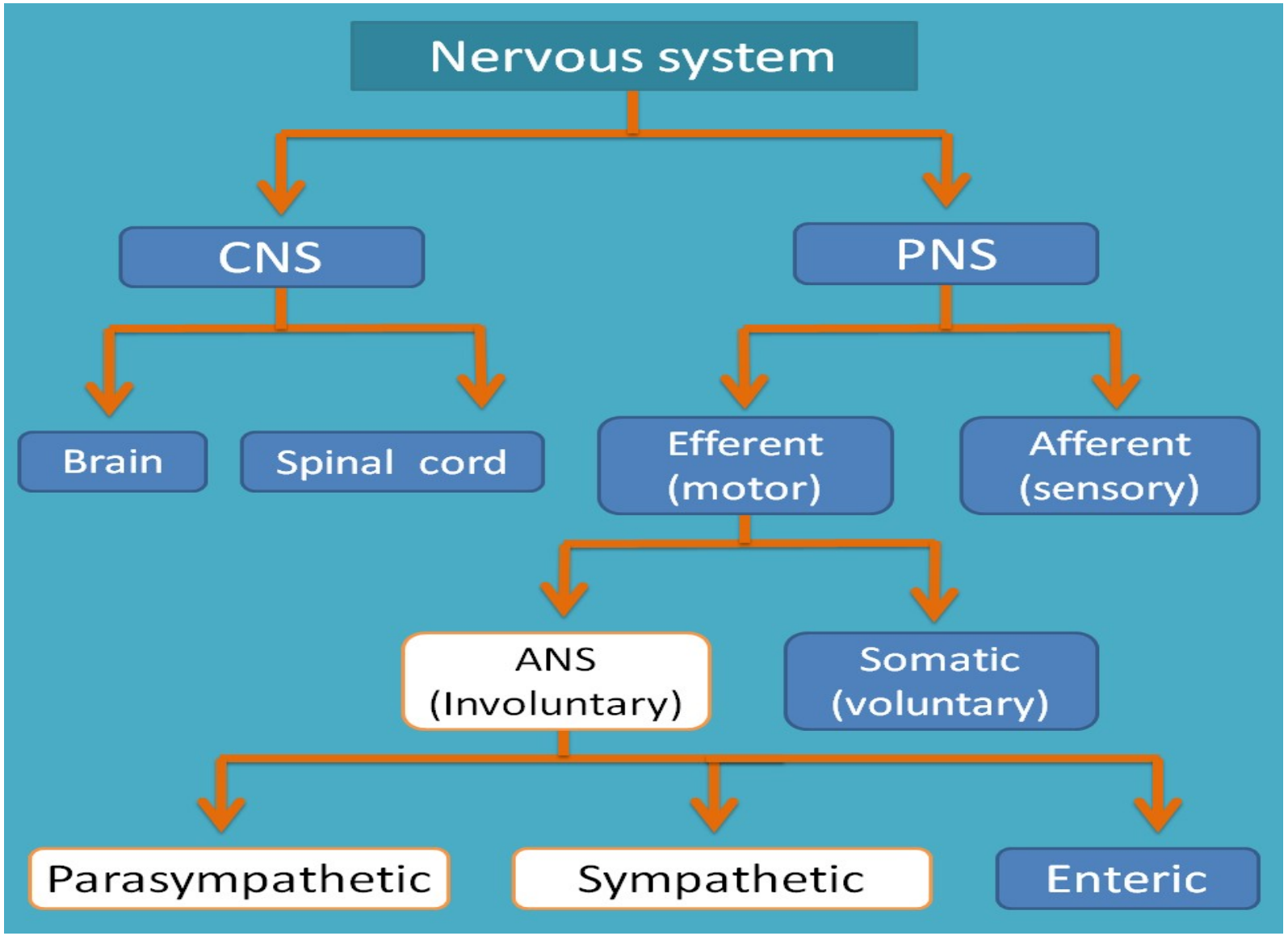
DRUGS ACTING ON AUTONOMIC NERVOUS SYSTEM
PART-I: ADRENERGIC SYSTEM AND SYMPATHOMIMETIC DRUGS

Presented By:
Dr. Joohee Pradhan

OUTLINE OF PRESENTATION

- **Adrenergic Neurotransmitters:**
  - Biosynthesis and catabolism of catecholamine.
  - Adrenergic receptors (Alpha & Beta) and their distribution.
- **Sympathomimetic agents:** **SAR of Sympathomimetic agents**
- **Direct acting:** Nor-epinephrine, Epinephrine, Phenylephrine*, Dopamine, Methyldopa, Clonidine, Dobutamine, Isoproterenol, Terbutaline, Salbutamol*, Bitolterol, Naphazoline, Oxymetazoline and Xylometazoline.
- **Indirect acting agents:** Hydroxyamphetamine, Pseudoephedrine, Propylhexedrine.
- **Agents with mixed mechanism:** Ephedrine, Metaraminol.

