Unit-4th

÷ Neurotransmitters & Their mode of Action ÷

÷ Neurotransmitters ÷

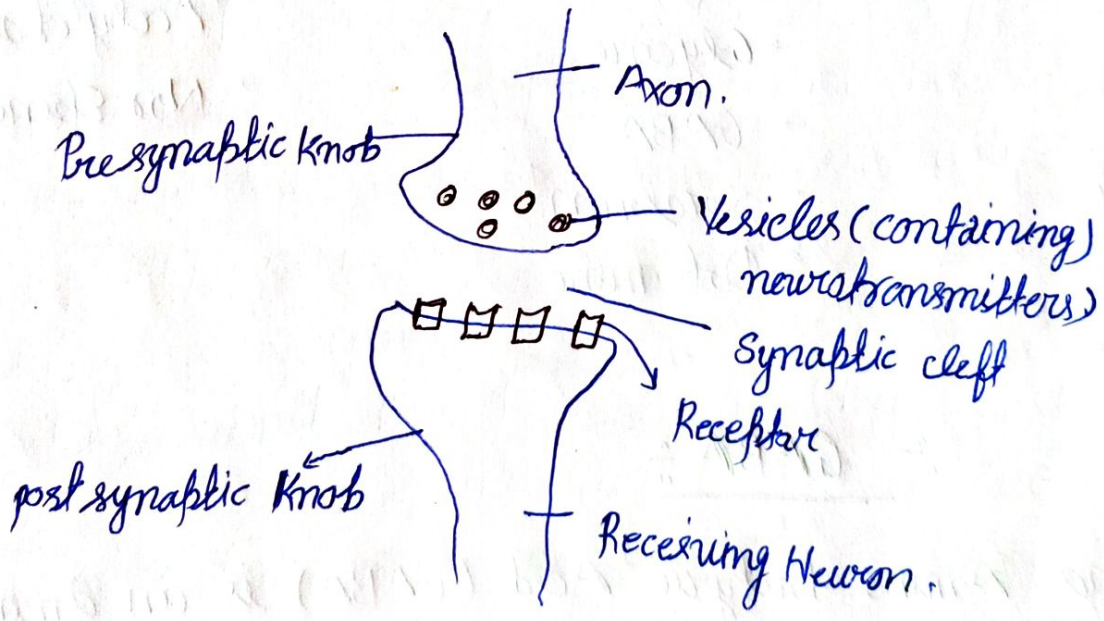
→ Neurotransmitters are chemical massenger that transmit signals from a neuron to a target cell across a synapse.

→ Target cell may be a neuron or some other king of cell like a muscle or gland cell.

→ Necessary for rapid communication in synapse.

→ Neurotransmitters are packaged into synaptic vesicles presynaptic side of a synapse.

÷ A schematic representation of a chemical synapse ÷



÷ Properties of Neurotransmitters ÷

→ (1) Synthesized in the presynaptic neuron.

(2) Localised to vesicles in the presynaptic neuron.

(3) Released from the presynaptic neuron under physiological condition.

(4) Rapidly removed from the synaptic cleft by uptake or degradation.

(5) Presence of receptor on the post synaptic neuron.

(6) Binding to the receptor elicits a biological response.

÷ Types of neurotransmitters ÷

÷ Types ÷

- Excitatory
  - → Glutamate
  - → Aspartate
  - → Nitric Acid
- Inhibitory
  - → Glycine
  - → GABA
  - → Serotonin.
  - → Dopamine.
- Both
  - → Acetylcholine
  - → Nor Epinephrine.

÷ GABA ÷

→ Gamma-Amino Butyric Acid (GABA) is an amino acid which acts as a neurotransmitter in the central nervous system.

→ It inhibits nerve transmission in the brain calming nervous activity.

→ Chemical formula - $C_4H_9NO_2$

→ GABA is a zwitter ion with deprotonated carboxyl group and protonated amino group.

(GABA → Gamma Amino butyric acid)

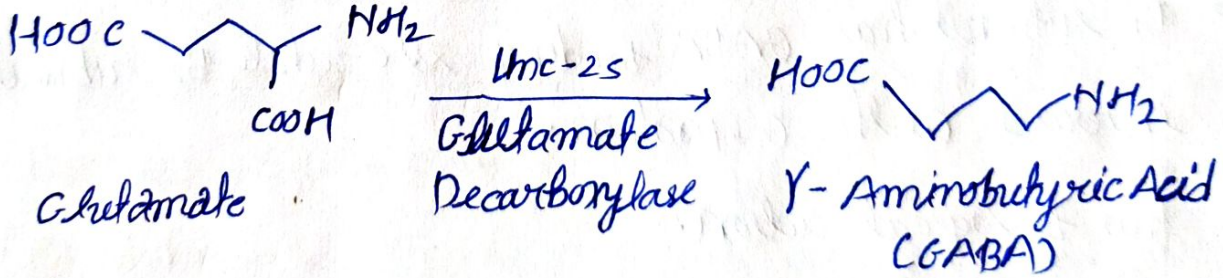
∴ Discovery ∴

→ In 19th century, was known as metabolite of plant and microorganism.

→ In 20th century - was isolated as amino acid in the brain of mouse through paper chromatography.

→ In 1950 Robert and Franked discovered that GABA act as Inhibitory neurotransmitter in human brain.

∴ Syntheses ∴



→ Synthesized from amino acid - L-glutamate acid in present of GAD.

→ Glutamic acid decarboxylase (GAD) present in neurons, pancreatic cells and in body fluid.

→ GAD acts as a catalyst that removes carboxyl group from glutamate and produce GABA.

÷ Classes of GABA Receptor ÷

GABA receptor is of two types ÷

(1) $GABA_A$ receptor.

(2) $GABA_B$ receptor.

÷ $GABA_A$ Receptor ÷

→ It has pentameric structure.

→ It has structural & functional similarity with ligand gated ion.

→ Each GABA - A receptor contain two alpha, two beta & one gamma subunit.

÷ $GABA_B$ receptor ÷

→ They are hetro dimers.

→ GABA - B has been cloned to b_1 & b_2 subunits.

→ B_1 subunit has GABA binding site while B_2 subunit interact with G-protein.

→ Two biological action.

- Decrease Ca^{2+} conductance
- Increase K^+ conductance

÷ Function of GABA ÷

→ Relieving Anxiety

→ Relieving Pain.

→ Regulating the release of sex harmones.

→ Treating ADHD (Attention deficit hyperactivity disorder)
→ Burning fat
→ Stabilizing blood pressure.
→ Decrease blood sugar level in diabetics

∴ Glutamic Acid or Glutamate ∴

→ Acidic nonessential amino acid.
→ Imp as the building block of protein synthesis.
→ As a neaurotransmitter in CNS.
→ Major Excitatory neaurotransmitter.
→ Called king of neurotransmitter.
→ Also called master switch of brain.
→ Concentration in brain is 10 mm, the highest of all amino acids and of all Neurotransmitter.

∴ Synthesis of Glutamate ∴

→ Given the excitatory effect of glutamate, it is excluded from the brain by BBB that is blood brain barries is impermeable to Glutamate.
→ Thus glutamate in the brain must be synthesised de novo from glucose.
→ TCA → Alpha Ketoglutarate → Glutamic Acid (via → transamination
→ Reuptake to storage vessels.
20% of glutamate turnover through Glutamate transporter. &
40% through glutamine cycle.

∴ Receptor of Glutamic Acid ∴

∴ Ionotropic receptors ∴

(i) NMDA Receptors ∴ (N-Methyl-D-Asparatate)

7 subunits ($GluN_1$, $GluN_2A$, $GluN_2B$, $GluN_2C$, $GluN_2D$, $GluN_3A$, $GluN_3B$).

