ATPase [Hsc 70, auxilin]
- Synaptosomal: Important for vesicle uncoating.
- Refilling of vesicle with neurotransmitter is done by transporters in the vesicle membrane.
- Neurotransmitter are removed from synaptic cleft by neurotransmitter transporter or by degradative enzymes.

Reversal potential in case of post synaptic neurons "is the potential at which a given nerve transmitter causes no net current flow of ions through that nerve transmitter receptor's ion channel". 3/11/2020

continued.

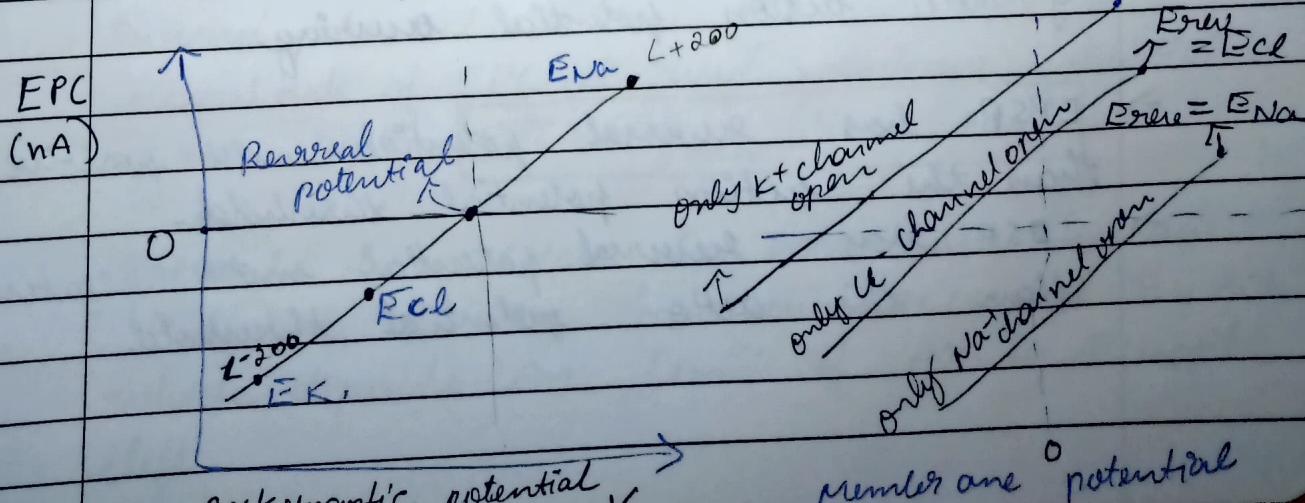
Neurotransmitter Receptors

- ① Ionotropic receptors or ligand-gated ion channels:
 - ⓐ Neuro transmitter binds transmitter binding
 - ⓑ Channel opens channel functions
 - ⓒ Ions flow across membrane into single cell into single cell
- Movement of ion depends on intervening metabolic steps.
- ② Metabotropic receptors or G-protein coupled receptors:
 - ⓐ Neuro transmitter binds (Now)
 - ⓑ G_i-protein is activated
 - ⓒ G_i-protein subunits or Intracellular messengers modulate ion channels.
 - ⓓ Ion channel opens.
 - ⓔ Ion flow across membrane.

→ Many transmitters can activate both ionotropic and metabotropic receptors to produce fast and slow postsynaptic potential.

→ The macroscopic current resulting from the summed opening of many ion channels is called the end plate current or EPC.

EPC is normally inward and causes post-synaptic membrane potential to depolarize $E_{\text{PSC}} = E_K$



