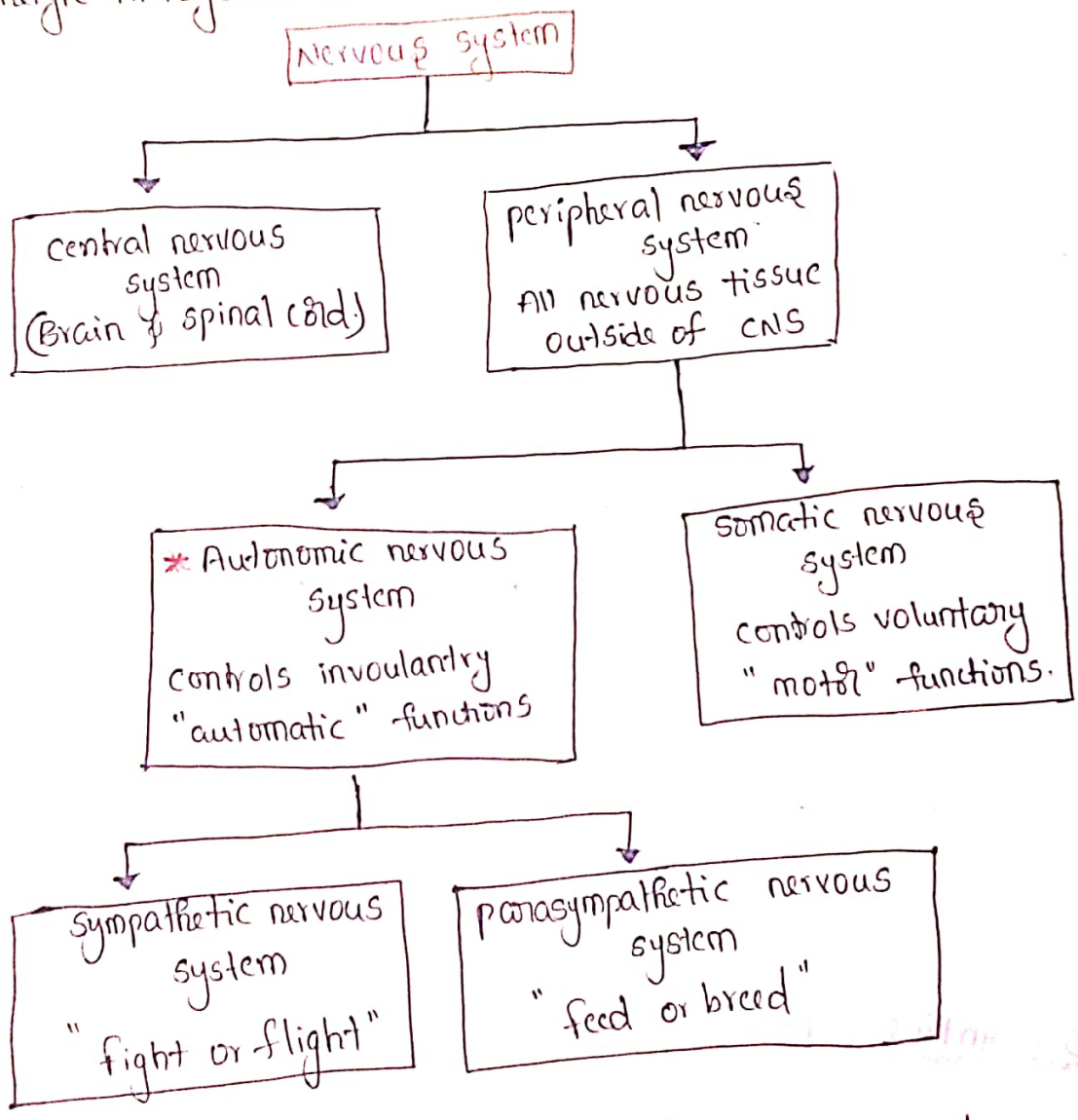
Drugs acting on Autonomic Nervous system

UNIT-2 (Topic 1)

* Adrenergic Neurotransmitters
* Sympathomimetic agents: SAR of sympathomimetics.
* Adrenergic Antagonists: Alpha adrenergic & Beta adrenergic blockers.



-> Adrenergic system is group of organs and nerves in which adrenaline / noradrenaline act as neurotransmitters.

Adrenergic Neurotransmitters :-

Neurotransmitters :- Neurotransmitters are the chemical substances released by the neurons to transfer the signals through synaptic cleft.

Adrenergic neurotransmitters :-

Adrenergic transmission is mediated by the sympathetic division of the ANS. There are three closely related endogenous catecholamines (CAs).

* Adrenaline [epinephrine]
* Noradrenaline [NA, Norepinephrine]
* Dopamine

Adrenaline → It is secreted by adrenal medulla and may have a transmitter role in the brain.

Noradrenaline → It acts as transmitter at post-ganglionic sympathetic sites and in certain areas of brain.

Dopamine → It is a major transmitter in basal ganglia, limbic system, or anterior pituitary etc.

Biosynthesis of catecholamines :-

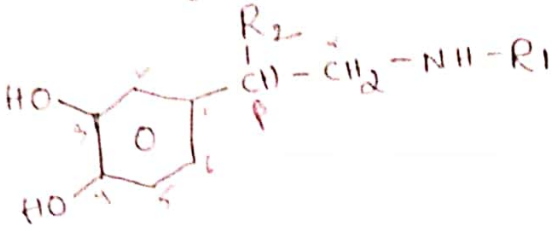
1 The adrenergic system produces neurotransmitters belonging to the class of substances known as catecholamine.

* These are derivatives of catechol with a β-aminoethyl side chain.

2 A catechol group is simply a benzene ring that has hydroxyl groups on two adjacent carbons.

4. Catecholamines biosynthesis takes place in adrenergic and dopaminergic neurons in the CNS, in sympathetic neurons in ANS and in the adrenal medulla.

Adrenaline & NBI adrenaline contain catechol function (3,4- Dihydroxy phenyl moiety) in their structure.



Name	R_1	R_2
Epinephrine	$-CH_3$	$-OH$
Norepinephrine	$-H$	$-OH$
Dopamine	$-H$	$-H$.

