Module Title	Pharmacology of Drug Acting on Central Nervous System
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Learning Outcome of Module-04

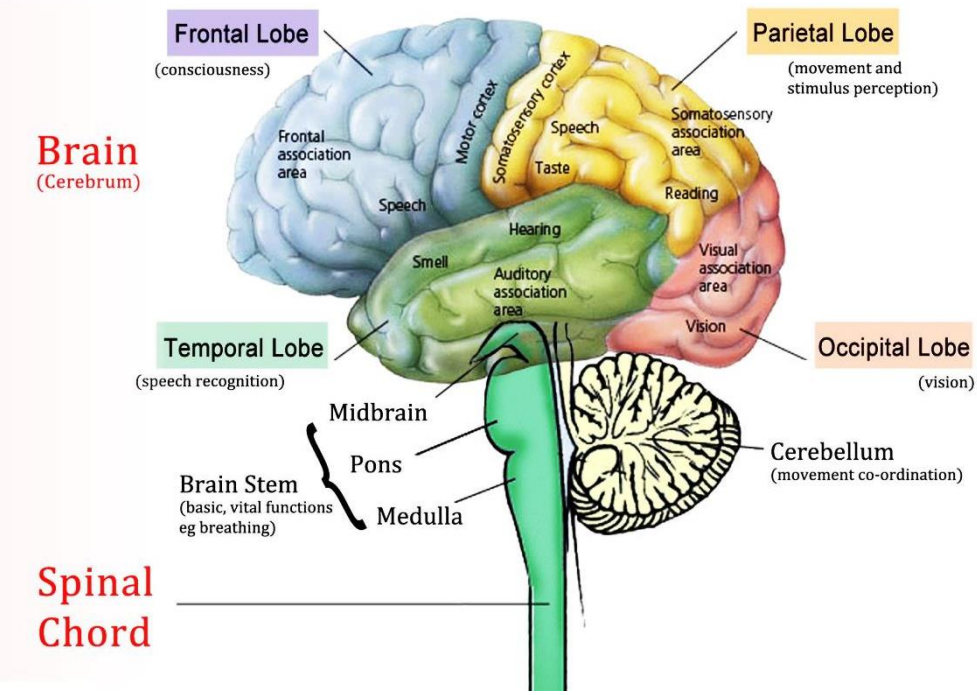
LO	Learning Outcome	Course Outcome Code
LO1	To Understand the importance of various neurotransmitters like GABA, Glutamate, Glycine, serotonin, dopamine.	BP404.4
LO2	To understand the MOA, Pharmacological action, Side effect of General anesthetics and pre-anesthetics.	BP404.4
LO3	To understand the MOA, Pharmacological action, Side effect of Sedatives and hypnotics	BP404.4
LO4	To understand the MOA, Pharmacological action, Side effect of Anti-epileptics, Alchol and Disulfiram	BP404.4
LO5	To Understand the MOA, Pharmacological action, Side effect of Drugs used in myasthenia gravis and glaucoma	BP404.5

Content Table

Topic
Pharmacology of Drugs Acting On Central Nervous System (CNS) • Neurohumoral transmission in the C.N.S. special emphasis on importance of various neurotransmitters like GABA, Glutamate, Glycine, serotonin, dopamine. • General anaesthetics' and pre-anaesthetics. • Sedatives and hypnotics • Centrally acting muscle relaxants • Anti-epileptics • Alcohols and disulfiram. • Drugs used in myasthenia gravis and glaucoma

NEUROHUMORAL TRANSMISSION IN CENTRAL NERVOUS SYSTEM

Neurohumoral transmission refers to the transmission of impulse through synapse and neuro-effector junction by the release of humoral (chemical) substances. The term 'conduction' stands for the passage of an impulse along an axon or muscle fibre.



Neurotransmitters: It is chemical secretions are called neurotransmitters, neuromodulators, neuromediators and neurotropic factors, respectively. It is synthesized in presynaptic neurons and are released into synaptic cleft to rapidly stimulate or inhibit postsynaptic neurons. eg. Ach, dopamine, norepinephrine (epinephrine in reticular formation), 5-hydroxytryptamine, gamma-amino butyric acid, glycine, glutamate, aspartate, endogenous opioids, cholecystokinin and tachykinins, etc.

Neuromodulators: These are released by neurons and astrocytes to produce slower pre-or postsynaptic responses. Neuromodulator generally relates to synaptic plasticity that means long-term changes in synaptic transmission, connectivity and efficacy following pathological damage or following physiological alterations in neuronal activity (as in learning and memory). eg. Carbon dioxide, locally released adenosine, some purines, peptides, sprostaglandins, arachidonic acid metabolites and Nitric oxide.

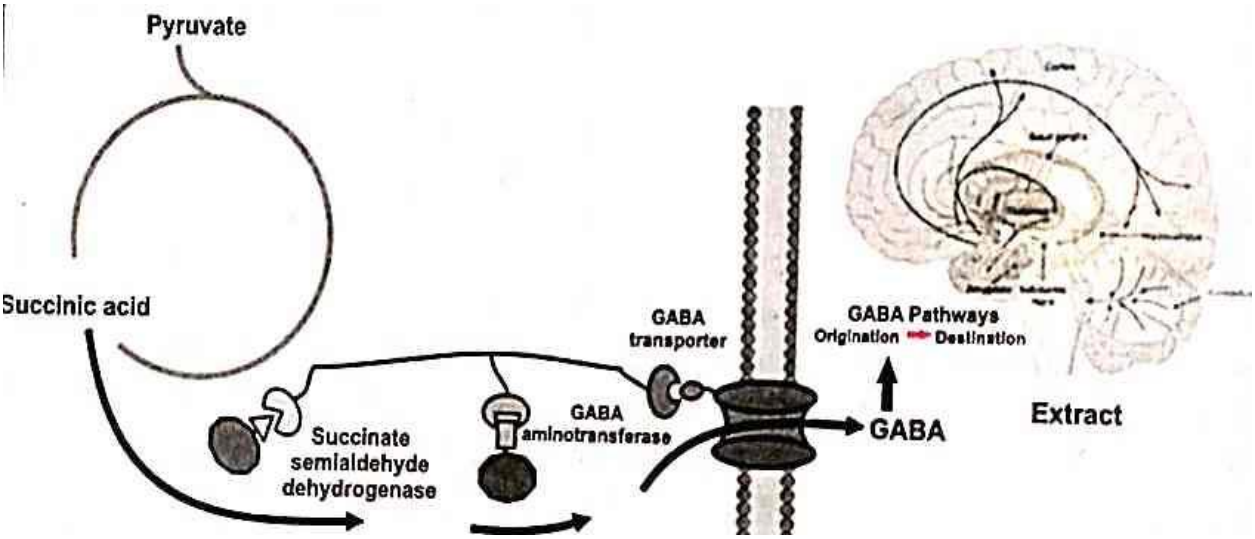
Neuromediators: These are second messengers that play crucial role in elicitation of postsynaptic responses produced by neurotransmitters. eg. CAMP, CGMP and inositol phosphate.

Neurotropic factors: These are mainly released by CNS neurons, astrocytes and microglia and act longer than neuromodulators to regulate the growth and morphology of neurons and control long-term changes in brain (synaptic plasticity, remodeling, phenotype characteristics) mainly by affecting gene transcription by acting through tyrosine kinase- linked receptors. eg. Cytokines, chemokines, growth factors.

GAMMA AMINOBUTYRIC ACID (GABA)

It is the chief inhibitory neurotransmitter in the mammalian central nervous system. Its principal role is reducing neuronal excitability throughout the nervous system. The brain functioning requires a fine-tuning between excitatory and inhibitory neurotransmission, a balance maintained through the regulation and release of glutamate and GABA.

Gamma aminobutyric acid pathway in CNS: Glutamate and GABA (gamma-aminobutyric acid) are the brain's most plentiful neurotransmitters. Since GABA is inhibitory and glutamate is excitatory, both neurotransmitters work together to control many processes, including the brain's overall level of excitation. Many of the drugs of abuse change the balance of glutamate or GABA, exerting tranquilizing or stimulating effects on the brain.



Systematic pathway of GABA Pathway

GABA is the major inhibitory neurotransmitter of the brain, occurring in 30-40% of all synapses (second only to glutamate as a major brain neurotransmitter). It is most highly concentrated in the substantia nigra & globus pallidus nuclei of the basal ganglia, followed by the hypothalamus, the periaqueductal grey matter ("central grey") and the hippocampus.

The GABA concentration in the brain is 200-1000 times greater than that of the monoamines or acetylcholine.

Function of GABA in the Brain:

(1)It has inhibitory effect in the brain.

(ii) GABA-mediated inhibition does not act solely as simple suppression of excitability (Tonic inhibitory input can transform firing pattern).

It inhibitory connections may be organized to provide negative feedback (recurrent inhibition) via networks of neurons.

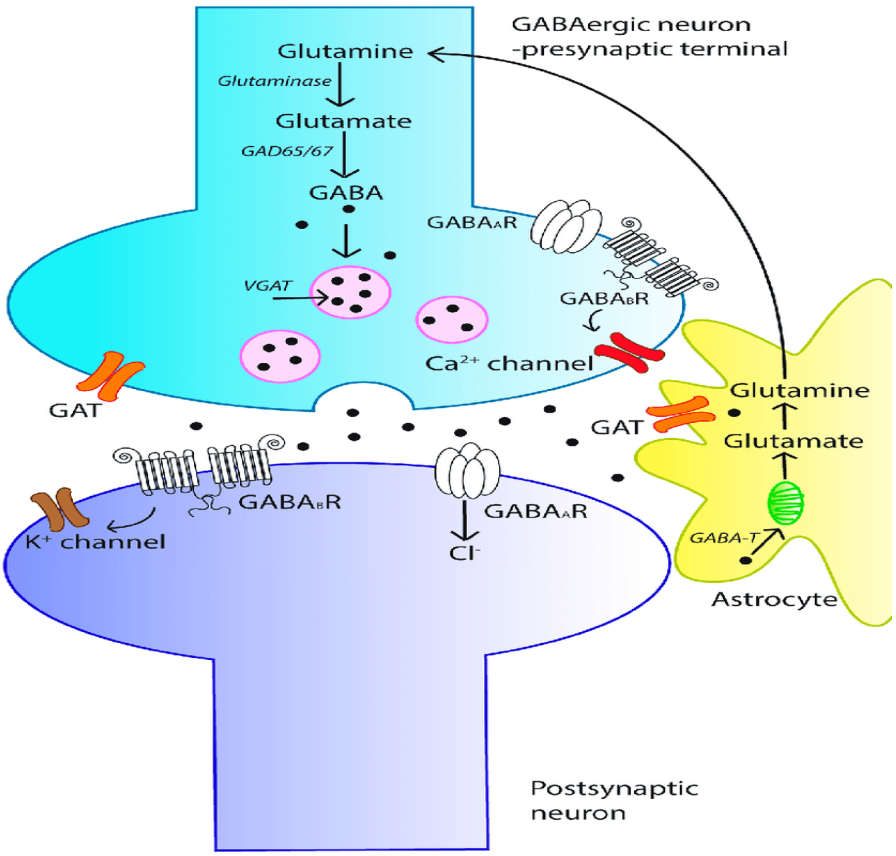
By controlling precise timing of firing in multiple tragets cells inhibitory interneurons may synchronize activity and even enhance the excitatory effect

Synthesis, storage, and release of GABA

Synthesis: Glutamate is actually a precursor for GABA synthesis. The following steps are involved in the synthesis of gamma amino butyric acid (GABA). It is converted into glutamate by an enzyme, glutaminase. It is formed by a-decarboxylation of glutamate. This reaction is catalyzed by a cytosolic enzyme, L-glutamic acid-1-decarboxylase (GAD), which is present almost exclusively in GABAergic neurons. When glutamate is released from glutamatergic synapses, it is taken up by nearby glial cells (usually astrocytes) and converted to glutamine. GABAergic neurons then take up glutamine and convert it to GABA. GAD is not present in neurons using glutamate as transmitter or in glia. It requires pyridoxyl phosphate (a form of vitamin B6) as a coenzyme.

Storage & release: Synthesized GABA is taken up into vesicles where it is stored and it is released into the synaptic cleft by exocytosis. After its release, GABA is taken up into presynaptic terminal via GABA transporters and repackaged into vesicles for subsequent use. It is also taken up into the glia via GABA transporters. In glia, GABA is converted to glutamate by a mitochondrial enzyme, GABA transaminase (GABA-T). Another enzyme, glutamine synthetase, converts glutamate into glutamine, which is then transported into the neighboring nerve terminals where it is processed to synthesize glutamate. Entry of Ca^{2+} ions inside the neurons. The action potential goes toward upwards. The synaptic vesicle move toward membrane side and exocitic explosion occurs. Then release the GABA neurotrosmitic, act on post sympatic membrane.

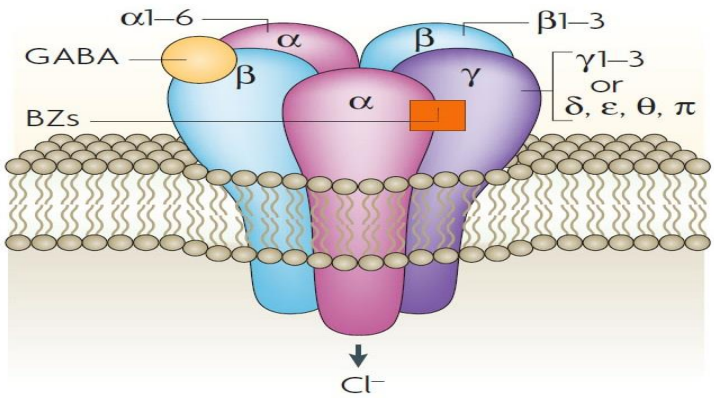
Distribution: GABA is found in high concentrations in the brain and spinal cord but is absent in peripheral nerves or peripheral tissues. Unlike glutamate, GABA is not an essential metabolite, and it is not incorporated into a protein.



Synthesis, storage, releases and termination of gamma intorcacid

For example, GABA is used as an inhibitory neurotransmitter by the Pericrise cells in the cerebellum. Alteration of GABAergic circuits has been implicated in neurological and Psychiatric disorders like Hunting-ton's choret, Parkinson's disease, senile dements, Alzheimer's disease, and schizophrenia.

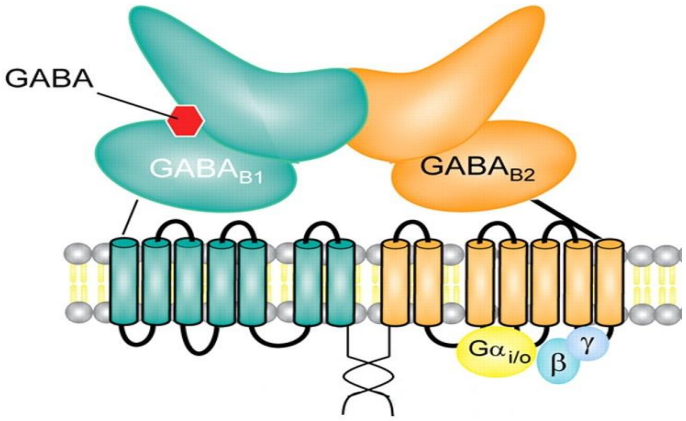
GABA Receptors: GABA modulates the inhibitory excizatory balance necessary for proper brain function in mature brains. There are two main types of GABA receptors, the ionotropic GABA receptor and the metabotropic GABA, receptor.



GABAa, Receptor. Fast ionotropic GABA, receptors are lizand-zated chloride ion channels comprised of a, B, Y and 6 subunits in a heteropentameric structure GABA, receptors with unique subunit compositions are distributed differentially in the mature bran Receptors containing a1 and 2 subunits localize in the synaptic cleft whereas receptors containing 4

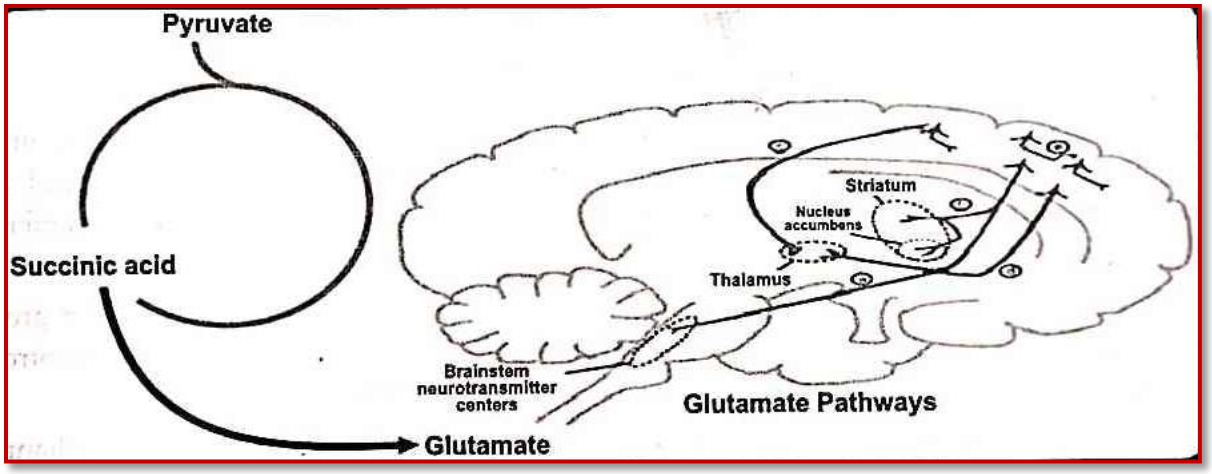
a5, a6, and 6 subunits localize extrasynaptically/perisynaptically. Extrasynaptic GABA, receptors are high-affinity GABA receptors implicated in tonic inhibition, whereas synaptic GABAA receptors are those involved in fast, phasic inhibition. When GABA binds to these receptors at the postsynaptic site, the ion channel opens and chloride (CH-) diffuses into the cell along its concentration gradient, thus hyperpolarizing the posi-synaptic mature neuron

GABAb, Receptors: It Regulate through G proteins couple receptor and are composed of two subunits, GABAnand GABAY GABAreceptors are responsible for the later and slower component of inhibitory transmission GABA, receptors are found both pre and post synaptically. Activation of these receptors is coupled to K and/or Cz2. channels via a G- protein mediated pathway or in a membrane delírnited manner.



GLUTAMATE NEUROTRANSMITTER (GLU)

Glutamate neurons that are begin in the frontal cortex and connect and project in to brainstem, midbrain, and limbic areas. In this way, neurons originating in the more modern frontal neocortex may penetrate into deeper areas of the brain to exert control over midbrain centers that are primarily responsible for creating and projecting neurotransmitter activity that are ultimately responsible for drive and affective initiation. These primary GLU neurons may project further to deeper brain areas such as the amygdala and nucleus accumbens creating appropriate perceptual balance versus psychosis.



Systematic pathway of Glutamate

There are five glutamate pathways have been identified.

(a) The cortical brainstem glutamate projection is a descending pathway that projects from cortical pyramidal neurons in the prefrontal cortex to brainstorm neurotransmitter centers (raphe, locus coeruleus, ventral tegmental area, substantia nigra) and regulates artist neurotransmitter release.

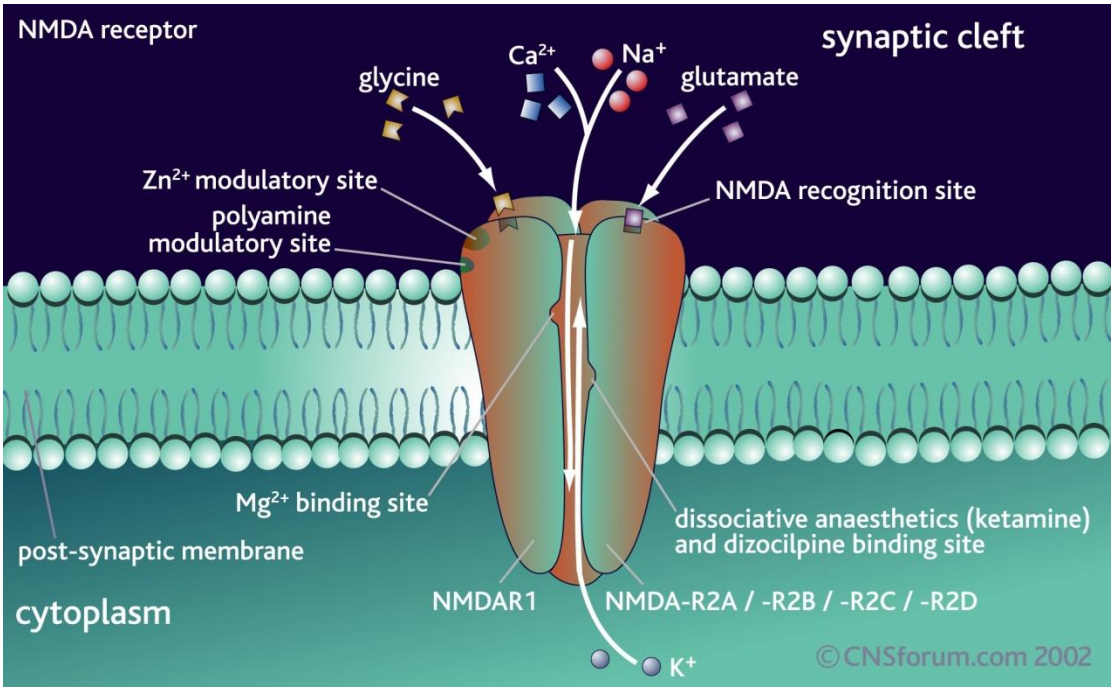
(b) Another descending glutamatergic pathway projects from the prefrontal cortex to the striatum (corticostriatal glutamate pathway) and to the nucleus accumbens (cortico- accumbens glutamate pathway), and constitutes the “corticostriatal" portion of cortico- striatal-thalamic loops.

(c) Thalamocortical glutamate pathways are pathways that ascend from the thalamus and innervate pyramidal neurons in the cortex.

(d) Corticothalamic glutamate pathways descend from the prefrontal cortex to the thalamus.

(e) Intracortical pyramidal neurons communicate with each other via the neurotransmitter glutamate. These pathways are known cortico-cortical glutamatergic pathways. Three of the five pathways project from the frontal cortex and penetrate into deeper brain areas where they exert control over the neuroanatomic structures residing there.

Glutamate receptor: There are several types of ionotropic glutamate receptors have been identified. Three of these are ligand-gated ion channels called NMDA receptors, AMPA receptors, and kainate receptors. These glutamate receptors are named after the agonists that activate them: NMDA (N-methyl-D-aspartate), AMPA (a-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate), and kainic acid.



NMDA and AMPA/kainate receptors. (A) NMDA receptors contain binding sites for glutamate and the co-activator glycine, as well as an Mg^{2+}-binding site in the pore of the channel. At hyperpolarized potentials, the electrical driving force on Mg^{2+} drives.

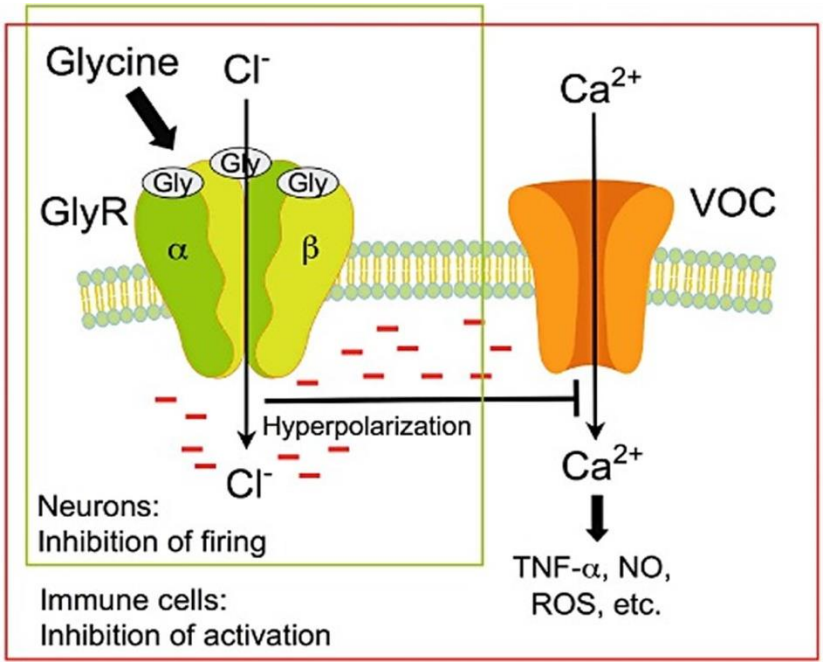
All of the ionotropic glutamate receptors are nonselective cation channels, allowing the passage of Na+ and K+, and in some cases small amounts of Ca2+. Like nACh receptors,the postsynaptic currents produced have a reversal potential close to 0 mV; hence AMPA, kainate and NMDA receptor activation always produces excitatory postsynaptic responses. And, like other ligand-gated channel receptors, AMPA/kainate and NMDA receptors are formed from the association of several protein subunits that can combine in many ways to produce a large number of receptor isoforms. While some glutamatergic synapses have only AMPA or only NMDA receptors, most have both AMPA and NMDA receptors. An antagonist of NMDA receptors, APV (2-amino-5-phosphono-valerate), is often used to differentiate between the two receptor types.