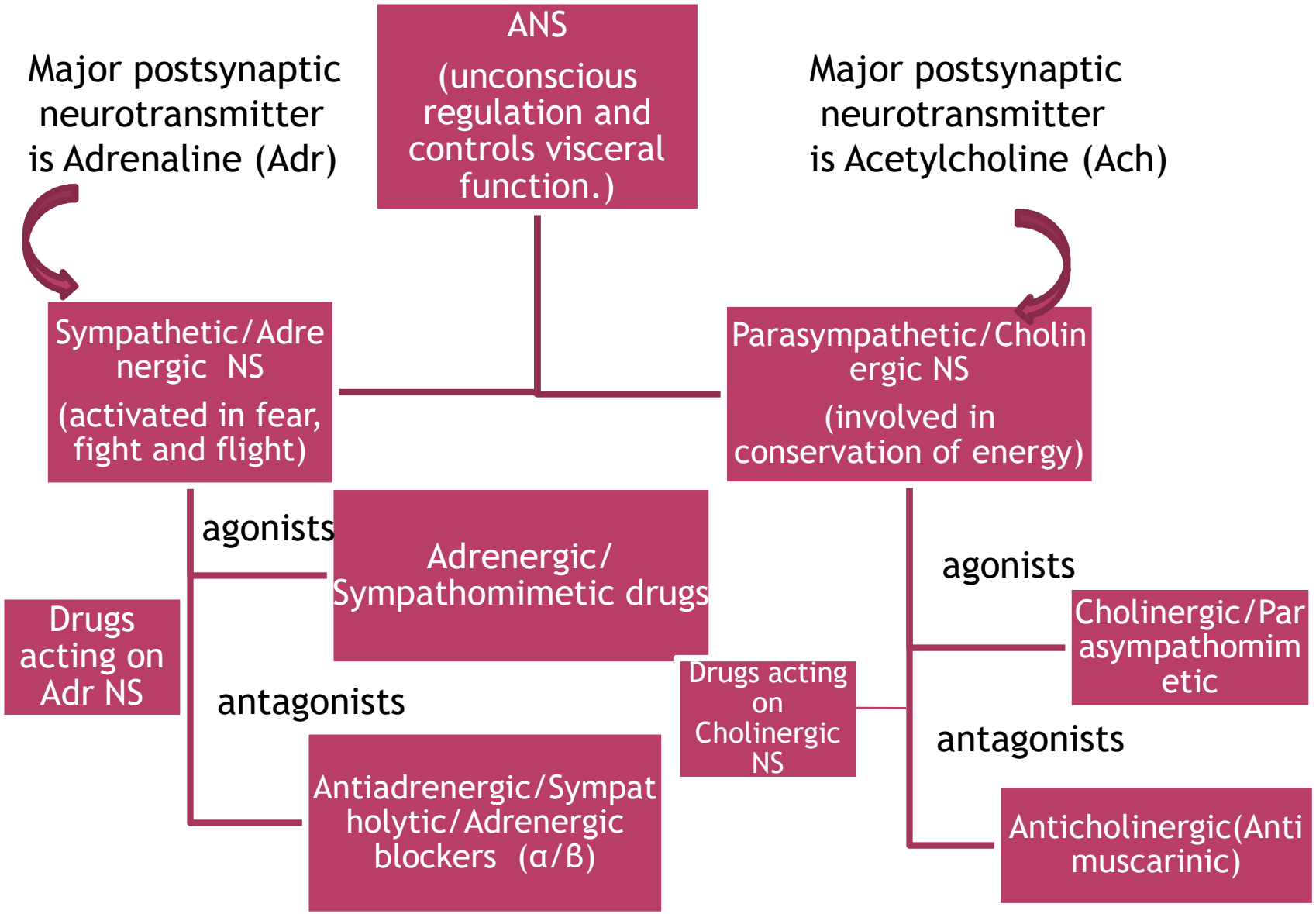
INTRODUCTION: NERVOUS SYSTEM

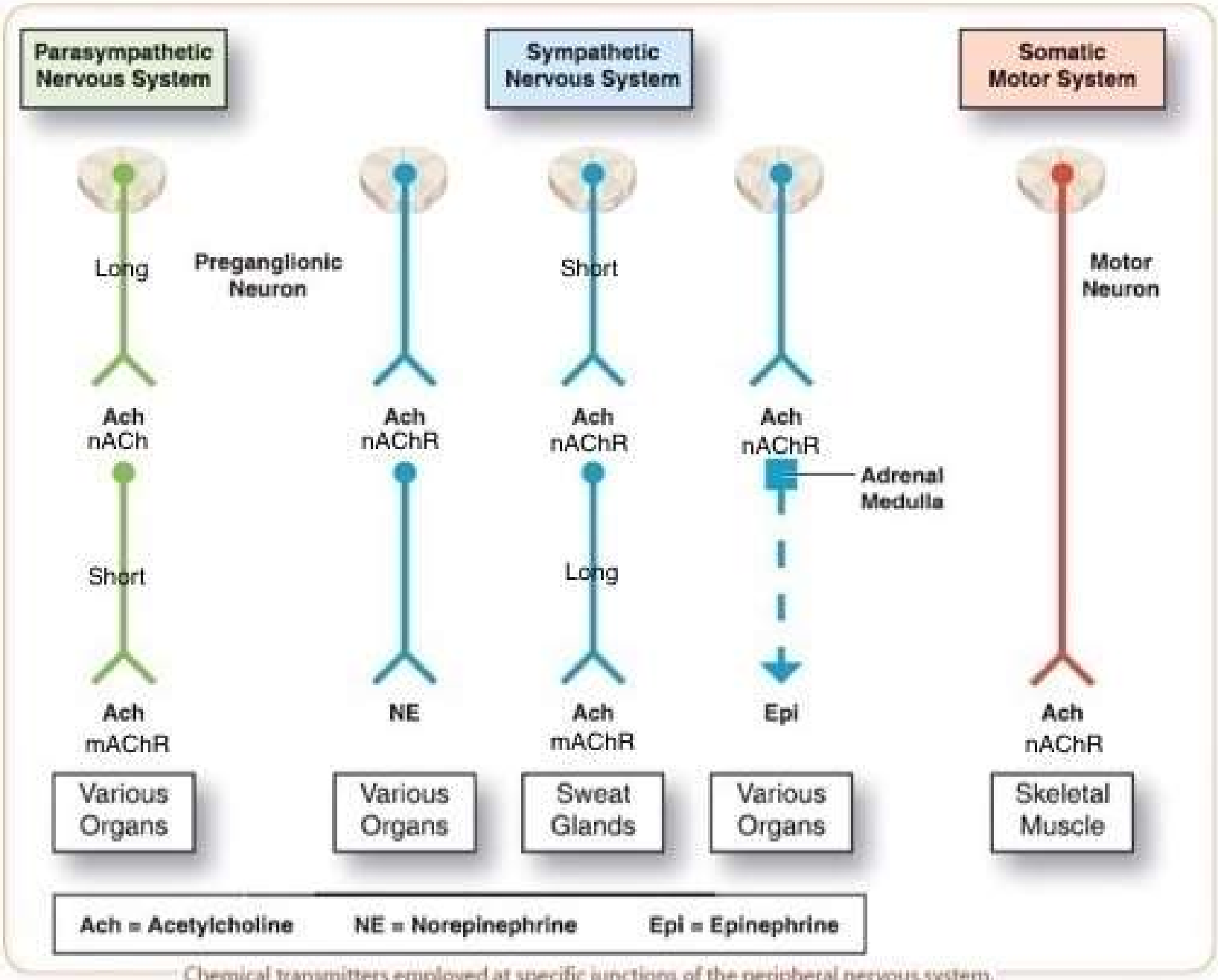


THE AUTONOMIC NERVOUS SYSTEM

- Autonomic nervous system (ANS) represents the unconscious regulation and controls the visceral function.
- It consists of afferent central connections, and autonomic efferents.
- Autonomic efferents are the principal peripheral connections that are divided into sympathetic and parasympathetic outflow.
- Neurotransmitter in all the pre and parasympathetic postganglion fibres is acetylcholine and in sympathetic postganglionic release is norepinephrine.
- ANS is composed of (1) sympathetic system and (2) parasympathetic system.

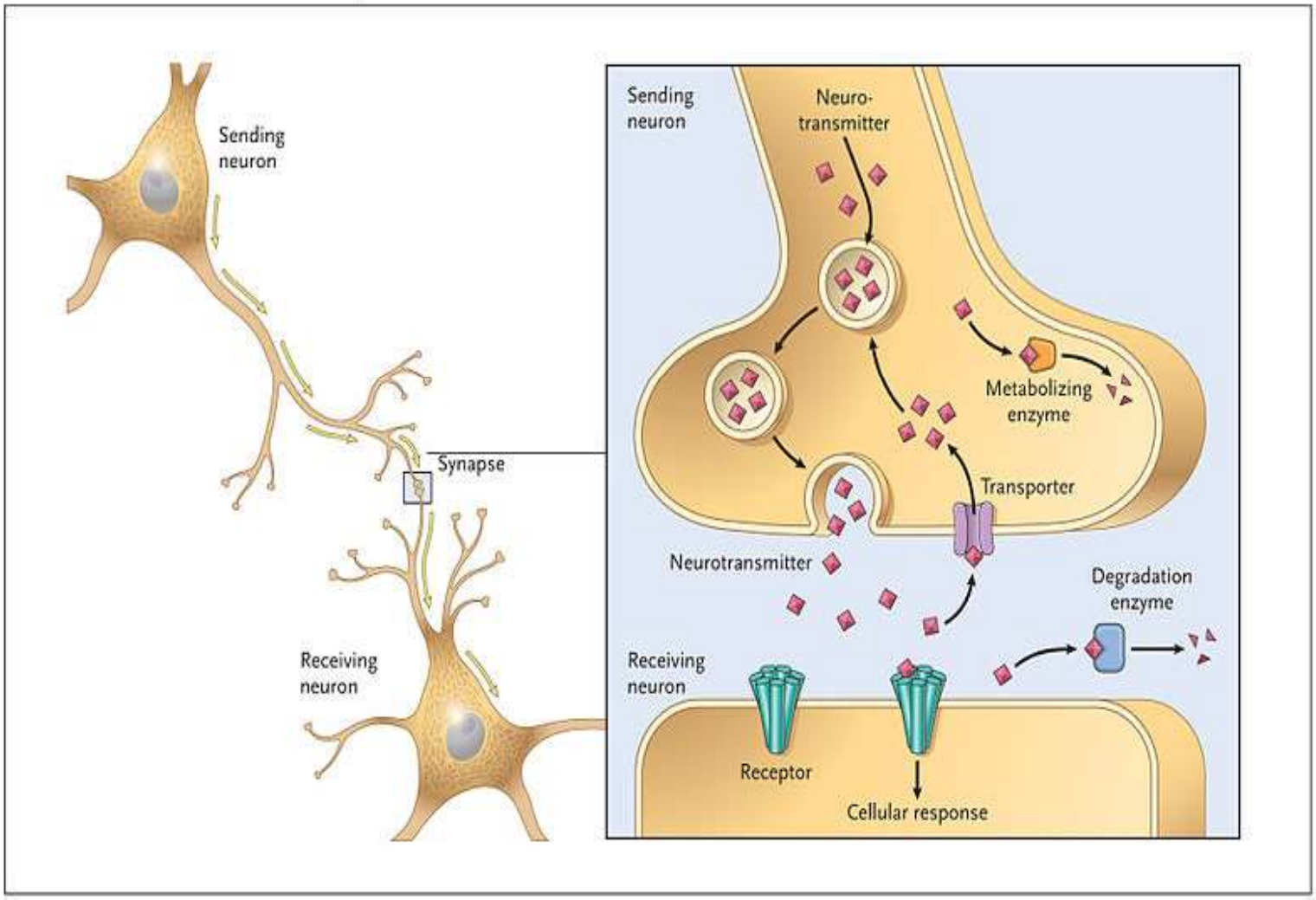
INTRODUCTION: ANS



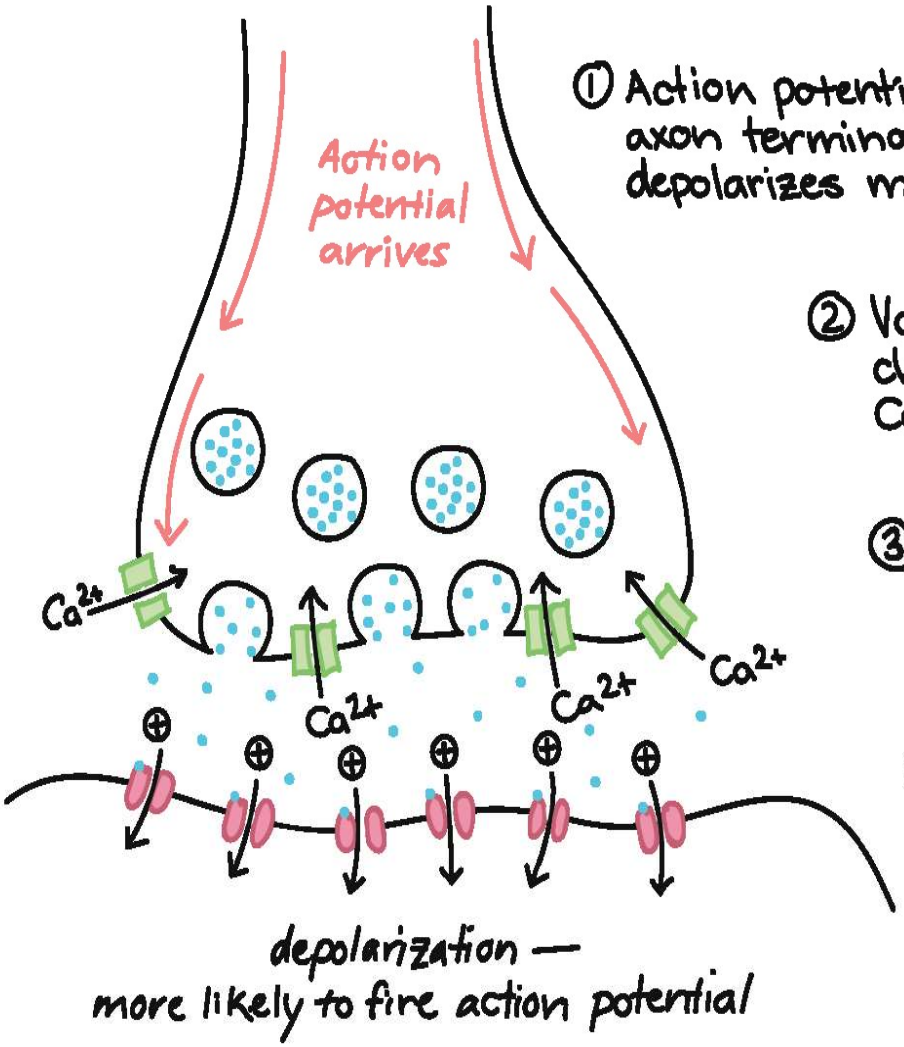


Chemical transmitters employed at specific junctions of the peripheral nervous system.

SYNAPTIC NEUROTRANSMISSION



ACTION POTENTIAL AND TRANSMITTER RELEASE



① Action potential reaches axon terminal and depolarizes membrane.