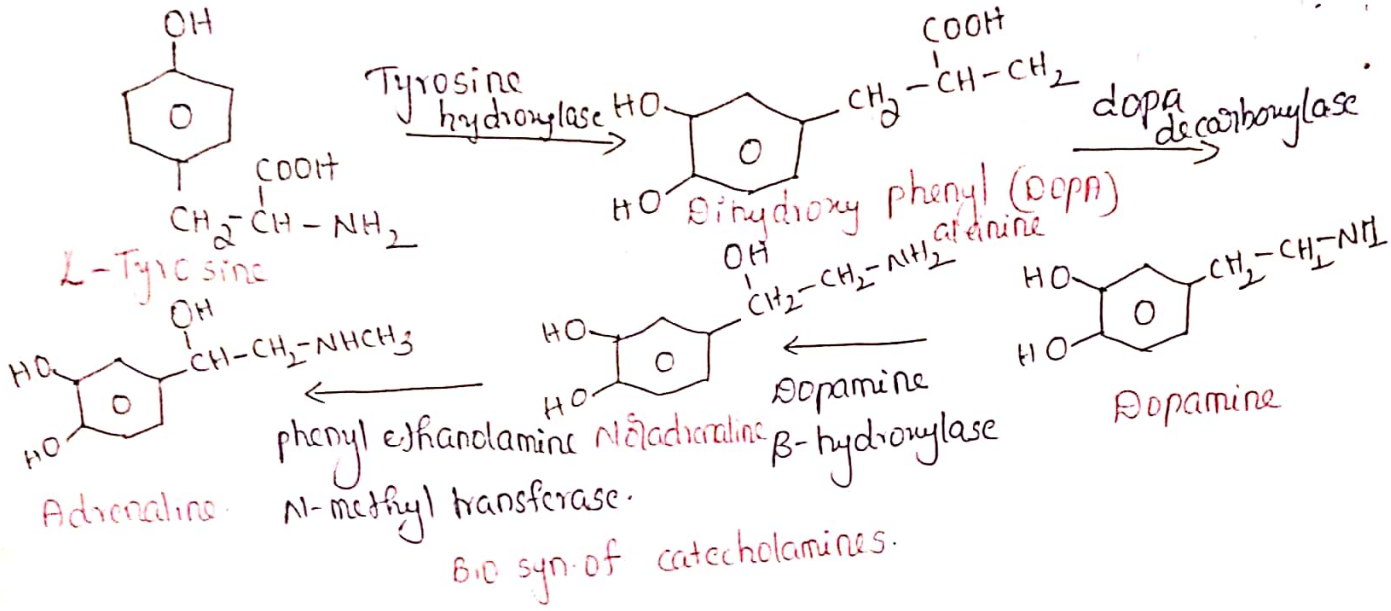
* The catecholamine biosynthesis involves the following steps :-

① The aromatic amino acid L-Tyrosine serves as a precursor. It is acted by Tyrosine hydroxylase to form L-dihydroxy phenyl alanine (L-dopa). This is the rate limiting step, so inhibition of Tyrosine hydroxylase is target for many drugs.

② The second step is the decarboxylation of L-dopa by L- aromatic amino acid decarboxylase to dopamine. (dopa decarbox

③ The dopamine formed in the cytoplasm of the neuron is transport into storage vesicle, where it is β-hydroxylated stereospecifically by the enzyme dopamine β- monooxygenase (dopamine-β-hydroxylase) in the side chain to Norepinephrine.

-> The NE formed remains stored in vesicles as its adenosine triphosphate complex.



Bio syn. of catecholamines.

Storage of catecholamines :-

-> NA is stored in nerve terminal / chromaffin cells contained in vesicles, only a little is free in the cytoplasm under normal circumstances.

-> The vesicular membrane actively takes up DA from the cytoplasm and final step of synthesis of NA takes place inside the vesicle which contains dopamine β-hydroxylase.

-> NA is then stored as complex with ATP which is adsorbed on a protein chromogranin.

-> In the adrenal medulla the NA thus formed with in the chromaffin granules diffuses out into the cytoplasm, is methylated and Adr so formed is again taken up by a separate set of granules.

-> The cytoplasmic pool of CAs is kept low by the enzyme MAO (mono amine oxidase) present on the outer surface of Mitochondria.

Release of catecholamines :-

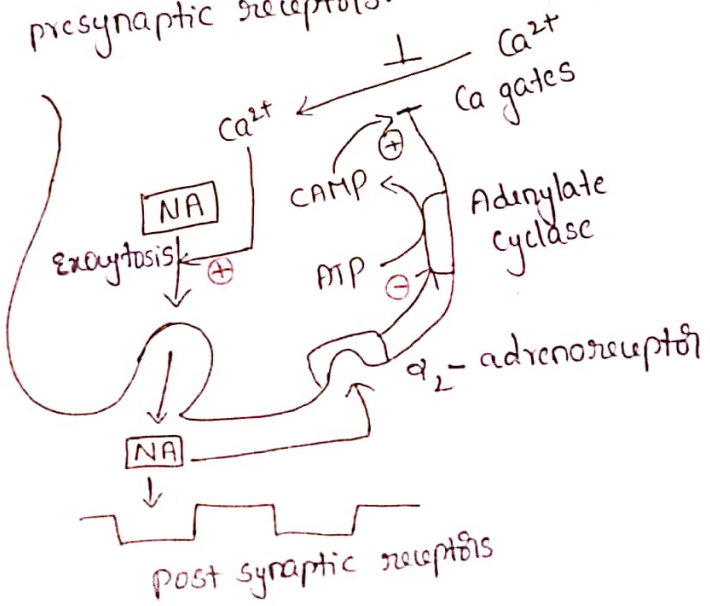
→ The nerve impulse coupled release of CA takes place by exocytosis and all the vesicular contents are poured out.

→ In case of vesicles which in addition contain peptides like enkephalin or neuropeptide Y, these contransmitters are simultaneously released.

→ The release is modulated by presynaptic receptors, of which α_2 inhibitory control is dominant.

→ with the arrival of nerve impulse, depolarisation and opening of calcium channels, calcium enters the terminal, promotes the fusion and discharge of synaptic vesicles.

→ The transmitter release can be controlled by a variety of substances that act on presynaptic receptors.



Uptake of catecholamines :-

There is very efficient mech by which NA released from the nerve terminal by which NA released from the nerve terminal is recaptured. This occurs in 2 steps. —> Uptake - 1
uptake - 2.

* Uptake - 1 Neuronal
  ① Axonal uptake
  ② vesicular uptake.

1. Axonal uptake :- An active amine pump (NET) is present at the neuronal membrane which transports NA by Na^+ coupled mechanism.

2. Vesicular uptake :- The membrane of intracellular vesicles has another amine pump the vesicular monoamine transporter (VMAT-2), which transports CA from the cytoplasm to within the storage vesicle. The VMAT-2 transports monoamines by exchanging with H^+ ions. The vesicular NA is constantly leaking out into the axoplasm & recaptured by this mech.

* uptake - 2 :-

-> Extraneuronal uptake of CAs is carried out by extraneuronal amine transporter (ENT / OCT3) & other org. cation transporters OCT1 & OCT2 into cells of other tissues.

Metabolism of catecholamines :-

-> endogenous & exogenous catecholamines are metabolised moiety by two enzymes : monoamine oxidase (MAO) & catechol-O-methyl transferase (COMT).

->MAO occurs within cells, bound to surface of mitochondria.

-> It is abundant in adrenergic nerve terminals.

->MAO converts catecholamines to their corresponding aldehydes, which in the periphery, are rapidly metabolised by aldehyde dehydrogenase to the corresponding carboxylic acid.