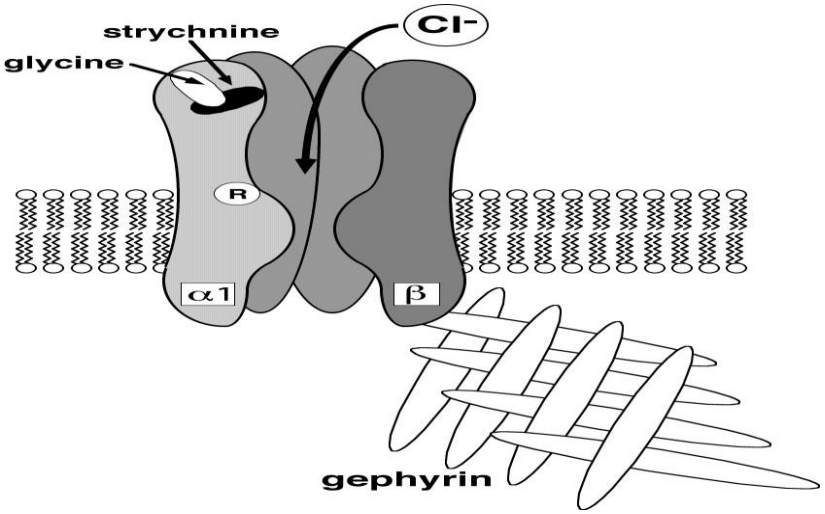
GLYCINE

Glycine is an important component and precursor for many macromolecules in the cells. Binding of glycine to the glycine receptor (a ligand-gated chloride channel) The chloride lens influx, membrane hyperpolarization, and thereby creating an inhibitory post-synaptic potential. In other hand, glycine also acts as a co-agonist, along with glutamate, facilitating an excitatory potential at the glutaminergic N-methyl-D-aspartic acid (NMDA) receptors. For example, involved in the generation of reflex responses, in the processing of sensorial inputs and in the sensation of pain.

The alkaloid strychnine is a potent competitive inhibitor of the glycine receptor acting already at micromolar concentrations. The neuronal glycine receptor is a pentamer presumably being composed of two a and three ß subunits. There are four different a subunits (al to a4) but only one ß subunit, encoded by separate genes. The scaffolding protein gephyrin binds to the ß subunits and connects the glycine receptor with filaments of the submembraneous cytoskeleton, mediating, among others, clustering of the receptor. In addition to its function an inhibitory neurotransmitter, glycine facilitates neurotransmission mediated by glutamate, the major excitatory neurotransmitter in the CNS. The NMDA (glutamate) receptor does not only have a specific recognition site for glutamate but also a second one for glycine. To activate the receptor, both recognition sites need to be occupied. The specific binding site for glycine within the NMDA receptor cannot be blocked by strychnine, and an impaired function of NMDA receptors has been proposed to contribute to psychiatric disorders.

Both glycine and GABAa receptors are anchored to the postsynaptic cytoskeleton by the protein gephyrin. Down regulation of this protein can affect inhibitory neurotransmission in the nervous system, resulting in neurons that are hyperexcitable, which can lead to disease states. For example, patients with temporal lobe epilepsy have abnormally low levels of gephyrin in their temporal lobes. Glycine receptors are mainly located in the spinal cord and brainstem

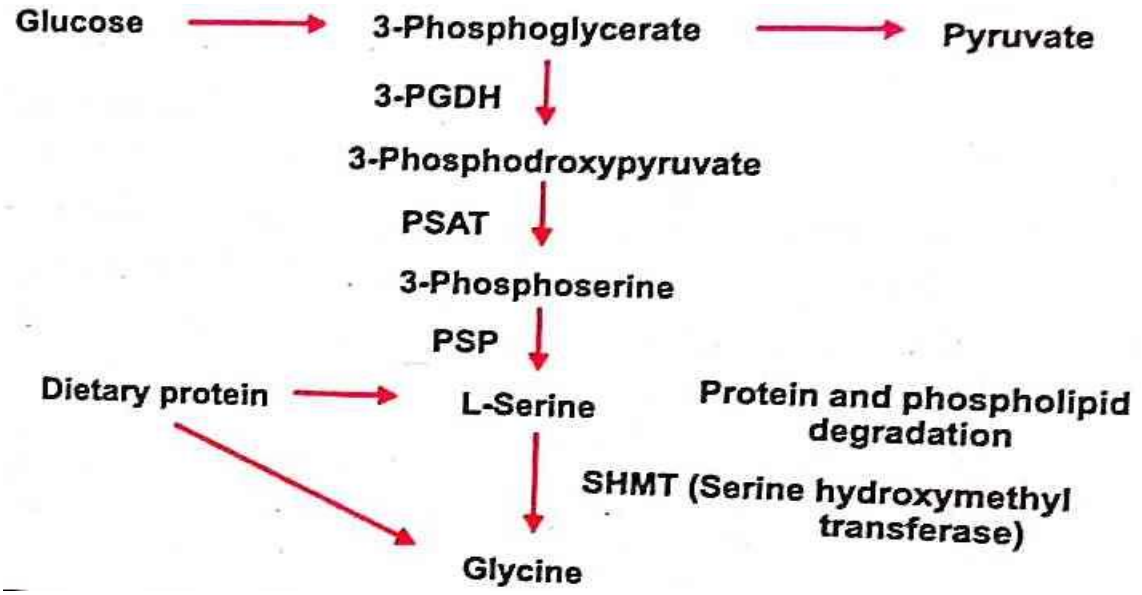




A systematic diagram of Glycine receptor

Synthesis: In the nerve terminal, serine is formed from an intermediate (3- phosphoglycerate) produced by glycolysis of glucose. Glycine is formed from serine by an enzyme, serine transhydroxymethylase. This reaction is folate-dependent.

L-Serine is classified as a nutritionally non-essential amino acid. While the main source of essential amino acids is from the diet, non-essential amino acids are normally synthesize by humans and other mammals from common intermediates. L-serine is biosynthesized from a glycolytic intermediate, 3-phosphoglycerate (3-PG), in a three-step process involving the enzymes: 3-phosphoglycerate dehydrogenase (3-PGDH), phosphoserine aminotransferase (PSAT), and phosphoserine phosphatase (PSP).



Synthesis of Glycine

Storage & release: After its release, glycine is taken up by neurons by an active sodium-dependent mechanism involving specific membrane transporters.

Distribution: Glycine is found in all body fluids and tissue proteins in substantial amounts.

It is not an essential amino acid, but it is an intermediate in the metabolism of proteins, peptides, and bile salts. It is also a neurotransmitter in the CNS.

FUNCTION OF GLYCINE

a. Glycine is known to attenuate the increase in fatty acids in rats fed on a high sucrose diet.

b. Inhibitory neurotransmitter in the adult central nervous system (preferentially in the brain stem and spinal cord).

c. Cytoprotective agent in against ischaemia-reperfusion injury. Glycine has anti- inflammatory effects during ischemia, injury, and transplantation.

d. Glycine subjectively and objectively improved sleep quality in humans who suffered from repeated sleep complaints.

DOPAMINERGIC PATHWAYS

Dopamine is a catecholamine neurotransmitter found in neurons of both the central and peripheral nervous systems. Dopamine interacts with specific membrane receptors to produce its effects.

Dopaminergic pathways: A dopaminergic pathway (dopaminergic projections) is composed of neurons that project or send their axons to distant regions of the brain. These neurons primarily use dopamine for neural transmission (communication) and are therefore called "dopamine" neurons. So specifically, the neurons that make up the dopaminergic pathway start around the brain stem, and run a continuous line of dopamine neurons all the way to the frontal lobe.

There are 4 main dopamine pathways in the brain: the Mesocorticolimbic projection, which is the combination of

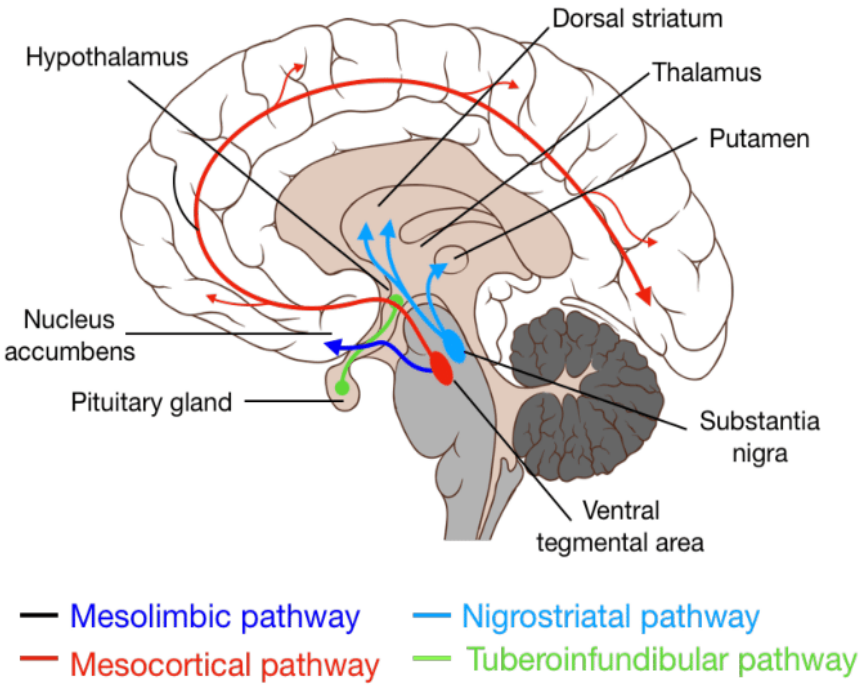
1. The mesolimbic: The mesolimbic DA system is composed of neurons located in the ventral tegmental area (VTA) that project to limbic structures including the nucleus accumbens located into the ventral part of the striatum (VS), the basolateral amygdala and the hippocampus

2. The mesocortical pathways: Finally, the DA mesocortical system is composed of neurons located into the VTA that project to cortical and cerebellar areas including the prefrontal cortex

(PFC), an area that plays a pivotal role in mediating cognitive functions (such as short term memory), attention, and executive functions (such as abstract reasoning and planning)

3. The Nigrostriatal pathway: The nigrostriatal system is composed of DA neurons located in the substantia nigra compacta that project into the dorsal striatum. This system is mainly involved in motor control.

4. The Tuberoinfundibular pathway: The tuberoinfundibular pathway starts down at the arcuate nucleus of the hypothalamus and then runs up to the median eminence of the hypothalamus. Dopamine released at the tuberoinfundibular pathway regulates the secretion of prolactin from the anterior pituitary gland. Mesolimbic system involving the VS is thought crucial for motivation and reward seeking while the DA system involving basolateral amygdala and hippocampus is implicated in long-term memory and emotion.



Schematic drawing of dopaminergic pathways

FUNCTION OF DOPAMINE

a) It has important roles in cardiovascular regulation through its effects on blood vessels and its renal actions, although its central role in blood pressure control remains unresolved.

b) Dopamine acts as an intrarenal natriuretic hormone and that intrarenal dopamine formation is defective in essential hypertension is of particular interest. This has led to the search for drugs which selectively stimulate peripheral D1 receptors to treat hypertension and congestive cardiac failure.

SYNTHESIS, STORAGE, RELEASE, AND TERMINATION OF DOPAMINE

Synthesis: Tyrosine (hydroxy-phenylalanine) is present in all food products and can be synthesized from phenylalanine. It enters the neuron by active transport. The tyrosine is converted into dihydroxyphenylalanine (DOPA) by the tyrosine hydroxylase enzyme. This enzyme is rate-limiting for the synthesis of all three catecholamines. The DOPA is converted to dopamine in the cytoplasm by the enzyme aromatic L-amino acid decarboxylase (DOPA-decarboxylase).

Storage: Dopamine is then actively transported into the storage vesicles by the vesicular transport mechanism. In the dopaminergic neuron, dopamine remains unchanged in the storage vesicles and is ready for release by exocytosis.

Release: Dopamine released into the synaptic cleft is actively transported back into the neuronal terminal. This process is called reuptake-1 and is the most important mechanism by which dopamine and other catecholamines are removed from the synaptic cleft. Some of the dopamine entering the neuronal terminal (about 50%) is transported into the vesicles for storage and release.

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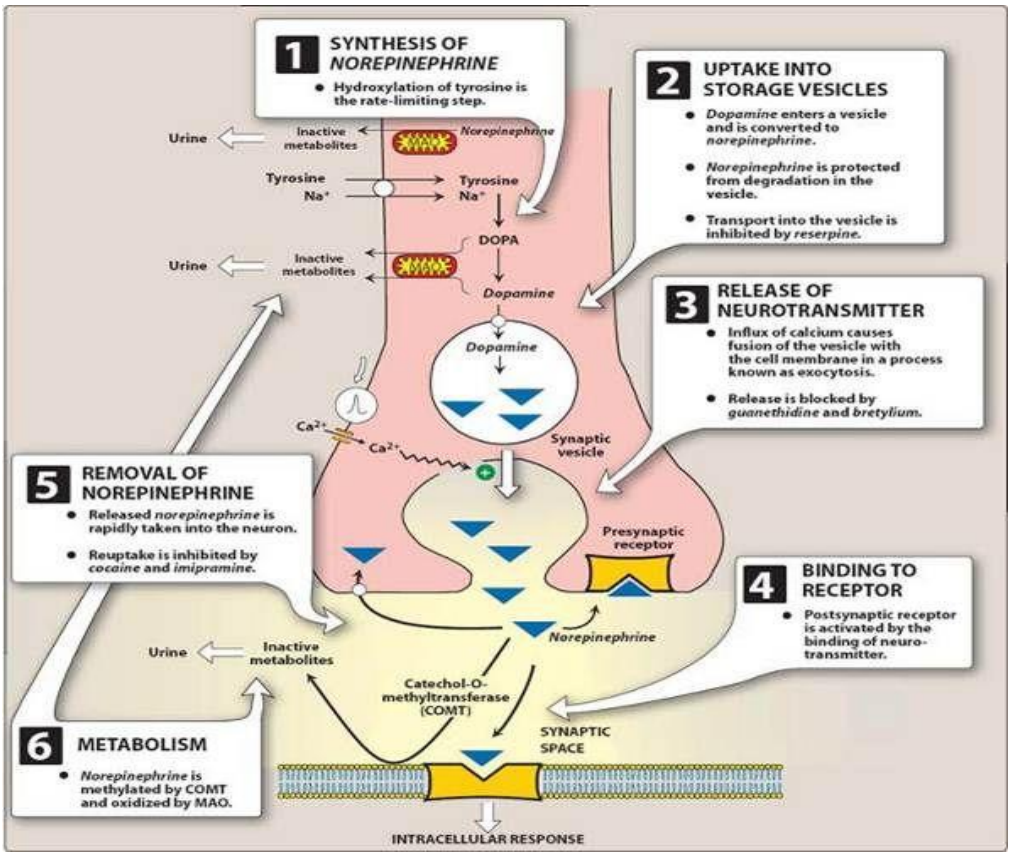


Steps involved in the synthesis and release of dopamine.

Termination: The dopamine that enters the neuronal terminal is destroyed by a mitochondrial enzyme, monoam-ine oxidase (MAO). The remaining dopamine in the synaptic cleft diffuses into the circulation and is destroyed in the liver by COMT and MAO. The end products of metabolism of catecholamine are organic acids and alcohols, which are excreted in urine.

COMT = catechol-O-methyltransferase. Monoamine oxidase.

Dopamine receptor: There are five subtypes of dopamine receptors, D1, D2, D3, D4, and D5, are members of the large G-protein coupled receptor super family. The dopamine receptor subtypes are divided into two major subclasses: types 1 and 5 are similar in structure and drug sensitivity, and these two receptors are referred to as the "Dl-like" group or class of receptors. Dopamine receptor types 2, 3, and 4 are also similar in structure and are, therefore, grouped together as the "D2like" group.

Receptors	Location	Type	Mechanism	Function
D1	Olfactory bulb Nucleus accumbens Striatum Amygdala Hippocampus Frontal cortex Substantia nigra Hypothalamus	Gs-coupled	Enhanced intracellular cAMP through activated adenylate cyclase	Attention Learning Locomotion Sleep Impulse control Regulation of renal function Memory
D5	Hypothalamus Substantia nigra Cortex	Gs-coupled	Adenylate cyclase	Motor Learning Cognition Decision Making Renin Secretion
D2	VTA Olfactory bulb Striatum Cerebral cortex	Gi-coupled	Increased level of cAMP intracellular by activating adenylate cyclase	Reproductive behavior Locomotion Sleep Attention
D3	Cortex Islands of Calleja Striatum	Gi-coupled		Locomotion Regulation of food intake Impulse control Cognition
D4	Hypothalamus Amygdala Frontal cortex Nucleus accumbens	1- Gi-coupled		Attention Impulse control Reproductive behavior

Dopamine receptors are typically couple to Gs and G; mediated transduction systems. The ultimate effect of D1-like activation (D1 and D5) can be excitation (via opening of sodium channels) or inhibition (via opening of potassium channels); the ultimate effect of D2-like activation (D2, D3, and D4) is usually inhibition of the target neuron. The effect of dopamine on

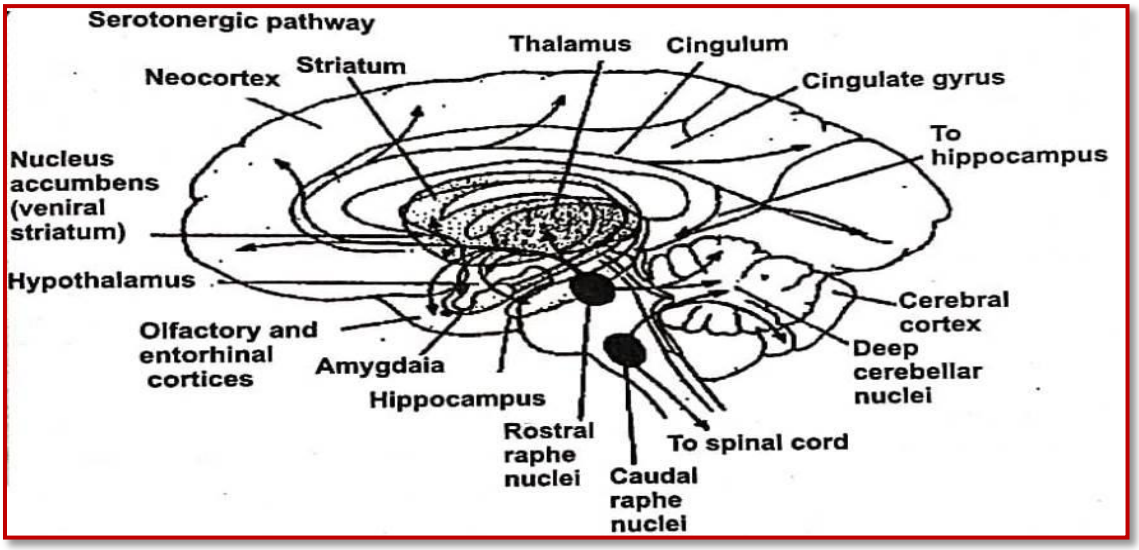
a target neuron depends on which types of receptors are present on the membrane of that neuron and on the internal responses of that neuron to the second messenger CAMP. D1 receptors are the most numerous dopamine receptors in the human nervous system and D2 receptors are the second most abundant receptors. D3, D4, and D5 receptors are present at significantly lower levels.D1 and D5 receptors mostly involved in post synaptic inhibition. D2, D3, and D4 receptors are involved in both pre-and postsynaptic inhibition. D2 receptors regulates mood, emotional stability in the limbic system and movement control in the basal ganglia.

SEROTONIN (5-HYDROXYTRYPTAMINE, 5-HT)

Serotonin was isolated from the blood serum as a substance causing powerful smooth muscle contraction. Only later was it demonstrated to be tryptamine with a hydroxyl group the 5-position. Only 1-2% of the serotonin in the body is in the brain, insofar as serotonin is widely distributed in platelets, mast cells, etc. But there is no equilibration between body serotonin and brain serotonin the serotonin in the brain is independently synthesized from tryptophan transported across the blood-brain barrier.

Serotonin pathways: Serotonin neurotransmitter neurons are located in the raphe nuclei.

The caudal (closer to the "tail") nucleus projects are largely to the medulla and spinal cord for the regulation of pain perception. The rostral (closer to the "beak") nucleus projects are extensively to the limbic structures and the cerebral cortex. In the limbic system, especially the projections are co-localized with norepinephrine receptors and the two transmitters seem to work in conjunction in the regulation of arousal.



A systematic pathway of serotonergic pathways

Serotonergic neurons innervate, these pathways are implicated in many functions, as listed above. The caudal serotonergic nuclei heavily innervate the spinal cord, medulla and cerebellum. In general, manipulation of the caudal nuclei (e.g. pharmacological, lesion, receptor knockout) that results in decreased activity decreases movement, while manipulations to increase activity cause an increase in motor activity. Serotonin is also implicated in sensory processing, as sensory stimulation causes an increase in extracellular serotonin in the neocortex. Serotonin pathways are thought to modulate eating, both the amount as well as the motor processes associated with eating. The serotonergic projections into the hypothalamus are thought to be particularly relevant, and an increase in serotonergic signaling is through to generally decrease food consumption (evidenced by fenfluramine, however receptor subtypes might make this more nuanced. Serotonin pathways projecting into the limbic forebrain are also involved in emotional processing, with decreased serotonergic activity resulting in decreased cognition and an emotional bias towards negative stimuli. The function of serotonin in mood is more nuanced, with some evidence pointing towards increased levels leading to depression, fatigue and sickness behavior, and other evidence point to the opposite.

SYNTHESIS, STORAGE, RELEASE AND TERMINATION OF SEROTONIN

Synthesis: Serotonin (5-hydroxytryptamine) synthesis is a 2-step process, the first step of which requires the enzyme tryptophan hydroxylase with oxygen, iron and THB as co- factors. Neither the enzyme nor the co-factors are rate-limiting for either step of these reactions virtually all brain tryptophan is converted to serotonin. Serotonin is also synthesized in the pineal gland as a precursor for the subsequent enzymatic formation of the pineal hormone melatonin (N-acetyl-5-methoxytryptamine).

Storage and release: Serotonin is principally found stored in three main cell types - i) serotonergic neurons in the CNS and in the intestinal myenteric plexus, ii) enterochromaffin cells in the mucosa of the gastrointestinal tract, and iii) in blood platelets. Serotonergic neurons and enterochromaffin cells can synthesize serotonin from its precursor amino acid L-tryptophan, whereas platelets rely upon uptake of serotonin for their stores. Likewise, serotonergic neurons also have the capacity for amine uptake via serotonin transporters.

Termination: Metabolism of serotonin is carried out primarily by the outer mitochondrial membrane enzyme monoamine oxidase (MAO), which occurs as two molecular subtypes called MAO-A and MAO-B. Both subtypes have a widespread occurrence in the brain and in peripheral

tissues, although they do show some differences, including species-related variations, with respect to the extent of their presence in certain tissues and cell types.

Serotonin receptor: The classification scheme proposes 7 subfamilies of 5-HT receptors. The main receptors and their subtypes, e.g., 5-HT; (5-HT1a, 5-HT1B, 5-HTD, 5-HTE and 5-HTP), 5-HT2 (5-HT2A, 5-HT2B and 5-HT2c), 5-HT3, 5-HT4, 5-HT5 (5-HT5A, 5-HT5B), 5-HT6 and 5-HT, have been identified.

