Unit-IV Pharmacology of drugs acting on Central Nervous System.

Neurohumoral transmission in the C.N.S :-

Most cell-to-cell communication in the CNS involves chemical transmission.

Chemical transmission requires several steps-

1. **Transmitter synthesis** - Small molecules like Ach and nor-epinephrine are synthesized in nerve terminals; peptides are synthesized in cell bodies and transported to nerve terminals.

2. **Transmitter Storage** - Synaptic vesicles store neuro-transmitters, often in association with various proteins and frequently with ATP.

3. **Transmitter release** - Release of transmitter occurs by exocytosis. Depolarization results in an influx of Ca^{2+}, which in turn appears to bind to proteins called synaptotagmins.
   - An active zone is established to which vesicles dock and then fuse with scaffoleding proteins on the pre-synaptic membrane. After fusing with the membrane and exocytotic release of their contents, synaptic vesicle proteins are recycled through endocytosis.

4. Transmitter recognition (bind on receptor)

Receptors exist on post-synaptic cells, which recognize the transmitter. Binding of a neurotransmitter to its receptor initiates a signal transduction event.

5. ~~Termi~~ Post synaptic Activity-

After binding with its receptor the neurotransmitter show its activity on the site of action.

- Activity may be — EPSP (Excitatory post synaptic potential)
  IPSP (Inhibitory post synaptic potential)

6. Termination of Action- A variety of mechanism terminate the action of synaptically released transmitter, including hydrolysis (for acetylcholine and Adrenaline).

Classification of Neurotransmitters

A large number of CNS neurotransmitter have been either tentatively or positively identified they may be consider under two main heads.

1. Fast point to point signaling- ↑ excitatory ↓ inhibitatory

(I) - Acetylcholine (↑ excitatory)

(II) Amino acids - (a) Glutamate - (↑)
(b) Glycine (↓)
(c) GABA (↓)
(d) Aspartate ↑

② Slow Diffuse Regulatory Signalling -

(I) Neuropeptides

(a) Substance P
(b) met-enkephaline
(c) Leu-enkephaline
(d) Angiotensin II
(e) Somatostain
(f) Leuteinizing hormone releasing hormone
(g) Calcitonin gene related peptide and others.

(II) Monoamines -

(a) Dopamine.
(b) Nor-adrenaline
(c) Adrenaline
(d) Serotonin.

(III) Acetylchaline (muscarinic effects)

(IV) Histamine

(V) Acetylchaline (Ach)

⇒ GABA (Gamma amino butyric acid) :-

GABA are inhibitory neurotransmitter which are tropically released from local interneurons in the mammalian CNS.

⇒ GABA are present throughout the CNS, including the spinal cord.

⇒ GABA is synthesized from glutamate by the action of enzyme L-glutonic acid-1-decarboxylase (GAD).

⇒ It is further metabolised by GABA transaminase to succinic semi-aldehyde and succinic acid.

Synthesis of GABA –

Glutamine
↓ Glutaminase
Glutomate
↓ Glutomate decarboxylase
GABA

metabolism of GABA –

GABA
↓
Succinic semi-aldehyde
↓ succinic semi-aldehyde decarboxygenase
Succinate

⇒ These are two types of GABA receptors –
(i) $GABA_A$.
(ii) $GABA_B$.

(i) $GABA_A$ receptors –
- These are ionotropic receptors.
- They are located post-synaptically and are linked with chloride ion Channel opening caused hyperpolarization and reduction in the membrane excitability.
- The major isoform of $GABA_A$ receptor in the

brain consist of 5 subunits. namely $2\alpha_1$, two β_2 & one γ_2 sub units.

(ii) $GABA_B$ receptor -

- It is a G-protein coupled receptor
- It's activation decrease formation of a cAMP
- These receptors cause pre & post synaptic inhibition by inhibiting calcium channel opening and increasing K^+ conductance Ca^{+2}
- The competitive antagonist for $GABA_B$ receptor is saclofen which has no clinical use

Glycine

It is an inhibitory neuro-transmitter, enrich in medulla, spinal cord, the lower brain stem & retina.