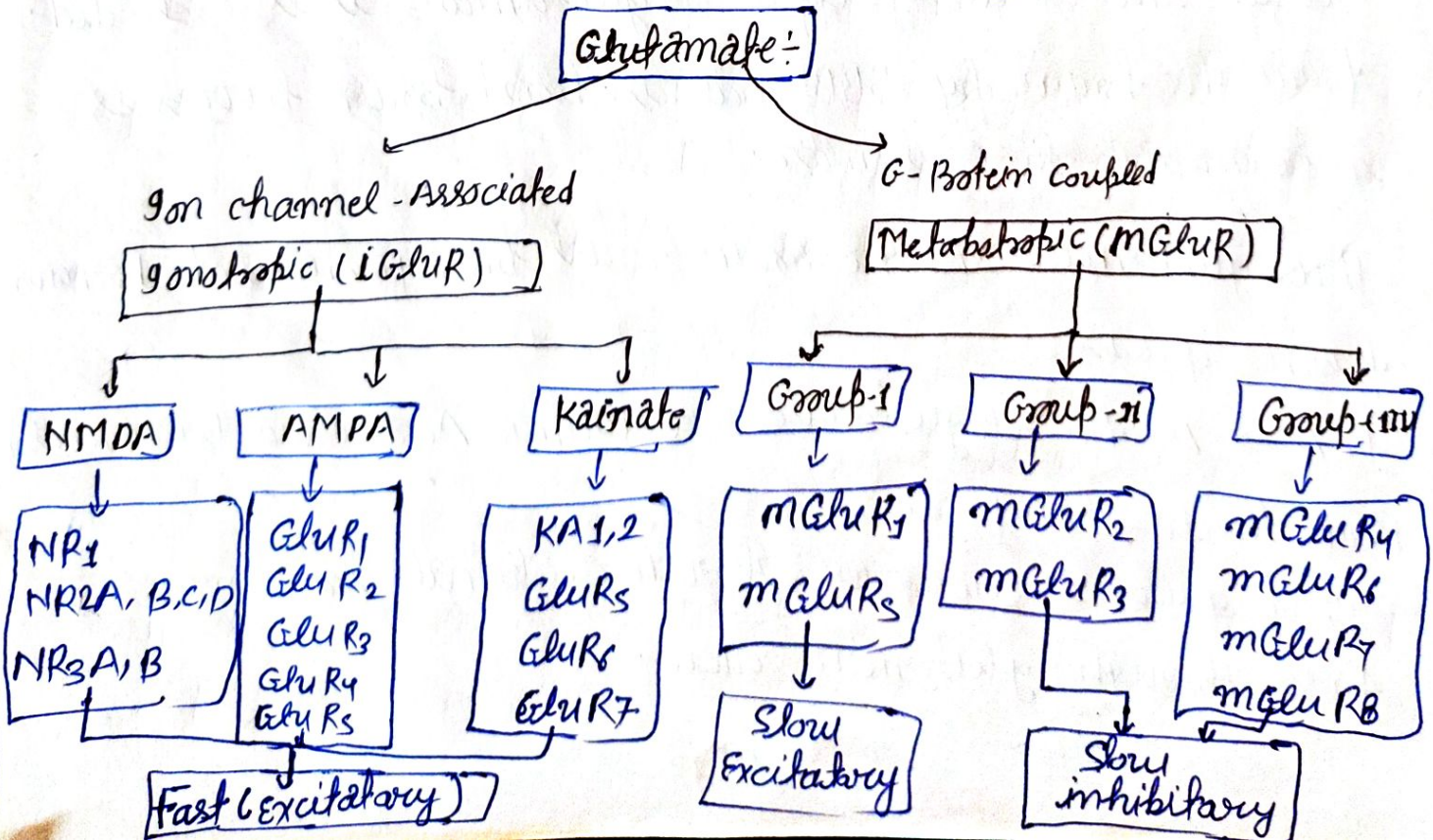
(ii) AMPA Receptors ∴ (α-Amino-3-hydroxy-5 methyl-4 isoxazale propionic acid)

4 subunits are present such as -

($GluA_1$, $GluA_2$, $GluA_3$, $GluA_4$)

(iii) Kainate Receptors ∴ There are 5 subunits are present. such as -

$GluK_1$, $GluK_2$, $GluK_3$, $GluK_4$, $GluK_5$



∴ Glycine Receptor ∴

→ Glycine is a simplest amino acid which is semiessential amino acid and is should be taken as a nutritional supplement.

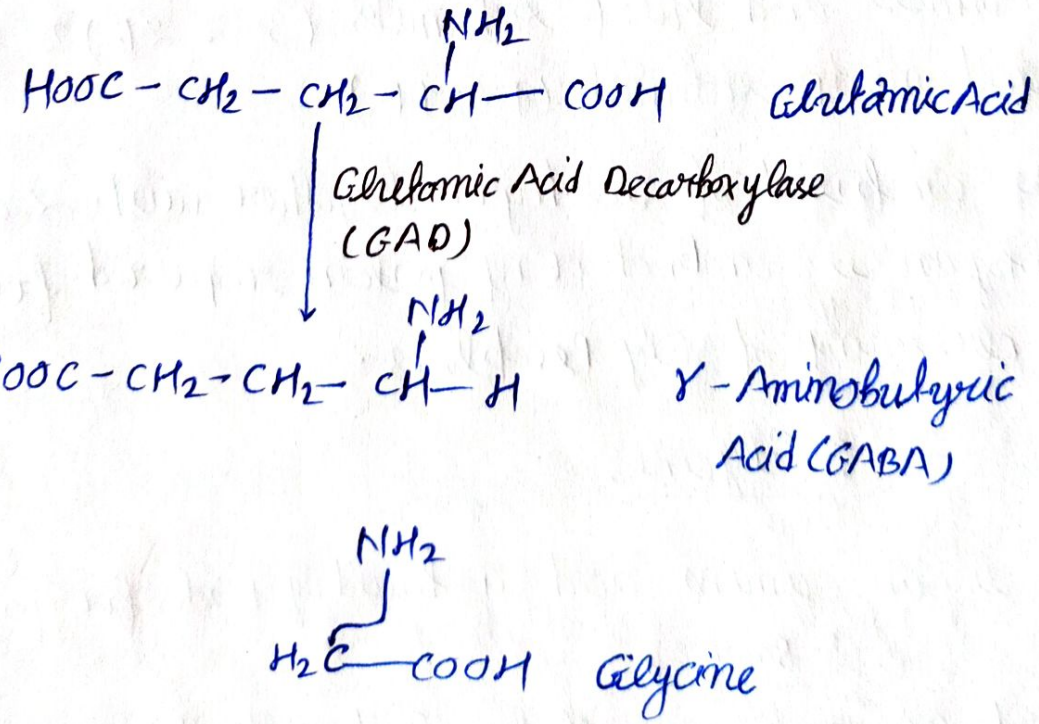
→ Glucine is also a major inhibitory neurotransmitter in the adult vertebrate central nervous system (CNS)

→ Glycinergic synapses are particularly abundant in spinal card and brain stem, but are also found in higher brain regions including the hippocampus.

→ Glycine receptor (GlyR) is a member of the nicotinicaid receptor superfamily.

→ It is also known as an inhibitory chloride channel protein.

∴ Synthesis ∴



Structure

→ Glycine receptors exist as pentameric proteins, homooligomers of the α isaforms (α_1, α_2, α_3, or α_4) or hetro oligomers which also contain the β- subtype variant β_1 which is essential for targetting the receptor to the synapse.

→ Receptors are arranged as five subunits surrounding a central pore with each subunit composed of four α helical transmembrane segments.

→ There are presently four k/w isoforms of the α subunit (α_1-4) of Gly-R that are essential to bind ligand. (GLRA1, GLRA2, GLRA3, GLRA4) and a single β-subunit (GlRB)

→ The adult of the Gly-R is the heteromeric $\alpha_1\beta$ receptor, which is believed to have a stoichiometry (proportion) of three α_1 subunits and two β subunits (3α : 2β) or four α_1 subunits and one β subunit (4α : 1β)

→ Gly-R is also composed of Gephyrin together with α and β subunits. Gephyrin is an Enchoring protein required for the postsynaptic clustering of Gly Receptors.

Glycine

→ Glycine is an amino acid a building blocks for protein.

Source

It is found primarily in gelatin and silk fibroin and used therapeutically as a nutrient.

÷ Mechanism of Action ÷

In the CNS, there exist strychnine sensitive glycine binding sites as well as strychnine insensitive glycine binding sites ~~the~~ is located on the NMDA receptor complex. The strychnine sensitive glycine receptor complex is comprised of a chloride channel and is a member of the ligand-gated ion channel superfamily. The putative antispastic activity of supplemental glycine could be medicated by glycine's binding to strychnine-sensitive binding sites in the spinal cord. This would result in increased chloride conductance and consequent enhancement of inhibitory neurotransmission. The ability of glycine to potentiate NMDA receptor-medicated neurotransmission raised the possibility of its use in the management of neuroleptic-resistant negative symptomes in schizophrenia.