Family	Type	Mechanism	Potential
5-HT_1	G-protein coupled.	Decreasing cellular levels of cAMP.	Inhibitory
5-HT_2	G protein coupled.	Increasing cellular levels of IP_3 and DAG.	Excitatory
5-HT_3	Ligand-gated Na^+ and K^+ cation channel.	Depolarizing plasma membrane.	Excitatory
5-HT_4	G-protein coupled.	Increasing cellular levels of cAMP.	Excitatory
5-HT_5	G-protein coupled.	Decreasing cellular levels of cAMP.	Inhibitory
5-HT_6	G-protein coupled.	Increasing cellular levels of cAMP.	Excitatory
5-HT_7	G-protein coupled.	Increasing cellular levels of cAMP.	Excitatory

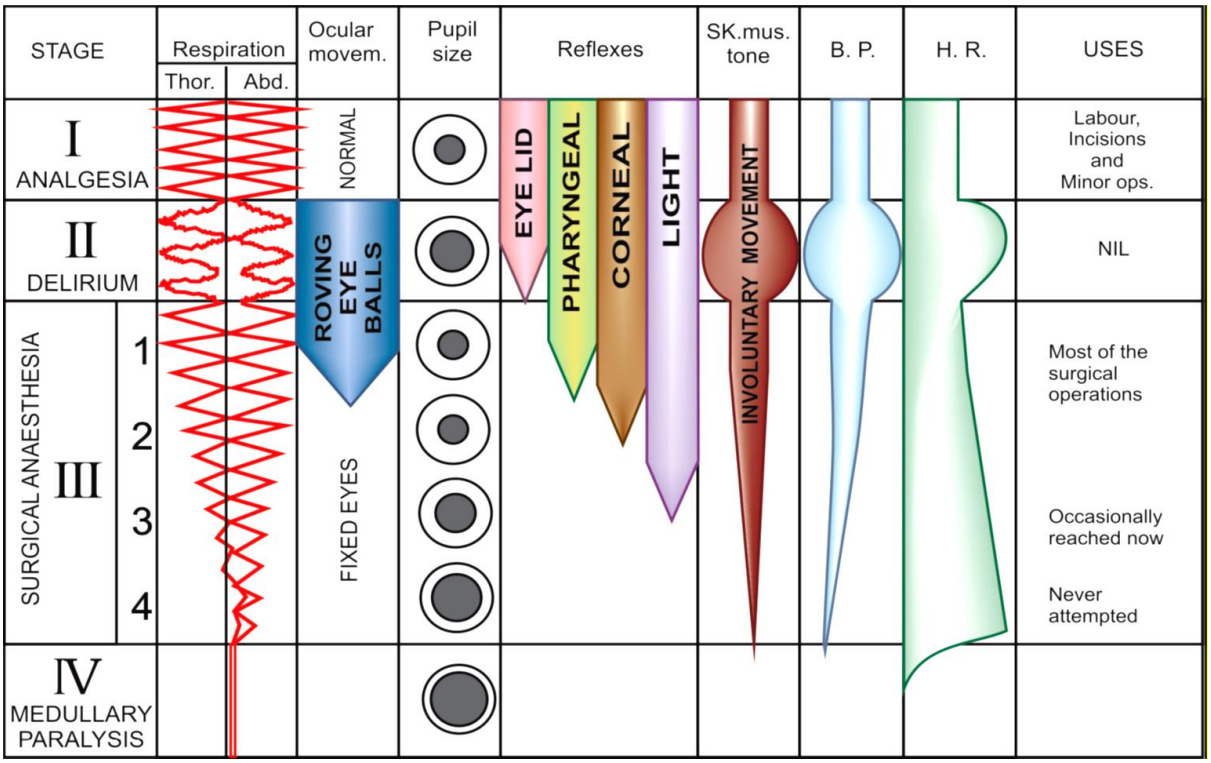
GENERAL ANESTHETICS

Definition: General anesthesia is the induction of a state of unconsciousness with the absence of pain sensation over the entire body, through the administration of anesthetic drugs. It is used during certain medical and surgical procedures. General anesthesia has many purposes including:

- Pain relief (analgesia)
- Blocking memory of the procedure (amnesia)
- Producing unconsciousness
- Inhibiting normal body reflexes to make surgery safe and easier to perform
- Relaxing the muscles of the body

"General anesthetics are agent which induces reversible loss of all sensation and consciousness".

Signs and stages of anesthesia: The signs and stages of anesthesia originate mainly from observations of the effects of diethyl enter, which has a slow onset of central action due to its high solubility in blood. Many of the signs refer to the effects anesthetic agents on respiration, reflex activity, and muscle tone. Traditionally, anesthetic effects are divided into 4 stages of increasing depth of CNS depression



STAGE OF ANESTHESIA

STAGE OF ANALGESIA

I. Stage of analgesia: Starts from anesthetic inhalation and lasts up to the loss of consciousness. Pain is slowly decreased but patient remains conscious and amnesia appear at the end. Respiration is normal during this stage.

II. Stage of excitement: During this stage, the patient often appears to be delirious and excited but definitely is amnesic. Consciousness during this stage is fully lost but patient may appear excited (muscle tone increases). Heart rate and BP may rise and pupils may dilate due to sympathetic stimulation.

III. Stage of surgical anesthesia: Starts from regular respiration to cessation of breathing. It basically involves Roving eyeballs and fixed at end, loss of corneal reflexes, and pupil starts dilating (light reflex lost). Four planes of stage III have been described in terms of changes in as.

Plane 1 Movement of eyeballs. In the last of this eyes become fixed.

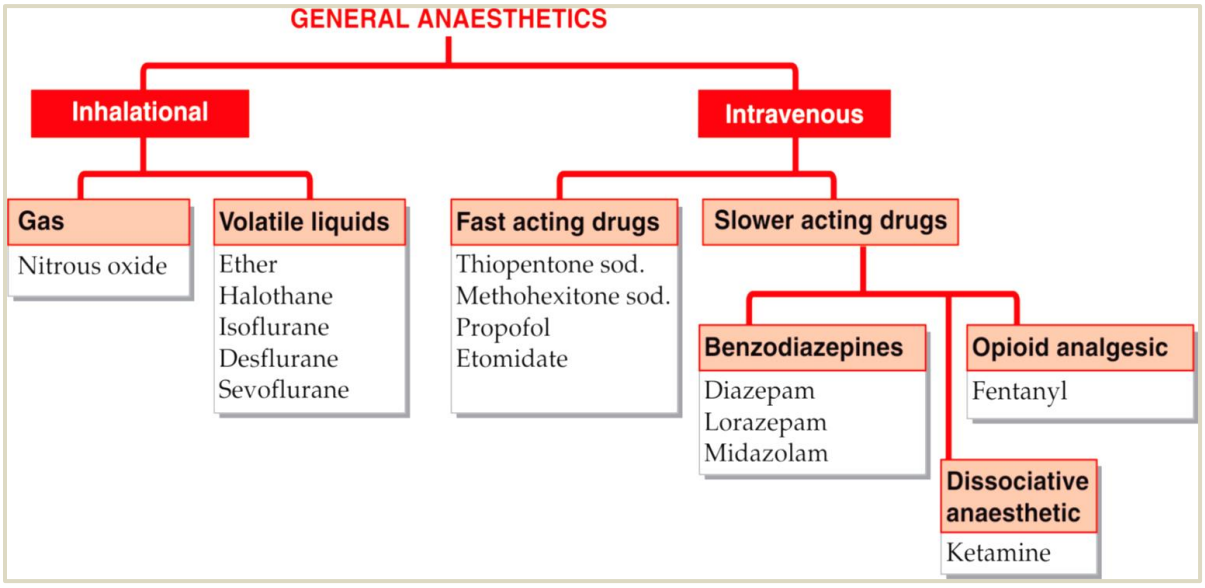
Plane 2 In the 2nd planes the corneal and laryngeal reflexes are loss

Plane 3 In this plain Pupil starts dilating and lost the light reflex

Plane 4 In this plain all reflex are loss, dilated pupil, shallow abdominal respiration and Intercostal paralysis,

IV. Stage of medullary depression: or overdose, is marked by hypotension or circulatory failure. Death may result if the patient cannot be revived quickly. Breathing stops and failure of circulation and this leads to death.

CLASSIFICATION OF GENERAL ANAESTHESIA



INHALATIONAL GENERAL ANAESTHETICS

These anesthetics diffuse across pulmonary and tissue barriers. The potency and partial pressure in brain decide the depth of anesthesia. The speed of induction of anesthetic effects depends upon:

1. Solubility: Large amount of anesthetics that are highly soluble in blood must be dissolved before PP is raised. The change in PP in blood leads to consequent induction and slow recovery. Drugs with low blood: gas partition coefficient (Nitrous oxide) induce quickly

2. Inspired Gas Partial Pressure: A higher partial pressure of the gas in lungs will result in more rapid achievement of anesthetic levels in blood. Thus, a quick induction can be made by administering the GA at high concentration at start

3. Ventilation rate: The greater the ventilation than there will be more rapid increase in alveolar and blood partial pressure of the anesthetic agent and more rapid will be onset of anesthesia.

4. Pulmonary blood flow: Higher the pulmonary blood flows, slower will be the rise in partial pressure of gas and thus onset of anesthesia is reduced. In contrast lower the blood flow rate, inset will be faster.

5. Cerebral Blood Flow: Gas is rapidly delivered to highly perfused organ (Brain). This can be hastened by inhalation of CO_2 which causes vasodilation which further leads to acceleration of induction and recovery.

Mechanism of action

- No specific receptor has been identified as the locus of general anesthetic action.
- Anesthetics increase the sensitivity of GABA receptors to the neurotransmitter GABA prolonging the inhibitory chloride ion current after GABA release, reducing the postsynaptic neurons excitability
- Anesthetics increase the activity of the inhibitory glycine receptors in the spinal motor neuron Anesthetics block excitatory postsynaptic nicotinic currents

PHARMACOLOGICAL ACTIONS O INHALED ANAESTHETICS

1. CNS: Inhaled anesthetics decrease brain metabolic rate. They generally reduce vascular resistance and increase cerebral blood flow and may increase intracranial pressure. 2. **2.Cardiovascular effects:** Inhalational anesthetics decrease arterial blood pressure moderately. Nitrous oxide is less likely to lower blood pressure than are other inhalational anesthetics.

3. Respiratory effects: Rate of respiration may be increased but the tidal volume is decreased which may cause increase in arterial CO2 tension. Nitrous oxide may or may not effect respiration while Halothane and Isoflurane causes greater depression of respiration

ADVERSE EFFECTS

- Prolonged exposure to nitrous oxide decreases methionine synthase activity and may lead to megaloblastic anaemia.
- Some Patients may develop malignant hyperthermia when exposed to halogenated anesthetics.
- Renal insufficiency may be one of the problem after using prolonged anesthesia.

NITROUS OXIDE (N_2O): Nitrous oxide, commonly known as "laughing gas", is a chemical compound with the chemical formula N_20. Nitrous oxide is a colourless heavier than air, odour characteristic, and taste faintly sweetish and noninflammable gas. It is kept compressed in metallic cylinders. It is non-toxic to liver, kidneys and brain. It is preserved in metallic cylinder painted blue and carry label stating name of gas N_20.

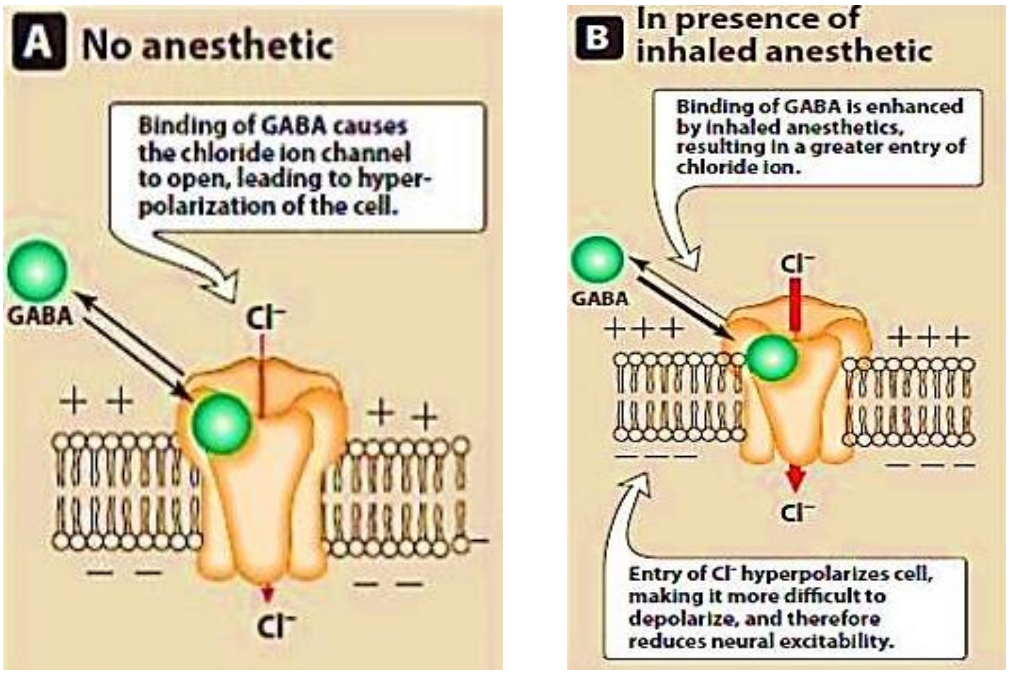
Mechanism of action: It indicate that nitrous oxide induces opioid peptide release in the brain stem leading to the activation of descending noradrenergic neurones, which results in modulation of the nociceptive process in the spinal cord.

Several receptor-effector mechanisms including dopamine receptors, a2 adrenoceptors, benzodiazepine receptors and -methyl--aspartate (NMDA) receptors have been implicated although the relationship of one with the other is not known.

Use: as an analgesic therapy, General anesthesia therapy / Adjunct to general anesthesia. It is used in surgery and dentistry for its anesthetic and analgesic effects.

HALOTHANE: (Fluothane): It is a colourless liquid with characteristic odour. It is a volatile liquid with sweet characteristic odour. It is non-inflammable and non-irritant. It is soluble in blood quickly. It is twice as potent to as chloroform and four times as potent as ether.

Mechanism of action: It causes general anaethesia due to its actions on multiple ion channels, which ultimately depresses nerve conduction, breathing, cardiac contractility. Its immobilizing effects have been attributed to its binding to potassium channels in cholinergic neurons. Halothane's effects are also likely due to binding to NMDA and calcium channels, causing hyperpolarization.



Uses: It is a general inhalation anesthetic used for induction and maintenance of general anesthesia. It reduces the blood pressure and frequently decreases the pulse rate and depresses respiration. It induces muscle relaxation and reduces pains sensitivity by altering tissue excitability.

Recovery from anesthesia is rapid.

The laryngeal spasm and shivering occurs occasionally, vomiting is unusual. Its use during labour can prolong delivery and increase post-partum blood loss.

It is currently the most popular anaesthetic used due to its property of non-irritating, non-inflammable pleasant and rapid action, particularly for maintenance anaesthetic in adults and children.

It is not a good analgesic or muscle relaxant. Urine formation is decreased during halothane anaesthesia due to low glomerular filtration rate resulted from fall in blood pressure.

Halothane may be administered by any usual method of inducing anaesthesia.

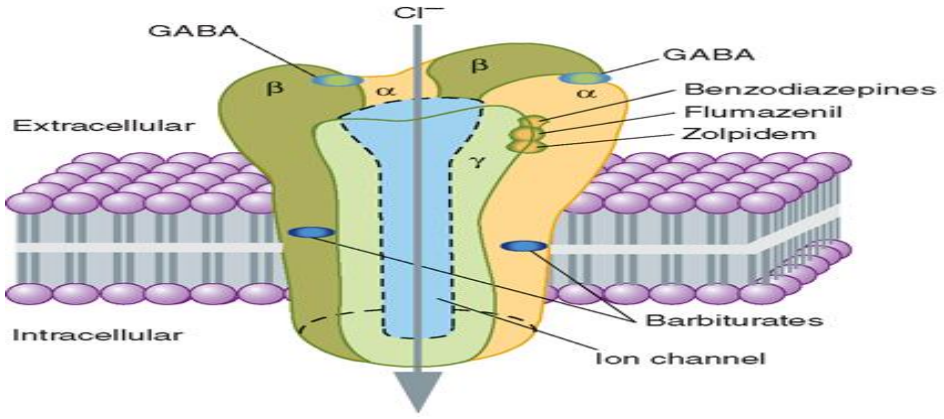
Poisoning with Halothane: The signs and symptoms of overdose with halothane are bradycardia and hypotension. This situation can be controlled with injection atropine 500 meg 1.V. and up to 10mg of methoxamine hydrochloride intravenously. If respiratory depression occurs, reduce dose of halothane.

INDUCING AGENTS :

These are the drugs which on administration as intra venous injection produce loss of consciousness. They are as under:

THIOPENTONE SODIUM :It is a very short acting thiobarbiturate. It is administered-intravenously for the induction of general anaesthesia. It is most useful for short surgical operations..

Mechanism of action: Thiopental binds at a distinct binding site associated with a Cl- ionopore at the $GABA_A$ receptor, increasing the duration of time for which the Cl- ionopore is open. The post-synaptic inhibitory effect of GABA in the thalamus is, therefore, prolonged.



A systematic diagram drug acting on GABA receptor

Side effects: Respiratory depression, broncho spasm, retrograde amnesia, hypotension, myocardial depression, coughing, sneezing, chills, shivering, necrosis, pain at injection site, irritability of muscles.

Indications: General anesthesia, narcoanalysis, induction anaesthesia before other anaesthetics.

Dosage: General anaesthetic

Adult I. V 50 to 75 mg at intervals of 20 to 40 seconds.

Narcoanalysis : Adult : Intravenously 100 mg per minute. Inj. Pentothane not to exceed 50 ml per minute.

Contraindications: Hypersensitivity to Barbiturates, status asthmaticus, liver disease, cardiovascular disease, renal disease, hypotension.

Pharmacokinetics: I.V. onset action 30 to 40 seconds. Plasma half life 4 to 8 hours. Crosses placenta excreted through urine unchanged.

Drug Interactions: Increase action with CNS depressants.

Uses: It is a barbiturate, is used for the induction of anesthesia prior to the use of other general anesthetic agents. Thiopental is an ultrashort- acting depressant of the central nervous system which induces hypnosis and anesthesia, but not analgesia.

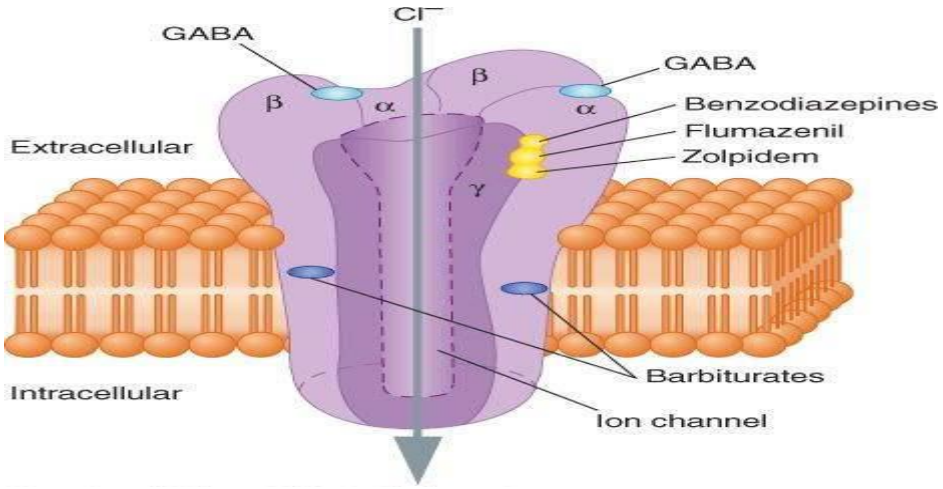
Brand names: Thiopentone : Injection Pentothal sodium, Anesthal, Pentone, Thipen, Thiosol 500mg, 1gm vial.

SLOW ACTING DRUGS

These are class of benzodzepines drugs. These drugs are used for endoscopy, cardiac catheterization angiographies, regional anaesthesia, fracture setting etc. The anaestheticaction of benzodiazepines can be rapidly reversed by flumazenil 0.5 mg to 2 mg intravenously administered.

DIAZEPAM: Its actions are mediated by enhancement of gamma-aminobutyric acid activity.

Mechanism of action: Benzodiazepines bind nonspecifically to benzodiazepine receptors which mediate sleep, affects muscle relaxation, anticonvulsant activity, motor coordination, and memory. As benzodiazepine receptors are thought to be coupled to gamma- aminobutyric acid-A (GABA) receptors, this enhances the effects of GABA by increasing GABA affinity for the GABA receptor. Binding of GABA to the site opens the chloride channel, resulting in a hyperpolarized cell membrane that prevents further excitation of the cell.



Uses: It is used in the treatment of severe anxiety disorders, as a hypnotic in the short-term management of insomnia, as a sedative and premedicant, as an anticonvulsant, and in the management of alcohol withdrawal syndrome.

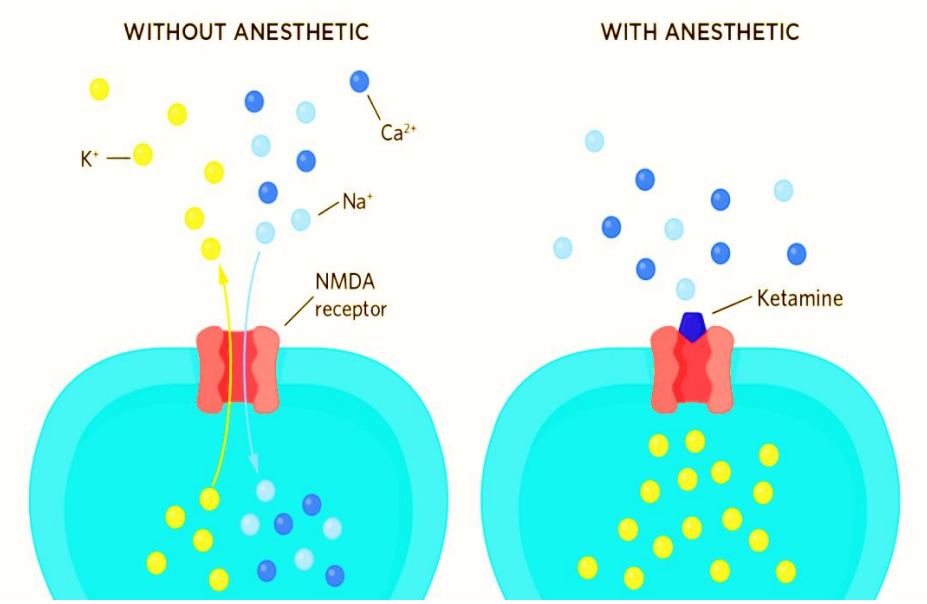
Brand names: Diazepam : Tablets Dizep, Lori, Dizep Calmpose, Valium, Placidox, Paxum 2mg, 5mg, 10mg tablets, Injection 5mg per ml.

KETAMINE :

It is an NMDA receptor antagonist with a potent anesthetic effect. It is a non barbiturate drug use as general anaesthetic.

Mechanism of action: Ketamine interacts with N-methyl-D-aspartate (NMDA) receptors, opioid receptors, monoaminergic receptors, muscarinic receptors and voltage sensitive Ca2+ ion channels. Unlike other general anaesthetic agents, ketamine does not interact with GABA receptors.

Uses: It is a rapid-acting general anesthetic producing an anesthetic state. It is used for operations of head, neck, in patients who do not want to lose consciousness and for short operations.



Mechanism of action ketamine

Indications : For operation on head and neck, in patient who have bled and for those patients who do not want to lose consciousness. For short operations, burn dressing, supplement low potency drug like nitrous oxide. For diagnostic/surgical procedures.

Contraindications: Hypersensitivity, severe hypertension, child below age 2 years, increased intra cranial pressure, pregnancy, seizure disorders, elderly.

Pharmacokinetics: I.V. injection peak concentration 40 seconds, duration 10 minutes, serum half-life 3 to 4 hour metabolized in liver.

Drug interactions: Increased action of ketamine with narcotic drugs, decreased cardiac output with halothane.