- It is structurally & functionally similar to $GABA_A$ receptor and is directly linked to chloride ion channel.

Synthesis -

Glutamic acid
↓ glutamic acid decarboxylase (GAD)
↓ γ-aminobutyric acid
↓
Glycine

* Release → exocytosis by Ca^{2+}

Glutamate

Aspartate

(A)

Glutamate are present in high concentration in the brain and are released in a Ca^{2+} dependent manner upon electrical stimulation in vitro.

→ Glutamate has powerful excitatory effect on neurons.

→ Glutamate is non-essential amino acids that do not cross the blood-brain barrier and synthesized from glucose

→ Excitatory synaptic transmission is mediated by glutamate, which is present in very high concentration in excitatory synaptic vesicles.

→ Glutamate is released into synaptic cleft by Ca^{2+}-dependent exocytosis.

→ The released glutamate acts on post-synaptic glutamate receptors and is cleared by glutamate transporters present on surrounding glia (glial cell).

→ In glia, glutamate is converted to glutamine by glutamine synthetase, released from the glia, taken up by the nerve terminal and converted back to glutamate by enzyme glutaminase.

⇒ The high concentration of glutamate in synaptic vesicles is achieved by the vesicular glutamate transporter (VGLUT).

⇒ Dopamine :-

Dopamine plays several important roles in the brain and ~~kidneys~~ body.

⇒ It precursor chemical L-DOPA, which is synthesized in brain & kidney.

⇒ Dopamine is also synthesized in the ~~brain~~ plant and animals.

⇒ In the brain, dopamine functions as a neurotransmitter — a chemical released by neurons to send signals to other nerve cells.

⇒ It show the therapeutic action of the antiparkinsonism drug (levodopa).

⇒ Five dopamine receptors have been identified and fall into two categories: D_1 (D_1 & D_5) and D_2-like (D_2, D_3, D_4).

⇒ All dopamine receptors are metabotropic

⇒ Dopamine generally exerts a slow inhibitory action on CNS neurons.

⇒ This action has been best characterized on dopamine-containing substantia nigra neurons, where D_2-receptor activation opens K^+ channels via the Gi coupling protein.

⇒ Synthesis- Tyrosine
↓ tyrosine hydroxylase
L-DOPA
↓ Dopa decarboxylase.
Dopamine

⇒ Serotonin (5-Hydroxytryptamine) (5-HT) :-

- It is a neurotransmitter in CNS, as a regulator of smooth muscle function in CNS and GIT and as regulator of platelets function.

Synthesis- Tryptophan
↓ tryptophan hydroxylase
5-hydroxy tryptophan
↓ decarboxylase
5-hydroxytryptamin (serotonin)

⇒ 5-HT is stored in specialised cells like entero chromaffin cells and neurons & as co-transmitter together with various peptide hormones like somatostatin, vasoactive intestinal peptides (VIP),.

⇒ Degradation of 5-HT occurs through oxidative deamination by MAO, to 5-hydroxy indole acetaldehyde followed by its oxidation to 5-hydroxy indole acetic acid, which is excreted in urine.

Pharmacological Action-

CNS

- regulation of mood, behaviour, sleep.
- thermoregulation

CVS -

- Contraction of vascular smooth muscle except in skeletal muscle and heart

GIT -

- stimulate peristalsis
- ↓ acid & pepsin

General Anaesthetics

General anaesthetia produce a reversible loss of all pain sensation and consciousness.

⇒ the important features of general anaesthesia-

(i) loss of all sensation especially pain.
(ii) sleep & amnesia (Lack of awareness).
(iii) Immobility & muscle relaxation
(iv) Abstraction of somation and autonomic reflexes.

Stages of Anaesthesia

(I) Stage of Analgesia -

- started from anaesthetic inhalation and lasts upto the loss of consciousness.
- Pain is progressively reduce.
- Patient remain conscious can hear and see.