÷ Pharmacokinetic ÷

It is absorbed from small intestine via an active transport mechanism and it is metabolized in liver

÷ Use ÷

- Glycine is used for treating schizophrenia, stroke, benign prostatic hyperplasia (BPH) and some rare inherited metabolic disorders.
- It is also used to protect kidneys from the harmful side effect of certain drugs used after organ transplantation as well as the liver from harmful effects of Alcohal.

→ Sometimes it can also be used to treat leg ulcers and heal other wounds by applying on the skin.

→ Glycine is also used as a sweetner, emollient emulsifying agent and solubilizing agent.

÷ Serotonin ÷

→ Serotonin is a naturally occurring amine synthesized from the tryptophan & commonly found in plants, some fruits, animal tissues & insect venoms. In human being, it is found in enterochromaffin cells in GIT & CNS.

→ Serotonin containing neurons are mainly found in limbic system, raphae nucleus, cortex hypothalmus, amygdala, caudal nucleus, mid brain vomiting centre & spinal cord.

→ These regulate sleep, body temp. & mood.

→ A harmone melatonin is derived from serotonin.

÷ Synthesis and degradation ÷

Tryptophan

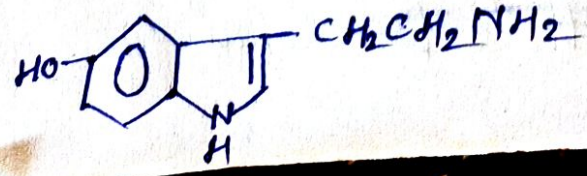
↓ Hydroxylase

5-Hydroxy Tryptophan

↓ Decarboxylase

5-HT —MAO→ 5-Hydroxy Indole Acelic Acid (5-HIAA)

5-HT —Dehydrogenase→ 5-Hydroxy tryptophol.



Pharmacological Action of Serotonin

← (5-HT → Hydroxy tryptophan) →

÷ Action on GIT ÷

- 5-HT act as a local harmone & to regulate peristelsis movement.

÷ Action on CNS ÷

→ It act as neurotransmitter in CNS.

÷ Action on CVS ÷

→ 5-HT produces positive ionotropic effect & chronotropic effect in myocardium.

÷ Action on smooth muscles ÷

→ 5-HT constrict the smooth muscles of bronchia and GIT.

÷ Action on blood vessels ÷

→ 5-HT dilate the blood vessels of skeletal muscles coronary arteries & capillary of skin.

÷ Action on Platelets ÷

→ It enhance the aggregation of platelets haemostasis.

÷ 5-HT- Receptors ÷

→ The 5-HT receptors are the receptors for serotonin They are located on the cell membrane of nerve cells and other cell types in animals, and mediate the effects of serotonin as the endogenous ligand.

- With the exception of the 5-HT_3 receptor, a ligand-gated ion channel, all other 5-HT receptor are G-protein-coupled seven transmembrane, (or-heptahelical) receptors that activate an intracellular second messenger cascade.

÷ 5-HT_2 receptors ÷

Occurs in CNS & many peripheral sites (especially blood vessels, platelets, autonomic neurons) Neuronal and smooth muscle effects are excitatory. Some blood vessel dilated as a result of nitric axide release from endothelial cells. 5 HT_2 - receptors acts through phosphoLipase C/inositol) triphosphate pathway.

÷ 5-HT_3-receptors ÷

Occurs in peripheral nervous system especially nociceptive afferent nervous and enteric neurons and in CNS. effects are excitatory mediated via direct receptor-coupled ion channel.

÷ 5-HT_4 receptors ÷

Occur mainly in the enteric nervous system (also in CNS). Effects are excitatory causing increased gastrointestinal motility. Act by stimulating adenylate cyclase.

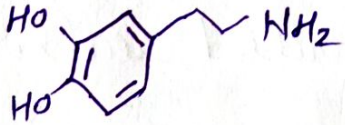
- Little is known so far about the function and pharmacology of 5 HT_{5-7} receptors.

Pathophysiological Roles

- Neurotransmitter
- Precursor of melatonin.
- Neuroendocrine functions.
- Nausea and Vomiting.
- Migraine.
- Haemostasis.
- Hypertension.
- Intestinal motility etc.

Dopamine

Introduction:- Dopamine belongs to the family of catecholamine



- Hormones, Epinephrine and Norepinephrine (other catecholamines) are derived from Dopamine.
- Significant role in learning, goal-directed behaviour, regulation of hormones motor control.

∴ Dopamine synthesis and Metabolism ∴

L Phenylalanine (Amino Acid from diet)

↓ Phenylalanine hydroxylase

L - Tyrosine

↓ Tyrosine hydroxylase (RLS

L - Dopa

↓ Dopa decarboxylase.

Dopamine (DA)

↓ Monoamine oxidase (MAO)
Catechol-o-Methyl transferase (COMT)

DOPAC + HVA

∴ Dopamine-Receptors ∴

Metabotropic G-protein coupled receptors.

D_1 - like family.

- Includes subtypes D_1 and D_5
- → Activation is coupled to G_s: Activates Adenylyl cyclase which leads to increase in concentration of CAMP.

D_2-like family.

- → Includes D_2 D_3 and D_4
- → Activation is coupled to G_i: Inhibits Adenylyl cyclase leading to decrease in concentration of CAMP.
- → Also open K channels & closes ca influs

Subtype	Location	Function.
D_1	Putamen nucleus Accumbens i.e nigrostrial pathway	Inhibition causes extrapyrimidal disorders.
D_2	Straiatum Substantia nigra pituitary	Control behaviar Voluntary prolactin release.
D_3	Midbrain Nucleus Accumbens & hypothalamus.	
D_4	Frontal cortex Medulla and Midbrain i.e mesocortical Pathway	
D_5	Hypothalamus Hippocambus.	

∴ General Anaesthetic ∴

General Anaesthetic are those agents which cause reversible loss of unconciausness this is used before the surgery.

∴ Classification of General Anaesthetic ∴

(1) → Inhaled → (A) Volatile liquid.
- → Ether
- → Halothane
- → Enflurane
- → Isoflurane
- → Desflurane
- → Sevaflurane.

(B) → Gases → Nitrous oxide.

(2) → Intravenus :- Thiopentone.
- → Propofol.
- → Etomidate
- → Benzodiazepine
- → Ketomine

:- Stage of Anaesthesia :-

(1) Stage of Analgesia.
(2) Stage of Delirium
(3) Stage of Surgical Anaesthesia.
(4) Stage of Respiratory paralysis.

:- (1) Stage of Analgesia :-

This is the first stage of Anaesthesia. In this stage the sensation pain and touch loss

(2) Stage of Delirium :-

In this stage the conciousness of body is slowly loss and patient goes into coma stage.

(3) Stage of Surgical Anaesthesia :-

In this stage the total body is Anaesthesia patient lost consciousness. but their respiration is normal

- This is the best stage for surgery.

(4) Stage of Respiratory paralysis :-

This is the lost and mast dengerous stage in this stage on longer.

- Those patient respiratory system can be paralysis and if patient remain in this stage for long time then death will occur.

:- Volatile liquid :-

(i) **Ether (Diethyl ether) :-** It is a colorless volatile liquid with a pungent odour.

- It is highly inflammable and explosive.
- It is quick absorbed and eliminated through lungs.

Advantages :- (i) It is a sale anaesthetics.

(ii) It produce satisfactary muscle relaxant.

(iii) It does not produce liver & kidney damage.

Disadvantage :- (i) Induction is slow and unpleasant.
(ii) It irritates mucus membrane and produce cough.
(iii) It increase Secreation of respiratary track.
(iv) Recovery is slow.

Desflurane

→ It is highly volatile and less soluble in blood tissues. so induction and are quick its pungent odur may cause irritation leading to coughing, and large spasm.
No liver are kidney toxicity suitable as an anesthetic for out patient.

Malignant hyper thermia

Is an imbartable to toxicity of halothane it is due to the release of calcium from the sarcoplastic Reticulam It is treated by the administration of dantroline A Directly acting muscle relaxant.

Advantages :- (i) It is non inflammable it does not irritate respiratary passages.
(ii) Induction and recovery are quick.
(iv) It induces controlled hypotension. So it produce blood less field for safe plastic surgery.

Disadvantage :- (i) Muscle relaxation is not adequate.
(ii) Respiratary depression at 20% concentration.
(iii) Cardiovascular depression and hypotension.

(B) Gaseous Anaesthesia:-

Nitrous oxide:- It is also called as is colorless laughing gas and sweet in taste it is heavier than air it is non inflammable but supports composition.