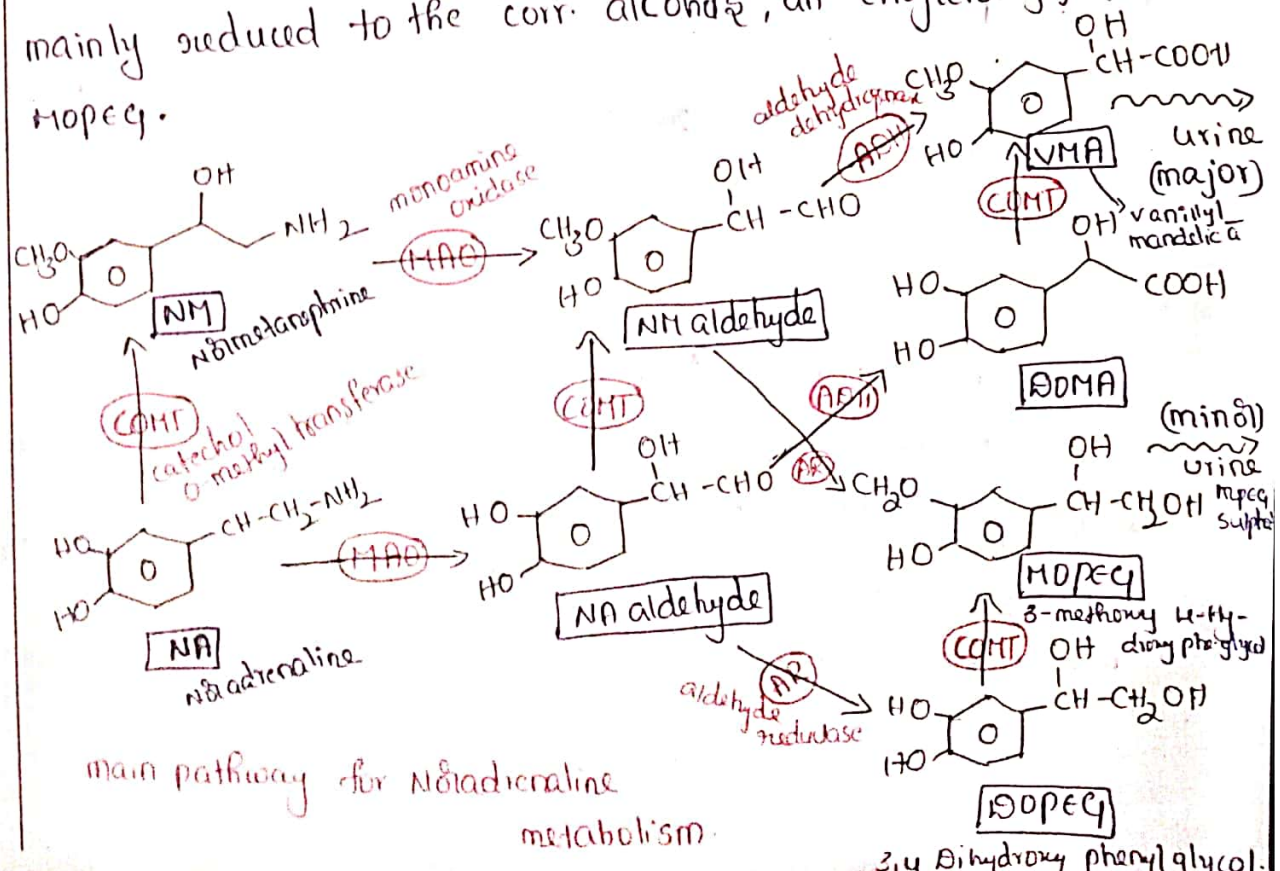
→ In the case of noradrenaline this yields dihydroxymandelic acid (DOMA).

→ 2nd major pathway for catecholamine metabolism involves - Methylation of one of the catechol - OH groups to give a methoxy derivative.

→ O- methylation of noradrenaline gives rise to the metabolite normetanephrine.

→ When this product, is acted by MAO, the product formed is 3- methoxy - 4- hydroxymandelic acid (VMA), which is the main final metabolite of adrenaline & noradrenaline.

→ MAO is more important as means of terminating transmitter action than it is in the periphery, and the resulting aldehydes are mainly reduced to the corr. alcohols, an ethylene glycol derivative MOPEG.



main pathway for Noradrenaline metabolism.

Adrenergic receptors

- Adrenergic receptors are the sites where adrenergic drugs bind and produce their effects.
- Adrenergic receptors are membrane bound G-protein coupled receptors which function primarily ↑ or ↓ intracellular production of second messengers cAMP / IP$_3$ / DAG.
- Adrenergic receptors are divided into alpha-adrenergic and beta-adrenergic receptors depending on whether they respond to epinephrine or norepinephrine
- Both alpha & beta-adrenergic receptors have subtypes designated 1 & 2

① Alpha receptors :-

* Alpha$_1$ - adrenergic receptors are located on the postsynaptic effector cells.
* Alpha$_2$ - adrenergic receptors are located on the presynaptic nerve terminals.

② Beta receptors :-

* Both beta adrenergic receptors are located on the postsynaptic effector cells.
* Beta$_1$ - adrenergic receptors are primarily located in the heart.
* Beta$_2$ - adrenergic receptors are primarily located in the smooth muscle of bronchioles, arterioles, & visceral organs.

Subtypes of Alpha1 Adrenergic receptors:-

$Alpha_{1A}$ – contraction of smooth muscle – high density in prostate gland, also found in arteries & veins

$Alpha_{1B}$ – most abundant type in heart

$Alpha_{1C}$ – found on coronary blood vessels & aorta.

$Alpha_{2A}$ – Inhibitory autoreceptor found on presynaptic nerve endings of sympathetic & also parasympathetic nerves & asso. with hypotension & nociceptive response

$Alpha_{2B}$ – found on peripheral blood vessels, low density, can produce constriction.

Alpha 2c :– predominately inhibitory – found in adrenal medulla on nerve endings to inhibit release of ϵ & dopamine.

Subtypes of Beta Adrenergic receptors:-

B_1 receptors:-

-> B_1 receptors are located in the:-
* Sinoatrial node
* Atrioventricular (AV) node
* ventricular muscles of the heart

-> produce excitation

-> sensitive to both noradrenaline & epinephrine

B_2 receptors

B_2 receptors located on:-
* vascular smooth muscle of skeletal muscle
* Bronchial smooth muscle
* walls of the GIT
* Bladder.

-> relaxation.

-> sensitive to epinephrine is more than to norepinephrine.

Adrenoceptors

α_1	α_2	β_1	β_2
– mydriasis	× ⊗ of NE release	> Tachycardia	✓ vasodilation
– vasoconstriction	* ⊗ of Ach release	> ↑ lipolysis	✓ ↓ peripheral resistance
– ↑ peripheral resistance	* ⊗ of Insulin	> ↑ myocardial contractility	✓ Bronchodilation
– ↑ B.P		> ↑ release of renin	✓ ↑ release of glucagon
			✓ Relaxed uterine smooth muscle

Sympathomimetic Agents [Adrenergic Drugs]

-> Sympathomimetic drugs/agents are stimulants compound which mimic the effect of endogenous agonist of the sympathetic nervous system.

-> Drug can make the action partially/completely or it may also be defined as the substance which sympathetic system is known as sympathomimetic agent or adrenergic agonist or adrenergic drugs.

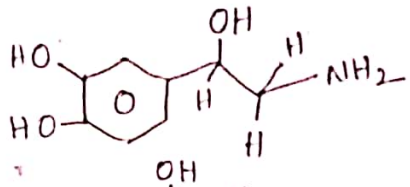
Classification of Sympathomimetic agents.