- amnesia develops by the end of this stage.
- Reflexes and respiration remain normal.

(II) Stage of delirium -

→ From loss of consciousness to begining of regular respiration.
→ Excitement is seen - patient may shout, struggle and hold his breath; muscle tone increase, jaws are tightly closed, breathing is jerky.
→ HR, BP may rise and pupil dilate due to sympathetic stimulation.
→ no any operative procedure carried out during this stage.

(III) Surgical Anaesthesia -

→ This has been divided into 4 planes which may be distinguished as:

Plane 1: → Roving eyeballs.
- This plane ends when eyes become fixed.

Plane 2 - Loss of corneal and laryngeal reflexes.

Plane 3: → Pupil starts dilating and light reflex is lost.

Plane 4: → Intercostal paralysis, shallow abdominal respiration, ~~lags~~ dilated pupil.

→ Muscle tone decrease, BP falls, HR increase with weak pulse.

(IV) Medullary paralysis :-

Cessation (end) of breathing to failure of circulation and death.

- pupil is widely dilated.
- muscles are totally flabby.
- ~~Pulse~~ pulse is thready.
- BP is very low.

* If eyelash reflexes is present and patient is making swallowing movements — stage II has not been reached.
* Loss of response to painful stimulus — stage III has been reached.

Properties of an Ideal Anaesthetics -

(A) For the surgeon, It should provide adequate analgesia, immobility and muscle relaxation.

(B) For the anaesthetist, Its administration should be easy, controllable and versatile.
→ Heart, liver and other organs should not be affected.
→ It should be cheap, stable and easily stored.

(C) For the patient, • It should be pleasant, non-irritating, should not cause nausea or vomiting.
→ Induction and recovery should be fast with no after effects.

Mechanisms of Anaesthesia-

A variety of ligand-gated ion channels, receptors and signal transduction proteins are modulated by general anaesthetics. Direct effect of anaesthetics exists for $GABA_A$ and NMDA receptors and the two-pore K^+ channels.

$GABA_A$ receptor -

Many inhalational anaesthetics, barbiturates, benzodiazepines and propofol potentiate the action of inhibitory transmitter GABA to open Cl^- channels.

General Anaesthetics bind with the inhibitory $GABA_A$ receptors

⇓

GAs. increase the sensitivity of $GABA_A$ receptor to GABA

⇓

Increases the influx of Cl^- through the Cl^- channel

⇓

Hyperpolarization

⇓

Enhancing inhibitory neurotransmission and depressing nervous system activity.

⇒ NMDA receptors - (N-methyl-D-aspartate) -

Ketamine inhibits NMDA receptors by binding to the ~~phen~~ phencyclidine site on the NMDA - receptor protein for anaesthetic actions. Nitrous oxide is potent and selective inhibitors of NMDA-activated currents. It inhibits the influx of Ca^{++} through the calcium channel.

Classification of General Anaesthetic

- Inhalational
  - Gas
    - Nitrous oxide
  - Volatile liquid
    - Ether
    - Halothane
    - Isoflurane
    - Desflurane
    - Sevoflurane
- Intravenous
  - Fast Acting drug
    - Thiopentone Sod.
    - Methohexitone Sod.
    - Propofol
    - Etomidate
  - Slower Acting drugs
    - Benzodiazepines
      - Diazepam
      - Lorazepam
      - Midazolam
    - Dissociative anaesthesia
      - Ketamine
    - Opioid analgesia
      - Fentanyl
      - Remifentanil

Pre- Anaesthetics :-

Pre-anaesthetic medication refers to the use of drugs before anaesthesia to make it more pleasant and safe. About an hour before a planned anaesthesia, some drugs are given this ~~procedure of~~ procedure of administering drug, is called pre-anaesthetic medication.

Aim of pre-anaesthetic medication -

① Reduction of Anxiety and Stress -

Anxiety and stress commonly occurs in the patient before surgical operation.

