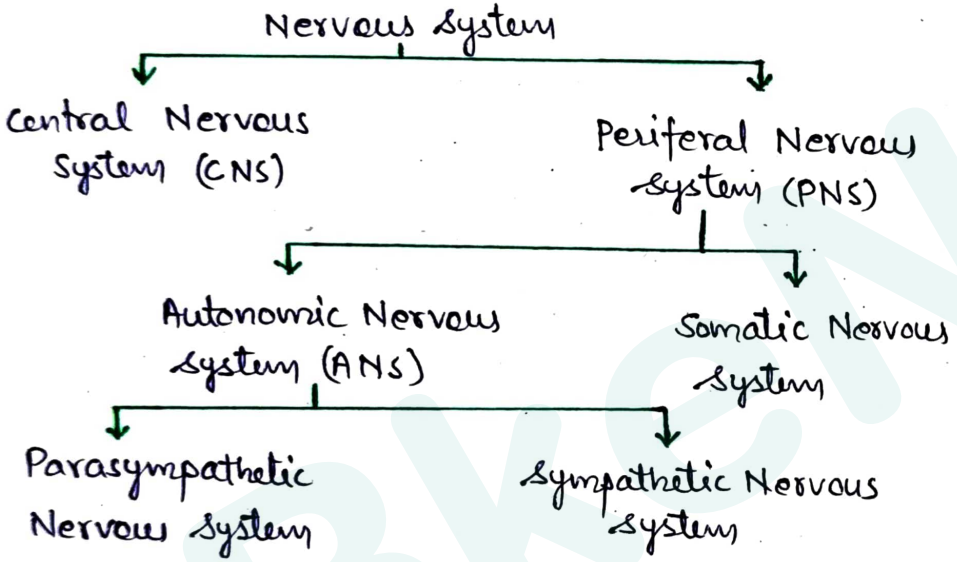
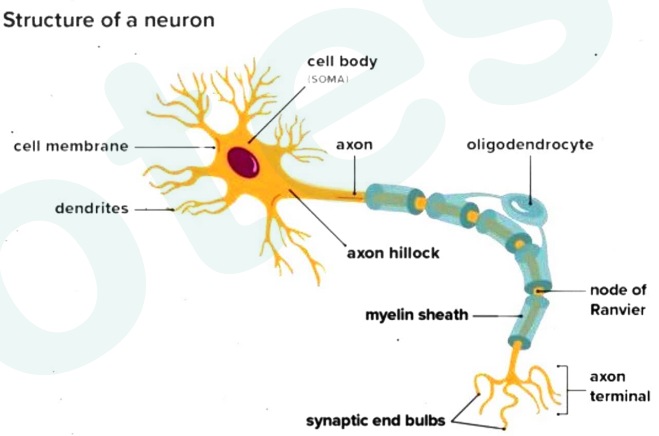
UNIT-2

Drugs Acting On Autonomic Nervous System



The CNS covers the brain and spinal cord. The PNS includes all neurons outside the CNS. Any sensory input of stumes from the periphery to the CNS is carried by afferent neurons and signals from the CNS are carried by efferent neurons to the periphery as a feedback. ANS controls and regulates the involuntary responses like breathing, digestion, etc.

A Neuron



A neuron is the fundamental unit of nervous system. They receive and transmit signals to different parts of the body.

Parts of neuron

Cell Body (or Soma) → Each neuron has a cell body with a nucleus, golgi body, ER, mitochondria, and other components.

Dendrites → These are branch-like structures that receive messages from the other neurons and allow the transmission of messages to the cell body.

Axon → Axon is a tube-like structure that carries electrical signals from the cell body to the axon terminals that pass the signals to another neuron.

Synapse → It is the chemical junction of b/w the terminal of one neuron and the dendrites of the other neuron.

Neurotransmitters

Neurotransmitter is a type of chemical messanger that transmits signals across a chemical synapse, from one neuron to another. The electrical signals that travel along the axon are briefly converted into chemical signals through neurotransmitters.

Sympathetic Nervous System (SNS)

SNS is triggered during stress, emergencies or fight or flight situations.

Neurotransmitters:

primary: Norepinephrine (noradrenaline)
secondary: Epinephrine (adrenaline)

effects of SNS: Increased heart rate, dilation of pupils, bronchodilation, elevated blood pressure and decreased digestive activity.

Parasympathetic Nervous System (PSNS)

PSNS eases out the situations triggered by SNS. PSNS and SNS works against the effects of each other.

Neurotransmitter: Acetylcholine (ACh)

Effects of PSNS

- slowed heart rate
- constriction of pupils
- bronchoconstriction
- increased digestive activity
- stimulation of salivary glands

Functions of neurotransmitters

→ Adrenaline make the heart beat faster (during stress)
→ Noradrenaline regulate attention, cognitive function.
→ Dopamine induces feeling of pleasure, addiction, movement and motivation.
→ Ach regulates cardiac contractions & blood pressure.

Adrenergic Neurotransmitters

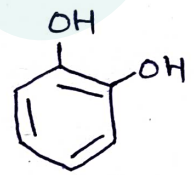
Adrenergic neurotransmitters are the part of sympathetic nervous system. The three adrenergic neurotransmitters are:

(1) Nor-epinephrine or Nor-adrenaline
(2) Epinephrine or Adrenaline
(3) Dopamine

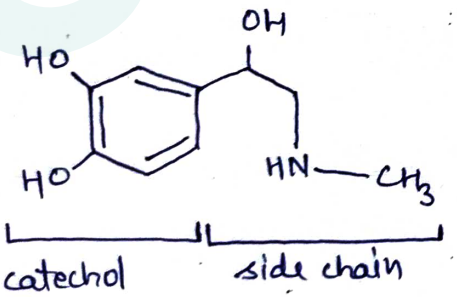
These all three are chemically catecholamines.