Sympathomimetic agents

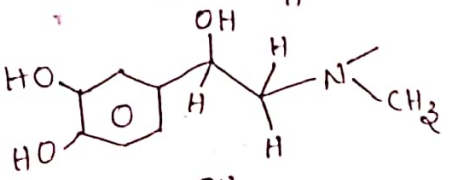
- **Direct acting**
  - Nor-epinephrine
  - Epinephrine
  - phenylephrine* (α_1)
  - Dopamine (β_1)
  - Methyldopa (α_2)
  - clonidine (α_2)
  - Dobutamine (β_1)
  - Isoproterenol (β_2)
  - Terbutaline (β_2)
  - Salbutamol* (β_2)
  - Bitolterol (β_2)
  - Naphazoline
  - Oxymetazoline (α_1) & xylometazoline.
- **Indirect acting**
  - Hydroxyamphetamine
  - pseudophedrine
  - propylhexedrine
- **Mixed acting**
  - Ephedrine
  - metaraminol. (α_1)

Direct acting :-

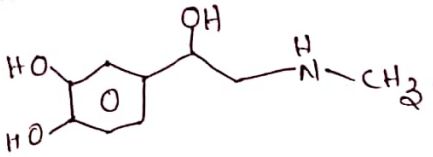
① Nôrepinephrine →



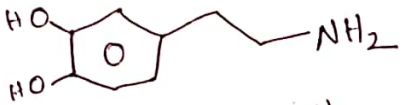
② Epinephrine →



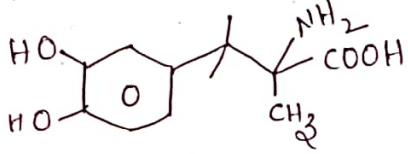
③ phenylephrine →



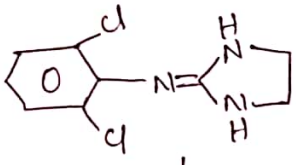
④ Dopamine →



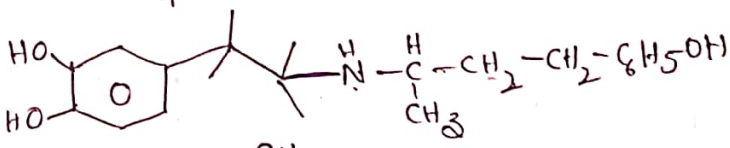
⑤ Methyldopa →



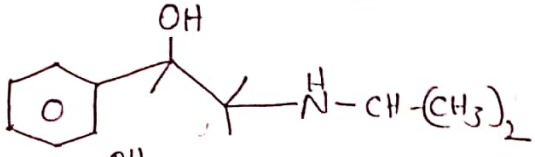
⑥ Clonidine →



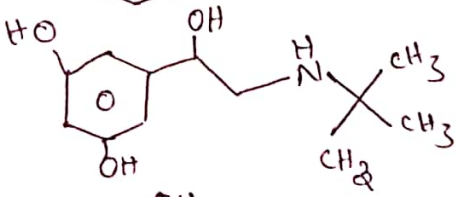
⑦ Dobutamine →



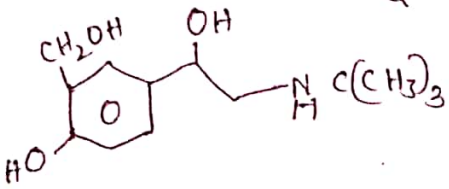
⑧ Isoproterenol →

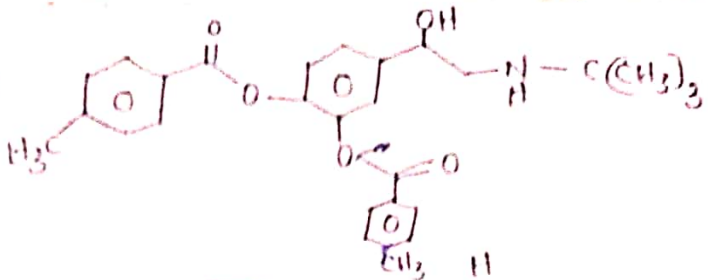


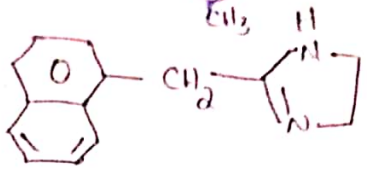
⑨ Terbutaline →

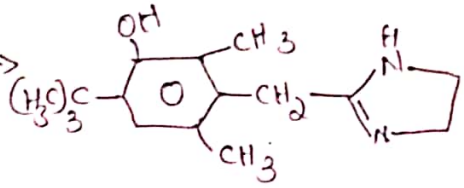


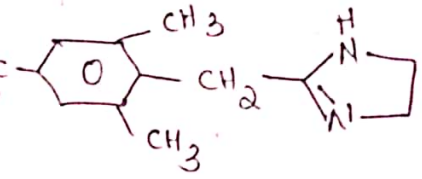
⑩ Salbutamol →



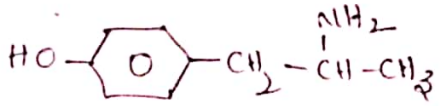
(11) Bitolterol → 

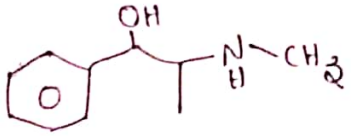
(12) Naphazoline → 

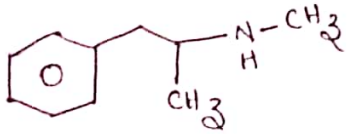
(13) Oxymetazoline → 

(14) Xylometazoline 

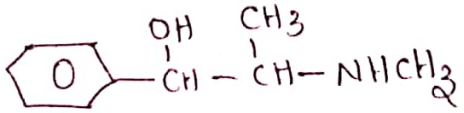
Indirect acting :-

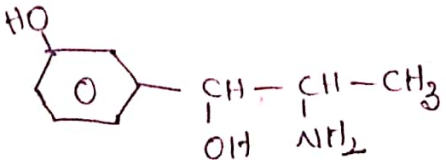
(1) Hydroxyamphetamine → 

(2) pseudo ephedrine → 

(3) propylhexedrine → 

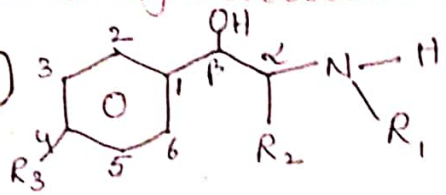
mixed acting :-

(1) Ephedrine → 

(2) Metaraminol → 

Structure Activity Relationship of Sympathomimetic Agents

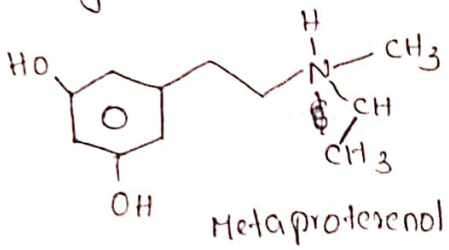
a. phenyl ring substitution: (R_3)



-> The naturally occuring noradrenaline has 3,4-dihydroxy benzene ring (catechol), active at both α & β-receptors.