→ Anxiety stimulates sympathy of adrenal system → tachycardia.

→ Anxiety also produces stress.

② Prevention of Gastroesophageal Reflux (GER):

GER may cause, spilling of the acid gastric content in oesophagus → aspiration, pneumonia.

③ Prevention of Excessive Salivation - Ether produces excess salivation → lung infection.

④ Reduction of the Dose of the General anaesthetics -

⇒ Following drugs ~~are~~ are used as pre-anaesthetics -

① Antiemetics - Ondansetron & Metoclopramide are used to enhancing gastric emptying and reduce vomiting and nausea.

(ii) Neuroleptics - Haloperidol, Chlorpromazine
cause → hypotension, respiratory depression.

(iii) Anticholinergics - Atropin & Hyoscine used

(iv) Sedative-antianxiety drugs - diazepam, or lorazepam

(v) Opioids - Morphine, pethidine

Sedatives and Hypnotics

Sedative - ~~Anti~~ Anxiolytic) agent should reduce anxiety and exert a calming effect.
- Sedative refers to decreased responsiveness to any level of stimulation, is associated with decrease in motor activity (CNS depression.)

Hypnotic - drug should produce drowsiness (insomnia) and encourage the onset and maintenance of a state of sleep.

⇒ Hypnotic effects involve more pronounced depression of the central Nervous system than Sedatives and this can achieved with many drugs in this class simply by increasing the dose.

Sleep:-

Sedative-Hypnotic Drugs

- Benzodiazepines
  - Hypnotic
    - Diazepam
    - Flurazepam
    - Nitrazepam
    - Lorazepam
    - Temazepam
    - Alprazolam
    - Triazolam
  - Antianxiety
    - Diazepam
    - Lorazepam
    - Alprazolam
    - oxazepam
    - Clonazepam
    - Chlordiazepoxide
  - Anticonvulsant
    - Clonazepam
    - Diazepam
    - Lorazepam
    - Clobazam
- Non-benzodiazepines
  - Zopiclone
  - Zolpidem
  - Eszopiclone
  - Zaleplon
  - Etizalam
- other hypnotics
  - Triclofos
  - melatonin
  - Ramelteon
  - Suvorexant
- Barbiturates
  - Long Acting
    - Phenobarbitone
  - Short Acting
    - Butobarbitone
    - Pentobarbitone
  - Ultra-Short acting
    - Thiopentone
    - methohexetone

(I) Barbiturates – It is substituted derivatives of Barburic acid.

⇒ These possess sedative, hypnotic and anticonvulsant sedative action.

Mechanism of Action –

→ Barbiturates act on the channel modulatory site of $GABA_A$ receptor and potentiate the GABA mediated inhibitory effect by increasing

the duration of Cl^- channel opening.
- At high doses, barbiturates directly increase the Cl^- ion conductance and exhibit GABA-mimetic action and not a GABA-facilitatory action.

Pharmacokinetics -

The rate of absorption of barbiturates depends on their lipid salubility.
- They are widely distributed depending on lipid solubility and regional blood flow.
- they are metabolised both phase I and phase II.
- They are excreted through urine but are readily reabsorbed from renal tubules.

Pharmacological Actions:

(1) CNS – Barbiturates produce dose-dependent effects:
sedation → sleep → anaesthesia → coma.

(2) PNS → Barbiturates selectively depress transmission in autonomic ganglia and reduce nicotinic excitation by choline esters.

(3) Respiration – It depress both the respiratory drive and the mechanisms responsible for the rhythmic character of respiration.

(4) CVS → It does not produce major effect on cardiovascular system (heart): Slight decrease in blood pressure and heart rate such as occurs in normal sleep.

(5) - Use

- As hypnotic & sedative they have been superseded by BZDs.
- To treat hyperbilirubinaemia.

Adverse effect -

→ Hangover was common after the use of barbiturates as hypnotic. On repeated use they accumulate in the body - produce tolerance and dependence.
→ Mental confusion, impaired performance and traffic accidents may occur.
→ Rashes, swelling of eyelids, lips etc.