② Voltage-gated Ca^{2+} channels open and Ca^{2+} flows in.

③ Ca^{2+} influx triggers synaptic vesicles to release neurotransmitter.

④ Neurotransmitter binds to receptors on target cell (in this case, causing positive ions to flow in).

SYMPATHETIC SYSTEM

- Preganglionic nerves of the sympathetic system arise from thoracolumbar division.
- They form ganglia in the vertebral chain called paravertebral chain ganglion and supply the postganglionic fi bres to effector organs.
- The principal neurotransmitter is adrenaline, so it is called adrenergic system.
- In adrenergic neurons (sympathetic postganglion), the neurotransmitter released is norepinephrine,which is also called noradrenaline (NA) or Adrenaline (Adr).
- There are closely related catecholamines (CAs), that is, adrenaline and dopamine that has minor effects secreted by adrenal medulla and in limbic system basal ganglia, respectively.

SYNTHESIS OF EPINEPHRINE AND NOREPINEPHRINE (CATECHOLAMINES)

- Catecholamines (CAs) are synthesized from amino acid phenylalanine. Tyrosine hydroxylase is the rate-limiting enzyme and its inhibition by α-methyl-p-tyrosine leads the CAs to dissipate.
- Other endogenous transmitter, that is, 5-HT produced by aromatic L-amino acid decarboxylase converts DOPA into dopamine and methyl dopamine, and then, it is converted by dopamine ß-hydroxylase to α-methyl norepinephrine.
- The steps involved in the synthesis of epinephrine and norepinephrine is depicted in Figure 1.1.

SYNTHESIS OF EPINEPHRINE AND NOREPINEPHRINE (CATECHOLAMINES)

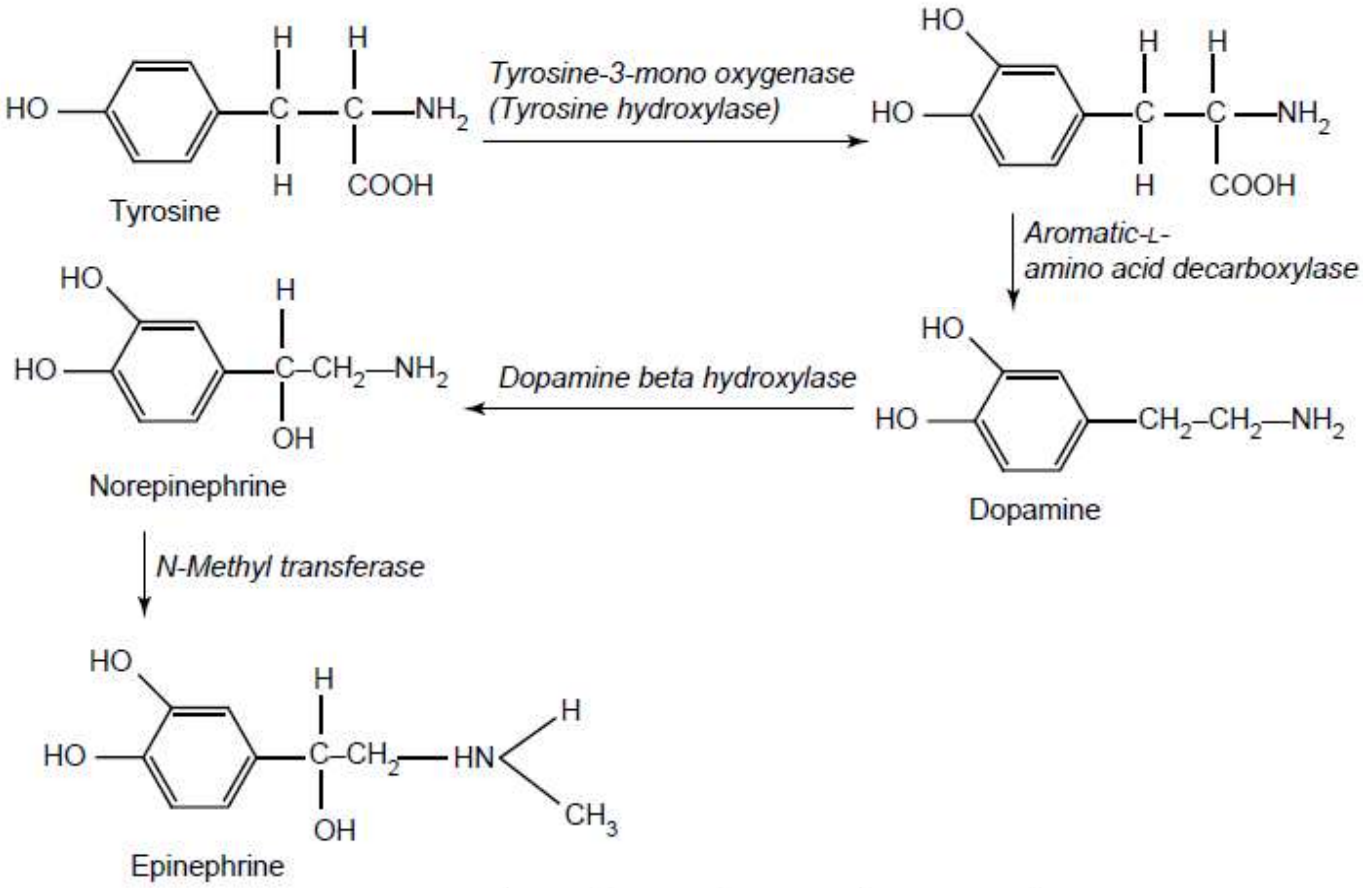
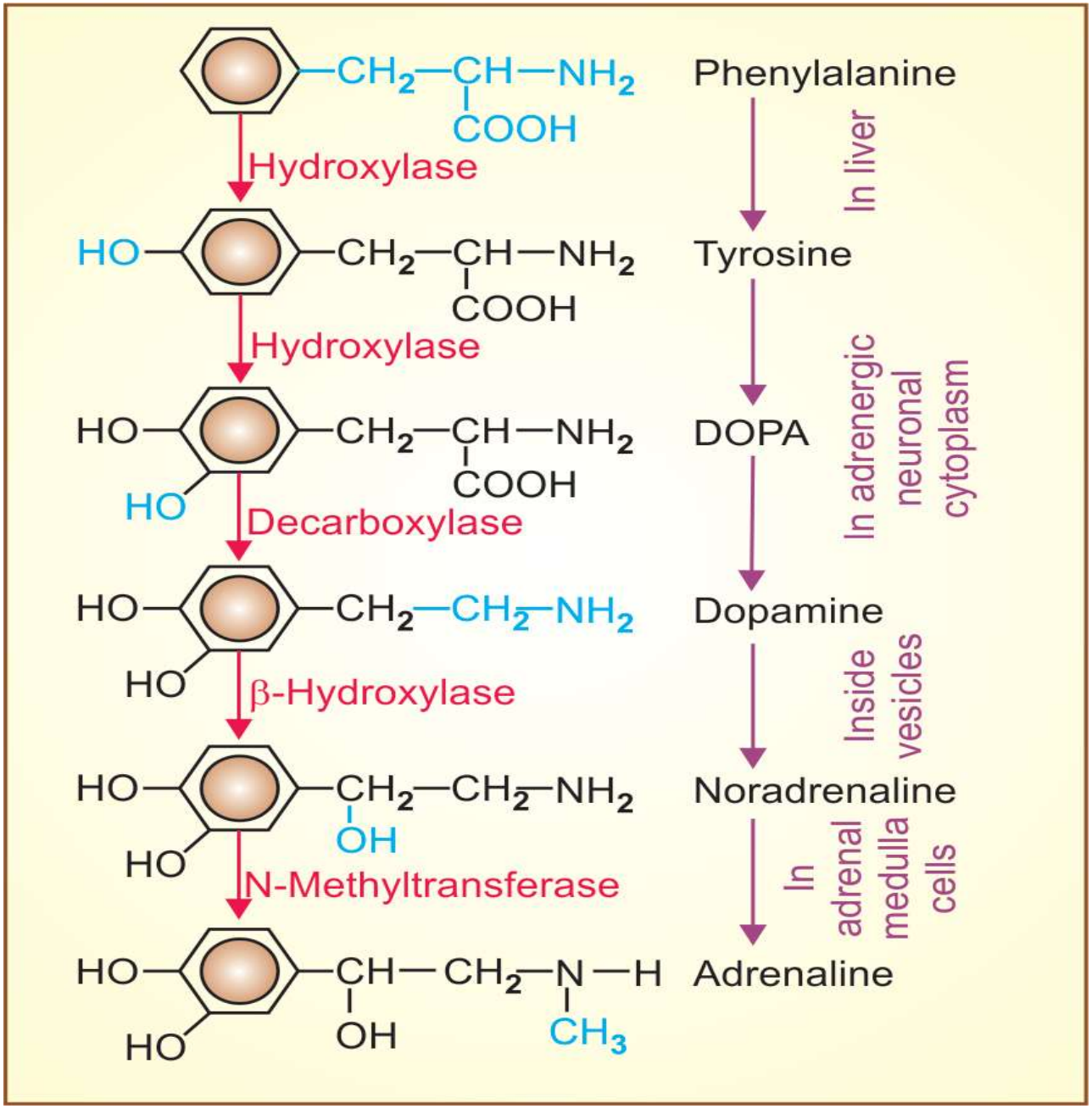


Figure 1.1 Biosynthesis of epinephrine and norepinephrine.


Phenylalanine
Hydroxylase
In liver
Tyrosine
Hydroxylase
DOPA
Decarboxylase
In adrenergic neuronal cytoplasm
Dopamine
β-Hydroxylase
Inside vesicles
Noradrenaline
N-Methyltransferase
In adrenal medulla cells
Adrenaline

REGULATION OF CATECHOLAMINES

- Noradrenaline is stored in the synaptic vesicles on the adrenergic nerve endings and released by exocytosis along with the stored adrenaline, ATP and dopamine ß-hydroxylase.
- The CAs are metabolized by monoamine oxidase (MAO) and catechol-*O-methyl transferase (COMT) in the liver and other tissues into vanillyl*mandelic acid (VMA) and 3-methoxy-4-hydroxy phenyl ethylene glycol with metaephrine and normetaephrine
- (Fig. 1.2).