-> But it has poor oral activity because it is rapidly metabolised by COMT, change in substitution pattern 3,5-dihidroxy as is in metaproterenol gives good oral activity.

-> This is due to its resistance to metabolism by COMT. It also provides selectively for β_2-receptors. It lacks cardiac stimulating prop's as found in isoproterenol.



Metaproterenol

-> other groups have also been found to impart oral activity.

eg:- Albuterol → 3 hydroxymethyl

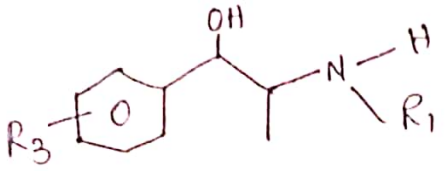
metabuterol → 3'-trifluoromethyl-4-amino,5'-chloro

-> One hydrogen bonding group is essential at the 4'-position for β-activity.

-> 3-OH substitution is req. for α-activity.

eg: phenylephrine

b Substitution at Nitrogen :- (R_1)



-> The receptor selectivity is dependent upon the size of alkyl groups present on nitrogen.

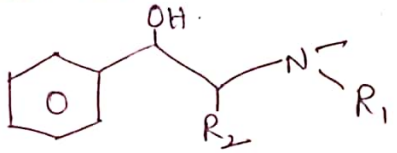
-> As the size is increased from hydrogen in noradrenaline to methyl in adrenaline to isopropyl in isoproterenol, activity of α-receptors ↓es and activity of β-receptors ↑es.

-> A large t-butyl group affords selectivity to β_2-receptors.

Eg:- Colteral is a selective β_2 agonist where as proterenol is a general β-agonist.

Ritrodine - with large, p-hydroxy phenyl ethyl subst is a selective β_2-agonist used to inhibit ~~contra~~ uterine contraction.

c Substitution on carbon on the side chain :- [R_2]



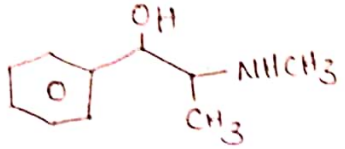
-> There are two 'c' atoms α and β to nitrogen function. Small alkyl groups methyl or ethyl, present on the α-carbon, slow metabolism by MAO

-> An ethyl group of this position diminishes α-activity.

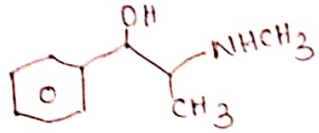
-> Substitutions on this carbon also introduces an asymmetric centre into these molecules producing pair of diastereomers.

Eg:- α-methyl noradrenaline → erythro stereoisomers with the (1R:2S) absolute configuration is active. ⑨

Ephedrine → The erythro enantiomer (1R,2S) & (1S,2R) are active.



(1R 2S)



(1S2R) ephedrine active

→ The beta carbon (C-2) bears a hydroxyl group in the R absolute configuration for minimal direct activity as in adrenaline & noradrenaline.

With respect to α-activity ~~of~~ this additional methyl group makes the direct acting 1R,2S stereoisomer of α-methyl norepinephrine more selective α-adrenoceptor than α_1 adrenoceptors.

Aromatic Substitution

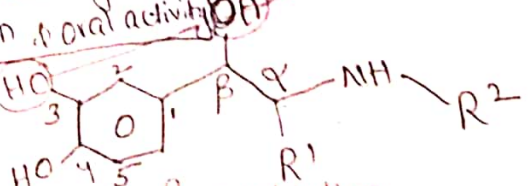
No subⁿ ↓ activity.

Both OH required α & β agonist action
easily metabolized by COMT
↓ durⁿ of action & oral activity
↓ CNS activity

more imp α activity.

↑ β activity
↓ α activity

R_2 branching in alkyl chain
↑ β_2 activity
↓ degrdⁿ by MOA.



Position of OH group & substitution

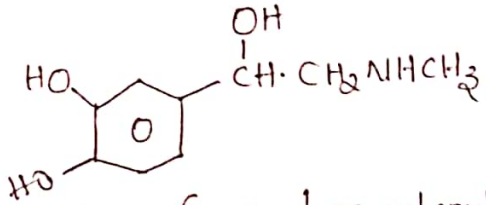
3,5 dio	↑ β_2 activity ↓ degradⁿ of COMT ↑ Oral & duration of activity.
3 only OH	

R_1 substitution

CH_3 subⁿ ↓ MOA degradⁿ
C_2H_5 ↓ α activity as compare to β
C_3H_5 ↑ CNS activity
↑ Oral activity.

→ more imp for β activity

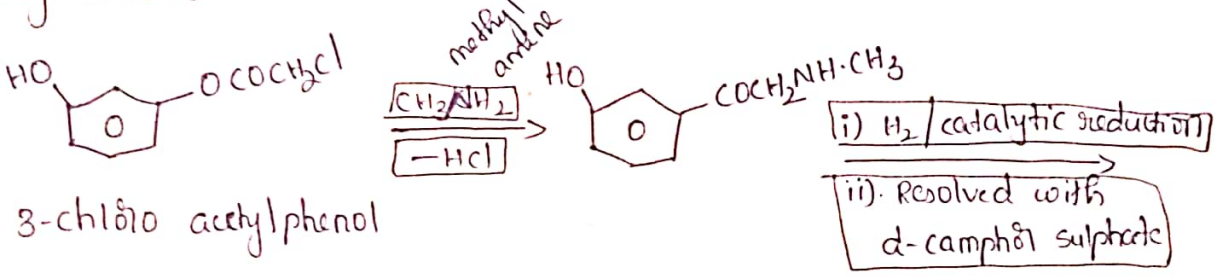
① phenylephrine



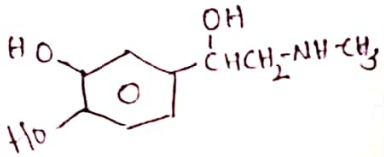
(−)-1-(3-Hydroxyphenyl)-2-methyl amino ethanol.

-> phenylephrine differs from Adrenaline only by lacking the H^th -OH group on the benzene ring and subsequently resistant to COMT & has predominantly α_1-agonist effect.

Synthesis:-



3-chloro acetylphenol



* (−)-phenylephrine

Uses:-

-> phenylephrine is selective α_1-receptor agonist
-> Oral absorption is not reliable and so it is given parenterally or topically as eye or nasal drops.
-> It is used as nasal decongestant, mydriatic & as a vasopressor agent.
-> It is also used in spinal anaesthesia, to prolong the anaesthesia and to prevent the drop in blood pressure during procedure.

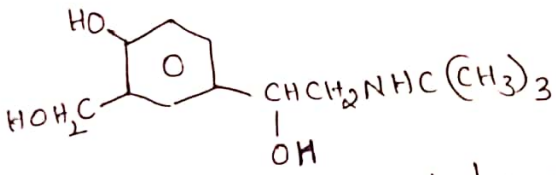
Mechanism of Action:-

-> It is a selective α agonist and has no action on β-receptors

-> Activation of α_1 receptors causes vaso constriction of arterioles, iris, and contraction of uterus.