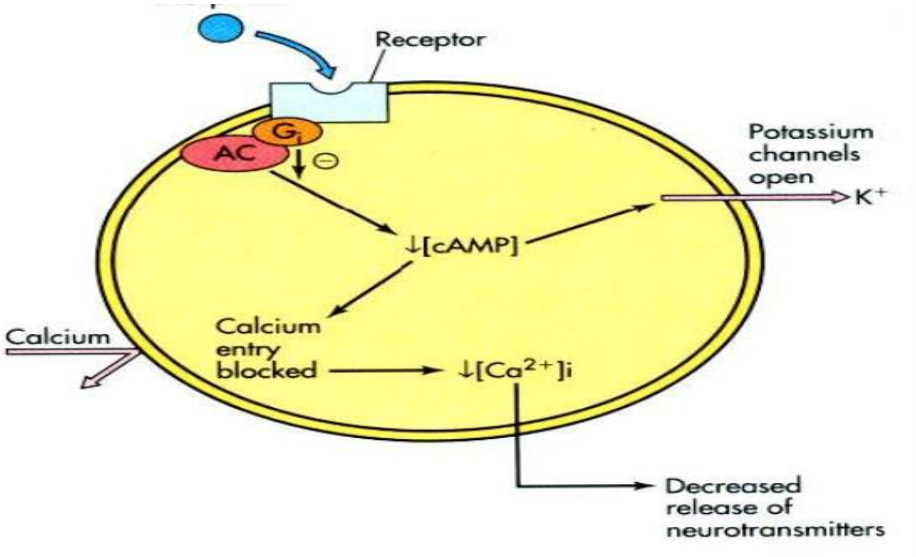
Dosage : Adult and child 1 mg to 4.5 mg per kg body weight over 1 minute.

Brand names: Ketamine : Injection Ketalar, Keta, Ketmin, Kotamin, Ketam, Ketolide 10mg, 50mg per ml.

OPOID ANALGESICS

FENTANYL: It is an synthetic opoid. It has rapid onset action and act for short duration of action. It is an opioid analgesic.

Mechanism of action: It interacts predominately with the opioid mu (u)-receptor but also binds to kappa (K) and delta (S)-type opioid receptors. Opiate receptors are coupled with G- protein receptors and function as both positive and negative regulators of synaptic transmission via G-proteins that activate effector proteins. Binding of the opiate stimulates the exchange of GTP for GDP on the G-protein complex. As the effector system is adenylate cyclase and cAMP located at the inner surface of the plasma membrane, opioids decrease intracellular CAMP by inhibiting adenylate cyclase. Subsequently, the release of nociceptive neurotransmitters such as substance P, GABA, dopamine, acetylcholine and noradrenaline is inhibited. Opioids also inhibit the release of vasopressin, somatostatin, insulin and glucagon. Fentanyl's analgesic activity is, most likely, due to its conversion to morphine. Opioids close N-type voltage-operated calcium channels (OP2-receptor agonist) and dependent inwardly rectifying potassium channels (OP3 and OP1 receptor agonist). This results in hypopolarization and reduced neuronal excitability.



Uses: Its primary actions of therapeutic value are analgesia and sedation. It may increase the patient's tolerance for pain and decrease the perception of suffering.

side effects : Vomiting, nausea, hypotension, respiratory depression, dizziness, muscle regidity, blurred vision, miosis.

Indications: Pre operatively, post operatively, induction and maintenance, as a general anaesthetic with oxygen.

Pre-operatively : Adult : 0.05 to 0.1 mg 30 to 60 minute before surgery, Intra muscular

Post operatively: Adult I/M 0.05 to 1 mg every 1 to 2 hours as required.

Children 1M 0.02 to 0.03 mg.

Contraindications : Respiratory depression, hypotension, hypovollmia, myasthenia gravis. Hypersensitivity to opiates, pregnancy, cardiac dysrhythmias.

Pharmacokinetics: IV onset action immediate. Peak plasma concentration 3 to 5 minutes. 1/M 7 to 8 minute peak serum concentration 30 minutes, plasma half life 1 to 2 hour. metabolized by liver, excreted by kidneys, crosses placenta, excreted in breast milk.

Drug interactions : Effect with CNS depressants may be increased. Alcohol, narcotic, sedative hypnotics antipsychotics also cause depression.

Dosage : Anaesthesia:

Adult IV 0.05 to 0.1 mg every 2 to 3 minute.

Brand names Fentanyl citrate : Injection Fendrop, Fent, Trofentyl, Durogesic 50mcg, 100mg per ml.

PRE-ANAESTHETIC MEDICATION

The term pre-anaesthetic medication refers to the use of drug prior to the administration of anaesthesia so that anaesthesia may be made safe and agreeable to the patient

Premedication aim is to provide following effects.

1) Pre medication is administered to produce sedation to reduce anxiety of patient before surgery. This effect of producing sedation can be achieved by sedatives, hypnotics, and tranquillizers.

2) Analgesia effect is achieved by morphine, pethidine. These analgesics reduce pain and also the amount of general anaesthetic required is decreased.

3) To control parasympathomimetic action of anaesthetic drugs like ether; decrease bronchial and salivery secretions.

COMPLETIONS OF GENERAL ANAESTHESIA

There are certain complication that arise during and after anaesthesia. There are marked drug interactions also

During anaethesia Complications

1) Respiration depression and hypercarbia.

2) Fall in blood pressure.

3) Asphyxia and laryngospasm.

4) Asystole, cardiac arrythmias.

5) There are low respiratory and salivation secretions. It is because mostly non irritant anaesthetics are used.

6) The patient have dreadful perception and recall of the events of before and during surgery. It is due to use of light anaesthesia, analgesia and muscle relaxants.

7) Aspiration of gastric contents cause acid pneumonitis.

8) The possibilities of fire and explosion are rare. These drugs due to use of non-inflammable drugs for anaesthesia.

9) Convulsions, delirium other excitatory effects are normally seen with intravenous anaesthetics.

After anaesthesia (complications)

1) Vomiting, nausea are common.

2) Organs toxicities, liver and kidney damage.

3) There is emergence delirium.

4) Due to over dose of anaesthetic drugs, and due to the faulty positioning there is occuring nerve palsies.

5) There is impaired psychomotor functions due to persistant sedation by anaesthetics.

6) There is atelectasis, pneumonia.

7) There as emotional disorders and change of attitude in some patients especially elderly due to undergone general anaesthesia of long duration.

Drug interactions

1) Opioid drugs, neuroleptics, mono amine oxidase inhibitors, potentiate action of anaesthetics.

2) Halothane sensitize heart to adrenaline.

3) If a patient is on anti hypertensive drugs and is given general anaesthesia blood pressure may fall markedly.

4) If a patient is on cortico steroids therapy and is to be given general anaesthesia, intra operatively 100mg hydrocortisone be given since anaesthesia is a stress which can precipitate adrenal insufficiency, there may be cardiovascular collapse.

5) If a patient is diabetic and is on oral hypoglycaemics drugs during anaesthesia. The need of insulin is increased so give plain insulin even if the patient is on oral hypoglycaemics.

HYPNOTICS & SEDATIVES

Hypnotics : These are the drugs which produce sleep resembling natural sleep.

Sedatives : These are the drugs which reduce excitement without producing sleep.

Sleep is naturally occuring phenomina. The duration and pattern of sleep varies among individuals. Age has also an important role and effect on quantity and depth of sleep. There are many theories and controversy regarding sleep, what, how and why about sleep. The necessity of adequate sound sleep is accepted universally. Sleep is essentially required to provide physical rest to the body and mental equilibrium (balance). During natural sleep persons change their position often during a night sleep. This movement occurs during second half of the night i.e., after mid night. The dream occurs during light or partial sleep. The condition of lack of sleep is called insomnia. Hypnotics are the drugs to treat this condition or otherwise called a disease (insomnia).

Hypnotics and sedatives both cause depression to the central nervous system; their difference is being in depth of depression produced to CNS. The sedative may be considered as mild hypnotics, and the hypnotics as mild sedatives.

Qualitatively hypnotics and sedative produce depression of central nervous system, the difference between them is quantitatively.

The sedatives, hypnotics are classified into two classes:

(I) Barbiturates

(II) Non Barbiturates

Organic hypnotics: Bromide

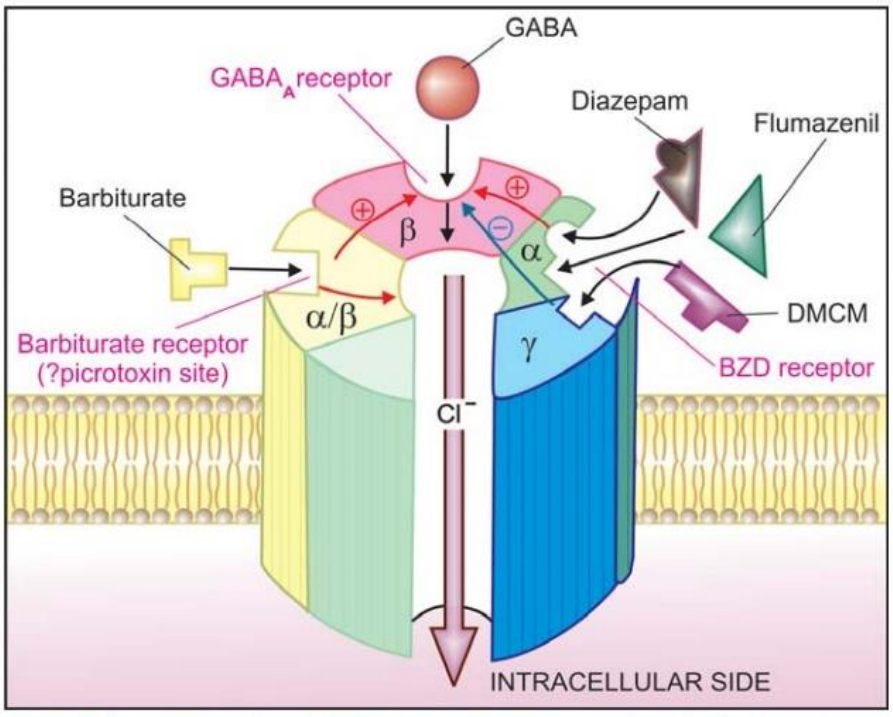
Bormides of sodium, potassium and ammonium have been used as sedatives. Bromides are not used for hypnosis due to concentration required for sleep cannot be attained by a single dose treatment. The large dose of bromides cause bromism characterised by headache, anorexia, dermatitis, conjunctivitis, gastric distress and neurological diseases/disturbance. Now a days bromides are not used now because better and safe drugs are available.

Classification of sedative-hypnotics

New non-benzodiazepine

BARBITURATES: These are organic hypnotics the Barbiturates are derivatives of barbituric acid (Malonyl urea) which has been prepared by the condensation of urea and malonic acid.

Mechanism of action: Barbiturates stimulating the inhibitory neurotransmitter system in the brain called the lgamma]-aminobutyric acid (GABA) system. The GABA channel is a Chloride channel that has five subunits at its gate. When barbiturates bind to the GABA channel they lead to potentiate, prolonged opening of the channel letting in Chloride ions into the cells in the brain. This leads to increased negative charge and hyperpolarisation. This change in voltage makes the brain cells resistant to nerve impulses and thus depresses them.



Mechanism of Barbiturate

PHARMACOLOGICAL ACTION OF BARBITURATES

Analgesic effect : Barbiturates do not act as analgesics. They do not relieve pain. In smaller dose they increase pain. Barbiturates enhance analgesic action of para amino phenol derivatives and salicylates.

Anaesthetic effect : Ultra short acting barbiturates when administered intravenously, produce anaesthetic effect (general anaesthesia). Thiopentene and methohexitone are useful for the purpose of general anaesthesia.

Action on Central Nervous System : Barbiturates produce CNS depression, mild sedation, hypnosis and anaesthesia. Hypnotic dose of barbiturates produces sleep which is said to be natural sleep. In fact no drug can induce natural and safe sleep. Natural sleep consists of periodic

cycles of REM (Rapid Eye Movement) and NREM (Non Rapid Eye Movements). Barbiturates induce sleep different from natural sleep by reducing REM time. Sedative doses of barbiturates cause depression, reduce excitement, relieve tension and anxiety state.

Action on Respiratory System : Sedative and hypnotic dose do not effect respiration. The larger doses depress respiratory system by depressing respiratory centre in medulla oblongata,that may cause respiratory collapse (paralysis) and may result death.

Action on liver : Normal doses of barbiturates do not effect liver. Anaes-thetic dose may produce hepatic dysfunction.

Action on Kidneys : Normal sedative and hypnotic dose produce no effect on kidney. Anaesthetic dose decreases urine output. This results in oliguria, by increasing ADH release.

Anti convulsant Effect : Long acting barbiturates like phenobarbitone have anti convulsant effect. Phenobarbitone is administered in combination with phenytoin in the treatment of epileptic convulsions.

Action on Cardiovascular system : Normal therapeutic doses of barbiturates may cause slight fall in blood pressure, and decrease heart rate. Higher and toxic doses produce hypotension.

Action on Gastrointestinal tract: Normal therapeutic doses do not effect intestinal motility. Higher doses decrease peristaltic movements.

Action on uterus : The toxic (higher) doses depress, force and frequency of uterine contractions.

Therapeutic uses of barbiturates

(1) Hypnosis to relieve insomina.

(2) Cause sedation (sedative effect) in case of anxiety.

(3) Used as pre anaesthetic drug to produce basal anaesthesia/general anaesthesia.

(4) Barbiturates has anti convulsant effect in the treatment of tetanus and status epilepticus.

(5) Useful in psychiatric treatment.

(6) Used to increase analgesic effect of salicylates.

Adverse effects

Intolerance :

(i) Intolerance includes excitement, vomiting, nausea, diarrhoea, headache.

(ii) Continuous long therapeutic use of phenobarbitone cause anaemia.

(iii) Barbiturates depress foetal respiration when administered during delivery. Barbiturates should be used with caution to lactating mothers, they decrease milk flow and small quantity present in milk may cause enzyme induction in infants.

(iv) The major adverse effect of barbiturates is "drug automatism". Repeated use for a long period causes forgetfulness. The patient may forget the dose taken and take drug repeatedly at night and may poison himself by taking over dose.

To avoid 'drug automatism' barbiturates should be given to patient by para medical, nursing staff or by a member of family of patient, as per schedule timing. Patient should not be permitted to take himself/herself the drug of this category.

Tolerance : Repeated use/administration of the barbiturates develops tolerance. It also produces cross tolerance to other CNS depressants.

Drug dependence : Barbiturates on repeated use develop both physical and psychological dependence. Sudden withdrawal of drug is difficult and causes disturbed sleep, insomnia which result from rebound increase in REM sleep. The withdrawal symptom develops like anxiety, weakness, tremors, excitement and even convulsions.

Barbiturate Poisoning : Accidental over dose taken or barbiturates consumed with suicidal tendency leads to barbiturates poisoning. Signs and symptoms of barbiturates poisoning are rapid and thready pulse, shallow breath, cold skin, paralytic dilatation of the pupils of eyes. The fatal complications are respiratory paralysis, collapse and death of the patient.

TREATMENT OF POISONING OF BARBITURATES

1. Gastric lavage : Simple aspiration of gastric contents is helpful if carried out within three hours of barbiturates ingested by the patient.

2. Endotracheal intubation : In barbiturates intoxication treatment adequate ventilation is important. Endotracheal intubation is used to maintain patients airway. Positive pressure respiration should be used to treat hypoventilation.

3. Alkalization : Systemic alkalosis reduces the plasma concentration of non ionized and diffusible form of barbiturates which leads to withdrawal of barbiturates from brain and Cerebrospinal Fluid (CSF). Sodium Bicarbonate ($NaHCO_3$) is used for this purpose. Barbiturates are weak acids. Force diuresis is effective for long acting barbiturates.

4. Intravenous fluids : (IV fluids) Intravenous fluids are helpful for forced diuresis to prevent dehydration. DNS Dextrose normal saline is used from intravenous fluids therapy. These IV fluids are useful for maintenance of blood volume and optimum blood pressure.

Diuresis : In case of barbiturates poisoning there is reduced urine out put. The barbiturate excretion can be increased by increasing urine flow. Forced diuresis should be avoided because it is dangerous procedure. It should only be considered for a patient whose chances of survival are

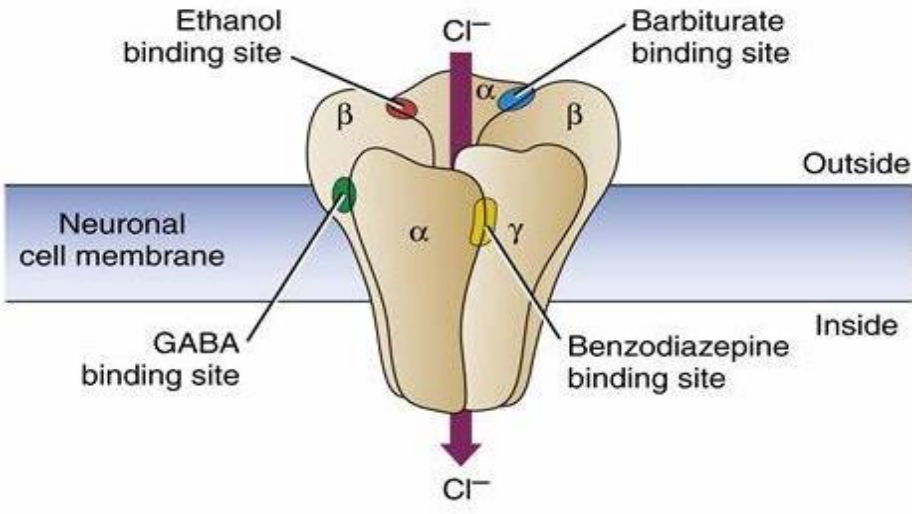
rare and other treatment does not seem to be effective. The diuretics like furosemide, mannitol are used for diuresis.

LONG ACTING BARBITURATES

Long acting barbiturates (action 8 hours and more):eg. Phenobarbitone,

PHENOBARBITONE SODIUM: It is an odourless, white, hygroscopic powder with a bitter taste. It is soluble in water. It decreases impulse transmission and increases seizure threshhold at cerebral cortex level.

Mechanism of action : GABA receptor-ion channel complex is made up of five subunits with the major form of the complex containing a, b, and y subunits. The benzodiazepines and barbiturates are believed to exert their effects on consciousness and sleep by facilitating the activity of y-aminobutyric acid (GABA) at various sites in the neuraxis. GABA, the most ubiquitous inhibitory neurotransmitter in the CNS, regulates the excitability of neurons in almost every neuronal tract. GABAA receptor-chloride ion channel has binding sites for benzodiazepines and barbiturates, as well as alcohols, steroids, and inhalational anesthetics.



A diagram shown drug acting on GABA receptor and open the chloride ions channel The GABA, chloride ion channel is a protein complex pentameric form that has varying combinations of a, b, and y subunits. GABA binds to a site near the junction of a and B subunits, and this causes conformational changes that open the chloride ion channel and lead to neuronal membrane hyperpolarization.

Side effects : Vomiting, nausea, skin rash, urticaria, angioedema, local pain, swelling, thrombophelebitis, paradoxic excitement (elderly) drowsiness, headache, lethargy, flushing.

Pharmacokinetics : I.V. on set action 5 minutes peak concentration 30 minutes duration 4 to 6 hours, 1M. SC onset action 10 to 30 minutes, duration 4 to 6 hours. Orally onset 20 to 60 minutes peak 8 to 12 hours duration of action 6 to 10 hours. It is metabolized in liver, excreted in urine, breast milk, crosses placenta, The plasma half life 100 hours in adults in children about 75 hours.

Indications : It is indicated in mania, all forms of epilepsy, insomnia, febrile seizures in children, sedation, status epilepticus.

Dosage : Insomnia : Adult : 100mg to 320 mg daily orally in 3 divided dose or by intramuscular injection. Child : Orally 6mg per kg body weight in equal three doses 8 hourly.

Sedation : Adult : 30 to 120mg daily by mouth in equal three doses, tid/eight hourly or by I/M. Child: I.M or orally 6mg per kg body weight in equal three divided doses.

Seizures :

Adult : Orally 100 to 200mg daily in three equal doses, or total dose H.S (at bed time).

Child : Orally 4 to 6mg per kg body weight in two equal divided doses 12 hourly or total dose at bed time (H.S.) as a single dose.

Pre operative sedation:

Adult: IM injection 100 to 200mg 1 to hour before surgery.

Child : By mouth 6mg per kg body weight per day in three divided doses.

Contraindications: Hypersensitivity, hepatic disease, diabetes, pregnancy, lactation, respiratory disease, hyperthyroidism, elderly patients.

Drug interaction : Increased effect with CNS depressants, chloramphenicol, alcohol, disulfiram, sulphunamides decrease effect of phenobarbitone with theophylline, metronidazole, oral anti coagulants , doxycycline, quinidine.

Brand names: Phenobarbitone : Tablet, Injection, Syrup Luminal, Gardenal, Fenobarb, Epinil, Fentoin ER, 30mg, 60mg, 100mg, 200mg tablets injection 200mg per ml, syrup 20mg per 5ml.

SHORT ACTING BARBITURATES

Short acting barbiturates (action 2 to 4 hours) : eg. Butobarbitone, Pentobarbitone

BUTOBARBITONE: Its belong to a group of medicines called the barbiturates may be used as mild sedative & hypnotic to relieve anxiety, nervous tension, and insomnia.

Mechanism of action: It binds at a distinct binding site associated with a Cl- ionopore at the GABAA receptor, increasing the duration of time for which the Cl- ionopore is open. The post-

synaptic inhibitory effect of GABA in the thalamus is, therefore, prolonged. All of these effects are associated with marked decreases in GABA-sensitive neuronal calcium conductance (gCa). The net result of barbiturate action is acute potentiation of inhibitory GABAergic tone. It also act through potent (if less well characterized) and direct inhibition of excitatory AMPA-type glutamate receptors, resulting in a profound suppression of glutamatergic neurotransmission.

Side effects: Drowsiness, Impaired concentration, Mental and physical sluggishness, Mental confusion (& Traffic accidents), Impaired performance, Hangover, Nausea, Dizziness, Idiosyncrasy, excitement, Porphyria, Hypersensitivity reactions e.g. Rashes, swelling of eyelids, lips, etc. Tolerance and Dependence.

Contraindications : Acute intermittent porphyria, Liver and kidney disease, Severe pulmonary insufficiency.e.g. emphysema, Obstructive sleep apnoea.

Pharmacokinetics: Plasma protein binding is 20%. And metabolism is reported hepatic. Renal excretion accounts for major and plasma half life is 40-55 hrs.

Adult Dosage: 15 to 30 mg Dose for sedation maintenance (routine daytime sedation), to relieve anxiety, tension or apprehension 50 to 100 mg dose for the short term treatment of insomnia and is given at bed time and recommended for Dose for preprocedure sedation induction and relief of preoperative anxiety and is given 60-9 minutes before surgery

PENTOBARBITONE: It is a short-acting barbiturate that is effective as a sedative and hypnotic (but not as an anti-anxiety) agent and is usually given orally

Mechanism of action: It binds at a distinct binding site associated with a Cl- ionopore at the GABAA receptor, increasing the duration of time for which the Cl- ionopore is open. The post-synaptic inhibitory effect of GABA in the thalamus is, therefore, prolonged. All of these effects are associated with marked decreases in GABA-sensitive neuronal calcium conductance (gCa). The net result of barbiturate action is acute potentiation of inhibitory GABAergic tone. Barbiturates also act through potent (if less well characterized) and direct inhibition of excitatory AMPA-type glutamate receptors, resulting in a profound suppression of glutamatergic neurotransmission

Use: It is used for the treatment of short term insomnia. It belongs to a group of medicines called central nervous system (CNS) depressants that induce drowsiness and relieve tension or nervousness.

Drug interactions: Administration of ethanol, benzodiazepines, opioids, antihistamines, other sedative-hypnotics, and other central nervous system depressants will cause possible additive effects.

Dose: 10 to 15 mg/kg given slowly over 1 to 2 hours; monitor blood pressure and respiratory rate.

ULTRA SHORT ACTING BARBITURATES

Ultra short acting barbiturates (action 15 to 30 minutes) : Thiopentone, Methohexitone.

THIOPENTONE SODIUM: It is a hygroscopic white powder with characteristic odour and a bitter taste. It is an ultra short acting thiobarbiturate

Mechanism of action : The drug Thiopentone sodium acts in reticular activating system and produces anaesthesia. It raises seizure threshold and is used short general anaesthesia. It binds at a distinct binding site associated with a Cl ionopore at the GABAA receptor, increasing the duration of time for which the Cl- ionopore is open. The post-synaptic inhibitory effect of GABA in the thalamus is, therefore, prolonged.

Indications : Induction anaesthesia before other anaesthetics, rapid control of convulsions, Narcoanalysis.

Dosage : Adult : I.V. 3 to 5mg per kg body weight or IV 210 mg to 280mg, it produces an unconsciousness in 15 to 30 seconds.