- It is insoluble in blood and it does not combine with hemoglobin.
- It is carried in blood in the form of physical solution.
- It does not decompose in the body. so the oxygen of nitrous oxide is not available for tissue respiration.
- It is excreated unchanged through the lungs. A small quality may be eliminated through skin.

Advantage:- Induction and recovery are quick.

- No irritation to mucus membrane.
- It is non toxic to liver and kidney

Disadvantage It is not a potent Anaesthetic muscle relaxation. is not Adequate special Apparatus is required for its use is produce euphoria.

:- Pre Anaesthetic Medication:-

- Before surgery are operation the groups of medicine which are given with the Anaesthetic is called pree Anaesthetic medicine and the process is known as pre Anaesthetic Medication.

⇒ (1) Sedation → Barbiturate - Sleep.

(2) Analgesia → General

(3) Inhibition of parasympathetic activity Atropin

Antimetic effect → Promethozine.

Anticoglent → Heparin → Blood Cloth.

÷ Drugs of general Anesthetics ÷

÷ Inhalational Anaesthetics ÷

(i) Nitrous Oxide ÷ (N_2O) It is a Colourless ÷ Odourless, heavier than air, noninflammable gas supplied under pressure in steel cylinders. It is nonirritating. but low potency Anesthetic Nitrous oxide is a good Analgesic. even 20% produces Analgesia equivalent to that produced by conventional doses of morphine. Muscle relaxation is minimal.

Nitrous oxide is generally used as a carrier and Adjuvant to other Anaesthetics. A mixture of 70% N_2O + 25-30% O_2 + 0.2 -2% another potent Anaesthetic is employed for most surgical procedures.

- As the sole agent, N_2O (50%) has been used with O_2 for dental and obstetric Analgesia. It is nontoxic to liver. kidney and brain. However.

prolonged N_2O Anaesthesia has the potential to depress bone marrow and cause peripheral neuropathy.

- Metabolism of N_2O does not occur it is quickly removed is cheap and commonly used.

(2) Ether (Diethyl Ether) It is highly Volatile:-

Liquid, produces irritating vapours which are inflammable and explosive ($C_2H_5-O-C_2H_5$)

- Ether is a potent Anaesthetic produces good Analgesia and marked muscle relaxation by reducing ACh output from motor nerve endings.
- The dose of competitive neuromuscular blockers should be reduced to about 1/3. It is highly soluble in blood.
- Induction is prolonged and unpleasant with struggling.
- Breathholding, salivation and marked respiratory secretions (Atropine must be given as premedication to prevent the patient from drowning in his own secretions) Recovery is slow postanaesthetic nausea vomiting and retching are marked.

(3) Halothane (Fluothane)

It is a volatile liquid with sweet odour, nonirritant and non-inflammable. Solubility in blood is intermediate→ Induction is reasonably quick and pleasant.

- It is potent Anaesthetic - precise control of Administered conc. is essential. for Induction 2-4%. and for maintenance 0.5-1% is delivered by the use of a special vaporizer. It is not a good Analgesic or muscle relaxant. but it potentiates competitive neuromuscular blockers.

Halothane (Prototype)

Advantages:- → Potent Anesthetic, rapid Induction & recovery.
→ Neither flammable nor explosive sweet smell, non irritant
- Does not augment bronchial and salivary secretions.
→ Low incidence of post operative nausea and vomiting
→ Relaxes both skeletal and uterine muscle and can be used in obstetrics when uterine relaxation in indicated.
→ Combined with its pleasant odor, this makes it suitable in children for inhalation induction.

Disadvantages:- Weak Analgesic (thus is usually coadministered with N_2O opioids.
→ Is a strong respiratory depressant
- Is a strong cardiovascular depressant halothane is vagomimetic and cause atropine-sensitive bradycardia.
→ Hepatotoxic is oxidatively metabolized in the liver to tissue toxic hydrocarbons (e.g trifluroethanol and bromide ion)
→ Malignant hyperthermia.

Intravenous Anesthetics:-

→ Potent Anesthetic but a weak analgesic.
→ High lipid solubility, quickly enter the CNS And depress function, often in less than one minute. and redistribution occur very rapidly as well to other body tissues. including skeletal muscle and ultimately adipose tissue (serves as a reservoir.

→ All barbiturates can cause apnea coughing chest wall spasm. laryngospasm and bronchospasm.

÷ Intravenous Anesthetics / Propofol ÷

Propofol ÷ Phenol derivative. It is an IV sedative-hypnotic used in the induction and or maintenance of Anesthesia.

→ Onset is smooth and rapid (40 sec)

→ Decrease BP without depressing the myocardium it also reduce intracranial pressure

→ It is widely used and has replaced thiopental as the first choice for Anesthesia induction and sedation, because it produces a euphoric feeling in the patient and does not cause post Anesthetic nausea and vomiting.

→ poor Analgesia.

÷ Intravenous Anesthetics / Ketamine ÷

→ Ketamine (Phencyclidine derivative) A short-Acting Anesthetic induces a dissociated state in which the patient is unconscious (but may appear to be Awake) And does not feel pain

→ This dissociative Anesthesia provides sedation amnesia and immobility.

→ Ketamine is also a potent bronchodilator.

→ Therefore. it is beneficial in patients in Asthmatics conversely it is contraindicated in hypertensive or stroke patients.

→ Ketamine is used mainly in children and elderly adults for short procedures.
→ It is not widely used because. It increase cerebral blood flow may induce hallucinations, particularly in young Adults.

Thiopentone Sodium

Barbiturate: Ultra short acting.

→ Water soluble
→ Alkaline
→ Dose - Dependent suppression of CNS Activity.
→ Dose 3-5 mg/kg iv (2.5%) solution - 15 to 20 seconds.

Pharmacokinetics: → Redistribution.
→ Hepatic Metabolism (Elimination half life (7-12 hrs)

→ CNS depression persists for long > 12 hr.

∴ Side effect of Thiopentone:

→ Pre Anaesthetic course — laryngospasm.
→ Noncompatibility - succinyl choline.
→ Tissue necrosis - Gangrene
→ Post - Anaesthetic Course - Analgesic

Thiopentone - Contained

Advantages:-

- Rapid induction.
- Does not sensitize Mycocardium to Adrenaline.
- No nausea and vomiting.
- Non explosive and non irritant.
- Short operations (Alone)
- other uses - Convulsion
- psychiatric patients and narcoanalysis of criminals.

Disadvantages:-

- Depth of Anaesthesia difficult to judge.
- Pharyngeal and laryngeal reflexes. persists - Apnoea - Controlled-Ventilation
- Respiratory depression.
- Hypotension (rapid & Shock and hypovolemia.
- poor analgesic and muscle relaxant
- Gangrene and necrosis.
- Shivering and delirium.

(4) Fentanyl:

- Neuroleptanalgesia - droperidol
- 4- Acylanilino derivative
- Opioid Analgesic
- Duration of Action 30 - 50 min.

Use:-

In combination with diazepam used in diagnostic endoscopic and Angiographic procedures.

- Adjunct to spinal and nerve block Anaesthesia.

Fentanyl contained:-

Advantages:-

- Smooth onset and rapid recovery

DisAdvantages

- Respiratory depression.

→ Suppression of vomiting and coughing.

→ Commanded operation

⇒ Less fall in BP and no sensitization to Adrenaline.

⇒ Increase tone of chest muscle.

⇒ Nausea vomiting and itching during recovery

∴ Sedative & Hypnotics ∴

→ Sedative and Hypnotics are those drugs which acts on the central nervous system and they reduce the mental excitement, mental depress, and produce the natural sleep and sound sleep. they are called basicaly sedative & Hypnotics.

→ Sedative are those drugs which do not produce sleep. but they reduce the excitement of brain and depression. and produce drowsiness.

→ Hypnotics are those drugs which have higher concentration than sedative they basically relax the brain completely and produce natural sleep or sound sleep.