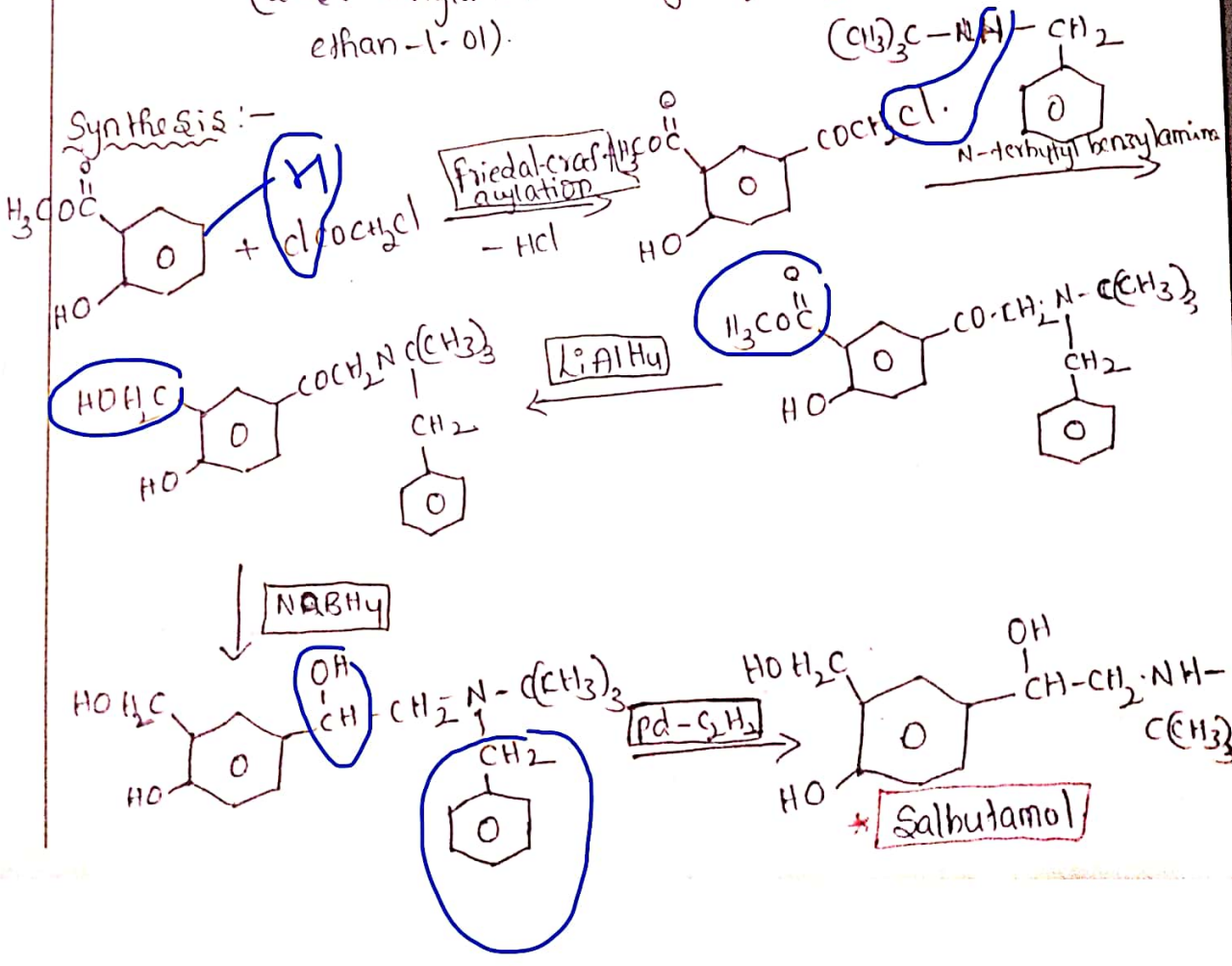
-> It produces its affects by contracting membrane present in animals.

(2) Salbutamol :- [Albutero]



(2-(t-butylamino-1[3-hydroxymethyl-4-hydroxy) phenyl] ethan-1-ol).

Synthesis :-



Mechanism of action :—

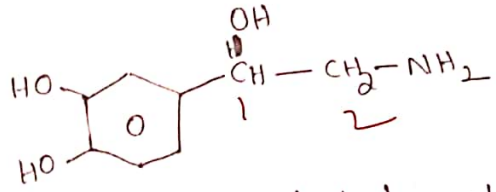
→ It is a strong β_2- adrenergic agonist

→ It is directly acting sympathomimetic drug having strong action on β_2- receptors.

Uses :—

1. Orally or as an inhalation it is used for symptomatic relief of bronchospasm associated acute / chronic asthma.
2. It is used in the treatment of bronchitis & other obstructive pulmonary diseases.
3. Infusions of salbutamol are used to arrest premature labours.

③ Nolepinephrine —



R - 2- Amino - 1 (3,4 di hydroxy phenyl) ethanol.

mechanism of action :—

→ It is a potent agonist at α- receptors and has little or no effect on β- receptors but has effect on β_1- receptors

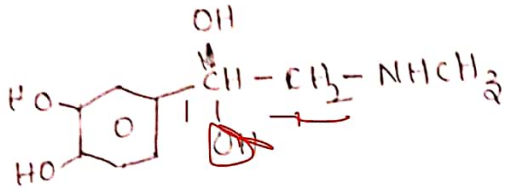
→ It is less potent than epinephrine

Uses :—

1. Nolepinephrine is used to reduced the absorption and to localise the effects of local anesthetics.
2. It ↓es the chances of haemorrhage during an operation.

3. It is given by intravenous infusion for the treatment of hypotension
4. It has strong vasoconstriction property.

(4) Epinephrine -



(R)-1(3,4-Dihydroxyphenyl)-2-methyl aminoethanol

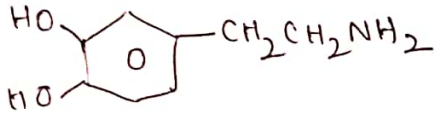
Mechanism of action:-

→ It is direct acting drug
→ It interacts directly with α, β_1 and β_2 receptors
→ It is highly potent among all the direct by acting drugs.
→ Epinephrine is inactive when given by mouth as it undergoes enzymatic degradation & first pass metabolism in the liver

Uses:-

1. It acts subcutaneously to produce vasoconstriction
2. It is mainly used in the emergency treatment of anaphylaxis and anaphylactic shock in the cardiopulmonary disease.
3. It relaxes bronchial muscle and used in the treatment of asthma Aq. soln of epinephrine can used as inhalation as a spray to reduce asthmatic spasms.
4. Adr is generally added to local anaesthetics to ↓ diffusion and to limit absorption.
5. It is also used in form of spray in acute allergic rhinitis, hay fever & sinusitis.
6. It is used in the management of glaucoma at it ↓es intraocular pressure.

⑤ Dopamine :-



4-(2-Aminoethyl) benzene-1,2-diol.

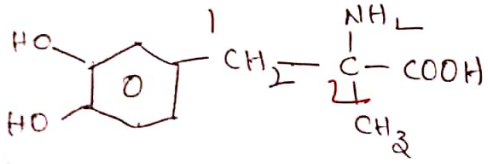
Mechanism of action :-

→ It interacts directly on β-adrenergic receptors and indirectly on α-adrenergic receptors.