A catecholamine is an organic compound that has a catechol nucleus and a side-chain amine.

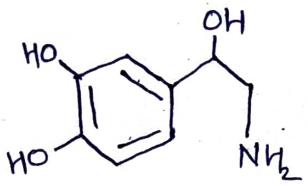
Different side chains attached to catechol form either Norepinephrine, Epinephrine or dopamine.



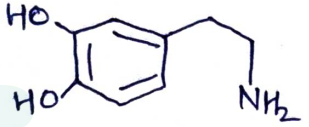
Catechol



Epinephrine

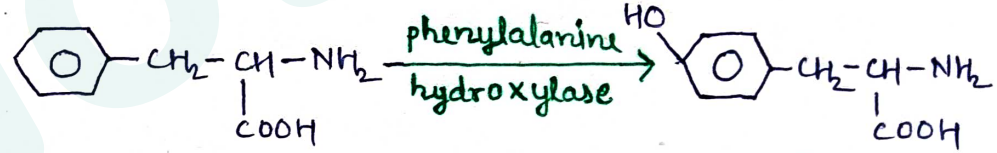


Norepinephrine



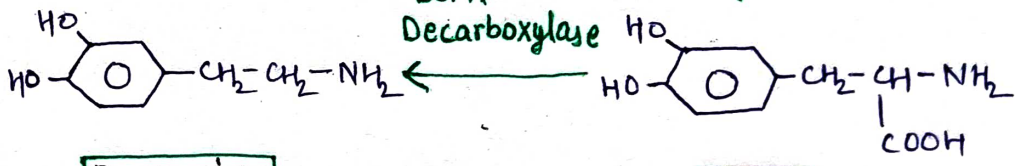
Dopamine

Biosynthesis of Catecholamines



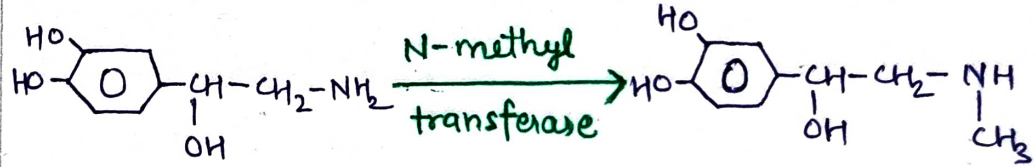
Phenylalanine — Tyrosine

Tyrosine hydroxylase



Dopamine — DOPA

β-hydroxylase



Noradrenaline — Adrenaline

Phenylalanine is an amino acid which acts as a precursor molecule for catecholamine.

→ Phenylalanine is hydrolysed into tyrosine in liver.
→ Tyrosine to DOPA to dopamine in neuronal cytoplasm.
→ Dopamine to noradrenaline inside granules
→ Noradrenaline to Adrenaline in adrenal medulla cells.

Catabolism of Catecholamines

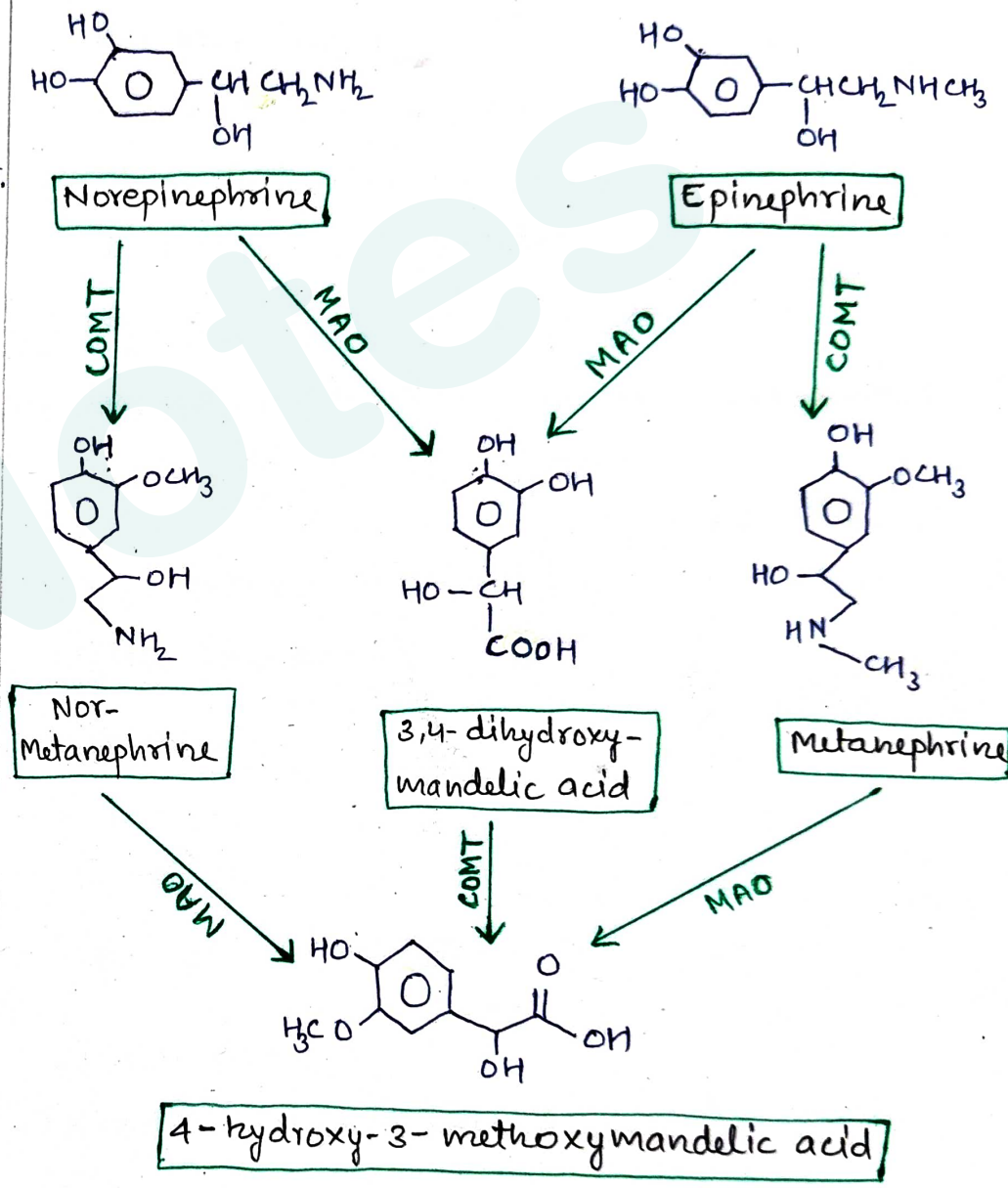
Catabolism results in the termination of action of catecholamines.