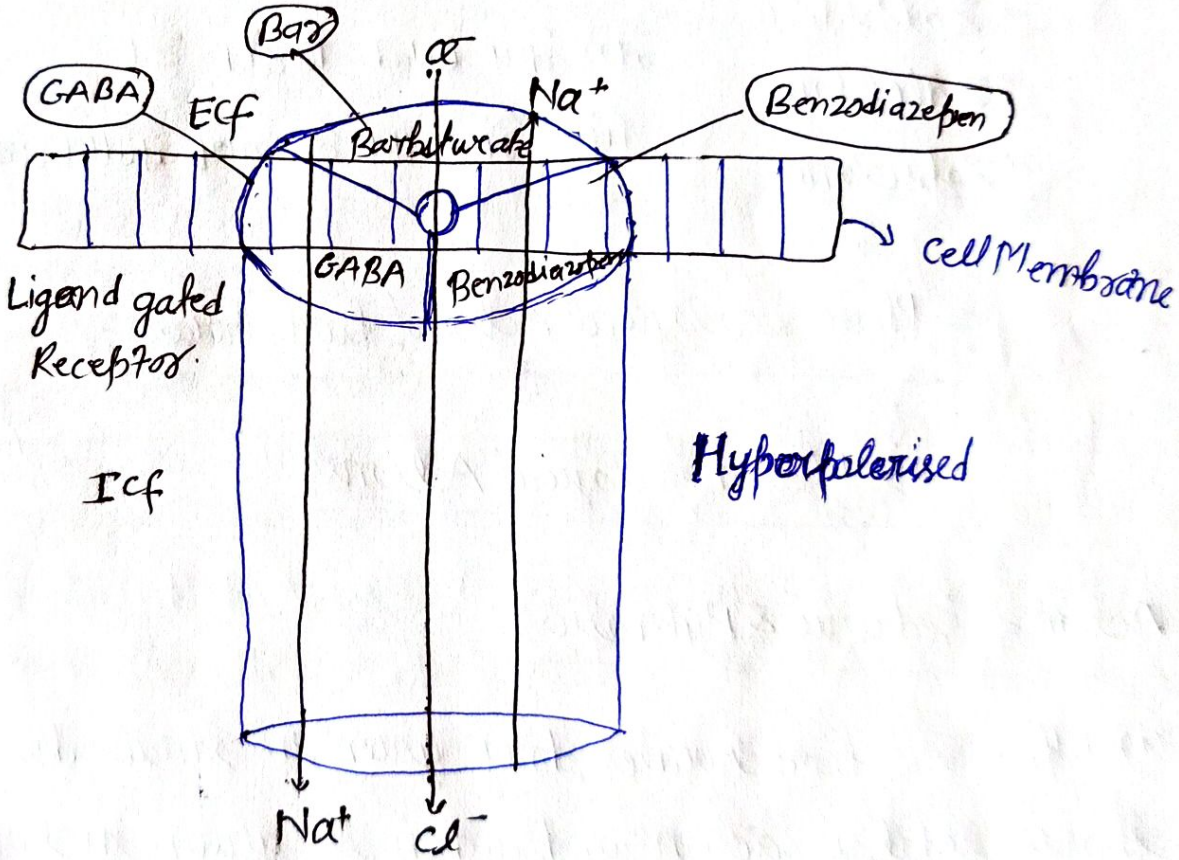
∴ Mode of Action of Sedative and Hypnotics ∴

→ Basically sedative and Hypnotics drugs are in of three category GABA Analog, Benzodiazepon. and Barbiturates.

⇒ When Benzodiazepon or barbiturate any of the drug bind with their receptor like benzodiazepon bind with
Selective

Benzodiazepen receptor and barbiturate bind with the barbiturate receptor and which these drugs bind the receptor the channels are becomes open and chloride ion goes from Extra cellular fluid to intra cellular fluid.

→ And when chloride ion moves the channels becomes hyperpolerised and when the receptor becomes hyperpolerised the transmission of N ion is completely stop and in that case brain becomes relax and the excitement of brain is reduce and sedative and hypnotics action produce in our CNS.



∴ Classification of Sedative & Hypnotics :-

(1) Barbiturates

Long Acting → Phenobarbitone

Short Acting → Butobarbitone

Ultra Short Acting → Thiopentone Methohexitone

अगर दवाई को सुलाना है तो फेन बूताबो थपकी दो माथे पर और मस्त दोन मे लोरी गाओ

(2) Benzodiazepines – Hypnotics:-

→ Diazepam
→ Flurazepam
→ Nitrazepam
→ Triazolam
→ Temazepam
→ Alprazolam

दिया को फ्लू हो गया था नाइट में पर त्रिपाठी को तमीज नहीं रात भर बेंजो पर अलाप गाता रहा ।

(3) Newer Nonbenzodiazepine hypnotics :-

→ Zolpidem
→ Zaleplon
→ Zopiclone

नए लोग जाल बिछाते हैं।
पिंड में प्लान के साथ क्लोन बनाते हैं।

:- Pharmacological Action of barbiturates :-

:- Pharmacological Actions :-

Action of Sedative & Hypnotics :-

(1) When the barbiturates drug given in small dose then it shows sedative action and when it given in large dose it shows Hypnotics Action.

→ And when barbiturates drugs give regularly for sedation then it may cause Addiction.

(2) Anaesthetic Effect :-

→ Some barbiturates drugs like "Theopental Sodium" when it is given IV form then it cause Anaesthetic effect.

→ And these drug is generally given in pree Anaesthetic medication.

(3) Anticonvulsent

→ Some category of barbiturates drugs is given for the treatment of epilepsy like Phenobarbitone and Methobarbitone

(4) Effect on Respiration:

→ Barbiturates drugs basically reduce the Hypoxic & Chemoreceptor responce and it causes the respiratory depression.

- And the rate of respiration becomes slow.

→ But when it is given in large dose they cause respiratory paralysis or death.

(5) Effect on Cardiovascular System:

- In general dose there are no effect on CVS.
- But after a long dose it may cause decrease in the heart rate and decrease in the cardiac output and blood pressure may also be reduce.

(6) Effect on Peripheral Nervous System:

→ When barbiturates drug is given then it affect the neurohumoral transmission in Ganglia of the peripheral Nervous System.

→ It reduce the both action of symathetic and Parasympathetic nervous system. basically it blocks the nicotinic receptor and reduce the cholinergic responce.

(7) Effect on Kidney

→ When barbiturate drug is given it shows effect on kidney it reduce the Glomerular filtration rate so the urine output is reduce.

(8) Effect on Spinal cord :-

→ When barbiturate drug is given it reduces the reflex action of spinal cord.

:- Pharmacokinetics :-

→ It is well absorb orally from stomach and GIT.
→ It is available in tablet form.
→ And it is also available in injection form.
→ Barbiturates are available in two form.
→ Ionic or Non Ionic form.
→ Ionic form is distributed slowly. And Unionic form drug
→ can easily distributed and pass into the brain.
→ It is metabolise in to the liver.
→ And excreate through urine.

:- Adverse Effect :-

→ Intolerance
→ Anaemia.
→ Allergy
→ Addiction.
→ Respiratory Depression.

∴ Pharmacology of Benzodiazepines ∴

→ Benzodiazepine drug is a sedative Hypnotics category drugs.

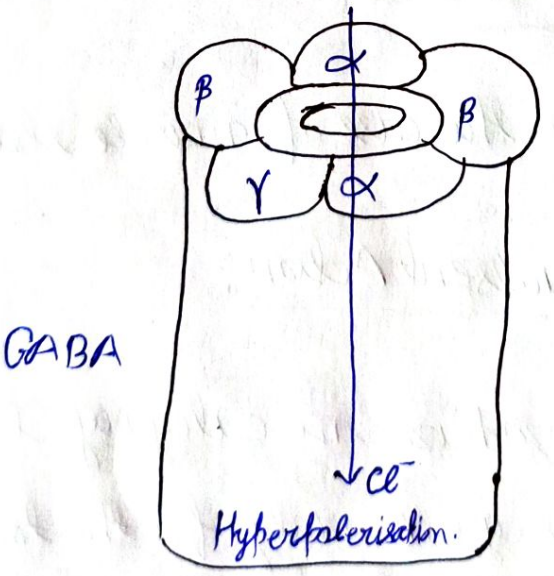
→ Basically benzodiazepines drugs bind with the GABA receptor.

→ GABA Inhibit the action of brain or It depress the brain.

→ When benzodiazepine drugs bind with the GABA receptor. then GABA receptor contain five pentameric form. two alpha two bita and one Gama.

→ And after binding with the drug benzodiazepine with GABA receptor. the chloride channel is open and Cl^- ion goes inside from ECF to ICF

→ And due to hyperpolerisation of Cl ion. the CNS become depress.



∴ Pharmacological Action ∴

(1) Sedative & Hypnotics Action ∴ Benzodiazepines drugs are used to treatment of Insomnia. It is given for sedative & Hypnotics Action.