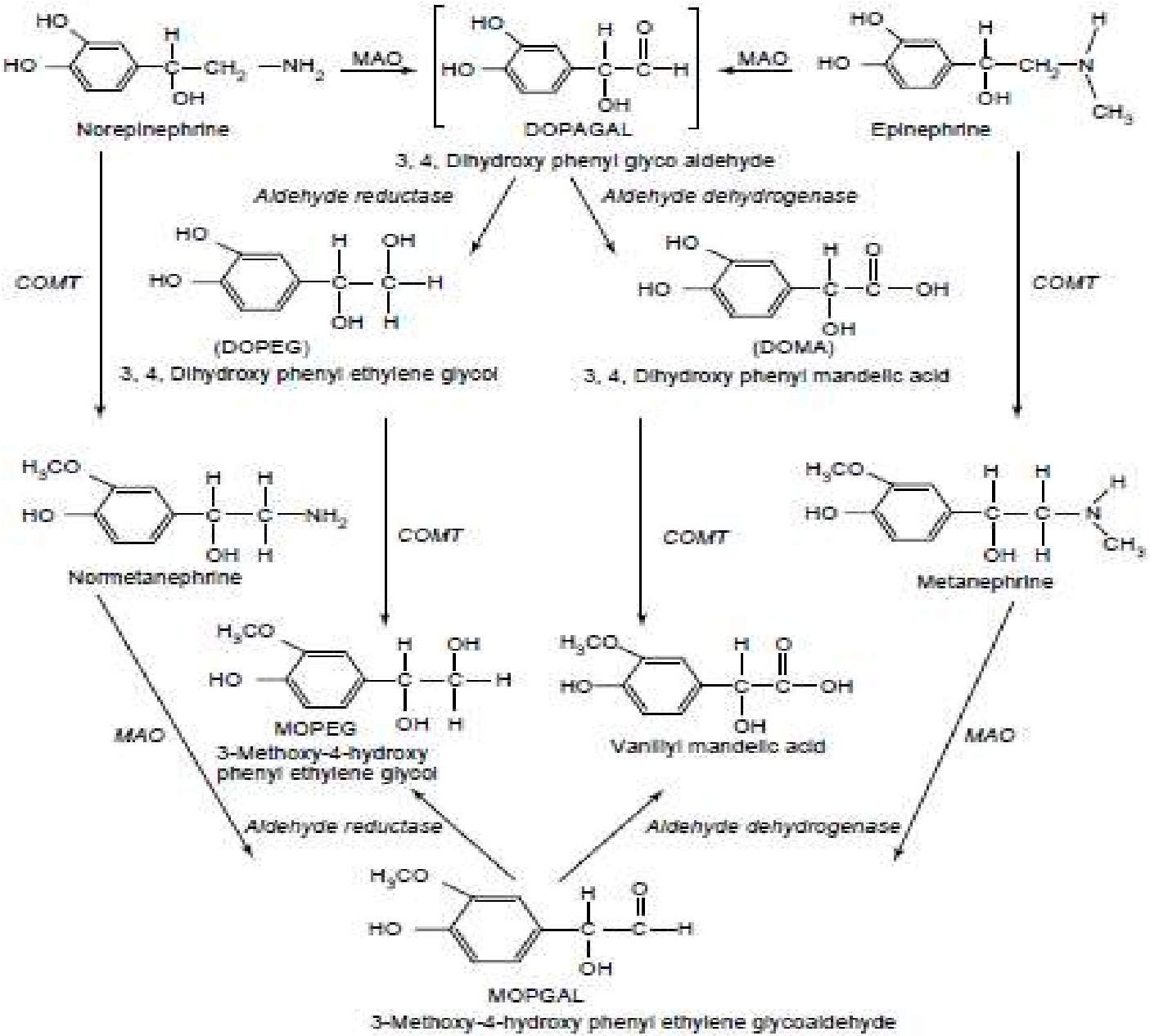
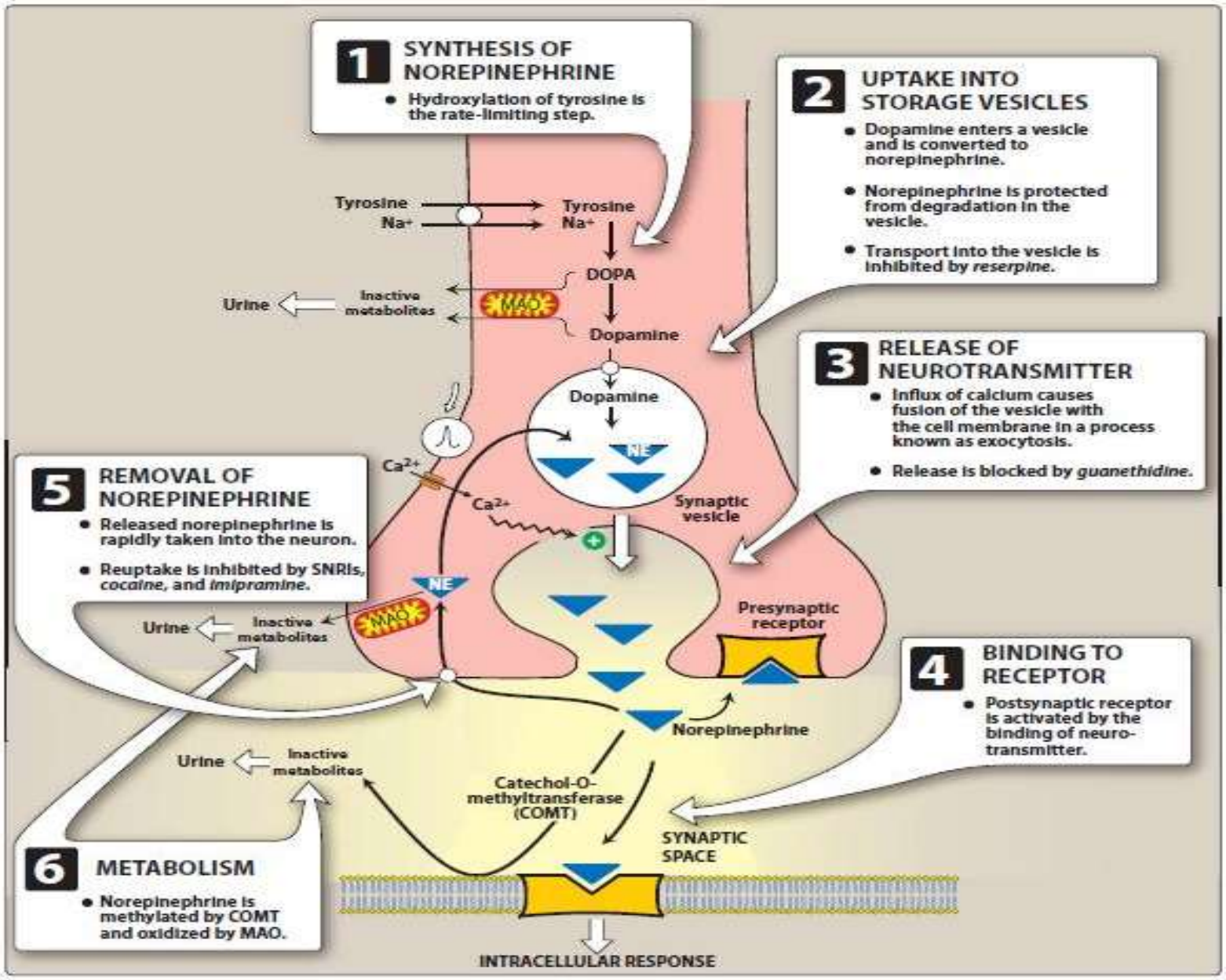


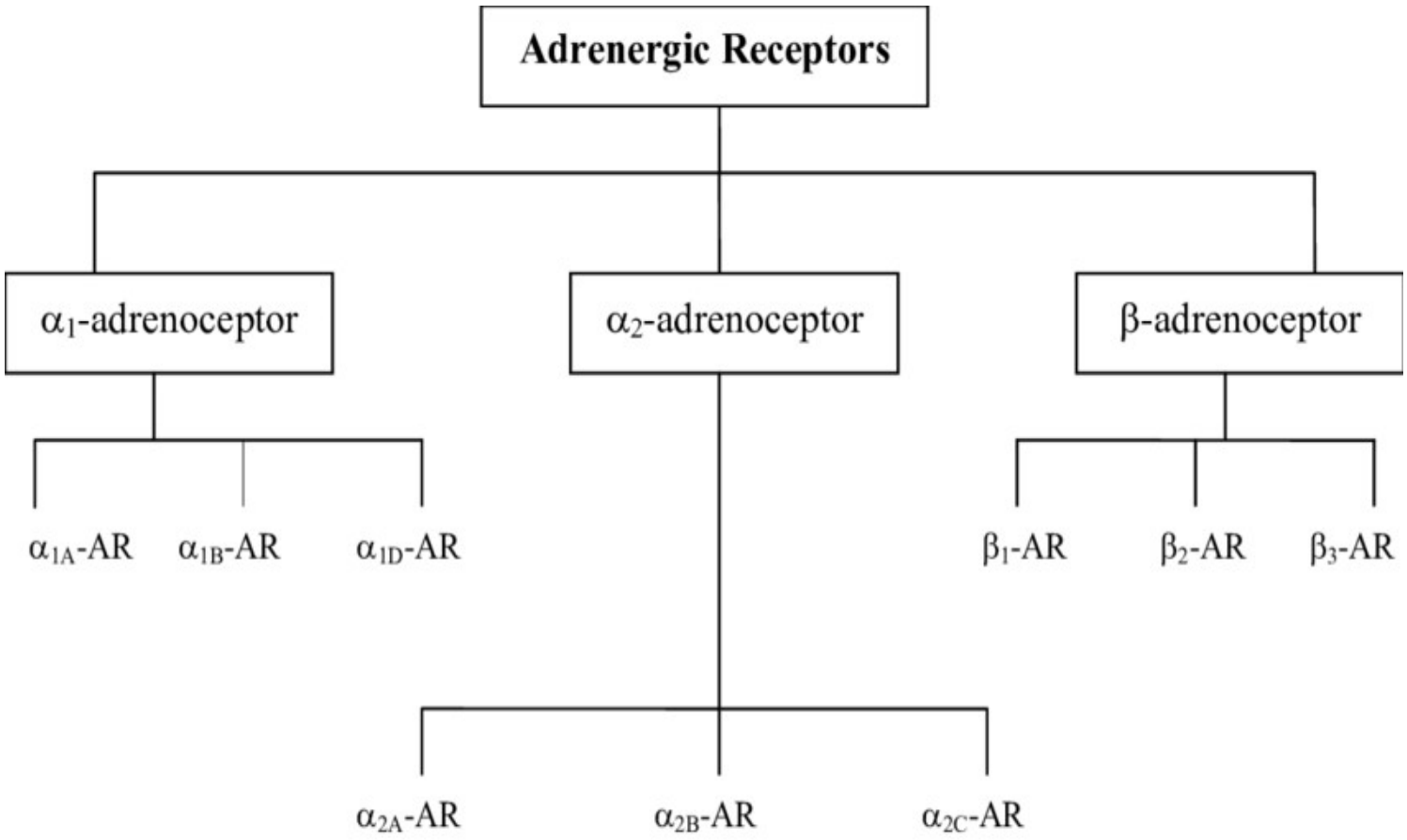
Figure 1.2 Metabolism of catecholamines.