Uses :-

1. Dopamine is used in patient of shock
2. It is used in severe congestive heart failure where it ↑es BP and urine out-flow
3. It is used intravenously in M.I, trauma, septic shock and cardiac surgery.

⑥ Methyl dopa



3-(3,4-Dihydroxyphenyl)-2-methyl-L-alanine

Mechanism of action :-

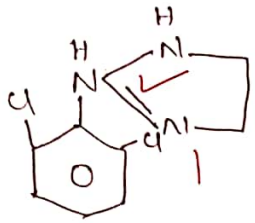
→ It is a competetive inhibitor of enzyme DOPA decarboxylase which results lower blood pressure and CNS effect like anxiety depression, or methyldopa is converted into α-methyl norepinephrine by enzyme dopamine β-hydroxylase

→ α-methyl norepinephrine is an agonist of α_2 adrenergic receptor and lower blood pressure. ⑥

Uses:-

1. It is used in the treatment of hypertension in combination with a diuretic
2. It is preferred in Gestational hypotension (pregnancy induced hypotension) by given orally or intravenously.

⑦ Clonidine:-



2-[(2,6-Dichlorophenyl)amino]-2-imidazoline.

Mechanism of action:-

→ It is centrally acting α_2 receptor agonist and also imidazoline receptor agonist leading to reduction in sympathetic outflow from CNS.

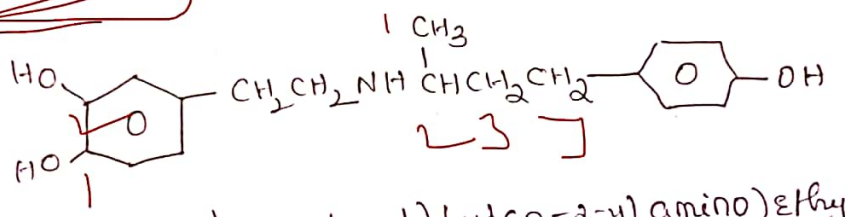
Uses:-

1. Clonidine is given orally/intravenously in treatment of all grades of hypertension alone or in combination with thiazide diuretic
2. In U.S. it is used in the treatment of attention deficit hyperactivity disorder [ADHD].
3. It can be used in treatment of Tourette syndrome.
4. clonidine may be used to ease withdrawal symptoms associated with long term of use of alcohol, narcotics, nicotine/benzodiazepines.

5. Due to its mild sedative action, clonidine can be used as premedication before surgery.

6. It can be used for migraine or in restless legs syndrome

(3) Dobutamine :-



4-(2-[4-(4-hydroxyphenyl) butan-2-yl amino) ethyl benzene 1,2 diol.

Mechanism of action :-

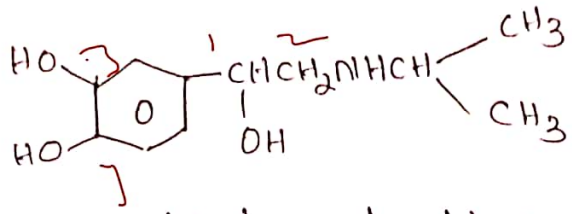
-> It directly stimulate β_1 receptor of sympathetic nervous system and α_1 receptors. ~~It is dual acting drug.~~

Uses :-

1. It is used in the treatment of congestive heart failure because of positive ionotropic effect.
2. It is also commonly used in the hospital setting as a pharmacological stress testing agent to identify coronary artery disease.

Dobutamine is active only by IV route due to rapid first pass metabolism and therefore its use is limited to critical care condition.

(9) Isoproterenol [Isoprenaline]



(RS) - 1-(3,4 dihydroxy phenyl)- 2- isopropylamino ethanol.

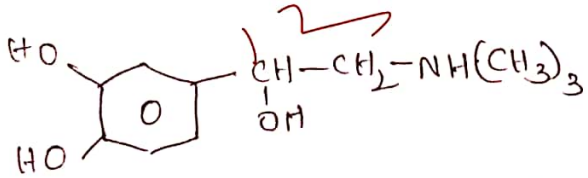
Mechanism of action:-

-> It acts on both β_1 and β_2 receptors. On stimulating β_1 receptors it increase cardiac output and on stimulating β_2 receptors it increase bronchodilation.

Uses:-

1. It is mainly used for symptomatic relief on bronchial asthma.
2. It is used in the treatment of bradycardia, as a stimulant following cardiac arrest.
3. It is also used in the form of solutions having 0.5% and 1% of drug as inhaler.

(10) Terbutaline



(2 t-butylamino-1-[3,5-dihydroxy phenyl] ethan-1-ol.

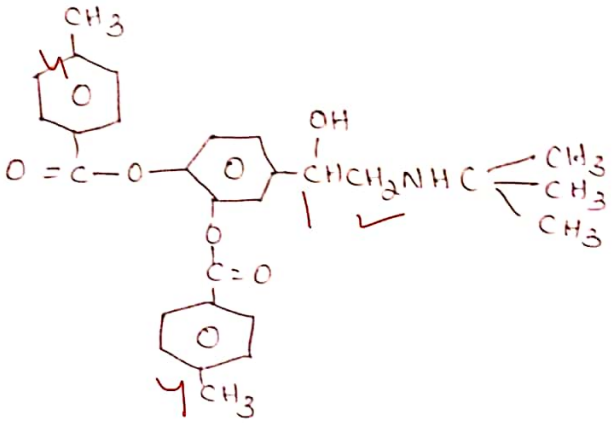
Mechanism of action:-

-> It is a selective β_2-agonist. It is much more effective than isoprenaline. It acts directly on this β_2 adrenergic receptor and produces response.

Uses:-

1. When given orally, it is very effective as bronchodilator and is used in the treatment of asthma and various bronchospasmodic disease
2. It is also used as an aerosol or inhalation.
3. It is also used to arrest premature labour.

(1) Bitolterol



[4-(1-Hydroxy-2-tert-butylamino-ethyl)-2-(4-methyl benzoyl)oxy-phenyl] 4-methyl benzoate.

Mechanism of action:-

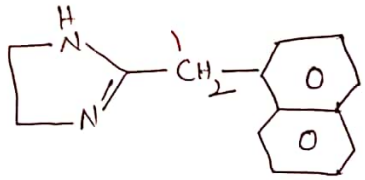
-> It is short acting β_2 adrenergic receptor agonist.

-> It is a direct acting sympathomimetic with mainly action on β_2-receptors.

Uses:-

1. Bitolterol is a bronchodilator and is used to treatment of asthma.
2. It is used treat bronchospasm associated with COPD.

12 Naphazoline:



2-(1-Naphthylmethyl)-2- imidazoline.

Mechanism of action:-

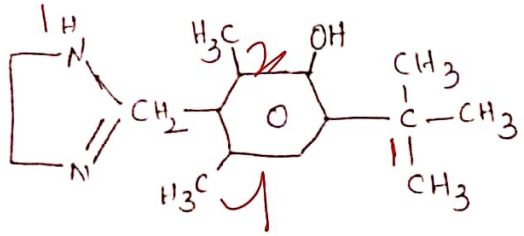
-> It is a powerfull α-receptor stimulant but it is different from most of the other sympathomimetic amines as it depresses inspite of stimulating CNS.