For the process of catabolism, it involves the action of mainly two enzymes:

(1) Monoamine oxidase (MAO) : removes amine group ($-NH_2$).

(2) Catechol-O-Methyl Transferase : addition of a methyl group

Catabolism involves nullification (no effect) of catecholamines by these enzymes.



The metabolites (products of catabolism) are excreted via urine.

Adrenergic Receptors and their Distribution

Adrenergic receptors are specialised proteins located on the surface of cells. These receptors bind to catecholamines (adrenaline and noradrenaline) to produce their action.

Types

α-1 Receptors

→ Located in smooth muscles of blood vessels.
→ Activation of α-1 receptors causes vasoconstriction, leading to an increase in BP.
→ Found in eyes' iris muscles, dilates pupil.

α-2 Receptors

→ located in pre-synaptic nerve terminals and pancreas.
→ their activation inhibits the release of further neurotransmitters.

β-1 Receptors

→ predominantly found in heart
→ their activation increases heart rate and force of contraction.

β-2 Receptors

→ Located in bronchial smooth muscle, blood vessels of skeletal muscles.
→ their activation causes bronchodilation and vasodilation, promoting increased blood flow to muscles.

β_3-Receptors

→ present in adipose tissue.
→ activation leads to lipolysis (the breakdown of fats for energy).

clinical significance

Medications that target α-receptors are used for conditions like hypertension, while those acting on β-receptors are used for heart and respiratory issues.

Sympathomimetic Agents (Adrenergic Agonists)

Sympathomimetic agents are the drugs that mimic the effects of the sympathetic nervous system, also known as fight and flight response.

They act on adrenergic receptors, thereby showing the same results as that of epinephrine and norepinephrine.

They are also called as adrenergic agonists.

Classification

(1) Direct-Acting Adrenergic Agonists

These drugs directly bind to adrenergic receptors and stimulate them to produce a biological response.

Norepinephrine, epinephrine and dopamine are naturally occuring molecules that bind to adrenergic receptors.

Examples of direct-acting drugs are xylometazoline, phenylephrine, methoxamine, etc.

(2) Indirect-Acting Adrenergic Agonists

These drugs act indirectly by first stimulating the release of norepinephrine from the terminal nerve endings, producing its actions.

Examples- amphetamine, tyramine, cocaine, etc.

(3) Mixed-Acting Adrenergic Agonists

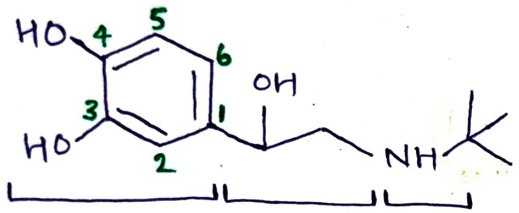
These drugs act both directly and indirectly.

Examples- ephedrine, mephentermine.

SAR of Sympathomimetic Agents

Structure-Activity Relationship (SAR) is an approach to find relationships between chemical structure and biological activity of a drug.

Modification in the structure of a drug alters the activity of drug. Like, suppose, a functional group already present is substituted by any other group, it may decrease or increase the activity of drug.

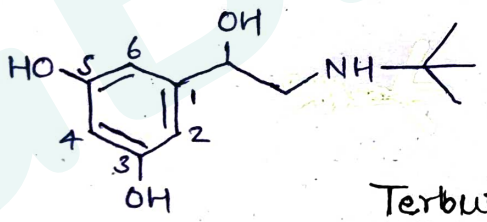


Substitution at different positions alter activity:

(1) Substitution of catechol ring

→ Compound having both 3,4-dihydroxy on benzene ring are active at both α and β receptors.

→ Change in substitution pattern to 3,5-dihydroxy as in terbutaline gives good oral activity.



Terbutaline

(2) Substitution at ethylene

→ Hydroxy group substitution on the β-carbon is essential for activity.

→ substitution at α-carbon decreases the metabolism by MAO.

(3) Substitution at amino group

→ substitution at nitrogen by any other group than alkyl group decreases activity.

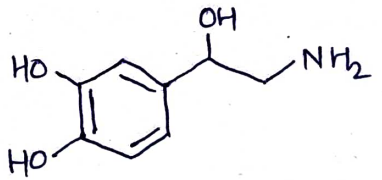
→ Primary (1°) and secondary (2°) amines have good adrenergic activity.

Major Sympathomimetic Drugs

Direct-Acting Drugs

Nor-Epinephrine

It is secreted by adrenal medulla.



MoA

It performs its action by being released into the synaptic cleft where it acts on adrenergic receptors.

on α-adrenergic receptors :- vasoconstriction

on β-adrenergic receptors :- (inotropic) stimulation of heart.