→ When benzodiazepine drugs are Given in small dose then it causes or produce the sedative Action

→ And when it is given is large dose it produce Hypnotics Action.

→ And when they are used more than four weeks. then it may produce Addiction effect.

(2) Reduction of Anexiety & Aggresstion :-

→ Basically benzodiazepine drugs are also used in Anexiety Reductionand Aggresstion.

- And it is given before the miner surgery and dental surgery for reducing the Aggresstion.

→ It is never be given After four week because it can cause Addiction and tolerance.

(3) Reduce Muscle tone :-

→ It is also given in the case of muscle spasm

(4) Anticonvalsent Action :-

→ Some drugs are benzodiazepine categary like Diazepam & Medazelam which is given oraly for the treatment of epilapsy or as a anticonvalsint drug.

(5) Anterograde Amensia

→ It is also used in the case of Amensia. ~~when the patient~~

→ This drug delete the old memories and create new

→ memory.

÷ Pharmacokinetics ÷

→ It is given orally.
→ It is well absorbed in stomach and intestine.
→ They are lipophilic in nature. so they can pass the BBB and effective in the CNS and distributed in the CNS.
→ It is metabolise in liver in the form of Glucoronic Acid and oxidation reaction.
→ It is excreate from the urine.

÷ Adverse Effect ÷

→ Drowsiness
→ Dizziness.
→ Reduce Alertness.
→ Reduce Concentration.

÷ Anticonvulsant / Antiepileptic ÷

÷ Epilepsy ÷

→ Most commonely seizure is also known as Epilepsy.
→ It is derived from greek word epilambanein means to seize.
→ It is a neurological disorder. in which neurohumoral transmission of brain is completely affected

→ In epilepsy the sensory and motor neuron abnormely discharge. The function of all organ or body. is completly change and seizure or Convulsion comes out which is called epilepsy.

÷ Symptoms of Epilepsy ÷

- → Chronic recurrent proximal changes.
- → Loss of conciousness.
- → Excess of Muscular Activity.
- → Abnormal Sensation.
- → Sec to min.

÷ Classification of Epilepsy ÷

(1) **Generalised Epilepsy ÷** In this seizure the entire brain envalue in the seizure it is not devolved from the any single part of the brain.

- It is of two types -

(i) Grandmal → Tonic clonic Seizure

(ii) Petimal → Absence seizure.

→ **Grandmal ÷** It is also called tonic clonic Seizure.

- → It this seizure starts from aura and then after bilateral muscular jurk.
- → In this seizure loss of conciousness completly involue. and muscle spasm
- → It remain two to five minute.

(ii) Petimal :- It is also called absence seizure.

→ It is basically seen in the children.

→ In this seizure the completely loss of conciousness.

- And the loss of speach is generally seen.

- It lost from 1 to 30 sec.

(2) Partial / focal Seizure :- This type of seizure generally seen in any one part of the brain basically temporal lobes and it not involves in the full brain.

→ And its symptoms start from local body organ.

it is of two types-

(1) Simple → Jacksonion Motar Epilepsy.

(2) Complex → Psychomotar.

(1) Simple :- It is also known as Jacksonion Motar Epilepsy.

→ It starts from certain part of brain cortex.

→ Some muscle are jump like thumb or toe.

→ And do not loss any type of conciousness.

→ Duration of time is 1 to 2 min.

Complex :- It is also called Psychomotar Epilepsy.

→ In this case body ~~solu~~ shows unusual behaviour. like Extensive, Swallowing, Chewing.

→ Shows confusion or bizzare

→ (3) Status Epilepsy :-

→ In this case the brain is damage.

→ And the ~~time~~ duration ~~of~~ time of these epilepsy for 30 minutes.

Classification of Antiepileptic

(1) Barbiturate → Phenobarbitone

(2) Deoxybarbiturate → Primidone

(3) Hydantain → Phenytain, Fosphenytoin

(4) Iminostilbene → ~~Car~~Carbamazepine Oxcarbazepine

(5) Aliphatic carboxylic → Ethosuximide

(6) Succinimide → Valproic Acid, Sodium Valproate, Divalproex

(7) Benzodiazepines → Clonazepam, Diazepam, Lorazepam, Clobazam

(8) Phenyltriazine → Lamotrigine

(9) Cyclic GABA → Gabapentin; Pregabalin

(10) Newer drugs :- → Topiramate, Zonisamide, Levetiracetam, Vigabatrin, Tiagabine, Lacosamide.

→ हाय बाबर देव अली इनमे सक्सेस पाना है तो बन जाओ सन्यासी इन सब चक्करो मे न पड़ो

Hydantion, Barbiturate, Deoxybarbiturate, Aliphatic carboxylic Acid, Iminostilbene, Succinimide, Phenyltriazine Newer drugs, Cyclic GABA, Benzodiazepines.

÷ Mechanism of Action ÷

It is of two types ÷

- Mechanism of Action
  - General Mech → Excitation of GABA.
    - Reducing discharge Rate
    - Hyperpolerisation by Cl^- ion.
  - Molecular Mech
    - Blockage of Voltage gated Na^+ channel
      - Phenytoin, Valproate, Carbazepine
    - Increase of GABA Enhancement.
      - Barbiturate and Benzodiazepine.
    - Blockage of T Type of Ca^+ channel.
      - Ethosuccimide. Gabapentin.
    - Reduce Glutamate Excitation.
      - Felbamate, Gabapentin.

÷ Brief Notes on Antiepileptic drugs ÷

÷ Hydantoins ÷

Phenytoin (Dilantin), Ethotoin (Peganone), Fosphenytoin (Cerebyx)

Pharmacological Effects (Mechanism of Action)

Limits the development of spontaneous seizure activity and reduces the spread of the seizure.

→ This effect is mediated by a slowing of the rate of recovery of voltage-gated sodium channels from inactivation, thus delaying repolarization and reducing excitability. This action is both voltage and use dependent

- Mechanism of Action of AEDs (Phenytoin, Valproate and carbamazepine) Acting on voltage gated sodium channels. phenytoin, carbamazepine, Valproate and other drugs prolong the inactivation of the Na^+ channels thereby reducing the ability of neurons to discharge high frequency firing. The channel opens for Na^+ influx when both (A) Activation gate and (I) Inactivation gate opens.

∴ Clinical Indications "Broad-Spectrum AED" ∴

Used for Generalised tonic/clonic (Grand mal) seizures partial seizures, status epilepticus may exacerbate absence seizure

∴ Pharmacokinetics ∴

Phenytoin is highly fat soluble highly protein bound (98)% readily absorbed from the GI tract metabolized in the liver by CYP2C9/10. It induces CYP2C/3A families. Oral bioavailability is variable due to first pass metabolism. Metabolism is nonlinear (See Box 2) since the metabolic enzyme is saturated at low concentrations the elimination of phenytoin follows zero-order kinetics. Thus a relatively small changes in dosage can produce a marked change in blood levels. Valproic Acid lowers phenytoin plasma levels because is displaces phenytoin from plasma protein-binding

sites and increases availability for metabolism. The metabolism of phenytoin is enhanced in the presence of Inducers of liver metabolism (e.g phenobarbital) and inhibited other drugs (eg. cimetidine) phenytoin should be used with caution in liver disease.

$T_{1/2}$ = 24 hr.

:- Advers effect :-

→ Gingival hyperplasia (20% - 40%) of patient. especially children coarsening of facial features hirsutism, skin rash, mental confusion, altered vitamin D and calcium metabolism.

→ Dizziness, Ataxia, (Inability to coordinate voluntary movement) nystagmus (Involuntary movement of eye) diplopia (double vision)

:- Teratogenic effect :-

Cleft palate congenital heart disease, Slowed growth and mental retardation "(fetal hydantoin syndrome)

:- Contraindication :-

Sinus bradycardia and SA block.

:- Succinamides :-

Ethosuximide (Zarontin)

:- Mechanism of Action :-

Inhibits low threshold voltage (T- Type) Calcium channel currents, especially in thalamic neurons that act a pacemakers to generate rhythmic cortical discharges. (3 - Hz SWDs)

Clinical Indications

Primary agent for the treatment of absence seizures.
Not effective in tonic clonic seizures.