-> It is partial agonist at both α_1 and α_2 receptors.

Uses:-

1. It is a vasoconstrictor
2. It helps in reducing swelling and congestion on application to mucous membrane
3. It helps in the relief of rhinitis and sinusitis.
4. Soln of Naphazoline is used in the eyes as conjunctival decongestant.

13 Oxymetazoline:-



3-[(4,5-dihydro-1H-imidazol-2yl)methyl-6-(1,1 dimethyl ethyl) -2,4- dimethyl phenol]

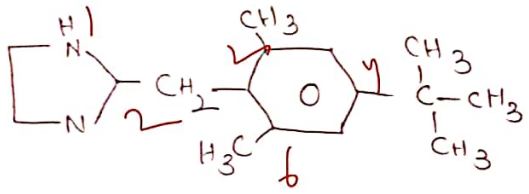
Mechanism of action :-

-> It is a partial agonist at both α_2 and selective agonist at α_1 receptors.

Uses :-

1. It is used as a topical decongestant in the form of nasal sprays
2. It has vasoconstriction prop's so it is used to treat nose bleeding and redness of eye due to irritation.
3. It is also used topically for the treatment of facial erythema.

(14) Xylometazoline :



2-(4-tert-Butyl-2,6 dimethyl benzyl)-2- imidazoline

Mechanism of action :-

-> It is an imidazole derivative and mimics the molecular shape of adrenaline.

-> It binds to both α_1 and α_2 receptors.

-> It causes stimulation of adrenergic receptors and produces constriction of large veins in the nose.

Uses :-

-> It is used to treat symptoms of nasal congestion, allergic rhinitis and sinusitis.

-> It's salt has been use as a conjunctival decongestant.

Direct acting Drugs:-

-> These agents produce a sympathetic response by interacting directly with adrenergic receptors. The actions produced are rapid onset and of short duration. The drugs effect both α and β receptors.

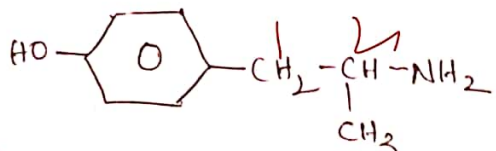
Indirect acting drugs:-

-> These drugs produce their effects mainly by releasing noradrenaline from storage sites in the sympathetic nerves to the effector organs.

-> The response produced by these drugs are similar to that of noradrenaline but have slower onset and longer duration of action.

-> These drugs donot themselves react which them interacts with receptors to produce effect.

(1) Hydroxyamphetamine:-



H- hydroxy -α- Methylphenylamine methylamine.

Mechanism of action:-

-> It is an indirectly acting drug. Though it is a der. of amphetamine, hydroxyamphetamine lacks CNS stimulant action.

-> It causes release of noradrenaline from nerve synapses and causes dilation of pupil.

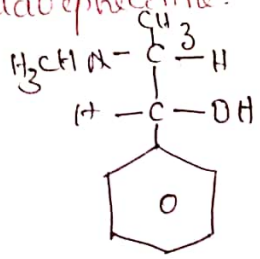
Uses:-

-> It is used as an eye drop to dilate the pupil.

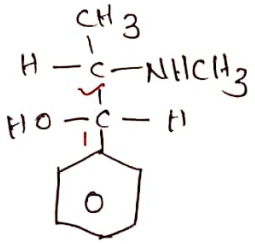
-> It is used as a diagnostic agent for testing Horner's syndrome (damage of nerves of eyes)

-> Its use helps in indicating whether lesions in eye is based on pupils response or not.

② Pseudoephedrine:-



(−) pseudoephedrine



(+) pseudoephedrine.

(1S, 2S)-2-methylamino-1-phenylpropan-1-ol.

Mechanism of action:-

-> It has both α and β adrenergic activity. It stimulates CNS.

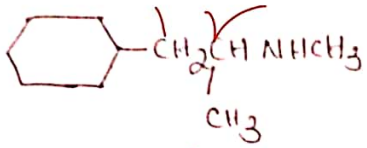
-> It increases blood pressure by increasing the cardiac output and by causing vasoconstriction.

Uses:-

1. It has less pressor activity and CNS effects, so mainly used as a nasal and bronchial decongestant.

2. It causes vasoconstriction so results in hypertension.

(3) propylhexedrine :-



1-cyclohexyl-N-methylpropan-2-amine.

Mechanism of action:-

-> It is an indirectly acting drug, it reverse the transporter for dopamine, norepinephrine and serotonin which leads to release of monoamines from presynaptic vesicles in turn increases their activity at their receptors.

-> It actions are similar to those of dexamphetamine.

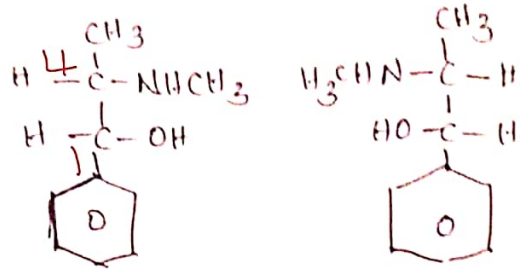
Uses:-

1. It has sympathomimetic, adrenergic, vasoconstructive, and psychostimulant effects.
2. It is used medicinally for relief of congestion due to colds, allergies, and rhinitis.

Mixed acting drugs:-

These drugs as the name indicates they act directly on the adrenergic receptors and also effect the release of noradrenaline. These drugs act some of the drugs belonging to this categogory are:-

① Ephedrine:-



(−) Ephedrine.

(+) Ephedrine

(1R, 2S)- 2-methylamino- 1-phenylpropan-1-ol.

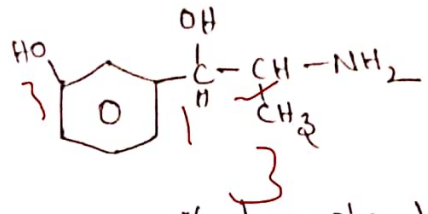
Mechanism of action:-

→ It has α and β- adrenergic activity. It has high stimulating effect on the CNS. It has both direct and indirect effects on adrenergic receptors.

Uses:-

1. It is used to control bronchial spasm in asthma when given orally.
2. It is used as a CNS stimulant in narcolepsy.
3. As inhalation as a spray or as an aerosol it is used in various allergic disease like hay fever & urticaria.
4. It is also used as a nasal decongestant in the form of nasal drops and nasal sprays.
5. It is also used as a mydriatic.

(2) Metaraminol :-



(1R,2S) – 2-amino -1- 3-hydroxy phenyl)- propan-1-ol.

mechanism of action :-

- It acts on both α and β -receptors and also stimulate the release of noradrenaline from sympathetic nerves.
- It is a mixed acting ~~actin~~ sympathomimetic drug.

Uses :-

1. It is used as a pressor agent in various hypotensive states.
2. It is used in the treatment of hypertension which is due to complication of anesthesia.

→ The structure activity relationship is the relation between the chemical or 3D structure of a molecule and its biological activity.

→ The analysis of SAR enables the determination of the chemical group responsible for evoking a target biological effect in the organism.

→ This allows modification of the effect or its potency of a bioactive compound (drug) by changing its chemical structure.

a