General anaesthesia : IV 50 to 75 mg administered at 20 to 40 seconds intervals.

Narcoanalysis : Adult : 100mg per minute intravenously.

Contraindications : Hypersensitivity, asthma, hepatic disease.

Side effects : Chills, shivering, necrosis pain at the site of injection, sneezing, coughing, bronchospasm, respiratory depression, retrograde amnesia, tachycardia, prolong somnolence hypotension.

Use with precautions : Myasthenia gravis, asthma, renal disease, liver disease, hypotension, severe cardiovascular disease.

Pharmacokinetics : IV onset action 30 to 40 seconds, serum half life 11 to 12 hours, crosses placenta.

Drug interactions : Increased effect with CNS depressants.

Brand names: Thiopentone : Injection Pentothal, Thipen, Pentone, Intraval sodium, Anesthal 500mg, 1000mg vials.

METHOHEXITONE: It is An intravenous anesthetic with a short duration of action that may be used for induction of anesthesia.

Mechanism of action: It binds at a distinct binding site associated with a Cl- ionopore at the GABAA receptor, increasing the duration of time for which the Cl- ionopore is open. The post-synaptic inhibitory effect of GABA in the thalamus is, therefore, prolonged.

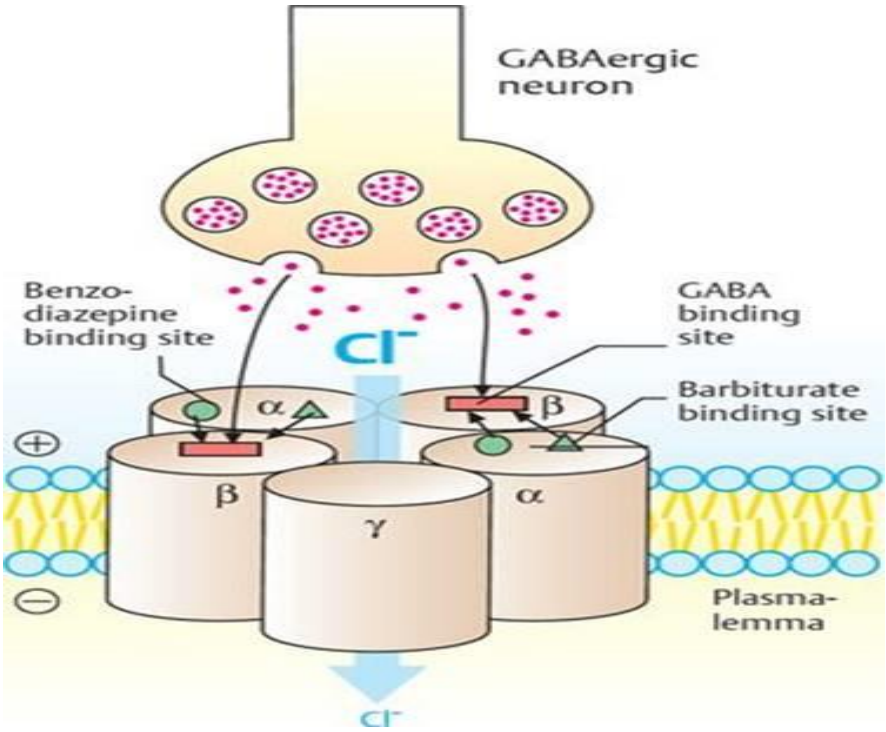
Uses: It is used for the induction of anesthesia prior to the use of other general anesthetic agents and for induction of anesthesia for short surgical, diagnostic, or therapeutic procedures associated with minimal painful stimuli. Little analgesia is conferred by barbiturates.

Dose: 6.6 to 10 mg per kg.im and iv dose 1 to 2 mg per kg of body weight

BENZODIAZEPINES

It is a group of structurally related drugs which acts on the central nervous system. The drugs of this group are effective for treatment of anxiety, anti convulsant and central muscle relaxants.. In the year 1960 Diazepam and Chlordiazepoxide were introduced as anti anxiety drugs.

DIAZEPAM: It is a white crystalline powder with slight bitter taste. It is slightly soluble in water. It has tranquilliser properties. It is used in the treatment of psychoneurotic disorders, anxiety, status epilepticus



Mechanism of action of benzodiazepine/Barbiturates and GABA

Mechanism of action It bind to an allosteric site formed by the cleft between a and y subunits, and this facilitates GABA binding and increases the frequency of chloride channel opening.

Barbiturates bind adjacent to a and B subunits and increase the duration of chloride channel opening

The resting member potential is-70mV benzodiazepine increased the membrane potential -80m V. Diazepam potentiates the action of gamma amino butyric acid. Its actions are mediated by enhancement of gamma-aminobutyric acid activity.

Indication : Sedative for surgical procedures, anxiety, tension, muscle spasm, psychosomatic and behaviour disorder, dysmenorrhea, cerebral palsy, labour, tetanus, eclampsia.

Dosage: 5 to 30mg daily in divided doses.

Contraindications: Hypersensitivity, psychosis, narrow angle glaucoma, orthostatic hypotension

Side effects : Headache, drowsiness, anxiety, confusion, fatigue, ECG changes, hypotension, mydriasis, tinnitus, dry mouth, anorexia, skin rash, itching.

Pharmacokinetics : Rapidly absorbed orally onset action 15 to 30 minutes duration of action 2 to 3 hours, metabolized by liver, crosses placenta, excreted in breast milk, serum half life 20-50 hours in Beta phase, in alpha phase half-life 1 to 10 hours has been recorded.

Drug interactions : CNS depressants, alcohol increases effect of diazepam, decrease effect of diazepam : oral contraceptives, rifampin, cimetidine, disulfiram, isoniazid, propranolol. Anxiety/covulsions : Adult 2 to 10mg bid to QID.

Orally : Child above 6 months age orally Img to 2.5mg 6 to 8 hourly. Status epilepticus : Adult IV 5 to 20mg, 2mg per minute may repeat after 5 to 10 minutes not to exceed 60mg per day.

Child: 0.1 to 0.3mg per kg body weight.

Uses: It is used as anticonvulsant, anxiolytic, sedative, muscle relaxant, and amnesic properties and a long duration of action. It is used in the management of alcohol withdrawal syndrome

Brand names: Diazepam : Tablet, Capsule, Injection Valium, Paxum, Placidox, Calmpose, Diazep, Calmtack, Diaz, Repam 2mg, 5mg, 10mg, Injection 10mg per 2ml.

FLURAZEPAM : It is a drug of class, Benzodiazipines, which it is slowly eliminated drug in which active metabolite occurs.

Mechanism of action : It produces central nervous system depression at the limbic, thalamic and hypothalamic level of brain. It is mediated by the neurotransmitter (gamma) amino butyric which result in the sedation, muscles relaxation, anxiolytic action and hypnosis. Indications anxiety, short term and transient insomnia.

Dosage: Orally 15 to 30mg at bed time.

Contraindications : Myasthenia gravis, Hypersensitivity, glaucoma, hypotension.

Side effects Drowsiness, drug dependence, blurred vision urinary incontinence.

Brand names: Capsule Nindral containing 15mg Flurazepam hydrochloride.

NITRAZEPAM : It is useful for patients having frequent nocturnal awakenings, when day time sedation is acceptable.

Mechanism of action: It depress subcortical level of central nervous system including lumbic system and reticular formation Useful in social phobia, depression

Indications : Insomnia, transient sleep disturbance.

Dosage: 5 to 10mg orally at bed time (before goint to sleep).

Contraindications : Myasthenia gravis, narrow angle glaucoma.

Side effects : Sweating, weakness, dry mouth, blurred vision, nightmares, behavior changes.

Brand names: Nitrazepam : Capsules, tablets Dormin, Nindral, Nitravet, Nitwan, Nitrosun, Stressban 10mg, 5mg tablets.

ALPRAZOLAM : It is a triazole analogue of benzodiazepine. It is effective in anxiety disorders, anxiety associated with depression.

Mechanism of action: It depress subcortical level of central nervous system including limbic system and reticular formation. It is useful in social phobia, depression.

Dosage : Orally 0.25 to 0.5mg thrice a day, maximum 3 to 4mg per day in divided doses 8

Indications : Anxiety disorders, anxiety associated with depression.

Contraindications : Hypersensitivity, narrow angle glaucoma.

Elderly : Dose should be reduced.

Side effects : Drowsiness, anorexia, memory impairment, loss of coordination, slurred speech, weakness, pruritis.

Brand names: Alprazolam : Tablet Alprazolam, Alzip, Alzolam, Quiet, Restyl, Anzilum, Alzot, Alzan, Zeptra, Zoldac, 0.25mg, 0.5mg, 1mg tablets.

The other drugs of this group are Temazepam, Triazolam, Midazolam. Midazolam is three times potent to diazepam, and is used in anaesthesia, 0.02 to 0.1mg per kg per hour i.v. infusion.

Therapeutic uses of Benzodiazepins

These drugs are useful therapeutically as anti anxiety and sedatives, anti convul-sants, muscle relaxants, and pre anaesthetic medication, in anaesthesia.

Adverse effects : Benzodiazipines cause light headedness, loss of coordination, ataxia, confusion, dry mouth, weakness, vertigo, blurred vision, joint pain, vomiting epigastric distress.

NON BENZODIAZEPINE DRUGS

ZOPICLONE : It is a non benzodiazepine hypnotic drug. It rapidly initiates sleep without changing total REM sleep and preserves normal slow wave sleep.

Indications : Short term treatment of insomnia, nocturnal awakening, early awakening, chronic insomnia.

Dose : Adult orally 7.5mg to 15mg shortly before going to bed (before retiring) elderly, reduce dose 3.75mg.

Contraindications: Myalsthenia gravis, respiratory insufficiency, pregnancy, lactation.

Side effects: Nausea, vomiting, urticaria, metallic taste, dry mouth.

Brand names: Zopiclone : Tab Zopivane, Zotic, Lyzop, Ziclone, Zona, Zolium, Zopitran 7.5mg tablets.

ZOLPIDEM : It is a non benzodiazepine sedative drug. It belongs to the imidazopyridine class. The sleep duration is prolonged in imsomniacs. It is to be used for 1 to 2 week duration. It has no side effect or have few side effects.

Mechanism of action : It produces central nervous system depression at limbic, thalamic and hypothalamic levels. It is mediated by neurotransmitter GABA aminobutyric acid and cause sedation, skeletal muscle relaxation, hypnosis, anxiolytic action and anticonvulsant action. It is useful in treating insomnia.

Indications : Short term treatment of insomnia.

Dosage : By mouth (orally) 10mg before bed time. Elderly and weak patient 5mg H.S.

Contraindications : Hypersensitivity, apnea, liver disease, respiratory depression, pregnancy, lactation.

Side effects : Headache, chest pain, drowsiness, amnesia, embolism, confusion, dry mouth, diplopia

Brand names: Zolpidem : Capsules, Tablets, Zleep, Ambiz, Dactive, Lypin, Sove, Soza, Zoldem, Zolpid 5mg, 10mg tablets.

CHLORAL HYDRATES: A hypnotic and sedative used in the treatment of insomnia. The safety margin is too narrow for chloral hydrate to be used as a general anesthetic in humans but it

is commonly used for that purpose in animal experiments. It is no longer considered useful as an anti-anxiety medication

MELATONIN RECEPTOR AGONIST

RAMELTON: It is the first selective melatonin agonist. It has an active metabolite that is less potent but circulates in higher concentrations than the parent compound.

Mechanism of action: It is a melatonin receptor agonist with both high affinity for melatonin MT, and MT2receptors, and lower selectivity for the MT3 receptor. Melatonin production is concurrent with nocturnal sleep, meaning that an increase in melatonin levels is related to the onset of self-reported sleepiness and an increase in sleep propensity. MT, receptors are believed to be responsible for regulation of sleepiness and facilitation of sleep onset, and MT2 receptors are believed to mediate phase-shifting effects of melatonin on the circadian rhythm. While MT, and MT2 receptors are associated with the sleep-wake cycle, MT, has a completely different profile, and therefore is not likely to be involved in the sleep-wake cycle.

It has no appreciable affinity for the gamma-aminobutyric acid (GABA) receptor complex of receptors that bind neuropeptides, cytokines, serotonin, dopamine, norepinephrine acetylcholine, or opiates.

Uses: It is used for insomnia, particularly delayed sleep onset. Ramelteon has not been shown to produce dependence and has shown no potential for abuse.

BENZODIAZEPINE ANTAGONIST

FLUMAZENIL: It is a benzodiazepines benzodiazepine receptor antagonist. It antagonizes action of on central nervous system.

Mechanism of action: It antagonise the action of Benzodiazepines on central nervous butyric acid and the benzodiazepine receptors end. It is useful in reversal of sedative effects system. It competitively inhibit action of benzodiazepines recognition site on Gama Amino of Benzodiazepine drugs.

Indications: Reversal of sedative effect of benzadiazepines.

Dosage : Benzodiazepine overdose

Adult IV 0.2mg/2ml give over 30 seconds. Wait for 30 seconds then give 0.3mg/3ml over 30 seconds if consciousness does not occur further dose of 0.5mg (5ml) be given over 30 seconds, at interval of 1 minute up to 3mg cumulative lose.

Contraindications : Hypersensitivity, pregnancy, lactation ambulatory patients.

Side effects: Headache, increased sweating, fatigue, rigors, dizziness, agitation, somnolence, nausea, vomiting chest pain, hypertension, palpitation, blurred vision, tinnitus.

CENTRALLY ACTING MUSCLE RELAXANTS

These are the drugs which act on central nervous system (CNS) and decrease skeletal muscle tone and involuntary muscle movements. These drugs are used for the treatment of acute muscle spasms, orthopedic conditions and tetanus. The drugs belongs to this group are

(1) Mephensin congener (2) Benzodiazepines (3) Gama amino butyric acid derivative

MEPHENESIN: It is a synthetic cresol glyceryl ether which produces transient muscle relaxation and paralysis via central nervous system depression It was the first drug found to cause muscle relaxation without producing unconsciousness.

Mechanism of action: The exact mechanism of action of mephenesin is not known. It has been observed to block both inward sodium and inward calcium currents in neurons. It reduced neuronal excitability leading to decreases action potentials to muscle fibers which ultimately produces a reduction in spasticity. It has a physiological effect which opposes that of strychnine.

Dose: The usual dose for mouth is 0.5 to 1 gram once daily to 6 times a day. The dose by I.M or I. V route is 0.1 to 1 gram.

Adverse effect : When it is administered by injection it causes thrombophelebitis, haemolysis and hypotension.

Uses. It is used in creams for local applications, Medicreme ointment. Mephenesin has irritant and muscle relaxant property provide relief of acute muscle spasm. It is not clinically used because it is gastric irritant and cause haemolysis.

Brand names: Mephensin : Relaxyl ointment 30gm tube.

CHLORZOXAZONE: It is centrally acting central muscle relaxant with sedative properties. It is better tolerated when given orally. It is a skeletal muscle relaxant drug.

Mechanism of action : It inhibits multisynaptic reflex acts. It inhibits degranulation of mast cells, subsequently preventing the release of histamine and slow-reacting substance of anaphylaxis (SRS-A), mediators of type I allergic reactions. It also may reduce the release of inflammatory leukotrienes. It acts by inhibiting calcium and potassium influx which would lead to neuronal inhibition and muscle relaxation.

Uses: It inhibits antigen-induced bronchospasms and, hence, is used to treat asthma and allergic rhinitis. It is also a centrally-acting agent for painful musculoskeletal conditions.

Indications : Skeletal muscle spasm, relieve pain.

Dosage : Adult : Orally 250 to 750 mg 6 to 8 hourly Child : orally 20 mg per kg body weightin euqal divided doses two or three times a day.

Contraindications

Hypersensitivity, hepatic dysfunction, use with precautions in pregnancy, lactation, elderly.

Side effects : Vomiting, nausea, constipation, hepatotoxicity, jaundice, urine discoloration, drowsiness, dizziness, headache, insomnia, malaise, rash, urticaria, petechiae, angioedema, anaphylaxis.

Pharmacokinetics: On set action 1 hour, peak concentration 3 to 4 hour duration 6 hour, plasma half life 1 hour metabolized in liver excreted in urine.

Drug interactions : Increased central nervous system depression with alcohol, tricyclic antidepressant, narcotics , sedatives, barbiturates, hypnotics.

Brand names: Chlorzoxazone : Tablet Cipzox, Parafon, Diclonac MR, Fendol, Inac MR, Mofax, Oxalgin plus, Pacizox, Flamar P.

CARISOPRODOL: It is a white crystalline powder sparingly soluble in water. It is a centrally acting skeletal muscle relaxant. The relaxant action of carisoprodol is 8 times more than mephenesin or meprobamate (studied by burger et al in 1959). In 1959 Kestler used this drug successfully in the relief of muscle spasm, pain and stiffness.

Mechanism of action : Carisoprodol depresses central nervous system by blocking inter neuronal activity in decending reticular formation, spinal cord, produce sedation.

Indications : Musculo skeletal disorders, to relieve pain, stifness in musculoskeletal disorders.

Dosage : Adults : 250 mg to 350 mg orally three times a day.

Contraindications : Hypersensitivity, intermittent porphyria. Use with precautions, drug dependence, alcoholism, pregnancy, lactation, elderly, renal and hepatic disease. Avoid long term use.

Side effects : Headache, drowsiness, dizziness, weakness, tremors, depression, insomnia, ataxia temporarily loss of vision, postural hypotension, tachycardia, vomiting, nausea, hiccups, skin rash, fever, facial flushing.

Pharmacokinetics: Onset action 30 minutes, duration of action 4 to 6 hours, serum half life 8 hours, corsses placenta, excreted in breast milk, excreted in urine.

Drug interactions : There is increased CNS depression with alcohol, tricyclic antidepressants, narcotics, sedatives barbiturates, hypnotics.

Brand names: Carisoprodol : Tablet Somaflam, Carisoma, Carisoma compound.

CHLORMEZANONE : It is a centrally acting muscle relaxants. It has anti anxiety and hypnotic action so it is also used for relieve of tension state.

Mechanism of action: It binds to central benzodiazepine receptors which interact allosterically with GABA receptors. This potentiates the effects of the inhibitory neurotransmitter GABA, increasing the inhibition of the ascending reticular activating system and blocking the cortical and limbic arousal that occurs following stimulation of the reticular pathways.

Indications : Used for musculo skeletal disorders, pain and stiffness.

Dosage : Adults: By mouth (orally) 250 to 350 mg thrice daily.

Contraindications : Hypersensitivity, pregnancy, lactation, elderly and paediatrics, reduce dose.

Side effects of chlormezanone. Drowsiness, nausea, weakness, dizziness, headache.

Drug interactions : Increased CNS depression with Alcohol, and other CNS depressants, narcotics, sedatives, barbiturates.

Use: It is a non-benzodiazepine muscle relaxant. But ban throughout the world due to toxicity on epidermal necrolysis.

Brand names: Chlormezanone : Tablet Mezonac, Dilofen MR, Ontac forte, Pamagin MR.

METHOCARBAMOL: It is a white crystalline powder, soluble in water. It is less sedative and long acting muscle relaxation drug. In 1962 crookshank administered methocarbamol orally and intravenously to patients of back strain. He found excellent results. He stated that in his experience this drug was safe and effective. It is a monocarbamate ester of the guaicol ether of glycerol.

Mechanism of action : It depress/block multisynaptic path ways in the spinal cord and cause skeletal muscle relaxation. Methocarbamol's exact mechanism of causing skeletal muscle relaxation is unknown. It has no direct action on the contractile mechanism of striated muscle, the motor end plate or the nerve fiber.

Indications : Skeletal muscle spasm, chronic neurological disease, tetanus management, relief of spasm and pain in musculo skeletal conditions.

Tetanus : Adult IV infusion 1 to 3 gm per Ltr of D5, not to exceed 3 gm per day.

Child : IV 15 mg per kg body weight, every 6 hourly.

Contraindications : Hypersensitivity, intermittent porphyria, child below 12 year age, coma, known brain damage. Use with precautions : in pregnancy, lactation, epilepsy, myasthenia gravis, alcoholism, renal and hepatic disease.

Side effects : Headache, tremors, insomnia, depression, seizures, drowsiness, weakness, hemolysis, diplopia, temporary loss of vision, postural hypotension, vomiting nausea, increased hemoglobin (I.V. use only). anorexia, metallic taste, brown, green or black colour urine, skin rash, fever, face flushing.

Pharmacokinetics : Onset action IM/IV onset rapid. Orally onset 30 minutes, peak 1 to 2 hours half life 2 hours, crosses placenta, excreted in urine.

Drug interaction : Increase CNS depression with alcohol, narcotics, sedative barbiturates.

Dosage : Pain : Adult: 1.5 gm orally 4 to 6 hourly, for 2 to 3 days. Then 1 gram 6 hourly. IM 500 mg gluteal muscles, 6 hourly.

Brand names: Methocarbamol : Tablet Robinax, Robiflam, Flexinol, Ibugesic M, Flexinol, Robilid tablets.

GAMA AMINO BUTYRIC ACID (GABA) DERIVATIVES

BACLOFEN : It is derived from gama amino butyric acid (GABA) and is very effective antispastic with a spinal site action. It is not effective in stroke, cerebral palsy, rheumatic, traumatic muscle spasms, ineffective in the treatment of parkinsonism.

Mechanism of action : Baclofen is a direct agonist at GABAB receptors. The precise mechanism of action of Baclofen is not fully known. It is capable of inhibiting both monosynaptic and polysynaptic reflexes at the spinal level, possibly by hyperpolarization of afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. It inhibit synaptic responses in the central nervous system by decreasing gama amino butyric acid which decreases neuro transmitter functions. It decreases senerity of muscle spasms.

Indications : Skeletal muscle spasticity of spinal and cerebral origin, spinal cord injury, spasticity in multiple sclerosis.

Dosage :

Adult : Orally: 5 mg 8 hourly for 3 days, then 10 mg thrice daily x 3 days, then 15 mg thrice daily for three days, then 20 mg three times a day for three days, dose not to exceed 80 mg per day.

Child :0.75 to 2 mg per kg in equal divided doses three times a day.

Contraindications : Hypersensitivity.

Side effects : Sedation, nausea, vomitting, respiratory depression, drowsiness, headache, tremors, disorientation, nasal congestion, blurred vision, tinnitus, hypotension, chest pain, oedema, constipation, increase AST (SGOT) alkaline phosphate, dry mouth, abdominal pain, skin rash, pruritis.

Pharmacokinetics : Orally peak serum concentration 2 to 3 hours, duration of action 8 hours. Serum half life 4 hours, metabolized in liver excreted in urine.

Drug Interactions : Increased CNS depression with alcohol, sedatives, hypnotics, barbiturates.

Use with precautions : In pregnancy, lactation, elderly, epilepsy, levodopa abrupt discontinuation, renal and hepatic disease, diabetes melitus, peptic ulcer disease, CNS depressants.

Brand names: Baclofen : Tablet, Injection Riclofen, Chinofen, Liofen, Lioresal, Tefsole 10mg, 25mg, 50mg tablets.

Precautions for patient :

Not to consume alcohol and other CNS depressant drugs to avoid over sedation.

The drug should not be discontinued quickly, spasticity, tachycardia will occur, drug to be tapered off for 7 to 15 days.

Avoid driving and work with machinery, as drowsiness occurs.

To avoid use of cough syrups, antihistamme drugs with treatment unless advised by doctor.

To take more fluid diet up to 2 litres per day (additional) with food to avoid constipation

Treatment of overdose: In conscious patient induce emesis, lavage.

BENZODIAZEPINES

DIAZEPAM, (valium, paxum, calmpose). Diazepam acts in the brain on specific receptors increasing gama amino butyric acid transmission. Muscle tone is reduced by spinal action. It is very well tolerated orally as well as by parenteral route, no gastric irritation occurs. It is valuable in tetanus and spinal injuries. It is administered in combination wth analgesics. It is effective in rheumatic disorders having muscle spasm. Refer page no 250.

Dose : Orally 5 mg three times a day. IV: 10 to 40 mg (in tetanus)

CENTRAL ALPHA 2 AGONIST

TIZANIDINE: This drug is recently introduced. It is an alpha-2 adrenergic agonist. It reduces muscle tone and frequency of muscle spasm without decreasing muscles strength. It is well

absorbed orally. It has no effect on blood pressure it should not be given to patients on hypertensive therapy with clonidine. It is centrally acting skeletal muscle relaxant drug. It has site of action in the spinal cord.