Pharmacokinetics

Not plasma protein bound but it metabolised by hepatic microsomal enzymes (does not induce these enzymes)

$T_{1/2}$ = 40–50 hr

Adverse Effect

Nausea and vomiting (onset of treatment) suspected Teratogen, most notably in combinations with barbiturates

Iminostilbene

Carbamazepine (Tegretal, Carbatral)

Mechanism of Action

Inhibits voltage-gated sodium channels, It may also be a partial agonist at adenosine A2A and/or A2B receptors antagonist at A_1 Adenosine receptors. Adenosine is generally A central inhibitory substance.

Clinical Indications "Broad spectrum AED

used for generalized tonic/clonic (Grand mal) seizures partial seizures, status epilepticus.

→ Treatment of choice for partial seizures in pediatric patients in controlled studies, it is similar to phenytoin for focal and major motor seizures and has the least

Congnitive impairment.

Pharmacokinetics

80% is plasma protein bound.

Metabolised to an epoxide that is as active as the parent compound by CYP3A4. Induces hepatic microsomal enzymes CYP2C, CYP3A and UGT

$T_{1/2}$ = 10-15 hr.

Adverse Effect

Diplopia, Ataxia.

May cause a rare but frequently fatal Aplastic Anemia. idiosyncratic

Toxicity

Liver toxicity. follow up with liver function test and CBC.

Contraindications

MAO inhibitor use within 2 weeks.

Benzodiazepines

Clonazepam (Klonopin) Diazepam (Diastat Valium) Lorazepam (Ativan) Clorazepate (Tranxene)

Mechanism of Action

Positive Allosteric modulators of GABA-A-receptors. Enhance the Action of the inhibitory neurotransmitter GABA by Acting Upon specific benzodiazepine sites located on the

GABA-A-receptor channel

Clinical Indication

- Adjunct for absence seizures myoclonic seizures Atonic seizure.
- Diazepam lorazepam and clorazepate are used for status epilepsies and as adjuncts for other anticonvulsants.
- Rectal Administrations of diazepam gel (Diastat) is Approved for intermittent use in adults as treatment of increased seizure activity while taking other AEDs
- Rectal diazepam (Diastat) in children may help terminate seizures activity (febrile seizures) and reduce emergency room visits.

Adverse Effect

Use is limited due to 1) sedation and 2) tolerance. These drugs can also cause respiratory depression and bronchial hypersecretion. They should be used with caution in patients with respiratory depression.

Clorazepate (Tranxene)

Mechanism of Action

Positive allosteric modulators of GABA-A receptors. Enhance the action of the inhibitory neurotransmitter GABA by acting upon specific benzodiazepine sites located on the GABA A-receptors channel.

Clinical Indication

- Adjunct for absence seizures, myoclonic seizures Atonic seizure.
- Diazepam, lorazepam and clorazepate are used for status epilepticus as Adjuncts for other anticonvulsants.
- Rectal administration of diazepam gel (Diastat) is approved for intermittent use in adults as treatment of increased seizure activity while taking other AEDs
- Rectal diazepam (Diastat) in children may help terminate seizures activity (febrile seizures) and reduce emergency room visits.

Adverse Effect

use is limited due to 1) sedation and 2) tolerance.

- These drugs can also cause respiratory and depression and bronchial hypersecretion they should be used with caution in patients with respiratory depression.

Carboxylic Acid

Valproic Acid (Depakene) Sodium Valproate)

Mechanism of Action

Exact mechanism unknown, possible mechanism proposed inhibits metabolism of GABA via down regulation of GAT-1 and GAT-3 transporter proteins thereby elevating CNS levels prolongs recovery of sodium channel inactivation some reduction of slow threshold (T-Type) Calcium Currents)

4. Clinical Indications- Broad spectrum AED:-

Absence seizures, tonic-clonic seizures myoclonic seizures partial seizures.

Pharmacokinetics:

- 70-90% plasma protein bound.
- Metabolised to a glucuronide conjugate by UGT Enzymes and beta oxidation. Inhibits UGT enzyme.
- Inhibits metabolism of drug that are substrates for CYP2C9 (Phenytoin and phenobarbital)

$T_{1/2}$ = 15 hr

Adverse Effect:-

- Nausea, Vomiting.
- Hepatotoxicity (Idiosyncratic)
- Can increase the blood levels of phenobarbital by as much as 40%
- Teratogen → Neural tube defects craniofacial skeletal cardiovascular urogenital and cerebral defects combination therapy including sodium valproate is thought to be the highest risk for developmental effect.

Toxicity:

Hepatotoxicity. Follow up with liver function test Adjust dose based on patient response and desired serum levels.

:- Contra Indication :-

Hepatic impairment, Hepatotoxicity, fetal risk and pancreatitis.

:- Cyclic GABA Analouge :-

Gabapentin (Neurontin)

: Mechanism of Action :-

Gabapentin binds to the $\alpha_2\delta_1$ and $\alpha_2\delta_2$ regulatory subunits of high voltage Activated calcium channels (HVAs are linked to calcium neurotransmitter release)

→ Gabapentin is also as Agonist at certain GABA receptors.

→ In addition gabapentin exhibits a complex interaction with NMDA receptors the drugs may either target certain combinations of NMDA receptors subunits or intracellular processes that affect the phosphorylation states of NMDA receptors

:- Clinical Indication :-

Adjunct for partial and tonic - clonic seizures.

: Pharmacokinetics :-

Is not plasma protein bound and does not induce liver microsomal enzymes therefore producing no interactions with phenytoin, valproic acid, phenobarbital or carbamazepine

Absorption in the GI tract shows saturability increasing the does not proportionately increase the amount absorbed.

÷ Adverse Effect ÷

Usually mild but include somnalence fatigue, ataxia dizziness.

→ Animal studies suggest that gabapentin is not teratogenic however, the clinical data does not have sufficient numbers to make a valid conclusion (Pregnancy category C)

÷ Lamotrigine (Lamictal) ÷

÷ Mechanism of Action ÷

Inhibits release of excitatory amino acids (i.e glutamate) probably by blocking voltage-gated sodium channels.

→ Lamotrigine also inhibits N-Type and P/Q type voltage gated calcium channels.

÷ Clinical Indication ÷

Adjunct therapy in patients with partial and tonic-clonic seizures with or without secondary.

Topiramate (Topamax)

÷ Mechanism of Action ÷

It reduce voltage-Gated Na^+ channels, may act on inactivated state.

→ It activates K^+ current and GABA-A receptors current

→ It also limits activation of AMPA-Kainate subtype receptors.

÷ Clinical Indications ÷

- Partial seizures.
- Primary generalized (tonic-clonic) seizures

÷ Adverse Effects ÷

Somnolence, fatigue, weight loss nervousness memory impairment, kidney stones.

÷ Contraindications

Alcohal use within 6 hours.

÷ Ethyl Alcohal (Ethanol) ÷

- Alcohals are hydroxy derivative of aliphatic hydrocarbons.
- When unqualified alcohal refer to ethyl alcohal or ethanol
- Pharmacology of alcohal is important for its presence in beverages which have been used since recorded history Alcoholism and for Alcohal intoxication, rather than as a medicinal substance.
- Alcohal is manufactured by fermentation of sugars.
- fermentation proceeds till alcohal content reached 15%
- Then the reaction is inhibited by alcohal itself.
- Starchy cereals, eg. barley, when soaked produce malt

$$\text{Starch} \xrightarrow{\text{Conversion}} \text{Maltose}$$

- Which can then be fermented by yeast to produce Alcohal.

→ The major source of commercial alcohal is mallases, a by product of sugar industry.

Alcohalic Beverages :-

Malted liquars :- Obtained by fermentation of germinating cereals are undistilled alcohal content is low (3-6 %.) e.g Beers. Stout. Now strong beers (upto 100%.) are also available

Wines :- Produced by fermentation of natural sugars as present in grapes and other fruits.

- These are also undistilled.
- → Alcohal content 9-12 %. cannot exceed 15 %.
- → **Spirits :-** These are distilled after fermentation e.g. Rum, Gin, Whiskey, Brandey, Vodha, etc.
- → Through the alcohal content of these can very form 40-55 %.

:- other form of Alcohals :-

Absolute Alcohal :- 99% W/W ethanol (dehydrated Alcohal)

Rectified spirit :- 90% W/W ethyl Alcohal Produced from fermented mallases, by distillation

- **Proof spirit :-** It is an old term.
  - → If whiskey is poured on gun powder and ignited and it explodes then it was labelled to be of proof strength,
  - → if water is mixed to it gun powder will not ignite
- → 100% proof spirit is 49.29% W/W or 57.1% V/v alcohal.