↳ muscular contractility

Uses

→ potent vasoconstrictor

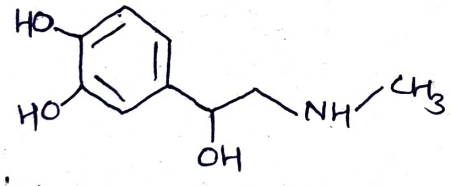
→ maintains BP in acute hypotensive states.

Epinephrine

Epinephrine is a hormone neurotransmitter.

MoA

It binds directly to adrenergic receptors which results in metabolic changes when it binds with α- adrenergic receptors.



Uses

(1) It stimulates the heart, increases heart rate, and BP and relaxes the muscles of intestine.

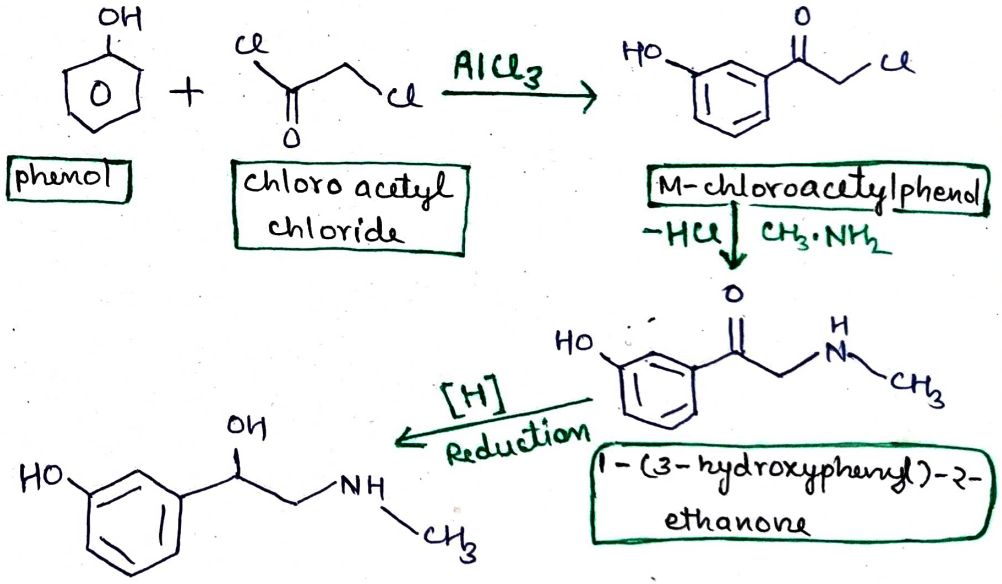
(2) Commonly used in acute allergic disorders.

Phenylephrine *

It acts mostly on α-adrenergic receptors.

It is a vasoconstrictor and used as a nasal decongestant and cardiotonic agent.

Synthesis



MoA

→ Phenylephrine acts selectively on α-1 adrenergic receptors.

→ shows no action on β- receptors.

Uses

→ used to treat nasal congestion, hypotension.

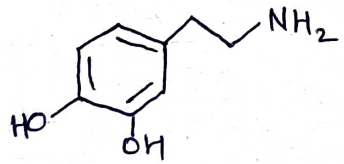
→ Also used in hypotension during spinal anaesthesia.

Dopamine

It does not cross the blood brain barrier and thus has minimal effect on the CNS. It produces a positive inotropic result on heart, i.e., increases the force of muscle contraction of heart.

MoA

It increases heart rate and cardiac contractility. This is done by binding to the β-adrenoreceptors and by releasing nor-epinephrine from the storage sites in sympathetic nerve endings.



Uses

(1) Used in acute congestive heart failure (CHF).

(2) Used in acute pancreatitis.

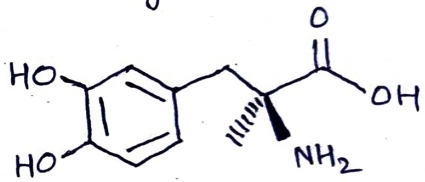
(3) Used in septic shock and surgical shock.

Methyldopa

Methyldopa is an α_2- adrenergic agonist which affects both CNS and PNS. It is mainly used as an antihypertensive agent.

MOA

Methyldopa is converted to methyl norepinephrine in CNS which decreases the action of α_2- adrenoreceptors, leading to the systemic blood pressure decrease.



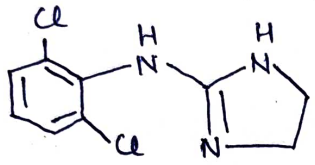
Uses

→ Reduces the levels of dopamine, epinephrine, nor-epinephrine and serotonin in tissues

→ Used in hypertension along with a diuretic.

→ Used in Raynaud's disease.

Clonidine



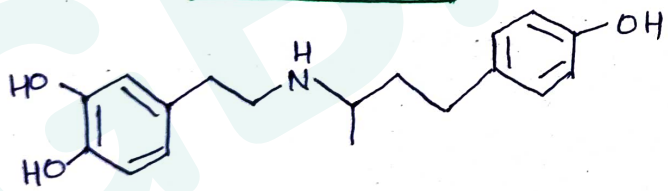
MOA

It is a centrally acting α_2-adrenergic agonist. It decreases blood pressure by crossing the blood brain barrier and acting on the hypothalamus.

Uses

→ Used to treat hypertension
→ Used for managing severe cancer pain
→ for managing the symptoms of menopause.

Dobutamine



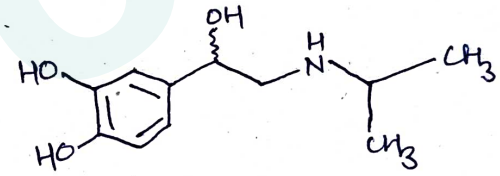
MOA

Dobutamine treats heart failure by strengthening your heart muscle. It increases cardiac output by increasing myocardial contractility and stroke volume through direct stimulation of β_1-receptors.