Mechanism of action: Tizanidine reduces spasticity by increasing presynaptic inhibition of motor neurons through agonist action at a2-adrenergic receptor sites.

Contraindications : Hypersensitivity, use with precautions in pregnancy, hypotension, lactation, liver disease, renal disease, children, elderly.

Pharmacokinetics : It is completely absorbed, peak concentration hour, plasma half life hour. metabolized in liver, excreted in urine, feces.

Drug interaction : Increased CNS depression with Alcohol oral contraceptives decrease action of tizanidine.

Indications : Painful muscle spasm, spasticity.

Use: It is a short-acting drug for the management of spasticity. It is an agonist at a2- adrenergic receptor sites and presumably reduces spasticity by increasing presynaptic inhibition of motor neurons.

Dosage : Painful muscle spasm.

Adult : 2 mg three times a day. not to exceed 24 mg per day.

Brand names: Tizanidine : Tablet Tizpa, Zatru, Tablet Nicip T, Tizam, Zulu forte, Nelsid MR tablets.

ANTI-EPILEPTIC DRUGS (Anticonvulsants)

Anticonvulsants (also commonly known as antiepileptic drugs or as antiseizure drugs) Antiepileptic's are a class of drugs that try and prevent rapid, repetitive, stimulation of the brain that causes seizure activity such as in epilepsy.

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 (convulsions), sensory or psychiatric phenomena. Epilepsies have been classified variously; major types are described below.

I. Generalized seizures

1. *Generalized tonic-clonic seizures* (GTCS, major epilepsy, grand mal): commonest, lasts 1–2 min. The usual sequence is aura—cry—unconsciousness—tonic spasm of all body muscles clonic jerking followed by prolonged sleep and depression of all CNS functions.

2. *Absence seizures* (minor epilepsy, petit mal): prevalent in children, lasts about 1/2 min. Momentary loss of consciousness, patient apparently freezes and stares in one direction, no muscular component or little bilateral jerking. EEG shows characteristic 3 cycles per second spike and wave pattern.

3. *Atonic seizures* (A kinetic epilepsy): Unconsciousness with relaxation of all muscles due to excessive inhibitory discharges. Patient may fall.

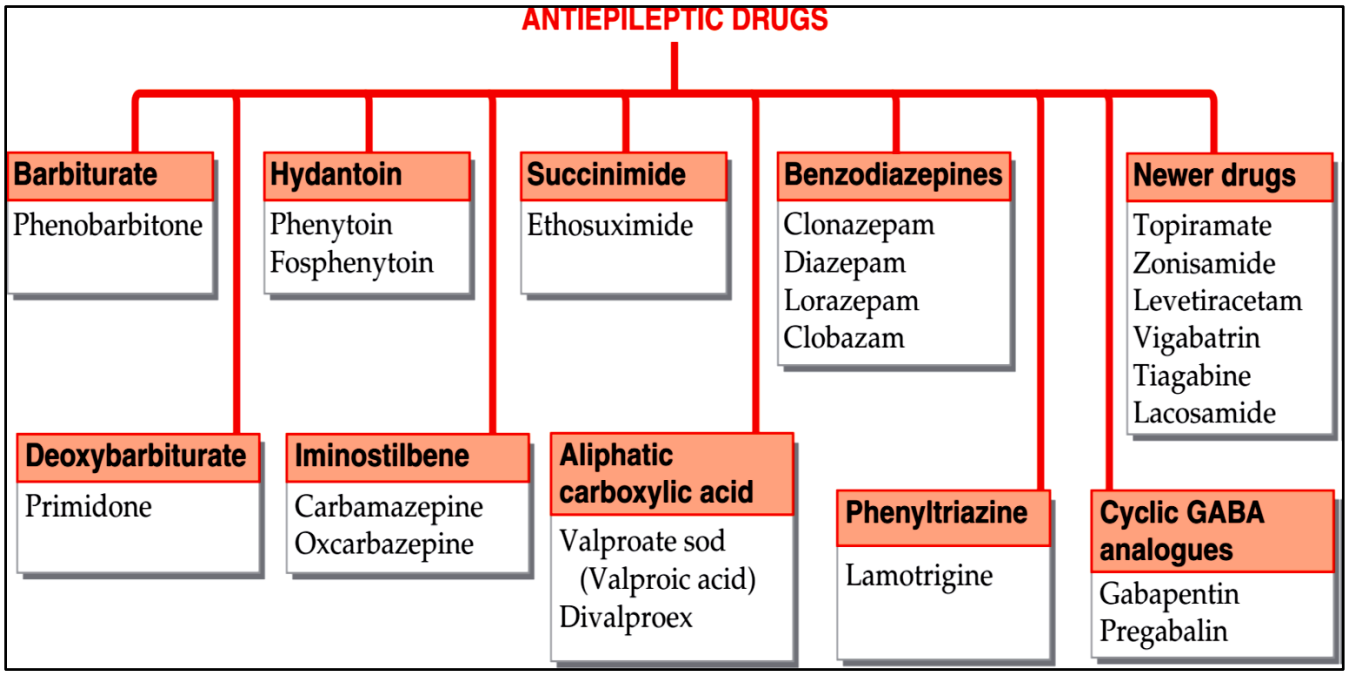
4. *Myoclonic seizures* Shock-like momentary contraction of muscles of a limb or the whole body.

5. *Infantile spasms (Hypsarrhythmia)* Seen in infants. Probably not a form of epilepsy. Intermittent muscle spasm and progressive mental deterioration. Diffuse changes in the interseizure EEG are noted.

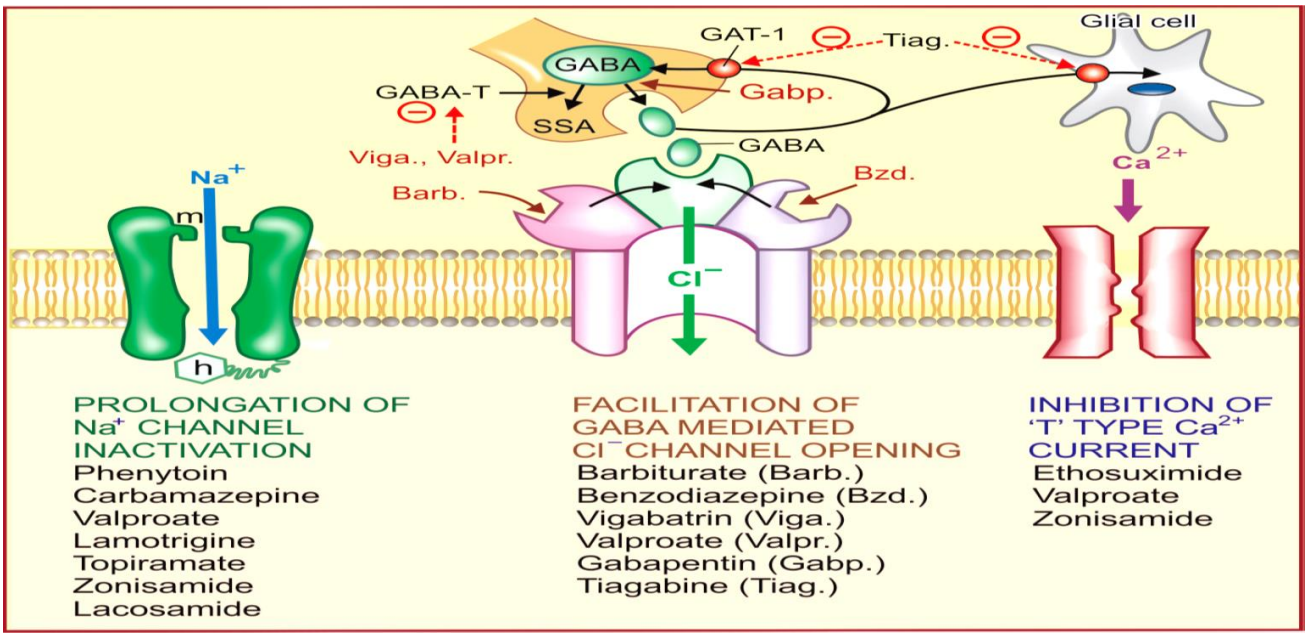
II. Partial seizures

1. *Simple partial seizures* (SPS, cortical focal epilepsy): lasts 1/2–1 min. Often secondary. Convulsions are confined to a group of muscles or localized sensory disturbance depending on the area of cortex involved in the seizure, without loss of consciousness.

2. *Complex partial seizures* (CPS, temporal lobe epilepsy, psychomotor): attacks of bizarre and confused behavior and purposeless movements, emotional changes lasting 1–2 min along with impairment of consciousness. An aura often proceeds. The seizure focus is located in the temporal lobe.



3. *Simple partial or complex partial seizures secondarily generalized* The partial seizure occurs first and evolves into generalized tonic-clonic seizures with loss of consciousness. The antiepileptic drugs are drugs which prevent the seizures are known as epilepsy.



A Systemic diagram mechanism of antiepileptic drugs

BARBITURATRE

PHENOBARBITONE: It is a barbituric acid derivative that acts as a nonselective central nervous system depressant.

Mechanism of action: It acts on $GABA_A$ receptors, increasing synaptic inhibition. This has the effect of elevating seizure threshold and reducing the spread of seizure activity from a seizure focus. It may also inhibit calcium channels, resulting in a decrease in excitatory transmitter release. The sedative-hypnotic effects of phenobarbital are likely the result of its effect on the polysynaptic midbrain reticular formation, which controls CNS arousal.

Uses: Phenobarbital, the longest-acting barbiturate, is used for its anticonvulsant and sedative-hypnotic properties in the management of all seizure disorders except absence (petit mal).

DEOXYBARBARTIONE

PRIMODONE: It is an antiepileptic agent related to the barbiturates; it is partly metabolized to phenobarbital in the body and owes some of its actions to this metabolite.

Mechanism of action: It is a GABA receptor agonist. The mechanism of Primidone's antiepileptic action is not known

Adverse effect: Overdose of primidone typically includes sluggishness, incoordination, and difficulty in thinking, slowness of speech, faulty judgment, drowsiness or coma, shallow breathing, staggering, and in severe cases coma and death.

Uses: It is a barbiturate with anticonvulsant properties. Primidone, either alone or used concomitantly with other anticonvulsants, is indicated in the control of grand mal, psychomotor, and focal epileptic seizures. It may control grand mal seizures refractory to other anticonvulsant therapy.

HYDENTOIN

PHENYTOIN (Diphenylhydantoin): The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. It reduces the maximal activity of brain stem centers responsible for the tonic phase of tonic-clonic seizures.

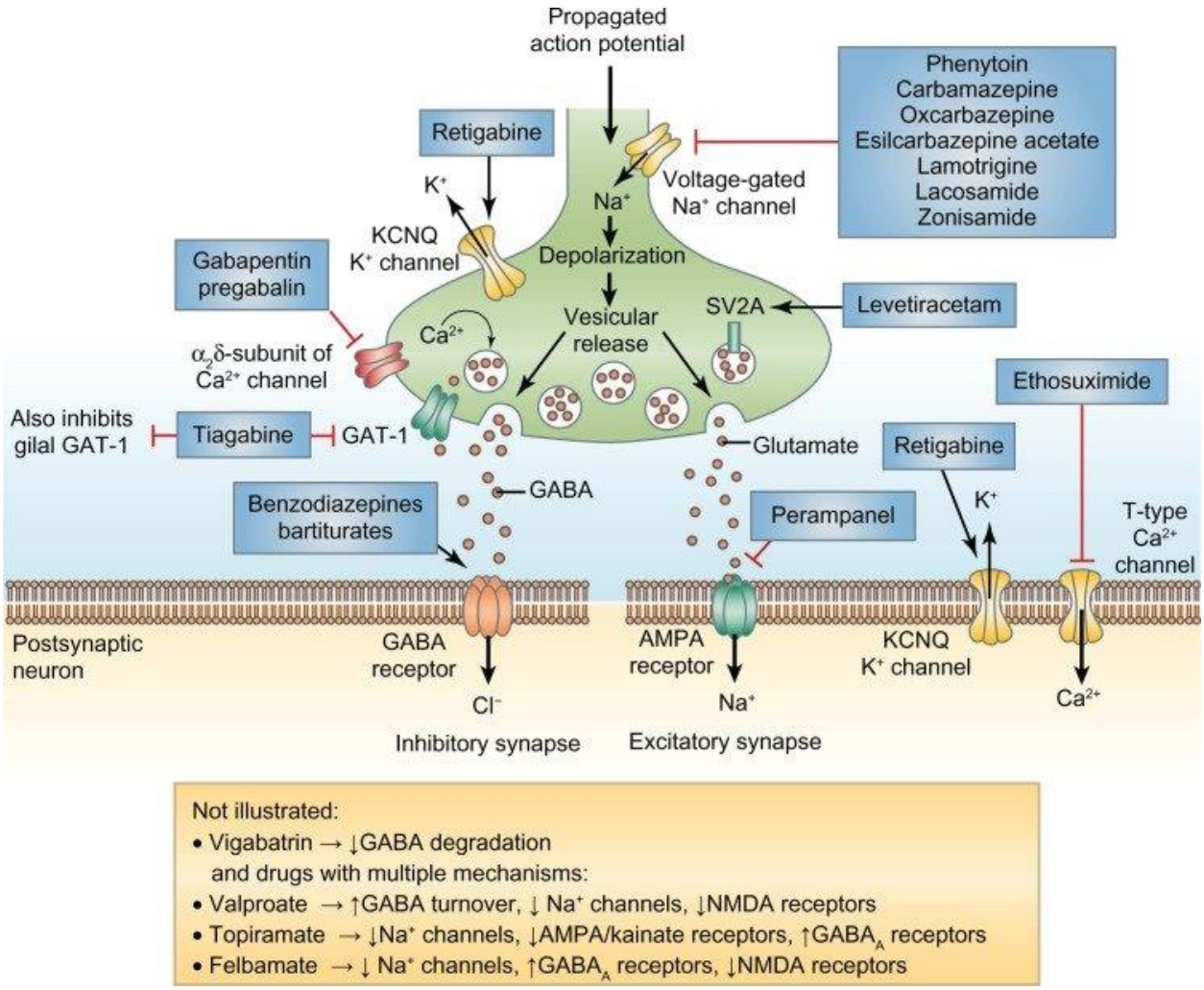
Mechanism of action: It acts on sodium channels on the neuronal cell membrane and limiting the spread of seizure activity and reducing seizure propagation. It promotes sodium efflux from neurons. It tends to stabilize the threshold against hyper excitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post-tetanic potentiation at synapses. Loss of post- tetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas.

Adverse effect: Rash (5% to 10%), Gum hypertrophy, Ataxia, slurred speech, Confusion, Drug-induced lupus, Agranulocytosis, Aplastic anemia, Hepatitis and Anticonvulsant hypersensitivity syndrome.

Drug interaction Phenytoin is an inducer of the hepatic cytochrome P450 microsomal isoenzymes CYP3A4, CYP2D6, CYP1A2, CYP2C9 and CYP2C19. It is metabolized primarily by CYP2C9 (major) and CYP2C19 (minor), thus several drugs may inhibit or induce the metabolism of phenytoin such as Amiodarone (increased level), Erythromycin (increased level),

Dose: Dilantin 25 mg, 100 mg cap., 100 mg/4 ml oral, suspension, 100 mg/2 ml inj; Epsolin 100 mg tab, 100mg/2 ml inj; Epton 50, 100 mg tab, 25 mg/ml syr; Fentoin-ER 100 mg extended release cap.

Use: It is anticonvulsant that is used in a wide variety of seizures. It is also an anti- arrhythmic and a muscle relaxant.



A systematic diagram mechanism of antiepileptic drugs'

IMINOSTIBENE

CARBAMAZAPINE: It is an anticonvulsant used to control grand mal and psychomotor or focal seizures.

Mechanism of action: It inhibits sustained repetitive firing by blocking use-dependent sodium channels. The pain relief due to blockade of synaptic transmission in the trigeminal nucleus and seizure control with reduction of post-tetanic potentiation of synaptic transmission in the spinal cord.

Adverse effect: The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting.

Drug Interaction: It concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Contraindications: It should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc.

Use: It an anticonvulsant structurally similar to tricyclic antidepressants.

It is used to treat partial seizures, tonic-clonic seizures, pain of neurologic origin such as trigeminal neuralgia, and psychiatric disorders including manic-depressive illness and aggression due to dementia.

It also possesses anticholinergic, central antidiuretic, antiarrhythmic, muscle relaxant, antidepressant, sedative, and neuromuscular-blocking properties.

SUCCINIMATE

ETHOSUXIMIDE: It is an anticonvulsant especially useful in the treatment of absence seizures unaccompanied by other types of seizures

Mechanism of action: It is binds to T-type voltage sensitive calcium channels. Voltage sensitive calcium channels (VSCC) mediate the entry of calcium ions into excitable cells and are also involved in a variety of calcium-dependent processes. It is selectively suppresses T current without affecting other type Ca^{2+} or Na^{+} current. It It also does not potentiate GABA therapeutic concentration.

Adverse effects Dose-related side effects are tiredness, headache, gastrointestinal, concentrate. intolerance, mood changes, agitation, drowsiness and inability to ensitivity reactions like rashes, and blood, dyscrasias are rare..

Dose: 20-30 mg/kg/day; Zarontin 250 mg/5 ml syr.

ALIPHATIC CARBOXYLIC ACID

VALPROIC ACID: (Sodium valproate): It has anticonvulsant properties used in the treatment of epilepsy.

Mechanism of action: It dissociates to the valproate ion in the gastrointestinal tract and then binds to and inhibits GABA transaminase. It increased the brain concentrations of gamma aminobutyric acid (GABA), an inhibitory neurotransmitter in the CNS, due to inhibiting enzymes block the reuptake of GABA into glia and nerve endings. It may also work by suppressing repetitive neuronal firing through inhibition of voltage-sensitive Na^{+} channels.

Pharmacokinetics: t is well absorbed into the bloodstream with bioavailability of 81-89%. The peak plasma concentration is 2 hours. It is highly bound to protein in the blood. The volume of distribution is 92L. Approximately 30-50% of the original active ingredient is excreted in the urine, and the remaining majority is first metabolized. The overall, the clearance of the drug ranges from 7-16 hours,

Adverse effects: The toxicity of valproate is low. Anorexia, vomiting, heart burn are common. Drowsiness, ataxia and tremor are dose-related side effects. Rashes and thrombocytopenia are infrequent hypersensitivity phenomena

Dose: Adults-start with 200 mg TDS, maximum 800 mg TDS; children--15-30 mg/kg/day.

Uses: It is drug of choice for absence seizures. Mania and bipolar illness: as alternative to lithium.

It has some prophylatic efficacy in migraine.

It is used in myoclonic and atonic seizures.

It is used in the treatment of mania and bipolar illness instead of lithium.

It has some prophylactic efficacy in migraine.

BENZODIAZEPINE

CLONAZEPAM: It is an anticonvulsant used for several types of seizures, including myotonic or atonic seizures, photosensitive epilepsy, and absence seizures, although tolerance may develop. It is seldom effective in generalized tonic-clonic or partial seizures.

Mechanism of action: It acts on benzodiazepine receptors and gamma-aminobutyric acid (GABA) receptors potentiate the effects of GABA. As GABA is an inhibitory neurotransmitter

Uses: It is used as an anticonvulsant in the treatment of the Lennox-Gastaut syndrome (petitmal variant), akinetic and myoclonic seizures. It can also be used for the treatment of panic disorders.

Brand name: Clonapam tab. 2 mg. Clonazepam tab.2 mg.

LORAZEPAM: It is a benzodiazepine derivaties used as an anti-anxiety agent with few side effects. It also has hypnotic, anticonvulsant, and considerable sedative properties and has been proposed as a preanesthetic agent.

Mechanism of action: It binds to an allosteric site on GABA-A receptors, which are pentameric ionotropic receptors in the CNS. It potentiates the effects of the inhibitory neurotransmitter GABA, which upon binding opens the chloride channel in the receptor, allowing chloride influx hyperpolarization in cell.

Uses: It is used to treat anxiety, status epilepticus, and for sedation induction and anterograde amnesia.

Brand Name: Ativan tab/inj. 1mg. oral/i.m

PHENYLTRIAZINE

LAMOTRIAZINE: It is an antiepileptic drug belonging in the phenyltriazine class used in the treatment of epilepsy and bipolar disorder.

Mechanism of action: It resembles the actions of phenytoin and carbamazepine in inhibiting voltage-sensitive sodium channes thereby stabilizing neuronal membranes and consequently suppress the presynaptic transmitter release of excitatory amino acids such as glutamate and aspartate.

Uses: It is used in partial seizures/primary generalized tonic-clonic seizures/generalized seizures of Lennox-Gastaut syndrome.

Brand Name: Lamictal tab. 5 mg, 100 mg. oral.

CYCLIC GABA ANALOGUE

GABA PENTIN: It is a drug used for the treatment of epilepsy. Now a days, It is widely used to relieve pain, especially neuropathic pain.

Mechanism of action: It interacts with cortical neurons at auxillary subunits of voltage-sensitive calcium channels. It increases the synaptic concentration of GABA, enhances GABA responses at non-synaptic sites in neuronal tissues, and reduces the release of mono-amine neurotransmitters.

Uses: It is used for the treatment of postherpetic neuralgia in adults and as adjunctive therapy in the treatment of partial seizures with and without secondary generalization seizure.

Brand name: Act Gabapentin 400 mg capsule, Gabapentin 400 mg. oral

NEW DRUG

VIGABATRIN: It is an analogue of gamma-aminobutyric acid, vigabatrin is an irreversible inhibitor of 4-aminobutyrate transaminase, the enzyme responsible for the catabolism of gamma-aminobutyric acid.

Mechanism of action: It increases brain concentrations of gamma-aminobutyric acid

(GABA), an inhibitory neurotransmitter in the CNS, by irreversibly inhibiting enzymes that catabolize GABA (gamma-aminobutyric acid transaminase, GABA-T). Duration of action is determined by rate of GABA-T re-synthesis. It may also work by suppressing repetitive neuronal firing through inhibition of voltage-sensitive sodium channels.

Uses: It is used an adjunct in treatment resistant epilepsy, refractory complex partial seizures, and secondary generalized seizures. It is also used as monotherapy in infantile spasms

Brand name: Sabril 500 mg tab. Sabril Pwr 3g/sachet 3 g.

ALCOHOL

DEFINITION

Alcohol is a chemical name for a group of related compounds that contain a hydroxyl group (-OH) bound to a carbon atom. The form of alcohol that is voluntarily consumed by humans is ethyl alcohol or ethanol and consists of two carbons and a single hydroxyl group (written as C2H5OH or CHO). It is a clear, colorless liquid rapidly absorbed from the gastrointestinal tract and distributed throughout the body. It has bactericidal activity and is used often as a topical disinfectant. It is widely used as a solvent and preservative in pharmaceutical preparations as well as serving as the primary ingredient in alcoholic beverages.

Substances included in this class: In terms of human consumption, all commercially available alcoholic beverages contain ethyl alcohol with concentrations depending upon the type of beverage. Beverages made by fermentation of sugar-containing fruits and grains include beer (3% to 8% ethanol by volume) and wines (11% to 13% ethanol by volume). Spirits are produced after distillation and generally contain at least 30% ethanol. Ethanol can be concentrated by simple distillation up to approximately 95%, while pure ethanol requires addition of benzene or related substances or desiccation using glycerol. Denatured alcohol contains additives or toxins to prevent human consumption. Rubbing alcohol is prepared from denatured alcohol or isopropyl alcohol and is used for topical purposes. (AGM)

Mechanism of action: Ethanol affects a large number of membrane proteins that participate in signaling pathways, including neurotransmitter receptors for amines, amino acids, opioids, and neuropeptides; enzymes such as Na+/K+-ATPase, adenylyl cyclase, phosphoinositide-specific phospholipase C; a nucleoside transporter; and ion channels. Much attention has focused on alcohol's effects on neurotransmission by glutamate and y- aminobutyric acid (GABA), the main excitatory and inhibitory neurotransmitters in the CNS. Acute ethanol exposure enhances the

action of GABA at $GABA_A$ receptors, which is consistent with the ability of GABA-mimetics to intensify many of the acute effects of alcohol and of GABAA antagonists to attenuate some of the actions of ethanol. Ethanol inhibits the ability of glutamate to open the cation channel associated with the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors. The NMDA receptor is implicated in many aspects of cognitive function, including learning and memory. "Blackouts"—periods of memory loss that occur with high levels of alcohol-may result from inhibition of NMDA receptor activation.