⇒ **Methylated spirit (Industrial)** Also called denatured spirit is produced by adding 5 parts of methy alcohal to 95 parts of rectified so as to render it unfit for drinking.

→ It is tinted blue by methylene blue dye for distinction.

⇒ It can be applied on the skin for Antiseptic cleaning and astringent purposes.

∴ Mode of Actions ∴

→ Alcohal has been shown to enhance GABA release at $GABA_AA$ sites in the brain

→ It is also inhibits NMDA and kainate type of excitatory amino acid receptors operating through cation channels.

⇒ Action of 5 HT on 5-HT inhibitory Autoreceptor (having an intrinsic ion channel) is augmented.

⇒ Some studies suggest that cerebral nicotinic cholinergic receptor (operating through Na channel) may also be one of the targets of Alcohal action.

⇒ Ethanol can indirectly reduce neurotransmitter release by inhibiting voltage sensitive neuronal Ca^{2+} channels.

∴ Pharmacological Action ∴

(1) **Local Actions ∴** Ethanol is a mild rubefacient and counterirritant when rubbed on the skin. by evaporation it produces cooling.

→ Applied to delicate skin (Scrotum) or Mucous Membranes it produces irritation and burning sensation

Concentrated Alcohal (Spirit) should not be applied in the mouth nase etc.

⇒ Injected S.C. it cause intense pain inflamation and nerozis followed by fibrosis.

⇒ Injected around a nerve it produce permanent damage

– Applied to the surface alcohal is an astringent precipitates surface proteins and hardness the skin.

⇒ By precipitating bacterial proteins it acts as and Antiseptic.

÷ CVS ÷

→ Alcohal is a neuronal depressant.

⇒ These are primarily inhibitary - Apparent excitation and euphoria are experienced at lower plasma concentrations 30 – 60 mg/dl.

→ Mood and feeling are altered anxiety may be Allayed impairment of attention memory blackouts occur.

⇒ 200 – 300 mg/dl result in stupor and above this unconsciousness prevails. medullary centres are paralysed and death may occur.

⇒ Alcohal can produce anaesthesia.

→ Driving is dangerous performance is impaired.

÷ CVS ÷

→ The effects are dependent on dose.

→ Small dose ÷ Produce only cutaneous (Especially on the face and gastric vasodilatation..

– skin is warm and BP is not affected

→ Moderate doses:- Cause tachycardia and a mild rise in BP due to increased muscular activity and sympathetic stimulation.

→ Large doses:- Cause direct myocardial as well as vasomotor centre depression and there is fall in BP.

- Blood :-

Regular intake of small to moderate amounts of alcohal 1-2 drinks has been found to raise HDL.

- Cholesterol levels and decrease LDL oxidation
- This may be responsible for the 15 - 35% lower incidence of coronary artery desease in such individuals

→ Mild anaemia:- is common in chronic alcoholics.

:- Body Temprature:-

→ Alcohal is reputed to combat cold.

→ It does produce a sense of warmth due to cutaneous and gastric vasodilation, but heat loss is actually increased in cold surroundings.

→ High doses temprature regulating centre.

:- Respiration:-

Brandy or whiskey are reputed as respiratory stimulants in collapse.

- They irritate buccal and pharyngeal mucosa which may transiently stimulate respiration reflexly.

However, it is better not to depend on this because the direct action of alcohal on respiratory centre is only a depressant one.

GIT

⇒ Dilute alcohal (optimum 10%) put in the stomach by Ryle's tube is a strong stimulant of gastric secretion (Especially of Acid)

⇒ Higher concentration (Above 20%) inhibit gastric secretion cause vomiting mucosal congestion and gasbutis.

Liver

Chronic Alcoholism exposes liver to oxidative stress. and causes cellular necrosis followed by fibrosis.

⇒ Acetaldehyde produced during metabolism of Alcohal Appears to damage the hepatocytes and induce inflammation, especially on chronic ingestion. of large amounts alcohalic cirrhosis.

⇒ Regular Alcohal intake induces microsomal enzyme.

Skeletal Muscle

⇒ Alcohal produces little direct effect.

⇒ Fatigue is allayed by small doses but muscle work is increased or decreased depending on the predominating central effect.

⇒ Weakness and myopathy occurs in chronic Alcoholism.

Kidney

- **Diuresis** Diuresis is often noticed after alcohal intake.
- This is due to water ingested along with drinks as well as alcohal induced inhibition of ADH secretion.
- It does not impair renal function.

Sex

- Aggressive sexual behaviour is due to loss of restraint and inhibition.
- However performance of the sexual act is often impaired
- Chronic Alcoholism can produce impotence testicular Atrophy, Gynaecomastia and infertility in both men and women.

Endocrine Effect

Moderate amounts of Alcohal increase Adr release which can cause hyperglycemia and other sympathetic effects

- However acute intoxication is often associated with hypoglycaemia and depletion of hepatic glycogen because gluconeogenesis is inhibited.
- Glucagon, thus fails to reverse it and glucose must be given to counteract hypoglycaemia.

Pharmacokinetics

- Absorption from intestine is very fast.
- Peak levels are Attained after 30 min.
- Limited first pass metabolism occurs in stomach and liver

→ Absorption of Alcohal from skin of Adults is minimum but may be significant in infants.

→ Alcohal gets distributed widely in the body (Val of distribution 0.7 L/kg) crosses blood brain barrier efficiently: conc. in brain is very near blood conc. It also crosses placenta freely.

→ Alcohal is oxidized in liver to the extent of 98%.

Ethyl Alcohal $\xrightarrow[\text{dehydrogenas}]{\text{Alcohal}}$ Acetaldehyde $\xrightarrow[\text{dehydrogenase}]{\text{Aldehyde}}$ Acetate $\rightarrow CO_2 + H_2O$

→ Excretion of Alcohal occurs through kidney and lungs.

→ concentration in exhaled air is about 0.05% of blood concentration.

÷ Contra Indications ÷

Intake of Alcohal should be Avaided by -

Peptic, Ulcer, hyperacidity and Gastroesophageal reflux patients (Alcohal increases Gastric secretion and relaxes LES)

→ Epileptics - Seizures may be precipitated.

→ Severe liver disease patients.

→ Pregnant women. Growth retardation, low IQ.

÷ Disulfiram ÷

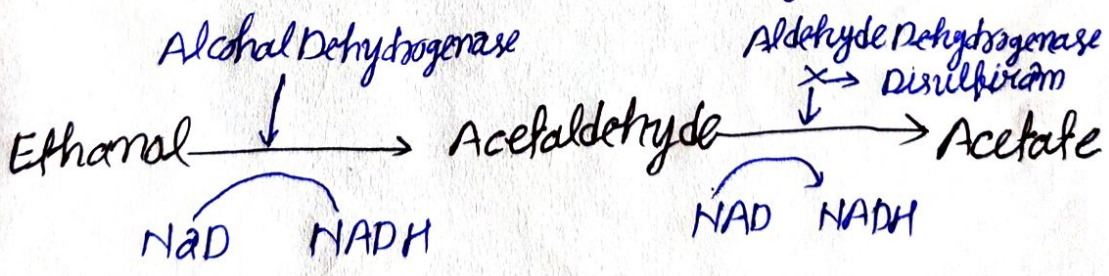
Disulfiram is an aldehyde dehydrogenase inhibitor. It prohibits the activity of Aldehyde dehydrogenase, an enzyme found in the liver in the United states disulfiram is sold under brand name Antabuse.

Purpose

Disulfiram is used as a conditioning treatment for Alcohal dependence. When taken with alcohal, disulfiram causes many unwanted and unpleasant effects and the fear of these is meant to condition the patient to avoid alcohal.

→ Disulfiram by itself is non toxic. if taken with alcohal however, it alters certain steps in the breakdown of Alcohal when alcohal is ingested it is converted first to a chemical called Acetaldehyde. Acetaldehyde is further broken down into acetate, (Aldehyde) In order for Acetaldehyde to be broken down into acetate, Aldehyde dehydrogenase needs to be Active Disulfiram is an Aldehyde dehydrogenase inhibitor. Since disulfiram blocks the activity of Aldehyde dehydrogenase Acetaldehyde can't be broken down and the levels of Acetaldehyde become five to ten times higher than the normal levels. This causes uncomfortable effects that encourage the person to avoid Alcohal.

Disulfiram comes in a 250 and 500 mg tablet.



Side effect:

The most common side effect of disulfiram includes drowsiness and fatigue. Many patients experience metallic or garlic-like after taste but most patients develope tolerance to this effect.