(2) Benzodiazepines :- (BZDs) :-

All benzodiazepines in clinical use have the capacity to promote the binding of the major inhibitory neurotransmitter γ- aminobutyric acid (GABA) to the $GABA_A$ subtype of GABA receptors, which exist as multi-subunit, ligand-gated chloride channels, thereby enhancing the GABA-induced ionic currents through these channels.

Mechanism of Action - same :

Pharmacokinetics -

- only midazolam is given either by IM or IV route.

⇒ All other BZDs are given orally.

⇒ BZDs like diazepam, oxazepam & chlordiazepoxide are more than 90% bound on proteins.

⇒ They have high volume of distribution they cross potential barrier and are to be used continously in prograncy.

⇒ Uses-

- To treat anxiety neuroses
- To treat insomnia
- For pre-anaesthetic medication and induction of anaesthesia.
- As skeletal muscle relaxant.
- Treatment of alcohal withdrawl.

Adverse effect-

- drowsiness, fatigue, tolerance develops slowly.
- depedence is mild.

③ Non-benzodiazepines hypnotics-

- Two type of BZDs receptors have been identified BZ_1 & BZ_2.
- BZ_1 receptors are found throughout the brain and in large concentration in the cerebellum. they are responsible for anti-anxiety, sedative and hypnotic effects.

- BZ_2 receptor are found mainly in the cerebral cortex, hippocampus and spinal cord and are associated with muscle relaxation, anti convulsant action & amnesia.
- These drugs have minimal muscle relaxant & anti convulsant action.

Centrally acting muscle relaxants

These are drugs which reduce skeletal muscle tone by a selective action in the cerebrospinal axis, without altering consciousness. They selectively depress spinal and supraspinal polysynaptic reflexes involved in the regulation of muscle tone without significantly affecting monosynaptically mediated stretch reflex.

- All centrally acting muscle relaxants do have some sedative property -

Classification -

(i) Mephenesin derivatives - Mephenesin, Carisoprodol, Chlorzoxazone.

(ii) Benzodiazepines - Diazepam & others.

(iii) GABA mimetic - Baclofen

(iv) Central α2 agonist - Tizanidine.

① Mephenesin –

It is a centrally acting muscle relaxant. It can be used as an antidot for strychnine poisoning.
- It was the first drug found to cause muscle relaxation in animals without producing unconsciousness and was called internuncial neurone blocking agent because its primary site of action is the spinal internuncial neurons which modulates reflexes maintaining muscle tone.

② Carisoprodol – It has a favourable muscle relaxant; sedative activity ratio with weak analgesic, antipyretic and anti-cholinergic properties.
- It is used in tissue injury, muscle sprains and disorders associated with local muscle spasm.

③ Chlorzoxazone – It is pharmacologically similar to mephenesin, but has a longer duration of action and better oral tolerance.

④ Chlormezanone – It has anti-anxiety and hypnotic action as well, and has been used for tension states associated with increased muscle tone.

⑤ Methocarbamol – It is less sedative and longer acting than mephenesin. Orally it has been used in reflex muscle spasms and

chronic neurological diseases.

⑥ Diazepam – It is the prototype of benzodiazepine (BZDs) which act in the brain on specific BZD receptor enhancing GABAergic transmission. - muscle tone reduced by supraspinal rather than spinal action, but muscle relaxant.

⑦ Baclofen – This is analogue of the inhibitory transmitter GABA acts as a selective $GABA_B$ receptor agonist. The GABA receptors have been divided into —

$GABA_A$ receptor – It is an intrinsic ion channel receptor which increase Cl^- conductance, and is blocked by bicuculline; facilitated by BZDs.

$GABA_B$ receptor – It is a G-protein coupled receptor, which hyperpolarizes neurones by increasing K^+ conductance and altering Ca^{+2} flux.

⑧ Thiocolchicoside – chemically related to colchicine, this muscle relaxant is believed to act as a GABA mimetic and glycinergic drug with additional analgesic action.