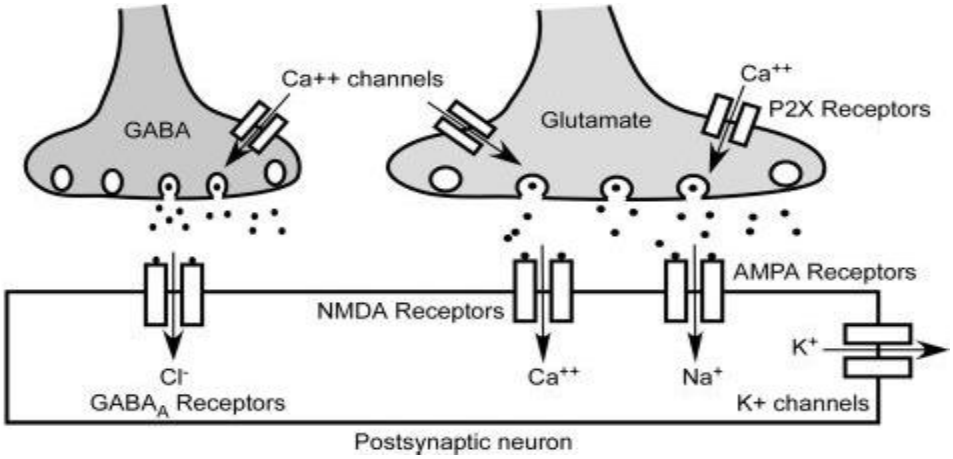
TABLE NO.3. Amount of alcohol in different beverages and relationship to a standard drink

Beverage	Volume(OZ)	% Alcohol (V:V)	No. of Standard Drinks
Beer			
Light Beer	**12**	**4.2%**	**-1**
Standard Beer	**12**	**5%**	**1**
Pint/Super	**16-20**	**5%**	**1.3-1.5**
Craft beer/Malt liquor	**12**	**7%-9%**	**1.5**
Wine			
Table Wine	**5**	**12%-14%**	**1**
Fortified	**3.5**	**17%**	**1**
Brandy	**1.5**	**35-50%**	**1**
Spiritis/Liquors			
80 proof shot	**1.5**	**40%**	**1**
100 proof	**1.5**	**50%**	**1.25**
190 proof	**1.5**	**95%**	**2.38**

Pharmacological action:

Central Nervous System: The CNS is markedly affected by acute alcohol consumption. Alcohol causes sedation, relief of anxiety and, at higher concentrations, slurred speech, ataxia, impaired judgment, and disinhibited behavior, a condition usually called intoxication or drunkenness. These CNS effects are most marked as the blood level is rising because acute tolerance to the effects of alcohol occurs after a few hours of drinking. For chronic drinkers who are tolerant to the effects of alcohol, higher concentrations are needed to elicit these CNS effects. For example, an individual with chronic alcoholism may appear sober or only slightly

intoxicated with a blood alcohol concentration of 300-400 mg/dL, whereas this level is associated with marked intoxication or even coma in a nontolerant individual. The propensity of moderate doses of alcohol to inhibit the attention and information-processing skills as well as the motor skills required for operation of motor vehicles has profound effects



Structure and regulation of alcohol-sensitive ion channels in the neuronal synapse

CVS: Alcohol has manifold effects on the cardiovascular system, and changes in contractility and function can follow both acute and chronic ingestion of alcohol. The deleterious effect of alcohol to the heart and other organ systems is countered by the protective effects of small amounts of alcohol on cardiovascular tissue. Thus, low to moderate alcohol use is associated with a reduced risk of coronary disease, and this may arise from alcohol-induced changes in plasma lipoproteins and alterations in cell protection pathways. Heart: Significant depression of myocardial contractility has been observed in individuals who acutely consume moderate amounts of alcohol, ie, at a blood concentration above 100 mg/dL.

Smooth Muscle: Ethanol is a vasodilator, probably as a result of both CNS effects (depression of the vasomotor center) and direct smooth muscle relaxation caused by its metabolite, acetaldehyde. In cases of severe overdose, hypothermia-caused by vasodilation-may be marked in cold environments. It also relaxes the uterus and-before the introduction of more effective and safer uterine relaxants (eg, calcium channel antagonists) —was used intravenously for the suppression of premature labor.

Liver: Liver disease is the most common medical complication of alcohol abuse; an estimated 15-30% of chronic heavy drinkers eventually develop severe liver disease. The risk of developing liver disease is related both to the average amount of daily consumption and to the

duration of alcohol abuse. The Chronic alcohol ingestion is well known to increase fat accumulation in the liver that can progress to severe liver damage and cirrhosis. Alcohol-induced liver damage is due in part the production of acetaldehyde that readily reacts with proteins, lipids, and other compounds leading to impaired mitochondrial function. Body temperature: Acute alcohol ingestion usually produces a feeling of warmth as cutaneous blood flow is increased, and this is accompanied by a reduction in core body temperature.

GIT: Gastric secretions are usually increased, although the concentration of alcohol ingested affects this response, with high concentrations (>20%) inhibiting secretions. Long-term ingestion of high concentrations of alcohol can lead to a variety of pathologies associated with the gastrointestinal tract including esophageal varices and bleeding, erosive gastritis, and diarrhea and malabsorption of nutrients and vitamins. Alcohol consumption is also associated with an increased risk of tumors in the GI system as well as in other tissues including lung and breast.

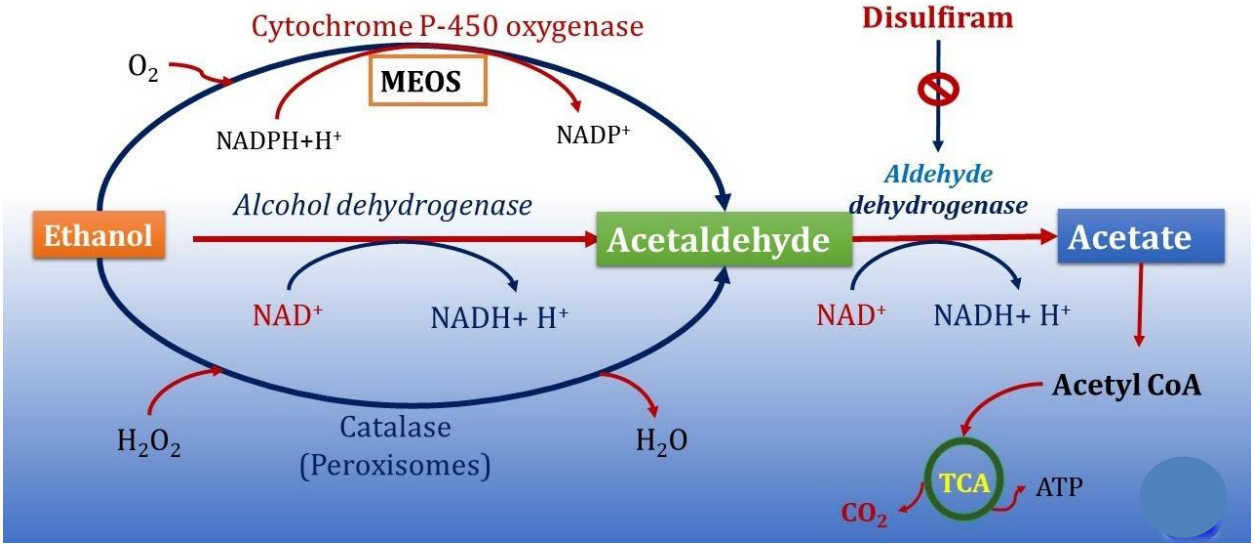
Sex Acute and chronic ingestion of alcohol generally decreases sexual performance in both men and women although sexual behavior may be enhanced due to loss of inhibitory control and judgment.

Uses:

1. As antiseptic
2. Rubifacient and counter irritant for sprains and joint pain
3. Rub into skin to prevent bedsores
4. As astringent
5. Alcohol sponges to reduce body temperature
6. Intractable neuralgias around the nerve cause permanent loss of transmission
7. Appetite stimulant
8. Reflex stimulation in fainting and hysteria
9. To treat methanol poisoning
10. Its bacteriocidal and antifungal action
11. It is also used as a cosolvent to dissolve many insoluble drugs and to serve as a mild sedative in some medicinal formulations.

Pharmacokinetics: Ethanol is a small water-soluble molecule that is absorbed rapidly from the gastrointestinal tract. After ingestion of alcohol in the fasting state, peak blood alcohol concentrations are reached within 30 minutes. The presence of food in the stomach is delays absorption by slowing gastric emptying. Distribution is rapid, with tissue levels approximating

the concentration in blood. The volume of distribution for ethanol approximates total body water (0.5-0.7 L/kg). After an equivalent oral dose of alcohol, women have a higher peak concentration than men, in part because women have a lower total body water content and in part because of differences in first-pass metabolism. In the central nervous system (CNS), the concentration of ethanol rises quickly, since the brain receives a large proportion of total blood flow and ethanol readily crosses biologic membranes. Over 90% of alcohol consumed is oxidized in the liver; much of the remainder is excreted through the lungs and in the urine.



Metabolism of alcohol

The primary pathway for alcohol metabolism involves alcohol dehydrogenase (ADH), a family of cytosolic enzymes that catalyze the conversion of alcohol to acetaldehyde. These enzymes are located mainly in the liver, but small amounts are found in other organs such as the brain and stomach. During conversion of ethanol by ADH to acetaldehyde, hydrogen ion is transferred from ethanol to the cofactor nicotinamide adenine dinucleotide (NAD+) to form NADH. As a net result, alcohol oxidation generates an excess of reducing equivalents in the liver, chiefly as NADH. The excess NADH production appears to contribute to the metabolic disorders that accompany chronic alcoholism and to both the lactic acidosis and hypoglycemia that frequently accompany acute alcohol poisoning. During chronic alcohol consumption, MEOS activity is induced. As a result, chronic alcohol consumption results in significant increases not only in ethanol metabolism but also in the clearance of other drugs eliminated by the cytochrome P450s that constitute the MEOS system, and in the generation of the toxic byproducts of cytochrome P450 reactions (toxins, free radicals, H2O2).

The Acetaldehyde Metabolism: The acetaldehyde formed from alcohol is oxidized in the liver in a reaction catalyzed by mitochondrial NAD-dependent aldehyde dehydrogenase (ALDH). The product of this reaction is acetate, which can be further metabolized to CO2 and water, or used to form acetyl-CoA. The oxidation of acetaldehyde is inhibited by disulfiram, a drug that has been used to deter drinking by patients with alcohol dependence. When ethanol is consumed in the presence of disulfiram, acetaldehyde accumulates and causes an unpleasant reaction of facial flushing, nausea, vomiting, dizziness, and headache. Several other drugs (eg, metronidazole, cefotetan, trimethoprim) inhibit ALDH and can cause a disulfiram-like reaction if combined with ethanol.

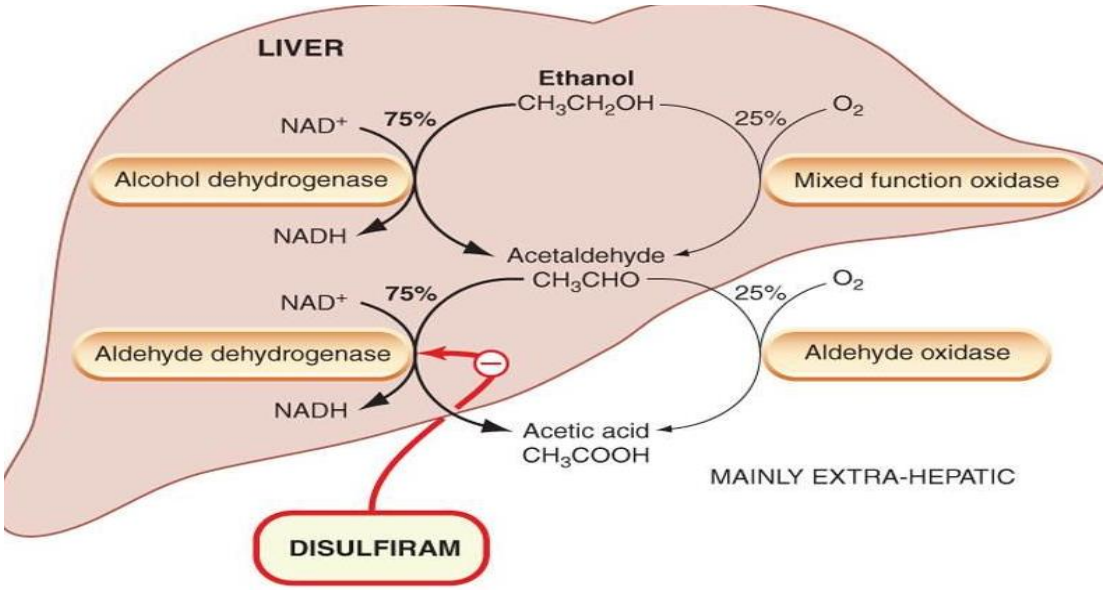
Use: Drug-Drug Interactions: Alcohol has depressant actions on the CNS that are similar to other centrally acting drugs such as barbiturates, benzodiazepines, general anesthetics and solvents, and anti-convulsants. Alcohol also enhances the sedative effects of antihistamines that are commonly used in the treatment of nasal congestion. Combining these medications with alcohol can result in significant CNS depression and reduced ability to safely carry out normal functions such as automobile driving. Alcohol can also enhance the hepatotoxic effects of acetaminophen (Tylenol) and the gastric irritating effects of NSAIDs, thus increasing the risk for development of gastritis and upper GI bleeding. Chronic alcohol use can interfere with the metabolism of certain drugs due to enhanced levels of liver enzymes.

DISULFIRAM

It is a carbamate derivative used as an alcohol deterrent. It is a relatively nontoxic substance when administered alone, but markedly alters the intermediary metabolism of alcohol.

When alcohol is ingested after administration of disulfiram, blood acetaldehyde concentrations are increased, followed by flushing, systemic vasodilation, respiratory difficulties, nausea, hypotension, and other symptoms (acetaldehyde syndrome). It acts by inhibiting aldehyde dehydrogenase.

Mechanism of action: It blocks the oxidation of alcohol at the acetaldehyde stage during alcohol metabolism following disulfiram intake causing an accumulation of acetaldehyde in the blood producing highly unpleasant symptoms. It blocks the oxidation of alcohol through its irreversible inactivation of aldehyde dehydrogenase, which acts in the second step of ethanol utilization.



A systematic diagram of Disulfiram inhibit the aldehyde dehydrogenase

In addition, it competitively binds and inhibits the peripheral benzodiazepine receptor, which may indicate some value in the treatment of the symptoms of alcohol withdrawal.

Pharmacological action: It produces a sensitivity to alcohol which results in a highly unpleasant reaction when the patient under treatment ingests even small amounts of alcohol. It blocks the oxidation of alcohol at the acetaldehyde stage during alcohol metabolism following disulfiram intake, the concentration of acetaldehyde occurring in the blood may be 5 to 10 times higher than that found during metabolism of the same amount of alcohol alone. Accumulation of acetaldehyde in the blood produces a complex of highly unpleasant symptoms referred to hereinafter as the disulfiram-alcohol reaction. This reaction, which is proportional to the dosage of both disulfiram and alcohol, will persist as long as alcohol is being metabolized. It does not appear to influence the rate of alcohol elimination from the body. Prolonged administration of disulfiram does not produce tolerance; the longer a patient remains on therapy, the more exquisitely sensitive he becomes to alcohol.

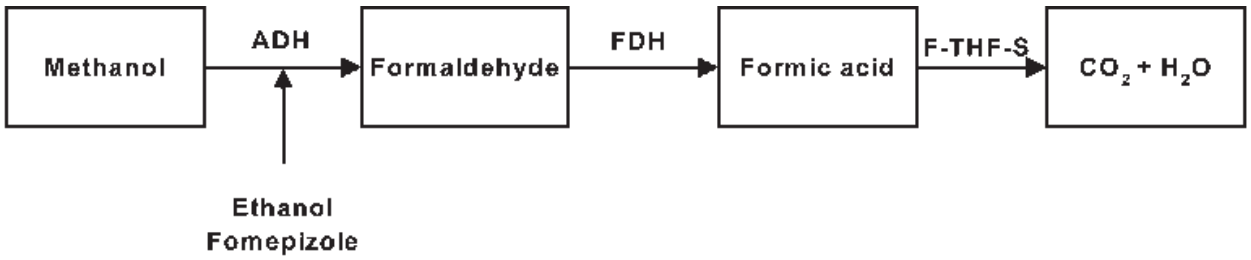
Treatments: The subsequently disulfiram is given 1 g on 1st day, 0.75 g on 2nd day, 0.5 g on 3rd and 0.25 g. It is sensitization to alcohol develops after 2-3 hours of first dose, reaches its peak at ~12 hours and lasts for 7–14.

Side effects of disulfiram (as such) are infrequent, include rashes, metallic taste, nervousness, malaise and abdominal upset. It inhibits a number of other enzymes as well including alcohol dehydrogenase, dopamine B hydroxylase and several cytochrome P450 isoenzymes. Thus, it prolongs t%2 of many drugs.

Drug: Esperal, Antadict 250 mg tab.

METHANOL

Methanol is a highly toxic alcohol that is found in a variety of commercial products, including antifreeze, windshield wiper fluid, some racing car fuels, paint thinner, and canned solid fuel for keeping food warm. There were 10 reported deaths from 1958 exposures to methanol in 2009 (Figure 1). The estimated minimum lethal dose for adults is approximately 15 – 30 ml. There are also reports of patients surviving ingestions greater than 400 ml without sequelae



ADH: alcohol dehydrogenase; FDH: formaldehyde dehydrogenase
F-THF-S: 10-formyl tetrahydrofolate synthetase

Metabolism of Methanol

It is metabolized to formaldehyde and formic acid by alcohol and aldehyde dehydrogenases respectively, but the rate is 1/7th that of ethanol. Like ethanol, it follows zero order kinetics and $t_{1/2}$ of 20-60 hours has been measured. It also is a CNS depressant, but less potent than ethanol. Toxic effects of methanol are largely due to formic acid, since its further metabolism is slow and folate dependent. A blood level of >50 mg/dl methanol is associated with severe poisoning. Even 15 ml of methanol has caused blindness and 30 ml has caused death; fatal dose is regarded to be 75-100 ml.

Manifestations of methanol poisoning are: vomiting, headache, epigastric pain, uneasiness, dyspnoea, bradycardia and hypotension. Delirium may occur and the patient may suddenly pass into coma. Acidosis is prominent and entirely due to production of formic acid. The specific toxicity of formic acid is retinal damage. Blurring of vision, congestion of optic disc followed by blindness always precede death which is due to respiratory failure.

LOCAL ANESTHETIC AGENTS

Local anaesthetics are drugs which cause reversible loss of sensory perception of pain in a particular area of the body. It is the temporary loss of sensation or pain in one part of the body produced by a topically applied or injected agent without depressing the level of consciousness.

CLASSIFICATION LOCAL ANESTHETIC AGENTS

Injectable anesthetic

Low potency, short duration

Procaine, Chloroprocaine

Intermediate potency and duration

Lidocaine (Lignocaine), Prilocaine

High potency, long duration

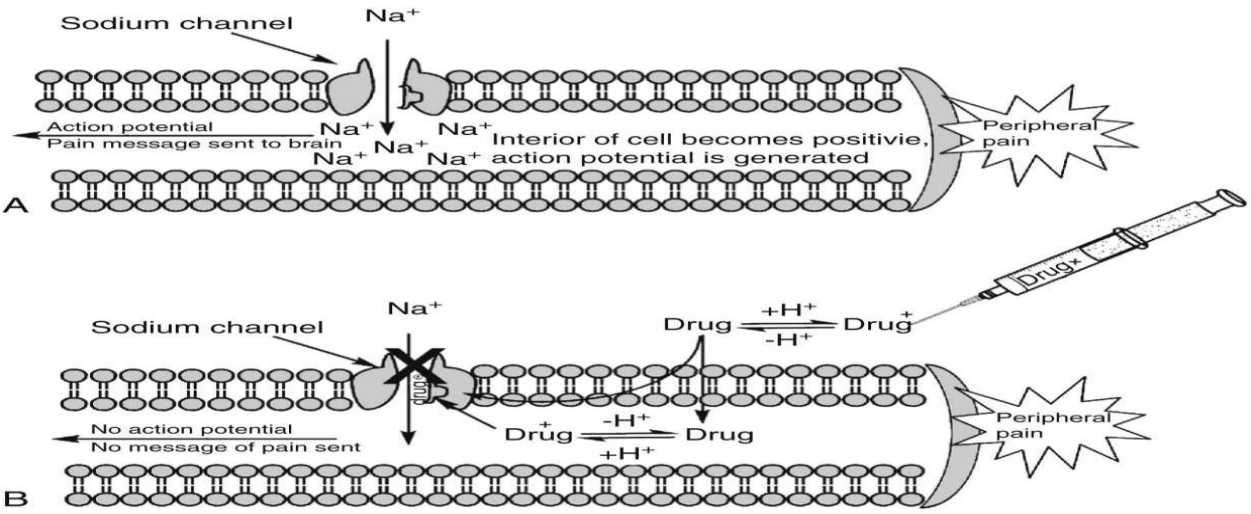
Tetracaine (Amethocaine), Bupivacaine, Ropivacaine

Surface anesthetic

Soluble: Cocaine, Lidocaine, Tetracaine.

Insoluble: Benzocaine ButylaminobenzoateOxethazaine

Mechanism of action:



The mechanism of local anesthetics connects with the ion channels, nerve, and depolarization. Local anesthetics block the conduction in peripheral nerves that inhibited the nerve to excited and created aesthesia. The anesthetic is a reversible reaction. It binds and activates the sodium channels. The sodium influx through these channels and depolarizes the nerve cell membranes. It

also created high impulses along the way. As a result, the nerve loses depolarization and the capacity to create the impulse, the patient loses sensation in the area supplied by the nerve.

Pharmacological action of LA:

CNS system: Local anaesthetics produce stimulation of central nervous system. This cause euphoria, restlessness and tremors. Cocaine causes addiction, which is due to its euphoric effect.

Cardiovascular system: Local anaesthetics produce vasodilatation and hypotension is occurred. Cocaine produces vasoconstriction due to which hypertensive effect occurs. All local anaesthetics produce a depressant effect on the myocardium.

Smooth muscles: Local anaesthetic produce relaxant effect on smooth muscles and there is neuro muscular blockade.

Blood vessels: LAs tends to produce in fall in blood pressure. This is primarily due to sympathetic blocked but higher dose cause direct relaxation of arteriolar smooth muscle

Absorption of local anaesthetics: Local anaesthetics are not absorbed from unbroken skin, absorption occurs through mucous membranes. The local anaesthetics are administered by subcutaneous infiltration. Vasoconstrictors like adrenaline prolong their duration of action.

They are metabolised in the liver and in plasma by hydrolysis.

Side effect of local anaesthetic drugs

i) Local anaesthetics cause cardiovascular symptoms like hypotension and there may be cardiac arrest.

ii) The allergic reactions occur due to intolerance like dermatitis, anaphylactic shock, asthmatic attack.

iii) They cause excitation, euphoria, restlessness, convulsions, tremors.

Uses of local anaesthetics:

1) They are indicated for systemic use for antiarrhythmic effect.

2) They are used as surface anaesthesia for reducing pain due to burns, ulcers, fissures.

3) As infiltration anaesthesia as local anaesthetic to anaesthetise nerve endings by biter administering as subcutaneous injection.

4) It causes nerve block anaesthesia when it is injected close to the specific nerve.

5) It is used for spinal anaesthesia when injected into sub arachnoid space.

Comparison features of General Anaesthetics and Local Anaesthetics

Site	General Anaesthetics	Local Anaesthetics
Site of action	CNS	Peripheral Nerves
Area of body involve	Whole body	Particular area
Major Surgery	Preferred	Cannot be used
Minor Surgery	Not Preferred	Preferred
Poor Health Patients	Risky	Safe
Consciousness	Lost	No effect
Non cooperative patient use	Possible	Not Possible
Care of vital organs	Essential	Not Needed

LOW POTENCY, SHORT DURATION

PROCAINE

It is an analog of cocaine.

It is a local anesthetic of the ester type that has a slow onset and a short duration of action.

Mechanism of action:

It acts mainly by inhibiting sodium influx through voltage gated sodium channels in the neuronal cell membrane of peripheral nerves.

The influx of sodium is interrupted, an action potential cannot arise and signal conduction is thus inhibited.