out +ve E_{Na}?
in -ve

14/11/2020

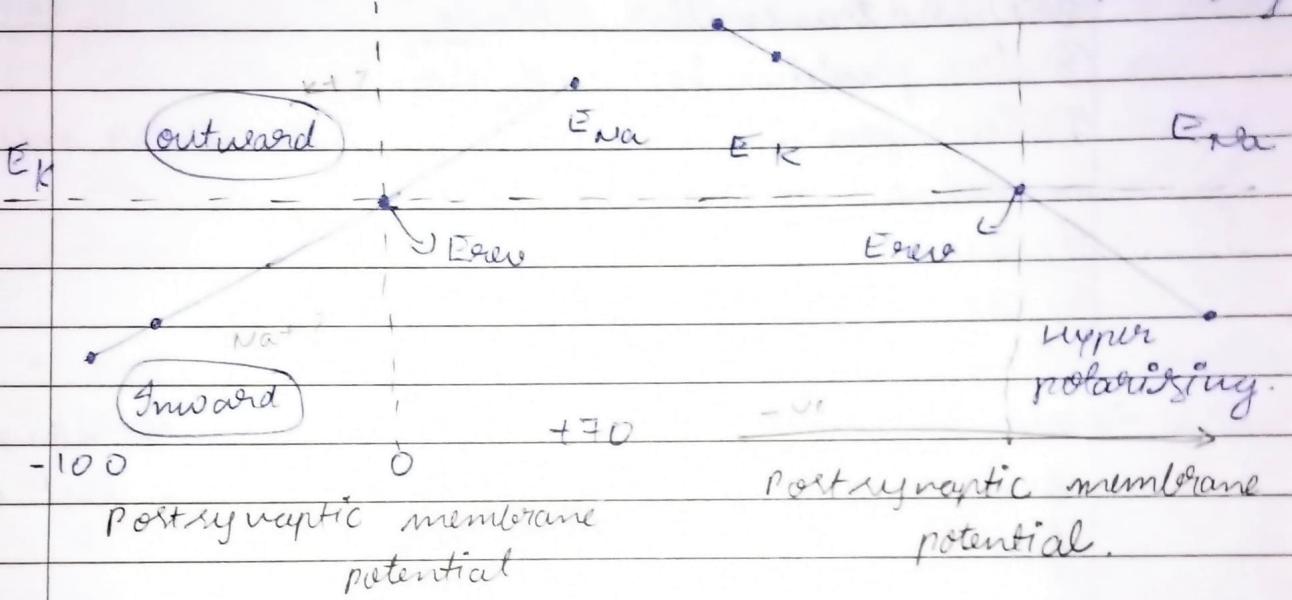
→ Potential where EPC occurs is called the reversal potential (0mV in case of neuromuscular junction).

$$EPC = g_{ACh} (V_m - E_{rev})$$

* Na^+ and K^+ movements.

↑ EPC (nA)

↑ EPP (mV)
Depolarizing



* Excitatory and inhibitory Post-synaptic potential:

- EPSP: If post-synaptic potentials (PSPs) increase the likelihood of post-synaptic action potential occurring.
- IPSP: If PSPs decrease the likelihood of post-synaptic action potential occurring.

→ EPSP has reversal potential more positive than the action potential threshold.

→ IPSP has reversal potential more negative than the action potential threshold.

EPSP ≠ Action potential

$\sum \text{EPSP} + \text{IPSP} > \text{threshold} \Rightarrow \text{Action potential}$

→ EPSP only depolarizes postsynaptic cell.

IPSP depolarizes as well as hyperpolarizes postsynaptic cell

* Postsynaptic membrane potential tries to move towards reversal potential.

IPSP If reversal potential is above threshold then membrane tries to hyperpolarize (w.r.t resting membrane potential $\sim -60/-70 \text{ mV}$)

EPSP If reversal potential is below threshold membrane tries to reach reversal potential which may be less than or greater than resting membrane potential ($-60/-70 \text{ mV}$).

→ EPSP produced by individual excitatory synapse may be only a fraction of a millivolt and usually are below threshold. PSPs produced by each active synapse can sum together - in space and time - to determine the behaviour of the postsynaptic neuron.

→ EPC is inward and depolarizes postsynaptic membrane potential.

→ Reversal potential = E_{rev} .

Magnitude of EPC at any membrane potential is given by, $E_{\text{PC}} = g_{\text{ACh}} (V_m - E_{\text{rev}})$.

g_{ACh} is insensitive to membrane voltage.

↳ depends on No. of channels opened by ACh which depends on "con" of ACh in synaptic cleft.

continued
(text book)Neurotransmitters and their Receptors

Main excitatory nerve transmitter = amino acid glutamate
 " " inhibitory " = γ -aminobutyric acid.
 γ ABA

- \Rightarrow "Cholinergic": Relative to or denoting nerve cells in which acetylcholine acts as a neurotransmitter.

15-11-2020

* Myasthenia gravis: Disease that interferes with transmission between motor neuron and skeletal muscle fibres. (Eye drooping, double vision)

\Rightarrow GABA excites its target cell in developing brain.
 ↳ Both ionotropic and metabotropic

Homeostatic function, cognitive phenomena: Attention.

* Bioactive Amines: (CNS and PNS)

① Dopamine (catecholamine):

\Rightarrow Corpus striatum: Major dopamine containing area

\Rightarrow Parkinson's disease: Dopaminergic neurons of the substantia nigra degenerate leading to motor dysfunction.

\Rightarrow Also involved in motivation, reward and reinforcement.

② Norepinephrine/Noradrenaline (catecholamine):

\Rightarrow Nerve transmitter in the locus caeruleus, a midbrain nucleus.

\Rightarrow Influences sleep, wakefulness, arousal, attention and feeding behaviour.

\Rightarrow Sympathetic ganglion cells employ norepinephrine as the major peripheral transmitter in this division of the neural motor system.