Uses

It produces inotropic action.

Isoproterenol



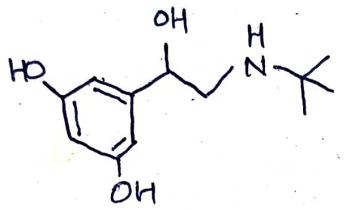
MOA

It relaxes the bronchial smooth muscles by stimulating the β-adrenergic receptors.

Uses

→ Used as a bronchodilator and in bronchial asthma.
→ Used in acute myocardial infarction.
→ It is topically used in ocular hypotension.
→ It is used to arrest premature labour.

Terbutaline



It is the most selective agent which stimulates B_2– adrenoreceptors.

MAD

Adenyl cyclase enzyme catalyses the conversion of ATP into cyclic adenosine monophosphate (cAMP) Terbutaline acts by stimulating intracellular adenyl cyclase, which increases the cAMP levels. Increased levels of cAMP further relax the bronchial smooth muscles.

Uses

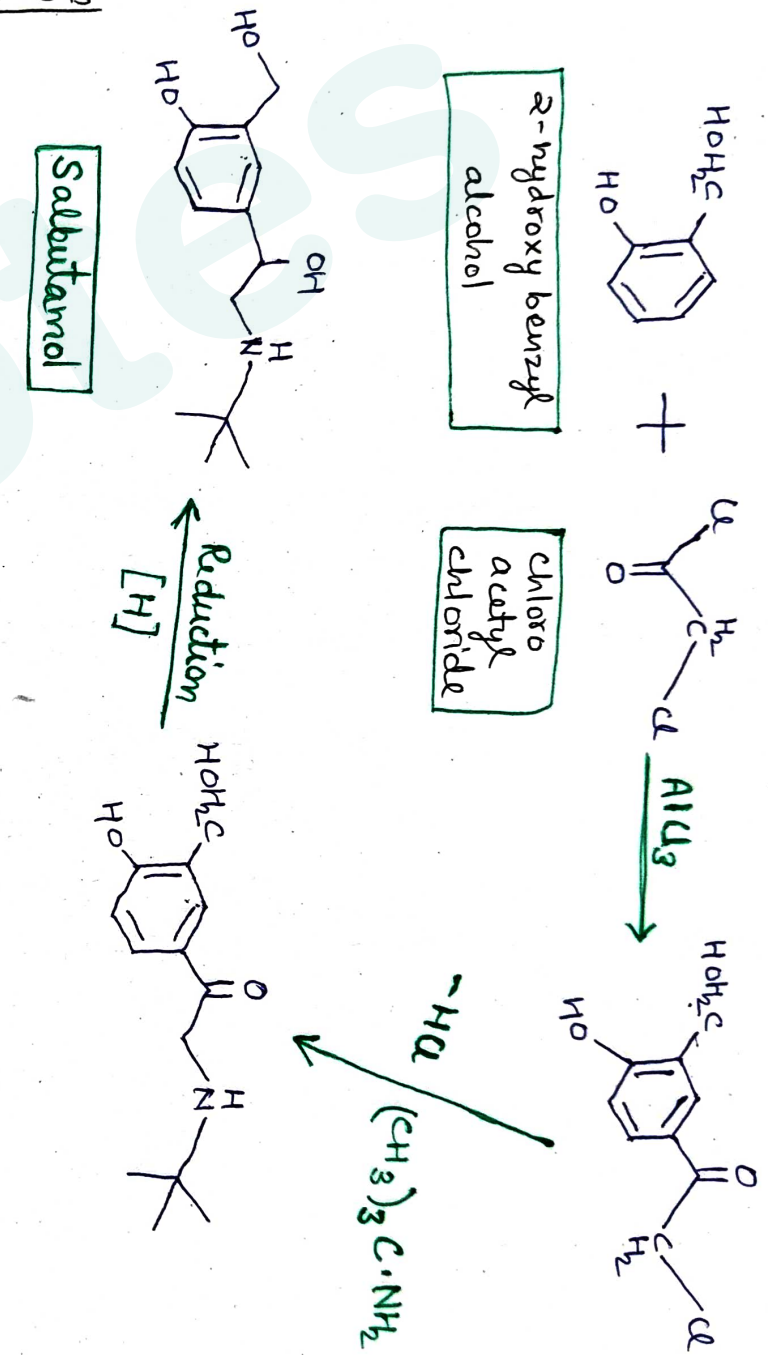
→ It is used in breathlessness and wheezing arising from lung problems.

Salbutamol *

Salbutamol (INN) is also known as albuterol (USAN).

It is employed in the management of bronchospasm seen in asthma and chronic obstructive Pulmonary Disease (COPD).

Synthesis



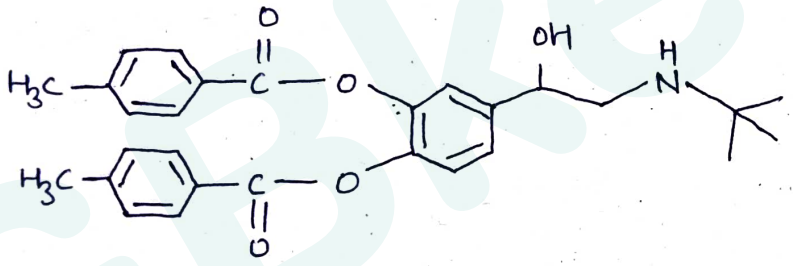
MoA

Salbutamol is a direct-acting sympathomimetic agent. It acts as a β-adrenergic agonist drug having a selective action on β_2-receptors.

Uses.

→ It is used in bronchial asthma.
→ Used in peripheral vascular diseases.
→ Used in the prevention of premature labour.