Pharmacokinetics: It is an ester anesthetic. It is metabolized in the plasma by the enzyme pseudo cholinesterase through hydrolysis into para-aminobenzoic acid (PABA), which is then excreted by the kidneys into the urine.

Side effects: It causes constant wetting of the skin, with the solution of procaine hydrochloride, dermatitis, dryness and cracking of the skin.

Uses: It is mainly used for infiltration anaesthesia, peripheral nerve block, and spinal block. It is used as a local anesthetic primarily in oral surgery.

Brand Name: Novocain 20 mg/ml,

Precautions

Before injecting the LA, Aspirate lightly to avoid intravascular injection.

Inject the LA slowly and take care not to exceed the maximum safe dose, especially in children.

Interactions

Propranolol (probably other B-blockers also) may reduce metabolism of lidocaine and other amide LAs by reducing hepatic blood flow.

Vasoconstrictor (adrenaline) containing LA should be avoided for patients with ischaemic heart disease, cardiac arrhythmia, thyrotoxicosis, uncontrolled hypertension, and those receiving blockers (rise in BP due to unopposed action) or tricyclic antidepressants (uptake blockade of Adr).

INTERMEDIATE POTENCY AND DURATION

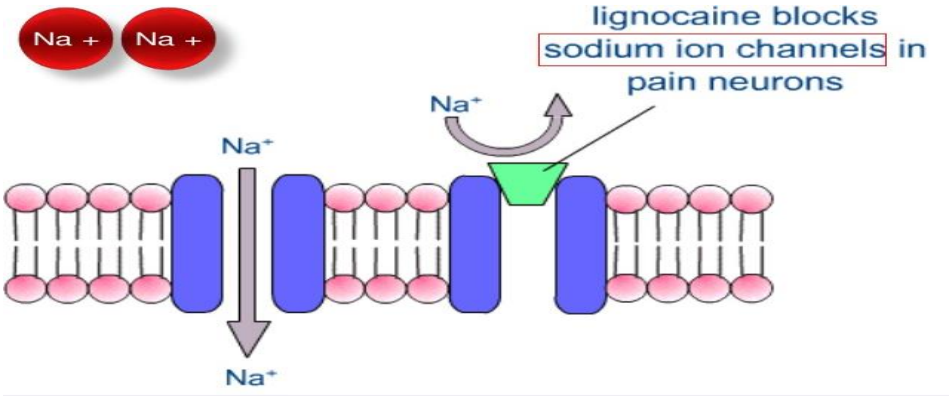
LIDOCAINE (LIGNOCAINE):

It is a local anesthetic and cardiac depressant used as an antiarrhythmic agent.

Its actions are more intense and its effects more prolonged than those of procaine but its duration of action is shorter than that of bupivacaine or prilocaine.

Mechanism of action:

It is stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses thereby effecting local anesthetic action.



It alters signal conduction in neurons by blocking the fast voltage gated sodium (Na+) channels in the neuronal cell membrane that are responsible for signal propagation.

With sufficient blockage the membrane of the postsynaptic neuron will not depolarize and will thus fail to transmit an action potential.

Indications: Peripheral nerve block, epidural, spinal, surgical anaesthesia, insect bites, minor burns, cystoscopy, painful cystitis.

Contraindications: Hypersensitivity, child below 12 years of age, elderly, hepatic impairment, pregnancy.

Side effects: Vomiting, nausea, blurred vision, tinnitus, constriction of the pupils of eyes, anaphylaxis, status asthamticus, urticaria, rash, edema, tissue necrosis, cardiac arrest, hypotension, fetal bradycardia, myocardial depression, tremors, shivering, drowsiness, loss of consciousness, convulsions, disorientation.

Pharmacokinects: Onset action 4 to 17 minutes, duration of action 3 to 6 hours, plasma half-life by i.v. injection is about 13 minutes by 1M injection 90 minutes; half-life is increased. It is metabolised by liver, crosses placenta, excreted in urine.

Drug interaction: It decreases the action of lidocaine. Lidocaine with other drugs like MAOI's tricyclic antidepressants, phenothiazine cause hypertension.

Dosage:. Lidocaine may be given by intra venous route 50 to 100mg alimentary bolus, followed by 20 to 40mg every 10 to 20 minutes or 1 to 3mg/minute infusion.

Uses: It is used as a local anesthetic and cardiac depressant. It is used as an antiarrhythmia agent.

PRILOCAINE: It is a local anesthetic that is similar pharmacologically to lidocaine.

Mechanism of action:

It binds to the intracellular surface of sodium channels which blocks the subsequent influx of sodium into the cell. Action potential propagation and never function is, therefore, prevented. This block is reversible and when the drug diffuses away from the cell, sodium channel function is restored and nerve propagation returns.

The antiarrhythmic actions are mediated through effects on sodium channels in Purkinje fibers.

Use: It is used as a local anaesthetic and is often used in dentistry.

Brand name: 4% Citanest Plain Dental 40 mg, Dentsply 4% Prilocaine Hydrochloride Dental Injection, Livixil Pak

HIGH POTENCY, LONG DURATION

BUPIVACAINE: Bupivacaine is local anaesthetics have similar action to lignocaine but duration is long. It is used in local and spinal anaesthesia. It may also be used to produce surface anaesthesia.

Mechanism of action: It binds to the intracellular portion of sodium channels and blocks sodium influx into nerve cells, which prevents depolarization. In general, the progression of anaesthesia is related to the diameter, myelination and conduction velocity of affected nerve fibers.

Clinically, the order of loss of nerve function is as follows:

(1) Pain

(2) Temperature

(3) Touch

(4) Proprioception, and

(5) Skeletal muscle tone.

The analgesic effects of Bupivicaine are thought to potentially be due to its binding to the prostaglandin E_2 receptors, subtype EP1 (PGE_2EP_1), which inhibits the production of prostaglandins, thereby reducing fever, inflammation, and hyperalgesia.

Indication: Local anaesthesia, spinal anaesthesia.

Side effects: Hypotension, respiratory depression, muscular twitchings, with over dosen convulsions may occur. Serious fetal bradycardia may be produced if used during labour.

Treatment of overdose: Injection atropine sulphate.

Brand names: Bupivacaine : Injection Bupivan, Marcain, Sensorcaine, Anawin, 5mg per ml.

ROPIVACAINE:

It is an local anesthetic drug. It can be used for nerve block for relief of post-operative and labour pain. It is a newer congener of bupivacaine. It is equally long acting and is mild cardio toxic drug.

Indication: Peripheral nerve block, central neural block vaginal block, spinal anaesthesia.

Dosage: Varies according to route of anaesthesia. It is available as injection 2mg, 5, 7.5mg per ml.

Contraindications: Hypersensitivity, liver disease, children below 12 years, elderly patients/persons. With precautions use in pregnancy and in patients having severe drug allergy.

Side effects: Vomiting, nausea, anaphylaxis, respiratory arrest, status asthma-ticus. Blurred vision, tinnitus, constriction drowsiness, tremors, shivering, convulsions, skin rash, urticaria edema, skin discoloration at injection site, tissue necrosis, cardiac arrest, fetal bradycardia, hypertension, cardiac arrest, myocardial depression, bradycardia.

Pharmacokinetics: Onset action 2 to 8 minute, duration of action 3 to 6 hour, metabolized by liver, excreted by kidneys.

Drug interactions: Hypertension is caused by drugs like tricyclic antidepressants, MAOI's phenothiazines, chloroprocaine decrease action of ropivacaine. Dysrhythmias is caused by epinephrine, halothane and enflurance.

SURFACE ANAESTHETIC

COCAINE: It was the first recognized LA. Its addictive properties and toxicity, i.e., psychological and physical dependence, mood alteration, CNS and cardiac excitation, and intense vasoconstriction preclude its clinical use in dentistry.

Mechanism of action: It produces anaesthesia by inhibiting excitation of nerve endings or by blocking conduction in peripheral nerves. This is achieved by reversibly binding to and inactivating sodium channels. Sodium influx through these channels is necessary for the depolarization of nerve cell membranes and subsequent propagation of impulses along the course of the nerve. It is the only local anesthetic with vasoconstrictive properties.

Indication: The only indication for cocaine is in ocular anaesthesia. It causes constriction of conjunctival vessels. It instilled into the eye it blanches the conjunctiva and dilates the pupil. It cause dilatation of the pupil, rise in body temperature, rise in blood sugar level and raises blood..

Side effects: Idiosyncrasy, headache, faintness, loosening of corneal epithelium and corneal erosion.

Poisoning: In acute cocaine poisoning, convulsions may be treated with diazepam, respiratory depression with the artificial respiration.

Uses: It is a local anesthetic indicated for the introduction of local (topical) anesthesia of accessible mucous membranes of the oral, laryngeal and nasal cavities.

Brand name: Cocaine Hydrochloride Top Sol 40mg/ml, Cocaine Hydrochloride Topical Sol 10%, pressure.

LOCAL ANAESTHESIA TECHNIQUES

1) **Surface anaesthesia:** It is produced by topical application of surface anaesthetics to mucous membranes. The superficial layer is anaesthetised. Except for lidocaine/prilocaine are capable to anaesthetizing the skin intact.

2) **Infiltration anaesthesia:** Dilute solutions of local anaesthetic is infiltrated under the skin in the area of surgical operation. It block sensory nerve endings. Lidocaine 30 to 60 minute, bupivacaine 120-180 minutes have duration of nerve block.

3) **Conduction block:** The local anaesthetic is injected around nerve so that the area distal to injection is anaesthetised and paralysed. Lidocaine 1-2% with intermediate duration of action is commonly used, for long lasting anaesthesia bupivacaine may be used. The main purpose of nerve block anaesthesia is to abolish pain and other sensations.

4) **Spinal anaesthesia**: The local anaesthetic is injected in the sub arachnoid space between L2-4 or L3-4 lumbar vertebra i.e. below the lower end of spinal cord. It cause anaesthesia to lower abdomen and limbs that are anaesthetised and paralysed. Spinal anaesthesia is used for surgery of lower limbs, pelvis, lower abdomen, fracture setting, obstetric treatment, caesarean operation. The duration of spinal anaesthesia depends on the drug used and its concentration. Women during late pregnancy need less dose for spinal anaesthesia. It is because inferior vena ceva compression results engorgement of vertebral column due to which there is decrease in the capacity of subarachnoid space.

The spinal anaesthesia has folowing advantages over general anaesthesia

(1) It is safe.

(2) It produces analgesia and muscle relaxants without loss of consciousness. (3) Diabetes, cardiac, renal disease, pulmonary disease do not interfere much and poses less problem in treatment.

Complications of spinal anaesthesia: The complications of S.A. are

(1) Headache: which is due to seepage of cerebrospinal fluid. Use small bore needle to minimise this effect.

(2) Vomiting and nausea: vomiting and nausea occurs after abdominal surgery. It is due to reflexes initiated by traction on abdominal viscera. It can be controlled with opioid analgesics.

(3) There is hypotension.

(4) Respiratory paralysis.

(5) **Cauda equina syndrom**

Septic meningitis, it is due to infection introduced/entered during lumbar puncture, though the chances are rare.

Spinal anaesthesia is contra indicated in uncooperative or mentally ill patients, infants and children, vertebral abnormalities like lumbar lordosis, kyphosis, and A patient with hypotension and hypovolamia. Lidocaine and bupivacaine are popular drugs for epidural abdomen surgery.

5) Epidural anaesthesia

Anaesthesia. Action of both drugs is prolonged by addition of adrenaline. Epidural anaesthesia is technically difficult than the spinal anaesthesia and large quantity of drug is needed. Epidural anaesthesia is of three types depending on the site of injection.

Thoracic injection is administered in the mid thoracic region. The epidural space in this region is narrow, smaller volume of needed and a wide segmental band of analgesia involving the middle thoracic dermatomes is produces. Thoracic anaesthesia is used for pain relief of thoracic or upper

Lumber anaesthesia: Large volume of drug is needed because epidural space is vide. It produces anaesthesia of lower abdomen, pelvis and hind limbs.

Caudal anaesthesia: Injection is given in the sacral canal through the sacral hiatus and produces anaesthesia of pelvic and perianal region. It is used for vaginal delivery, a rectal and genitourinary operation.

Precautions for local anaesthetics

- The local anaesthetic injection should be administered slowly, take care not to inject excess dose. The maximum safe dose should be given to patient, adult as well in children during local anaesthetics.
- Before injecting the local anaesthetic drug aspirate to avoid intra vascular injection.
- The drugs like propranolol may reduce metabolism.
- If the patient is suffering from ischaemic heart disease or thyrotoxicosis vaso constrictors local anaesthetics containing adrenaline should be avoided, also incase of uncontrolled hypertension, patient receiving tricyclic antidepressants.

When the patient is to be given anaesthesia. The following points must be remembered:

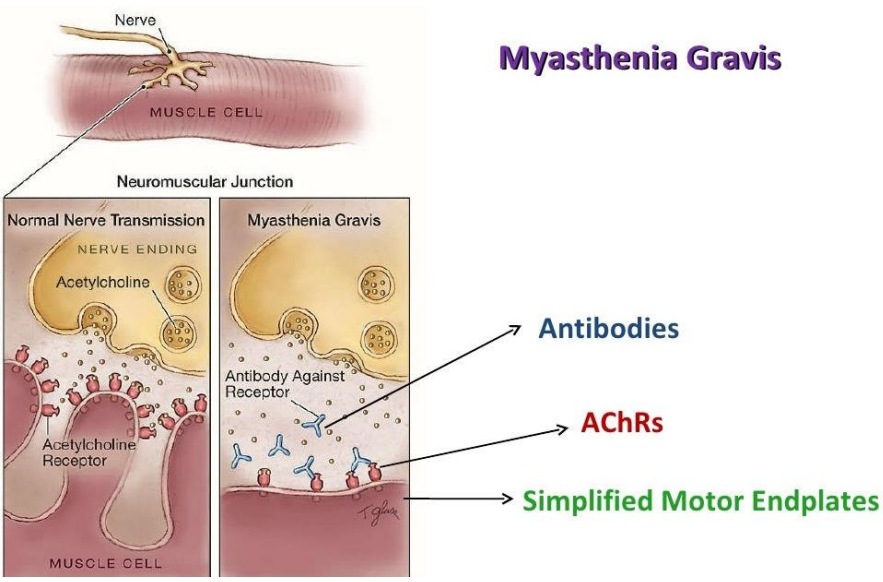
- The Psychology, Physical condition with reference to respiratory system liver, kidney any be checked disease and of cardiovascular system, CNS system functions, disease if any be checked and kept in mind.
- The patient suffering from disease like Hypertension, Diabetes mellitus, Diabetes insipid us and the treatment taken by the individual be recorded before anaesthesia is to be given.

- The anxiety state of individual by noted and observed. There is difficulty of anaesthesia in anxiety state more dose is needed. There is risk of arrhythmia in some anaesthetic patients.
- The opioids in small doses act synergistically to make the patient calm.
- It should be observed that in case of allergy to patient with anaesthetic drug. The drugs like Diphenhydramine promethazine also cause sedation and acts as antiemetic to the patient.
- The proper medicines cause help in induction of smooth and deep anaesthesia. The dose is also less required.
- During course of anaesthesia provide more dose of insulin to diabetes mellitus patients. The drug halothane sensitizes to our heart to adrenaline and cardiovascular collapse may occur.
- Increase the patient is on corticosteroid treatment, give the patient injection Hydrocortisone 100mg to avoid stress of anaesthesia and also avoid cardiovascular collapse.

DRUG USED IN MYASTHENIA GRAVIS

Myasthenia gravis is a condition where muscles become easily tired and weak. It is due to a problem with how the nerves stimulate the muscles to tighten (contract). The muscles around the eyes are commonly affected first. This causes drooping of the eyelid and double vision. Treatment is usually effective. Each muscle is supplied by a nerve which splits into smaller nerves that spread along the muscle fibres. There is a tiny gap between the ends of the nerves and the surface of the muscle. This gap is called the neuromuscular junction.

The brain sends messages down the nerves to the muscles it wants to tighten (contract). The nerve endings release a chemical called a neurotransmitter into the neuromuscular junction. This neurotransmitter is called acetylcholine. The acetylcholine quickly attaches to receptors on the muscles. This in turn triggers the muscle to tighten. There are many acetylcholine receptors on each muscle fibre. Myasthenia Gravis is an autoimmune disorder affecting about 1 in 10000 populatoin. It is due to development of antibodies directed to nicotinic receptors at muscle end plate which reduction in number of free Nm cholinreceptor to 1/3 of normal or less.



Myasthenia gravis

DRUGS USED IN TREATMENT OF MYASTHENIA GRAVIS

(A). Anticholinesterase medicines: These medicines delay the breakdown of acetylcholine when it is released from the nerve endings. More acetylcholine is then available to compete against the abnormal antibodies for the muscle receptors, which then improves the strength of the muscles. These medicines work best when the disease is mild and the level of antibody is low. The most commonly prescribed anticholinesterase medicine is called pyridostigmine.

(B) Removal of the thymus (thymectomy) This is an option in some cases. A thymectomy can improve symptoms for some people with myasthenia gravis.

Steroid medication: Steroid medication such as prednisolone tablets is often used in the treatment of myasthenia gravis. Steroids suppress the immune system and prevent the abnormal antibodies from being made. A low dose, often on alternate days, is usually enough for people where symptoms only affect muscles around the eye. Higher doses may be needed to prevent symptoms if muscles other than around the eyes are affected. It may take several months to bring symptoms under control with steroids. Once improved, the dose is commonly reduced gradually to find the lowest dose needed to prevent symptoms. In some people, the dose of steroid needed to control the disease may be quite high and lead to side-effects.

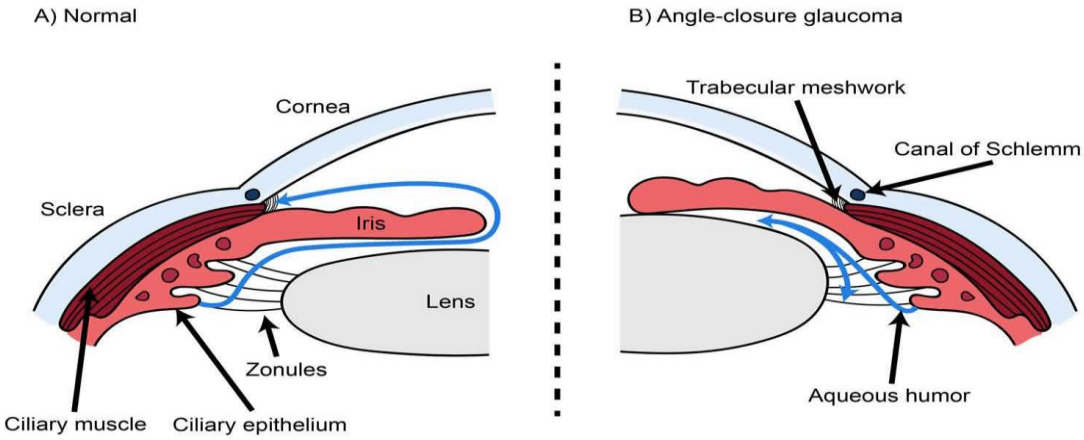
Immunosuppressant medicines: An immunosuppressant medicine such as azothiaprine may be advised in addition to steroid medication. These medicines work by suppressing theimmune system

Combinations of medicines: A steroid plus an immunosuppressant tends to work better than either alone. Also, the dose of steroid needed is often less if an immunosuppressant is added which reduces the risk of side-effects with steroids

Other: Some drugs can interfere with neuromuscular transmission and exacerbate the symptoms of myasthenia gravis. Those most often implicated include aminoglycoside antibiotic, ß-adrenoceptor antagonists, phenytoin, chloroquine and penicillamine. There is also altered sensitivity to neuromuscular junction blockers, with increased response to competitive (non-depolarising) neuromuscular junction blockers but resistance to depolarising neuromuscular junction blockers.

DRUG USED IN GLAUCOMA

Glaucoma is a disease that damages the eye's optic nerve. It usually happens when fluid builds up in the front part of the eye. That extra fluid increases the pressure in the eye, damaging the optic nerve.



A systematic presentation of open angle and narrow glaucoma

Primary open-angle glaucoma: This is the most common type of glaucoma. It happens gradually, where the eye does not drain fluid as well as it should (like a clogged drain). As a result, eye pressure builds and starts to damage the optic nerve. This type of glaucoma is painless and causes no vision.

Angle-closure glaucoma: It is (also called "closed-angle glaucoma" or "narrow-angle glaucoma").

This type happens when someone's iris is very close to the drainage angle in their eye.

The iris can end up blocking the drainage angle. You can think of it like a piece of paper sliding over a sink drain. When the drainage angle gets completely blocked, eye pressure rises very quickly. This is called an acute attack.

DRUGS USED IN THE TREATMENTS OF GLAUCOMA

ATROPINE

Atropine is a naturally occurring "belladonna alkaloid" that can be extracted from plants such as deadly nightshade (Atropa belladonna), Jimson weed & mandrake. It is a competitive antagonist of all five known muscarinic receptors (m1-m5), and when administered systemically, it antagonizes the "rest and digest" effects produced by the parasympathetic nervous system. It has numerous medical uses, including temporary relief from bradycardia or AV-block, as an antidote for cholinesterase poisoning or poisoning by mushrooms containing muscarine.

SCOPOLAMINE . It is a belladonna alkaloid that is well absorbed through the skin, and readily crosses the blood brain barrier (much more than atropine & most other belladonna alkaloids). It is most commonly used for preventing motion sickness and nausea associated with the use of opioid analgesia.

TROPICAMIDE & HOMATROPINE . These are short acting antimuscarinic drugs commonly applied as eye drops prior to retinal exams. They produce mydriasis by inhibiting the contraction of the iris sphincter muscles that are under control of the parasympathetic nervous system. They are sometimes co-administered along with eye drops containing a sympathomimetic (such as phenylephrine), which also produce mydriasis by causing contraction of the dilator or radial muscles of the iris that are under sympathetic control.

IPRATROPIUM BROMIDE It is a quaternary analog of atropine that is used in an inhaled dosage form for preventing bronchospasm associated with COPD and asthma.

GLYCOPYRROLATE : A quaternary analog of atropine used most commonly as a pre-operative medication to reduce salivary & respiratory secretions, and in combination with neostigmine to reverse the effects of non-depolarizing skeletal muscle relaxants (e.g. pancuronium) at the end of surgery.

MISCELLANEOUS:

Numerous prescription & over-the-counter medications have anticholinergic properties or side effects. While the impact of a single drug may be relatively small, the cumulative effect of multiple drugs taken concomitantly (e.g. for different clinical indications) can be significant, especially in elderly patients.

Long answer type Questions (10 Marks)

1).What are the different stages of general anesthetics.

2).Write the Classification of Barbiturates. Explain the mechanisun of action, pharmacology and uses of barbiturates.

3).Write the classification of skeletal muscle relaxant. Explain the pharmacology and uses of any one of centraly acting muscle relaxant.

4).Write the classification of anti epileptics with examples. Explain the pharmacology, side effects and uses of phenytoine.

5).Explain the steps involved in the neurohumoral transmission in the CNS.

6). Explain the steps involved in the neurohumoral transmission of GABA

7).What are the stages of general anesthetics.

8).Explain the pharmacology, side effects and uses of alcohol .

9).Write the Classification of Barbiturates. Explain the mechanisum of action pharmacology and uses of any one benzodiazepine.

Short answer type questions (5Marks)

1).Write the mechanism of action and pharmacology of sodium valproate.

2).Write the pharmacology of gabapentin.

3). What is the therapeutic application of Disulfiram .

4).What is the role of GABA in central nervous system.

5).What is the role of glycine in central nervous system.

6).Write the classification of antiepleptics with examples.

7) Write the classification of general anesthetics with examples.

8).Explain the pharmacology of ketamins.

9).What is the role of glutamate in central nervous system.

10) What is the role of serotonin in central nervous system.

11).What is the role of dopamine in central nervous system.

12).Write a note on pre-anesthetic medication

Very Short answer type questions (2 Marks)

1. What are general anaesthesia
2. Define pre-anaesthesia medication.
3. What is the chief complication of general anaesthesia.
4. Define Neurohumoral transmitter
5. Discuss the GABA.
6. Explain the function of GABA in the brain.
7. Define Disulfiram
8. Derscribe Glycine.
9. What is Mesolimbic and Mesocortical Pathway
10. Explain the function of Dopamine.
11. Classify the serotonin receptor
12. Define following term
13. Define Myasthenia Gravis
14. Define Glaucoma
15. Define Sedative and Hypnotics
16. Define Glutamate neurotransmitter
17. What is Alcohal.
18. Explain Methenol