3 catecholamine

(3) Epinephrine / adrenaline (catecholamine)

- Epinephrine containing neurons are in the lateral tegmental system and in the medulla and project to the hypothalamus and thalamus.
- Regulate respiration and cardiac function.

(4) Histamine:

- Found in neurons in the hypothalamus that send sparse but widespread projections to almost all regions of the brain and spinal cord.
- Mediates arousal and attention, reactivity in vestibular system.

(5) Serotonin:

- Found in the raphe regions of the pons and upper brainstem.
- Regulates sleep and wakefulness.

* ATP and other purines: (N.T + N.T.R)

- ATP acts as an excitatory neurotransmitter in motor neurons of the spinal cord, sensory and autonomic ganglia.
- 3 classes of purinergic receptors are known.
- 'P2X' receptor is one class of purinergic ionotropic receptors.
- Plays role in mechanosensation and pain.

Molecular signalling within Neurons

* Type of chemical signalling.

- ① Synapses
- ② Paracrine Signalling: Acts over a longer range than synaptic transmission and involves secretion of chemicals onto a nearby target cells.
- ③ Endocrine signalling: Secretion of hormones into the blood stream , they affects targets throughout the body.

Signalling → Signal → Receptor → Effector → Response.
 cell molecule

* Categories of cellular receptor:

- ① Channel linked receptors .
- ② Enzyme linked receptors .
- ③ G_i- protein - coupled receptors .
- ④ Intracellular receptors .

* Second messengers: (As intracellular signals)

① Calcium [Ca²⁺]:

→ In cytosol - 50 - 100 nM (10^{-9} M)

→ In blood stream and cerebrospinal fluid 10^{-3} M

② Cyclic nucleotides: Cyclic AMP (cAMP) is a derivative of the abundant cellular energy storage molecule ATP, and is produced when G_i-proteins activate adenylyl cyclase in plasma membrane.

③ Diacylglycerol and IP₃ (membrane lipids)

* Protein Kinases: Catalytic subunit - regulatory subunit

- ① CAMP-dependent protein kinase (PKA): PKA is primary effector of CAMP actions in neurons
- ② Ca^{+2} / calmodulin-dependent protein kinase, type II (CaMKII). This kinase is the most abundant component of the postsynaptic density, a structure important for postsynaptic signaling. (12 subunits)
- ③ Protein kinase C (PKC): Tumor-promoting compounds called phorbol esters mimic DAGs and cause a prolonged activation of PKC that is thought to trigger tumor formation.
- ④ Protein tyrosine kinase: Important for cell growth and differentiation.
- ⑤ Mitogen-activated protein kinase (MAPK). Also called extracellular signal-regulated kinases (ERKs)

* Protein Phosphatases:

- ① Protein phosphatase 1 (PP1): PP1 influences neuronal electrical signalling by dephosphorylating K^+ and Ca^{+2} channels, as well as neurotransmitter receptor such as AMPA-type and NMDA-type glutamate receptors
- ② Protein phosphatase 2A (PP2A): Although PP2A is constitutively active, its activity can be regulated by phosphorylation and other post-translational modifications of both catalytic and regulatory subunits.

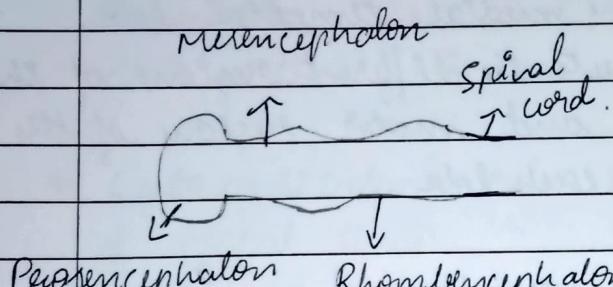
(3)

Protein phosphatase 2B (PP2B):/ Calcineurin.

Diphosphorylation of AMPA - type glutamate receptors by PP2B is thought to play a central role in signal transduction during long - term depression of hippocampal synapses.

Organizing principles: The basic principle of structure and function that will apply to nearly all of the sensory system:

* Embryological origins:



Prosencephalon Rhombencephalon

- Retina in our eye is derived from Diencephalon.
- There are around 20 - 30 discrete nuclei in Thalamus
- Thalamus receives many inputs from ascending sensory signals and relays this info to the prefrontal cortex.
- All major sensory and motor pathways have a midline crossings "decussations". This is due to each cerebral hemisphere receiving input from the opposite side of the body.

Embryological origins

- The dorsal and posterior part of the diencephalon becomes the thalamus.
- The ventral and anterior part becomes the hypothalamus.
- Thalamus is a component of the forebrain.

Anatomical localization

- w.r.t whole brain: Thalamus is near the center of the whole brain.
- w.r.t internal capsule: Thalamus is medial to the posterior limb of the internal capsule.
- w.r.t lateral ventricle: Thalamus is floor of the