⑨ Tizanidine – This clonidine congener has minimal cardiovascular effects, but is a

central α_2 adrenergic agonist which inhibits release of excitatory amino acids in the spinal inter-neurones.

- Tizanidine is absorbed orally, undergoes first pass metabolism and is excreted by kidney.
  $t_{1/2}$ = 2-3 hours.

Centrally Acting Skeletal Muscle Relaxants

- Mephenesin congeners
  - → Carisoprodol
  - → Chlorzoxazone
  - - Chlormezanone
  - → Methocarbamol
- Benzodiazepines
  - → Diazepam, etc.
- GABA mimetic
  - → Baclofen
  - - Thiocolchicoside
- Central α_2 agonist
  - - Tizanidine.

Anti-Epileptics

Epilepsies – These are a group of disorders of the CNS characterized by paroxysmal cerebral dysrhythmia, manifesting as brief episodes (seizures) of loss or disturbance of consciousness, with or without characteristic body movements.

⇒ These episodes are unpredictable and their frequency is highly variable.

⇒ Epilepsy has a focal origin in the brain, manifestations depend on the site of the focus, regions into which the discharges spread and postictal depression of these region.

Classification of seizures -

(I) Generalised seizures - They have a diffuse origin involving both hemispheres of the brain; manifestations and EEG abnormalities are bilateral.

(1) Generalised tonic-clonic seizures (GTCS), - lasts 1-2 min. (major epilepsy)
The usual sequence is aura - cry - unconsciousness. and patient falls - tonic spasm of all body muscles.

(2) Absence seizures - (minor epilepsy) → prevalent in children → lasts about 1/2 min.
⇒ No or only momentary loss of consciousness, no fall, patient apparently freezes and stares in one direction, no muscular component or minimal bilateral jerking or blinking of eyes;

(3) Atonic seizures - (Akinetic epilepsy) -
- Brief loss of consciousness with relaxation of all muscles due to excessive inhibitory discharges.
⇒ Patient may fall.

(4) Myoclonic ~~spasm (Hypsarrhythmia)~~ - seizures -
Shock-like momentary contraction of muscle of a limb or the whole body.

EEG = Electroencephalogram → recording brain activity. - used to

(5) Infantile spasms (Hypsarrhythmia) :-

⇒ Seen in infants.

⇒ Probably not a form of epilepsy.

(II) Partial seizures-

They have an unilateral localized origin in the brain, but may spread to small or large area or to the whole brain.