Bitolterol



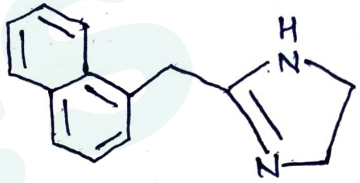
MOA

Bitolterol agonises β_2- adrenergic receptors by relaxing the smooth muscles surrounding the airway tubes. This increases the diameter of tubes and increases airflow.

Uses → in asthma and COPD (dilates air passages)

Naphazoline

Naphazoline decreases the congestion of conjunctiva through its vasoconstrictor action and is present in many OTC eye drops.

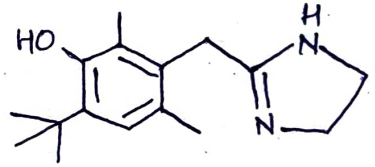


Uses

→ It is a decongestant that relieves redness, itchy/watery eyes due to cold, allergies.
→ used for corneal vascularity.

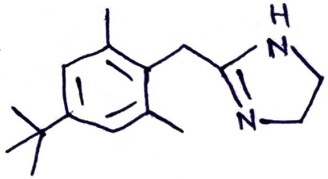
Oxymetazoline

It is used for its vasoconstrictor action in nasal congestion (blockage).



Xylometazoline

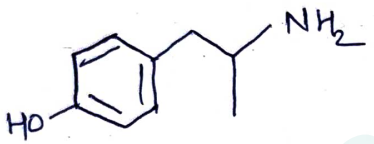
It is also used in nasal congestion.



Indirect - Acting Drugs

Hydroxyamphetamine

It is a powerful vasoconstrictor which stimulates the α-receptors but lacks any CNS activity.



MoA

It causes mydriasis by releasing nor-epinephrine from adrenergic nerve terminals.

mydriasis → dilation of pupil.

Uses

→ It is used in narcolepsy (sudden attack of sleep)

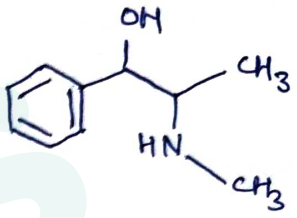
→ It is used in children having hyperkinetic syndrome.

Pseudoephedrine

It is a α- and β- adrenergic agonist which increases norepinephrine release.

MoA

It stimulates β_2- adrenergic receptors and relaxes the bronchial smooth muscles.



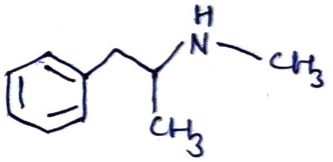
Uses

→ It is used in nasal, sinus and eustachian tube congestion.

→ Also used in priapism (prolonged erection of peni

Propylhexedrine

a nasal decongestant.



MoA

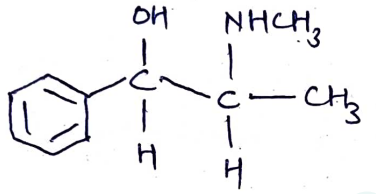
Propylhexedrine acts by reversing the direction of flow of nor-epinephrine, serotonin and dopamine.

Uses

It is used to treat nasal congestion due to common cold, allergic rhinitis or sinusitis through its vasoconstrictive effect.

Mixed-Acting Drugs

Ephedrine



MoA.

→ It acts both directly and indirectly.

→ indirectly stimulate the adrenergic receptor by increasing norepinephrine release.

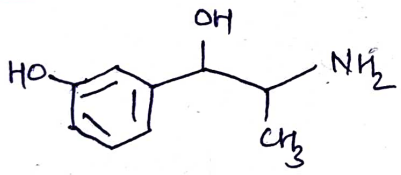
Uses

→ used in allergic disorders, colds.

→ applied locally for nasal decongestion.

→ asthma, hay fever, and urticaria (rashes).

Metaraminol



MoA

→ acts on both α & β receptors by stimulating the release of norepinephrine.

Uses

used in severe hypotensive state.

Adrenergic Antagonists

The term antagonist means the opposite of agonist. so, agonists drugs activate the adrenoreceptors and antagonists are the drugs that blocks responses produced by adrenoreceptor activation.

so, adrenergic antagonists are the drugs which inhibit the effect of sympathomimetic agents (agonists) by blocking the receptor.

Two types

(1) α-adrenergic antagonists / blockers

These are those drugs which blocks the α-receptors and antagonises the effects produced by the catecholamines and other drugs acting on α-adrenergic receptors.

Alpha adrenergic blockers: Tolazoline*, Phentolamine, Phenoxybenzamine, Prazosin, Dihydroergotamine, Methysergide.

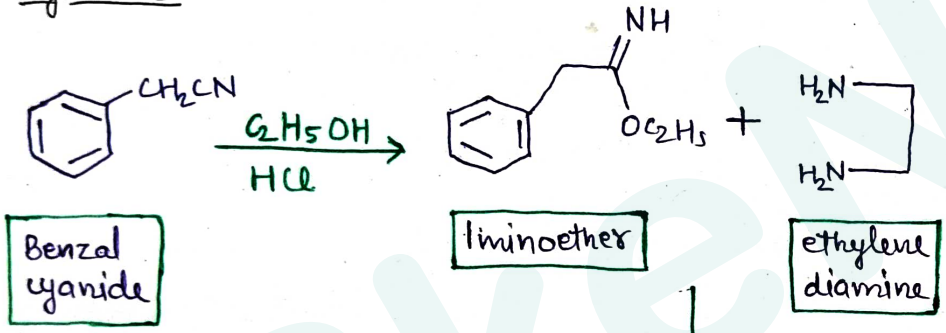
Tolazoline *

→ It is a white crystalline powder, which is freely soluble in water.

→ It is a non-selective α- adrenergic blockers.

→ It is competitive inhibitor of α- adrenoceptor.

Synthesis



MoA

Tolazoline causes vasodilation (opposite effects than α-agonists).