SUMMARY OF ADRENERGIC TRANSMISSION



ADRENERGIC RECEPTORS

Membrane bound G-protein coupled receptors and classified as α (alpha) and ß (beta) adrenoceptors.

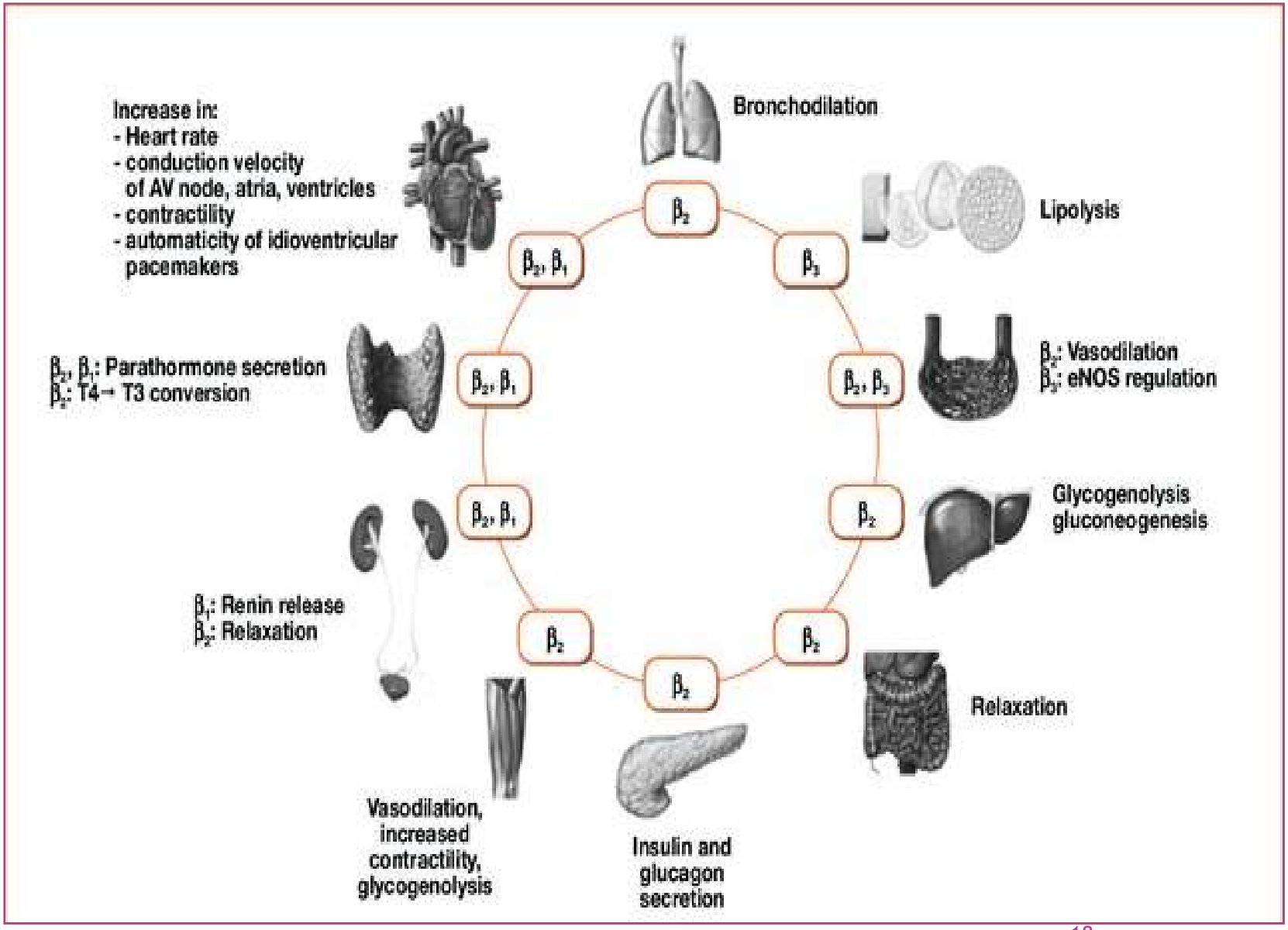


DISTRIBUTION OF ADRENOCEPTORS

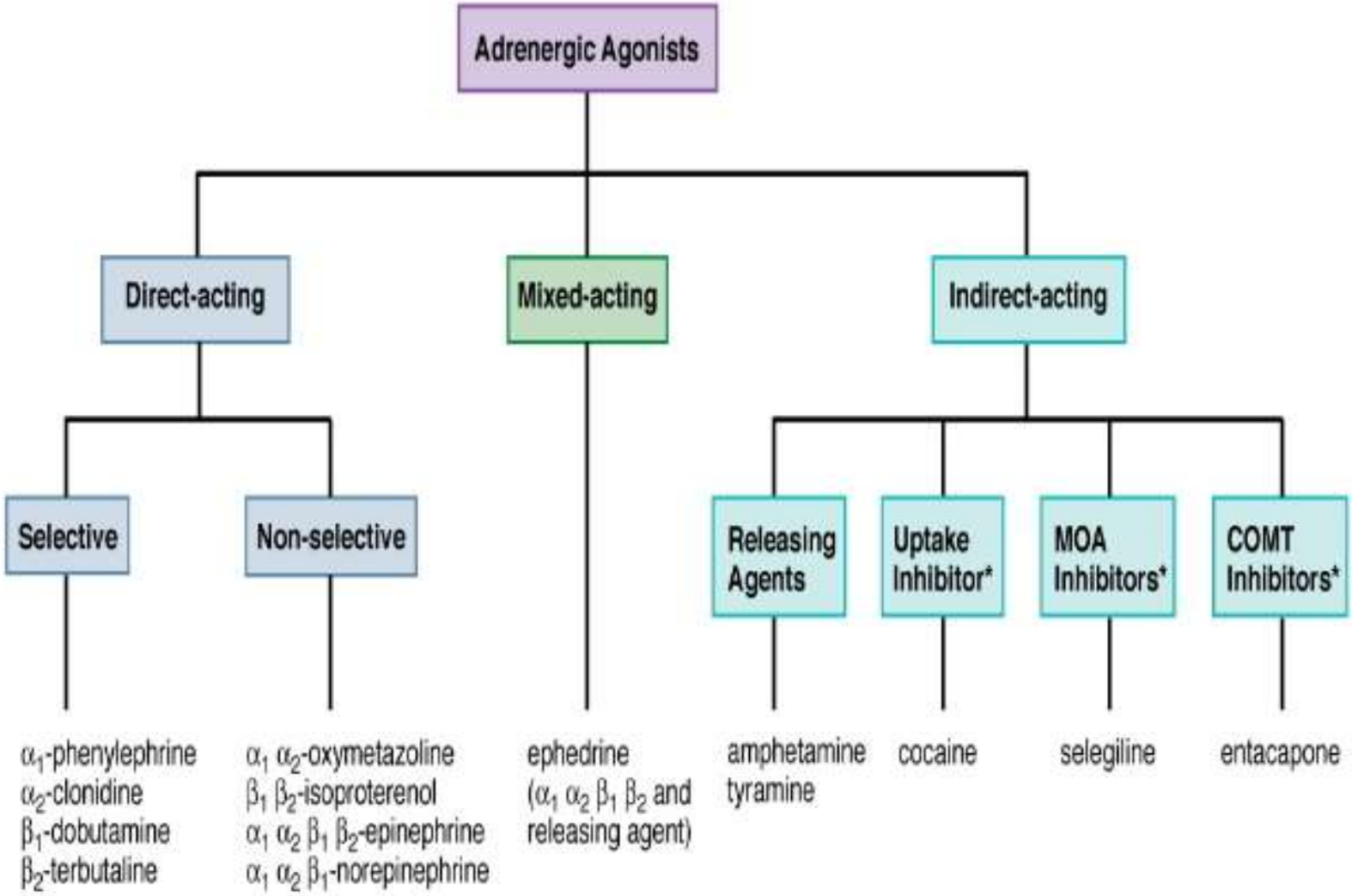
Receptor Type	Tissue Distribution	Mechanism of Action	Agonist Potency	Physiological Effects	Agonist	Antagonist
α1	Vascular Smooth Muscles, Visceral smooth Muscles	Gq-protein coupled activates Phospholipase C, IP3+DAG	Epi ≥ NE >> Iso	Smooth muscle contractions, Gluconeogenesis, Vasoconstriction	Norepinephrine, Phenylephrine, Methoxamine	Doxazosin, Phentolamine, Prazosin
α2	Pre-synaptic terminals, pancreas, platelets, Ciliary epithelium, Salivary Glands	Gi-protein coupled inhibits Adenyl cyclase	Epi ≥ NE >>Iso	Inhibits release of Neurotransmitter	Clonidine, Monoxidine	Yohimbine, Idazoxan, Tolazoline
β1	Heart, Kidney, some pre-synaptic terminals	Gs-protein coupled activates Adenyl cyclase +PKA	Iso > Epi ≥ NE	Increase heart rate and Renin secretion	Isoproterenol, Norepinephrine, Dobutamine	Propranolol, Metoprolol, Atenolol
β2	Visceral smooth muscles, Bronchioles, Liver, Skeletal Muscles	Gs-protein coupled activates Adenyl cyclase +PKA, Ca-channels	Iso > Epi >> NE	Vasodilation, Bronchodilation, Inhibits insulin secretion	Isoproterenol, Salbutamol, Salmeterol, Albuterol, Formoterol, Terbutaline, Levalbuterol	Propranolol, ICI-118,551, Nadolol, Butoxamine
β3	Adipose Tissue	Gs-protein coupled activates Adenyl cyclase +PKA	Iso = NE > Epi	Increase lipolysis	Isoproterenol, Amibegron, Solabegron	SR59230A