(1) Simple partial seizures (SPS) :-

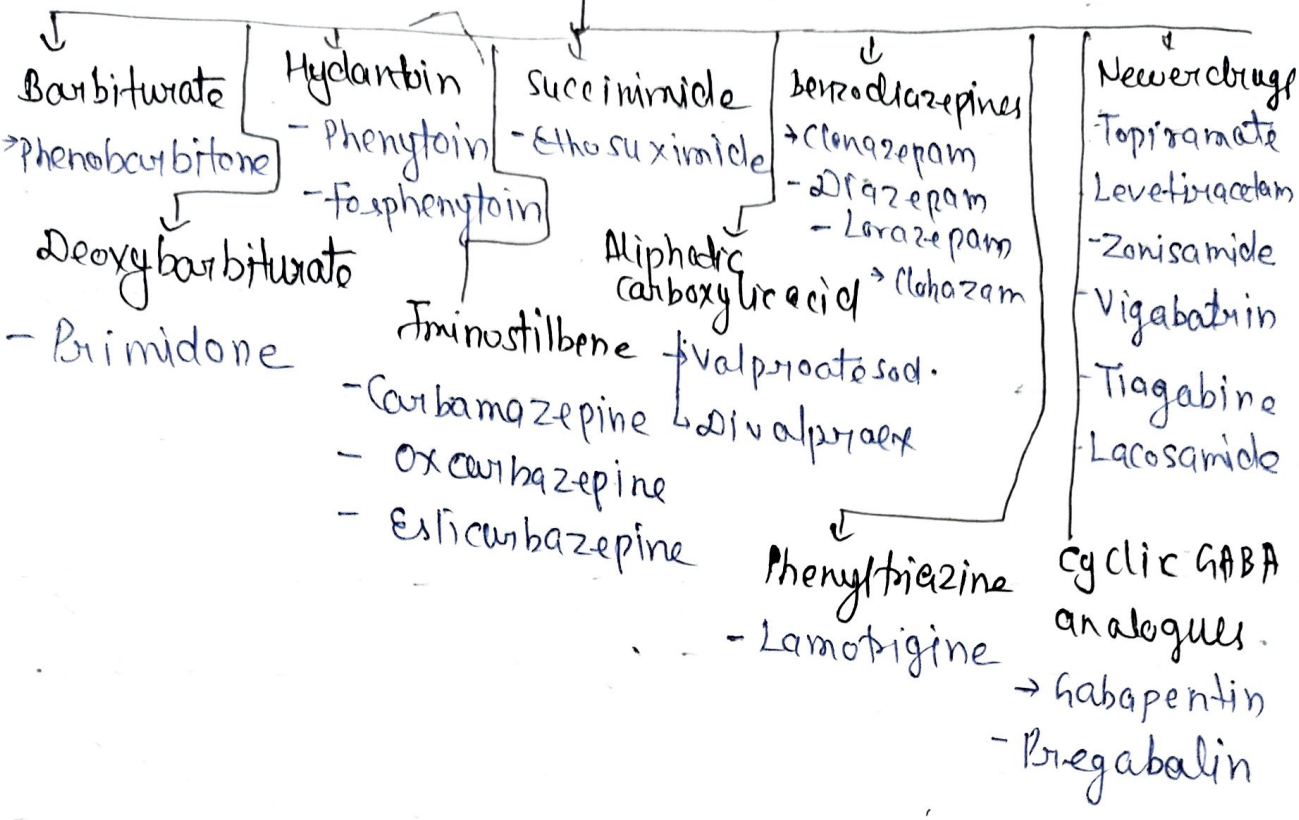
These are sudden onset unilateral clonic jerking of a group of muscles or a limb lasting 30-90 sec,

⇒ The patient remains conscious and aware of the attack.

(2) Complex partial seizures (CPS)

→ Confused behaviour, dream-like state and purposeless movements, or even walking unware, emotional changes. lasting → 1-2 min along with impairment of consciousness.

Antiepileptic drugs



Mechanism :-

Mechanism are classified into two types.

(i) mechanism in Grand mal and Partial seizures

(ii) mechanism in petil mal (absence seizures)

⇒ Mechanism in Grand mal & Partial seizures -

They are further sub-classified into following sub-types -

(a) Inhibition of use-dependent sodium (Na^+) ion channels.

- drug like phenytoin, carbamazepine etc block voltage gated Na^+ channels.

(b) Enhancement of GABAergic action.

- drug like phenobarbital & benzodiazepines

activate GABA$_A$ receptors to facilitate opening of Cl^- channels.

(c) Blockage of NMDA or AMPA receptors.

- drug like - felbamate block NMDA receptors.
- drug like phenobarbital block AMPA receptors

(d) ~~Blockage~~ Blockage of ~~NMDA~~ voltage gated N' type calcium channels.

(e) selective blocking of synaptic vascular protein

(f) By blocking effects of neurotropic factors.

(ii) Mechanism in petil mal (absence seizures) -

- It involves inhibition of T-type calcium channels.
- drugs like ethosuximide inhibit calcium channels

Alcohols and disulfiram

- Alcohols (ethanol) are hydroxy derivatives (-OH) of aliphatic hydrocarbons.
- Pharmacology of alcohol is important for its presense in beverages, alcoholism and for alcohol intoxication, rather than as a medicinal substance.