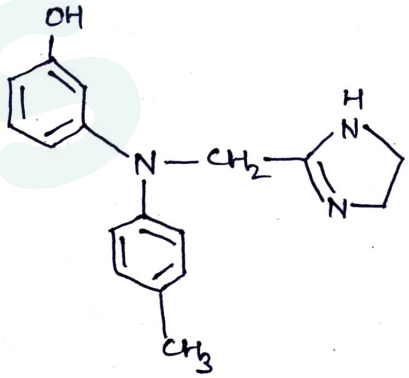
Uses

→ vasodilator, stimulate heart and cause mydriasis

→ used to treat pulmonary hypertension in new-born.

Phentolamine

Tolazoline and phentolamine have both α-1 and α-2 blocking activity and produce tachycardia.

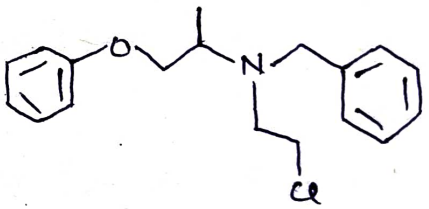


Uses

→ vasodilator, used to treat hypertension.

Phenoxybenzamine

It is a α-adrenergic antagonist with long duration of action



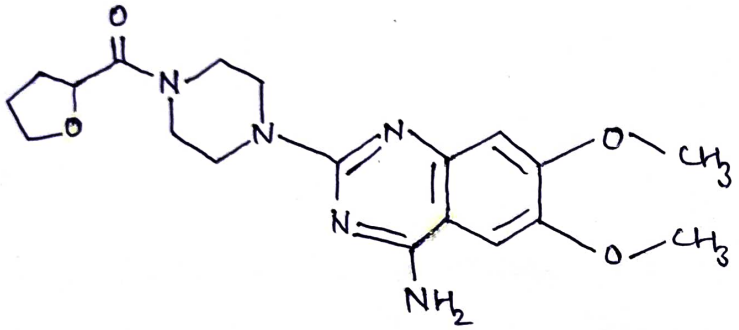
MoA

Phenoxybenzamine widens blood vessels and relaxes muscles by blocking α- receptors. Blood pressure reduces due to widened vessels.

Uses

anti-hypertensive and a peripheral vasodilator.

Prazosin



It is highly specific antagonist of α-1 receptors.

MoA

It causes vasodilation by inhibiting the effect of catecholamines.

Uses

→ treatment of hypertension and heart attack.
→ Also improve urination flow rate.

Dihydroergotamine

→ α- adrenoreceptor antagonist.
→ used in the treatment of migraine headaches.
→ treat cluster headache episodes.
→ treat medication overdose headache.

Methysergide

It is a serotonin antagonist acting on the CNS and causing vasoconstriction by directly stimulating the smooth muscles.

→ It is used for treating vascular headache.

Beta-Adrenergic Blockers

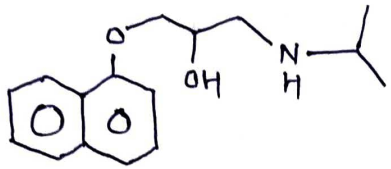
These are those drugs which blocks the β-receptors and antagonises or opposes the effects of drugs which show their effect after binding with β-receptors.

B-blocker drugs are most widely used as anti-hypertensive agents.

Most of the β-blocker are in the chemical class of aryloxypropanolamines.

SAR of Aryloxypropanolamines (β-blocker)

The basic drug in this category is Propranolol.



Propranolol

(1) Oxy group acts as a bridge between aromatic ring and propanolamine side chain, which is essential for beta-blocking activity.

(2) Most of the drugs have substituted phenyl rings in place of naphthyl ring which shows good β-blocking activity. e.g. Metipranolol.

(3) Substitution by CH_3 or OCH_3 or NO_2 groups on the phenyl ring shows good antagonistic activity.
e.g. Metipranolol

(4) Isopropyl and t-butyl groups on the amino side chain shows β-antagonistic activity.
e.g. Atenolol.

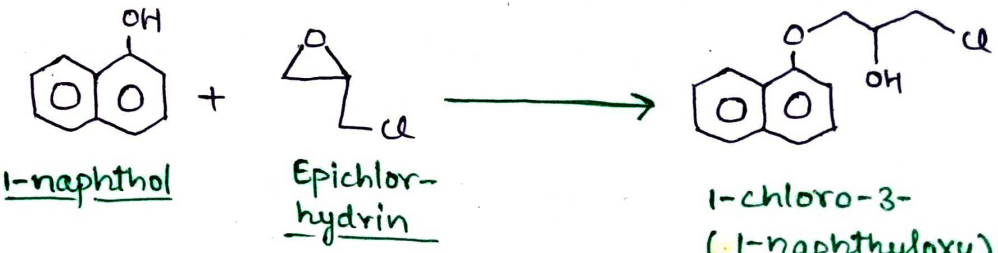
Propranolol *

It is a non-selective β-blocker which means it blocks the β-1 and β-2 receptors with equal affinity.

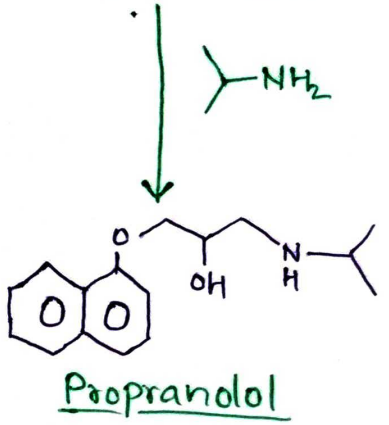
MOA

Propranolol inhibits the effect of catecholamines. This inhibition reduces the resting heart rate, cardiac output, systolic and diastolic BP.