NE: Norepinephrine, **Epi:** Epinephrine and **Iso:** Isoproterenol

DISTRIBUTION AND FUNCTIONS OF BETA - ADRENERGIC RECEPTOR

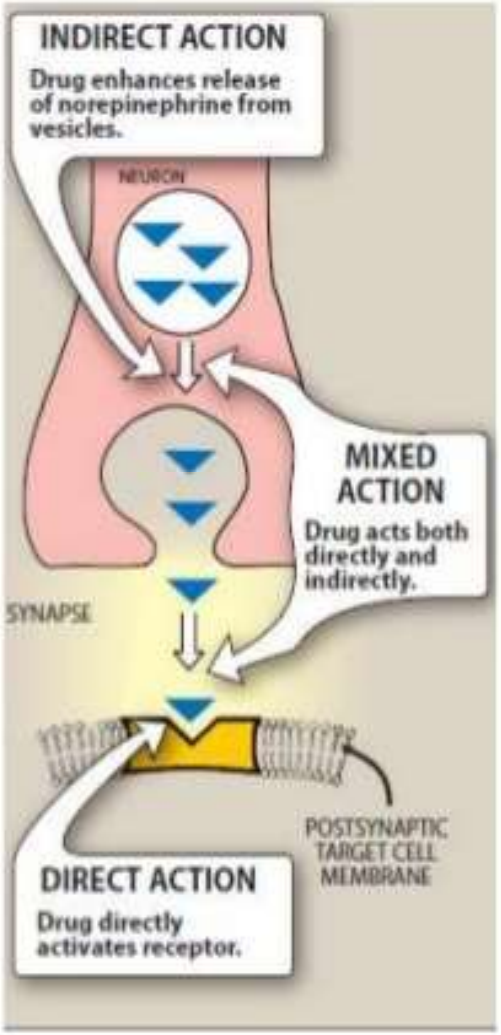


SYMPATHOMIMETIC AGENTS (ADRENERGIC DRUGS): CLASSIFICATION



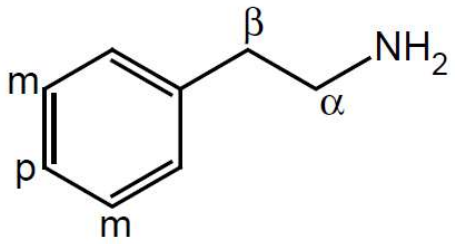
MECHANISM OF ACTION

1. **Direct acting agonist**
   - epinephrine
   - norepinephrine
   - isoproterenol
   - phenylephrine
2. **Indirect acting agonist**
   - cocaine
   - amphetamines
3. **Mixed agonist**
   - ephedrine



STRUCTURAL-ACTIVITY RELATIONSHIP (SAR)

Many of the sympathomimetic drugs contain ß-phenyl ethylamine as parent structure.

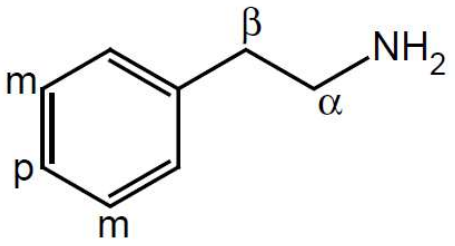


β–Phenyl ethylamine

Following substitutions affect the pharmacological activity:

1. Substitution at Phenyl ring
2. Substitution at Nitrogen
3. Substitution at carbon chain

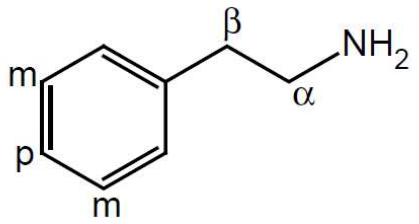
I. PHENYL RING SUBSTITUTION



β–Phenyl ethylamine

- Substitution on the meta and para positions of the aromatic ring and on the amino, α, and ß positions of the ethylamine side chain influences the mechanism of sympathomimetic action and the receptor selectivity of the drug.
- Maximal activity is seen in ß-phenyl ethylamine derivatives, containing hydroxyl groups in the meta and para positions of the aromatic ring (catechol) and a ß-hydroxyl group of the correct stereochemical configuration on the ethylamine portion of the molecule.
- Although the catechol moiety is an important structural feature to obtain maximal agonistic activity at adrenergic receptors, it can be replaced with other substituted phenyl moieties to provide selective adrenergic agonism.

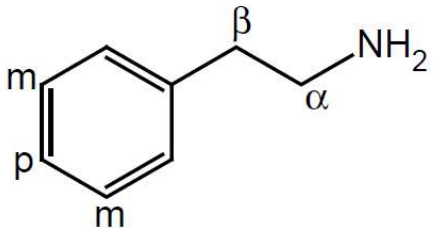
I. PHENYL RING SUBSTITUTION



β–Phenyl ethylamine

- For example, replacement of the catechol function of isoproterenol with the resorcinol structure gives the drug metaproterenol, which is a selective ß2-receptor agonist.
- In an other approach, replacement of the meta hydroxyl of the catechol structure with a hydroxymethyl group afforded Salbutamol, which shows selectivity to the ß2 receptor.
- The naturally occurring noradrenaline has 3, 4-dihydroxy benzene ring (catechol) active at both α and ß receptors. However, it has poor oral activity because it is rapidly metabolized by COMT, the change in substitution pattern 3, 5-dihydroxy as in metaproterenol gives good oral activity. This is due to its resistance to metabolism by COMT. It also provides selectivity for ß2 receptors.

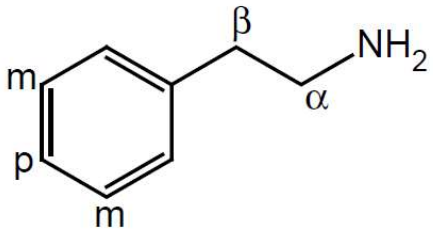
II. SUBSTITUTION AT NITROGEN



β–Phenyl ethylamine

- Amino group in phenylethylamines is important for direct agonistic activity.
- The amino group should be separated from the aromatic ring by two carbon atoms found among the potent direct-acting agonists.
- As the bulk of the nitrogen substituent increases, α-receptor agonistic activity decreases and ß-receptor activity increases. Thus, NE that is an effective ß1-receptor agonist is also a potent α-agonist, while epinephrine is a potent agonist at α, ß1, and ß2 receptors.
- *N-tertiary butyl group* enhances ß2 selectivity. As the size increases from hydrogen in noradrenaline to methyl in adrenaline,isopropyl in isoproterenol, the activity of α receptor decreases and ß receptor increases.
- Primary and secondary amines are more potent direct-acting agonists than 3° or 4° amines.

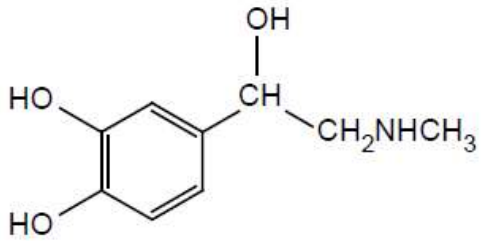
III. SUBSTITUTION ON THE CARBON SIDE CHAIN



β–Phenyl ethylamine

- Methyl or ethyl substitution on the α-carbon of the ethylamine side chain reduces direct receptor agonist activity at both α and ß receptors.
- Importantly, an α-alkyl group increases the duration of action of the phenylethylamine agonist by making the compound resistant to metabolic deamination by MAO.
- α-substitution also significantly affects receptor selectivity.
- Another effect of α-substitution is the introduction of a chiral centre, which has pronounced effects on the stereo-chemical requirements for activity.

EPINEPHRINE (ADRENALINE)



(3,4-Dihydroxy phenyl) -2-methylamino ethanol

Action:

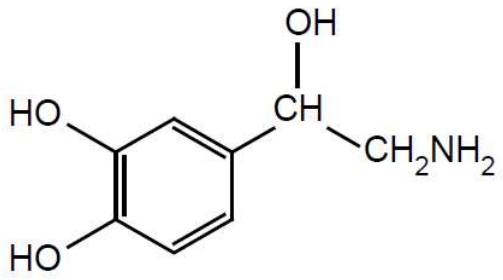
Adrenaline is a catecholamine and belongs to the family of biogenic amines. It is a direct acting potent stimulant for both α and β receptors, predominately on the β1 receptor of myocardium and pacemaker. The mechanism of rise in blood pressure is by

- direct myocardial stimulant (positive ionotropic action)
- increase in heart rate (positive chronotropic action)
- vasoconstrictor in the vascular beds.

Uses:

1. It is used as a sympathomimetic, broncholytic, and antiasthmatic.
2. It is used to prevent bleeding during surgery or in case of inner organ bleeding.
3. It is used in the treatment of heart block or circulatory collapse and open-angle glaucoma.
4. It is usually the drug of choice in acute allergic disorders and histamine reactions.