⇒ Alcohol is manufactured by fermentation of sugars:

$$\text{Sugar} \xrightarrow[\text{Yeast}]{\text{zymase}} \text{starch} \xrightarrow{\text{convertase}} \text{maltose} \xrightarrow{\text{Yeast}} \text{alcohol}$$

$$\underset{\text{(Glucose)}}{C_6H_{12}O_6} \xrightarrow[\text{(in yeast)}]{\text{Zymase}} 2CO_2 + 2\underset{\text{Ethanol}}{C_2H_5OH}$$

Alcoholic Beverages :- (Types)

(A) Malted liquors – obtained by fermentation of germinating cereals; these are unclistilled – alcohol content is low (3–6%)

eg- Beers, stout.

- Now strong bees (upto 10%) are also available.

(B) Wines – Produced by fermentation of natural sugars as present in grapes and others fruits

Eg- Light wines, claret, Cider; alcohol content 9-12%, can not exceed 15%.

(C) Spirits :- These are produced by distillation of the fermented broth;

eg. Rum, Gin, Whiskey, Brandy, Vodka etc.

Through the alcohol content of these beverages can vary from 40-55%, in India for all licenced brands it is standardized to 42.8% v/v or 37% w/v.

Pharmacological Actions :-

① Local actions – Applied to the surface, alcohol is an astringent - precipitates surfaces proteins and ~~hardnets~~ hardens the skin -
- By precipitating bacterial proteins it acts as an antiseptic.
- By evaporation it ~~coo~~ produce cooling.

② CNS – Alcohol is a neuronal depressant.
Alcohol & ether → conscious → anaesthesia → death.
- ~~Ag~~ Any measurable conc. of alcohol produce a measurable slowing of reflexes; driving is dangerous.

③ CVS – The effects of alcohol are dependent on the dose.
- Small doses: produce only cutaneous (face) and gastric vasodilation. Skin is warm and flushed and BP is not affected.
- moderate doses: cause tachycardia and mild rise in BP due to increased muscular activity and Sympathetic stimulation.
- Large dose: cause direct myocardial as well as vasomotor centre depression and there is fall in BP.

④ Blood - Regular intake of small to moderate amount of alcohal (1-2 drinks) has been found to raise HDL- cholesteral level.

⑤ Body temperature - It does produce a sense of warmth due to cutaneous and gastric vasodilation but heat loss is actually increased in cold surrounclings.

⑥ Respiration - Brandy or whiskey are reputed as respiratory stimulants in collapse.

⑦ GIT - Alcohalic beverages have variable effect on gastric secretion depending on the beverage itself and whether the individual likes it.

⑧ ~~Kidney~~.

Pharmacokinetics -

Rate of alcohal absorption from the stomach is dependent on its concentration but is generally quite slow.

- Absorption from intestine is very fast;
- Alcohal gets distibuted widely in the body, cross blood-brain-barrier efficiently
- Metabolism of alcohal follows zero order kinetics.
- Excretion of alcohal occurs through kidney and lungs.

1 drink = 50 ml of spirits = 150 ml of wines = 400 ml of beer.

⇒ side effects of moderate drinking –
Nausea, vomiting, flushing, hangover, traffic accidents.

⇒ Acute alcoholic intoxication – Unawareness, unresponsiveness, hypotension, gastritis, collapse, coma and death.

⇒ Chronic alcoholism – On chronic intake, tolerance develops to subjective and behavioural effects of alcohal.

Disulfiram

It inhibits the enzyme aldehyde dehydrogenase probably after conversion into active metabolites.

⇒ When alcohal is ingested after taking disulfiram, the concentration of acetaldehyde in tissue and blood rises and a number of highly distressing symptoms are produced promptly.

⇒ When alcohal is consumed in the presence of disulfiram, conversion of acetaldehyde to acetic acid is significantly reduced.

⇒ Hence acetaldehyde accumulates to cause effects like facial flushing, nausea, vomiting, dizziness & headache.

⇒ Adverse reactions of disulfiram include skin rashes, metallic taste and abdominal upset. (LOS)