Synthesis



1-naphthol + Epichlorhydrin → 1-chloro-3-(1-naphthyloxy)-2-propanol

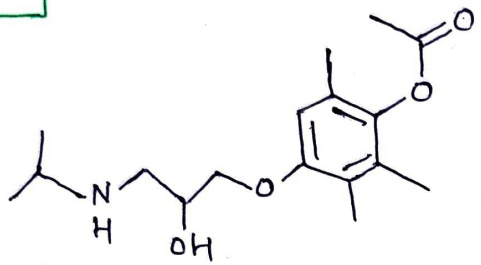


Propranolol

Uses

Tremor, angina, hypertension, heart rhythm disorders

Metipranolol



effective for both β-1 & β-2 receptors.
It acts as an antiarrhythmic, antihypertensive and anti-glaucoma agent.

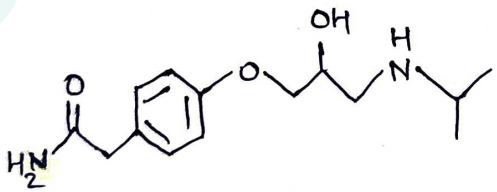
MOA

It has myocardial depressant activity and weak local anaesthetic activity.

Uses

→ used in ocular hypertension.

Atenolol



Atenolol is a competitor of sympathomimetic neurotransmitters (catecholamines) in binding at β-1 adrenergic receptors in the heart and vascular smooth muscles, thereby inhibiting sympathetic stimulation.

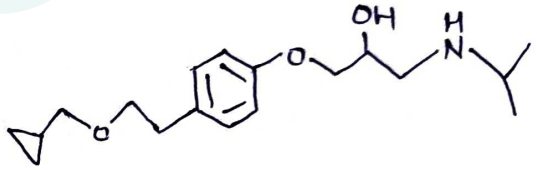
Uses

→ It is used in angina pectoris and hypertension for long-term treatment.

Betaxolol

It is a selective β-1 adrenergic antagonist.

MOA

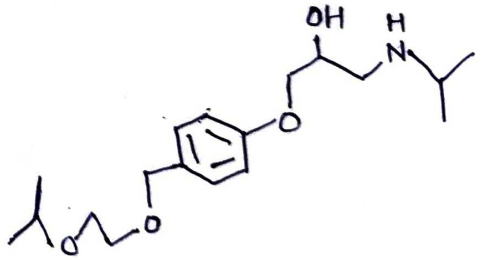


It binds to β-1 adrenoreceptors in the heart and blocks them, therefore the cardiac contractility is reduced which further reduces cardiac output and blood pressure.

→ It is used for managing hypertension.

Bisoprolol

It is also a selective β-1 adrenoceptor antagonist.



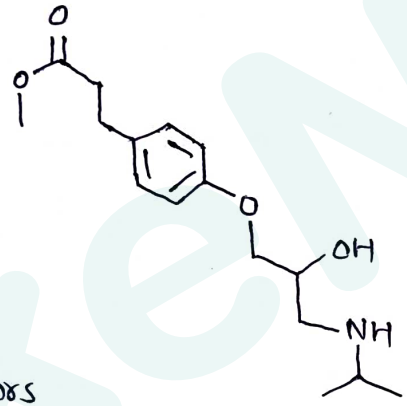
MOA

similar mechanism of action as betaxolol.

Uses

It is used for managing heart failure, angina pectoris, mild to moderate hypertension.

Esmolol



→ selective β-1 blocker

→ rapid and short duration of action.

MOA

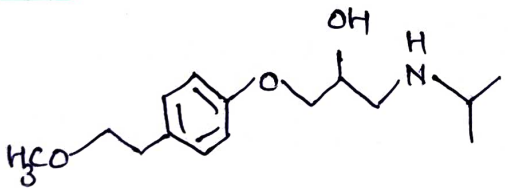
Blocks β-1 receptors at low doses and β-2 receptors at higher doses.

Uses

→ control rapid heart rate

Metoprolol

selective β-1 adrenergic receptor.



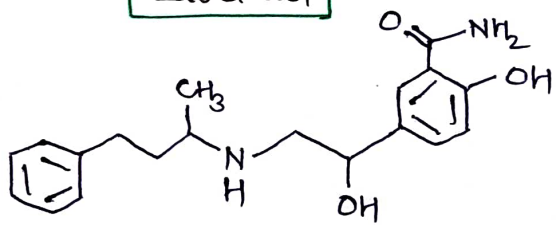
MOA

Metoprolol competes with the catecholamines to bind with β-1 adrenergic receptors in heart. Heart rate, cardiac output, BP are reduced as a result of β-1 receptor blockade.

Uses

Used in the treatment of myocardial infarction, hypertension, angina and heart failure.

Labetalol

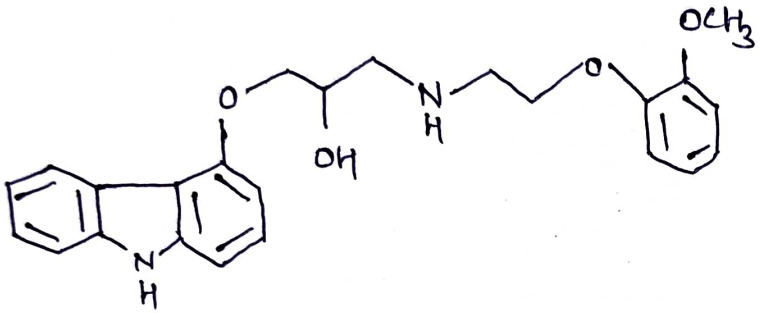


Labetalol is a non-selective blocker of α-1 and β- adrenergic receptors.

Uses

→ used for managing hypertension

Carvedilol



MAO

→ non-selective β-blocker prescribed for treating congestive heart failure

Uses

→ treat moderate heart failure of ischemic region.