NORADRENALINE (NOREPINEPHRINE, NEPHRIDINE)

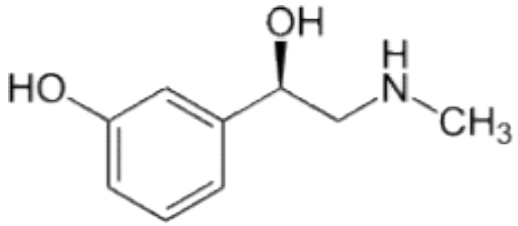


L-1-(3,4 Dihydroxy phenyl)-2-amino ethanol

Action and uses:

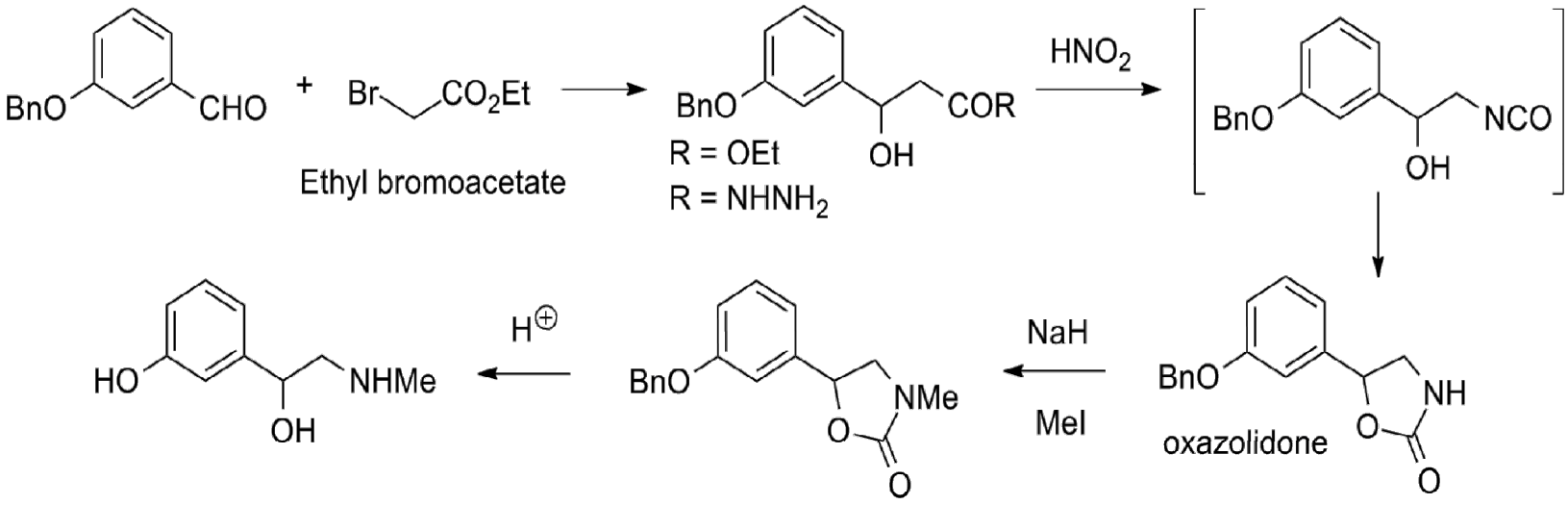
- Noradrenaline differs from adrenaline only by lacking the methyl substitution on the amino ethanol.
- L-isomer is pharmacologically active.
- Noradrenaline is a potent agonist for α1 receptors and has relative
- actions on β2 receptors.
- By acting on these receptors, the systolic and diastolic pressures, and usually, pulse pressure are increased.
- It increases the peripheral vascular resistance.
- Its principle use is to support blood pressure in various acute hypotensive states, especially in myocardial shock.
- It is used as a vasoconstrictor in some local anaesthetic solutions for dental use.

PHENYLEPHRINE



(*R*)-3-[-1-hydroxy-2-(methylamino)ethyl]phenol

- Synthesis:

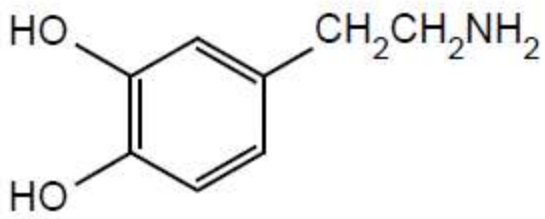


3-(benzyloxy)benzaldehyde reacts with ethylbromoacetate to give ethyl3-(3-(benzyloxy)phenyl)-3-hydroxypropanoate. The latter compound undergoes nitration to give an intermediate compound which gives oxazolidone later. The compound is then reacted with sodium hydride in presence of methyl iodide to give 5-(3-(benzyloxy)phenyl)-3-methyloxazolidin-2-one which on reduction gives phenylephrine.

ACTIONS AND USES OF PHENYLEPHRINE

- Phenylephrine is a selective alpha-1 adrenergic receptor agonist used to treat hypotension, dilate the pupil, and induce local vasoconstriction.
- Phenylephrine is used to relieve nasal discomfort caused by colds, allergies, and hay fever. It is also used to relieve sinus congestion and pressure.
- In the setting of IV administration, phenylephrine is a commonly used anesthetic vasopressor for patients with normal cardiac function

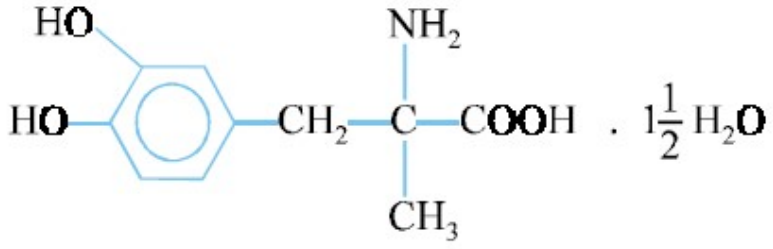
DOPAMINE



2-(3,4-Dihydroxy Phenyl)-1-amino ethane

- Dopamine is used in the treatment of shock.
- It is ineffective orally in large parts because it is a substrate for both MAO and COMT. Dopamine exerts the CVS effects by interacting with D1-dopaminergic receptors especially in the renal, mesenteric, and coronary beds.
- At high concentrations, dopamine acts on β1 adrenergic receptors and causes positive ionotropic effects and also dopamine causes the release of norepinephrine.

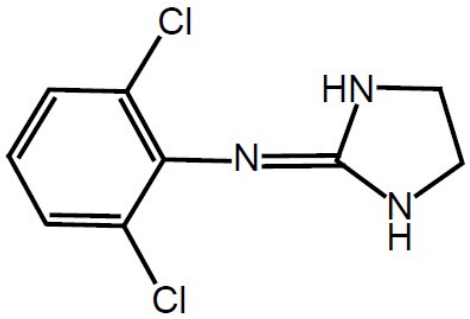
METHYLDOPA



L-3-(3, 4-Dihydroxyphenyl)-2-methylalanine sesquihydrate

- Methyldopa is a potent antihypertensive agent that acts centrally by stimulating α-adrenergic receptors.
- It also helps to minimize the tissue concentrations of adrenaline, noradrenaline and serotonin.
- It is widely employed to treat patients having moderate to severe hypertension by reducing the supine blood pressure as well as the standing blood pressure.

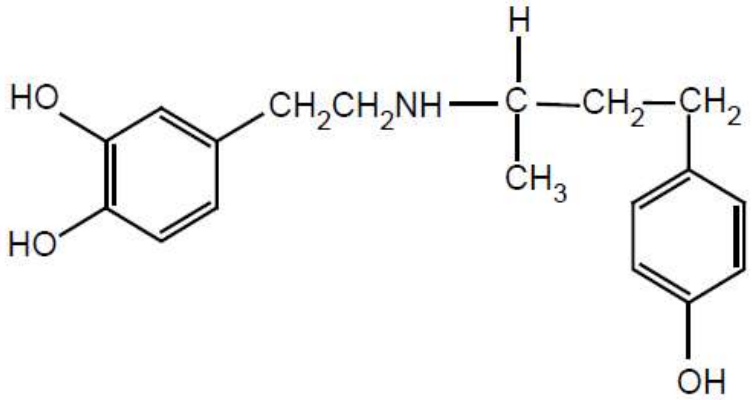
CLONIDINE



2-(2, 6-Dichloroanilino)-2-imidazoline hydrochloride

- Clonidine is selective alpha-2 agonist that lowers blood pressure and heart rate by relaxing the arteries and increasing the blood supply to the heart.
- The compound was initially investigated as a nasal vasoconstrictor but incidentally has shown to be an effective drug in the *treatment of mild to severe hypertension and prophylaxis of migraine headache*.

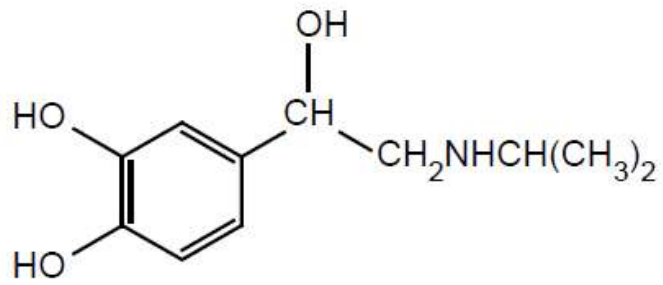
DOBUTAMINE



N-[1-Methyl-3-(4-hydroxy phenyl)propyl]3,4-dihydroxy phenyl ethylamine

- Dobutamine resembles dopamine chemically, but possesses a bulky aromatic residue on the amino group despite the absence of a ß-OH group.
- This substitution gives a compound that possesses an asymmetric carbon atom. Thus, dobutamine exists as a pair of enantiomers possessing a distinct pharmacology.
- The (+) enantiomer is a potent agonist at both ß1 and ß2 receptors. The (-) enantiomer is 10 times less potent at ß1 and ß2 receptors. The (-) enantiomer is a potent agonist at α1 receptors.
- It acts by directly interacting with α and ß adrenergic receptors.
- Racemic dobutamine increases the inotropic action due to α1 receptor when compared to chronotropic actions, and the effects are mediated by ß receptors.
- It enhances the automaticity of SA node.

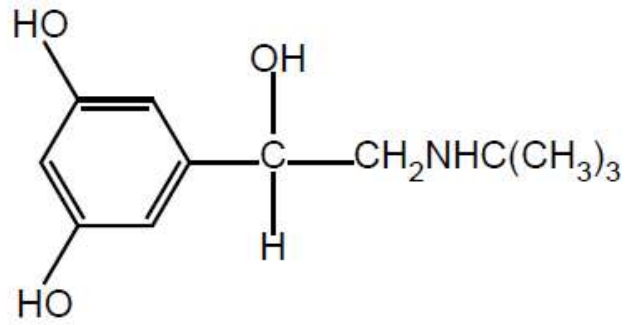
ISOPROTERENOL (ISOPRENALINE)



1-(3,4-Dihydroxy phenyl)-2-isopropylamino ethanol

- It is a synthetic Isopropyl analogue of adrenaline, acting almost exclusively at ß-receptor.
- It stimulates the action of adrenaline and has the advantage of being effective when given orally.
- It is a nonselective ß agonist and has strong ß1 and ß2 agonist activity.
- Its primary use is in the treatment of bronchial asthma. It is used as an antiarrhythmic agent and in the treatment of shock to increase heart rate.

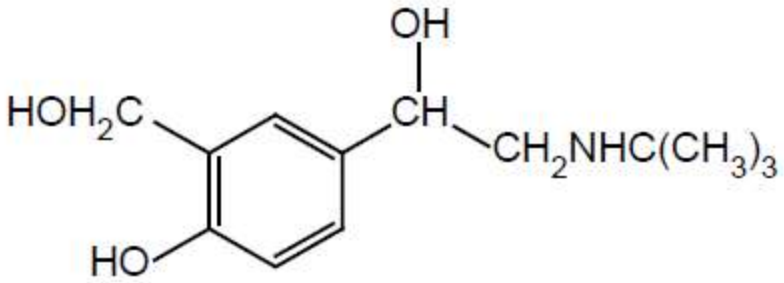
TERBUTALINE



5-(2-(Tert-butylamino)-1-hydroxyethyl)benzene-1,3-diol

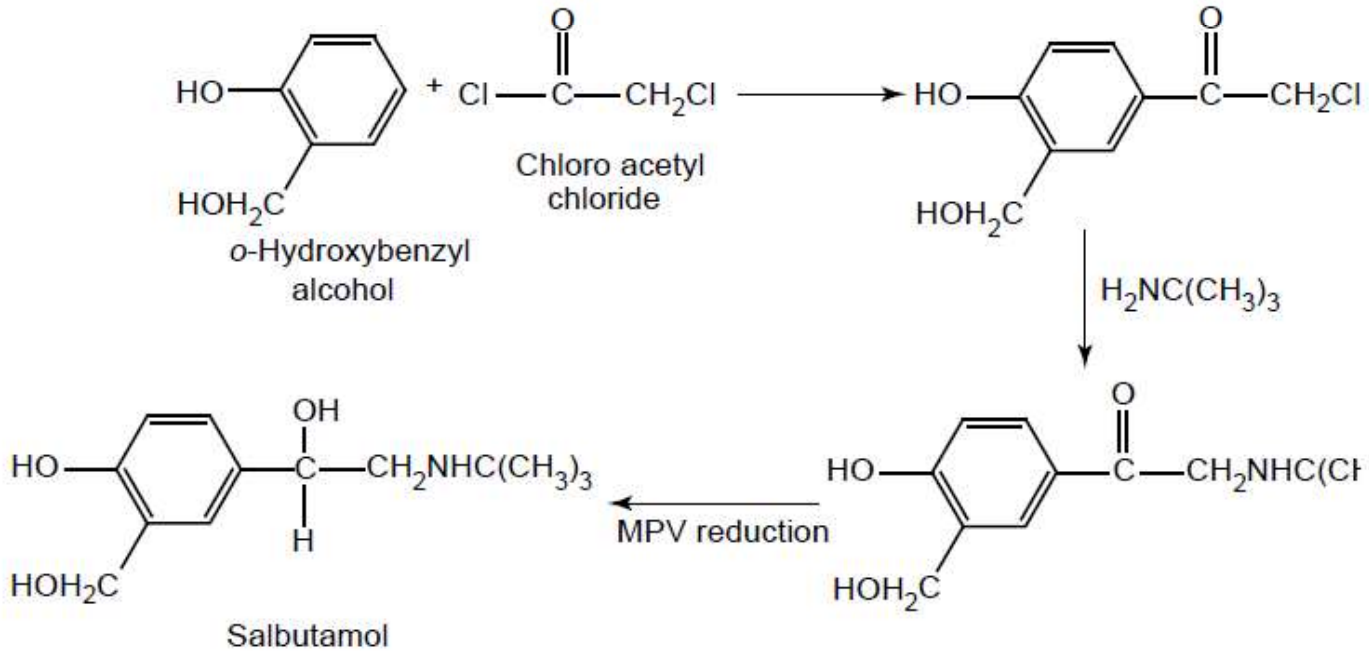
- The drug exhibits the properties of a direct-acting sympathomimetic agent, having predominantly ß2 adrenergic activity, and has a selective action on the ß2 receptors (i.e. ß2 agonist).
- It is used only as a bronchodilator and in the treatment of asthma. It possesses strong ß-agonistic activity.

SALBUTAMOL*



4-Hydroxy-3-hydroxy methyl-alpha-[(tert butylamino)methyl]benzyl alcohol

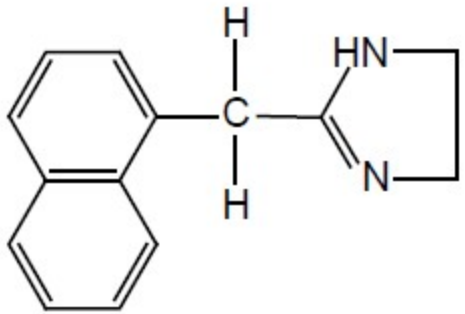
Synthesis:



SALBUTAMOL

- Salbutamol has strong β2 adrenergic activity. It is useful in the treatment of acute myocardial infarction,severe left ventricular failure.
- It has been used to arrest premature labour and is effective in ocular hypotension by topical application.
- It is used only as a bronchodilator and is the drug of choice in the treatment of bronchial asthma.

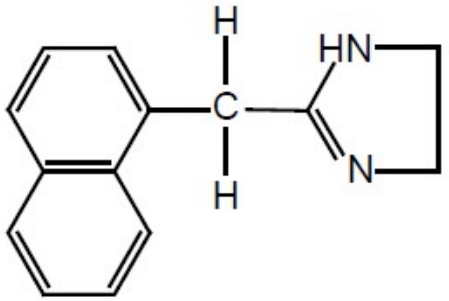
NAPHAZOLINE



2-(1-Naphthyl methyl)-2-imidazoline

- It is a directly acting sympathomimetic drug, which is mostly used as a local vasoconstrictor for the relief of nasal congestion due to allergic or infarction manifestations.
- It is also employed as an ophthalmic solution for the relief of ocular congestion and blepharospasm.

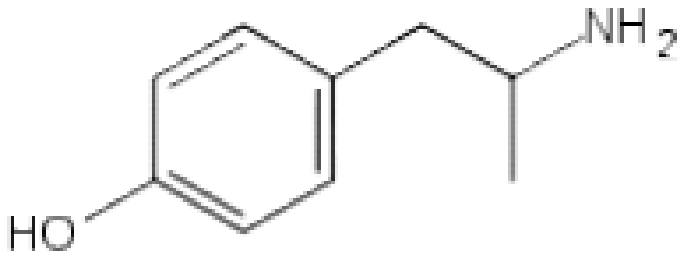
NAPHAZOLINE



2-(1-Naphthyl methyl)-2-imidazoline

- Naphazoline is a directly acting sympathomimetic drug, which is mostly used as a local vaso-constrictor for the relief of nasal congestion due to allergic or infarction manifestations.
- It is also employed as an ophthalmic solution for the relief of ocular congestion and blepharospasm.

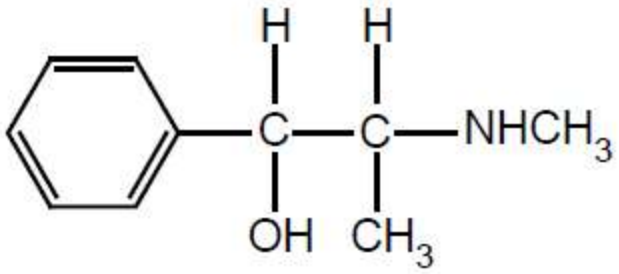
HYDROXYAMPHETAMINE



4-(2-Aminopropyl)phenol

- Hydroxyamphetamine is a drug that indirectly stimulates the sympathetic nervous system.
- It is used medically in eye drops to dilate the pupil (a process called mydriasis), so that the back of the eye can be examined.
- It is also a major metabolite of amphetamine and certain substituted amphetamines.

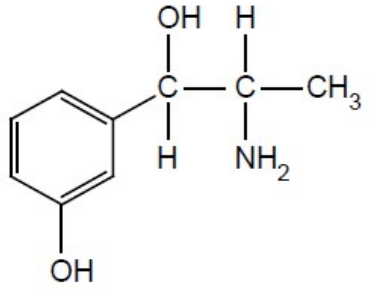
EPHEDRINE



2-Methylamino-1-phenyl propan-1-ol

- Ephedrine is obtained from the plant Ephedra sinica and other members of the genus Ephedra.
- Most of the l-ephedrine produced today for official medical use is made synthetically as the extraction and isolation process from *E. sinica* is tedious and no longer cost effective.
- Ephedrine has two assymetric carbon atom and four optical isomers.
- The erythro- racemate is called Ephedrine.
- It has both α and ß-adrenergic agonistic effect.
- It is used in a variety of conditions, such as allergic disorder, colds, hypotension conditions, and narcolepsy.
- Also, occasionally, used to treat enuresis to dilate the pupil.

METARAMINOL



2-Amino-1-(3´-hydroxy phenyl) propanol

- Metaraminol is structurally similar to phenylephrine.
- It enhances cardiac output, peripheral resistance, and blood pressure.
- It helps to increase the coronary blood flow thereby decreasing the heart rate.
- The drug is employed frequently in acute hypotensive states, such as anaphylactic shock or shock secondary to myocardial infarction and trauma.

THANK YOU……

KEEP LEARNING