Drugs acting on Adrenergic nervous system

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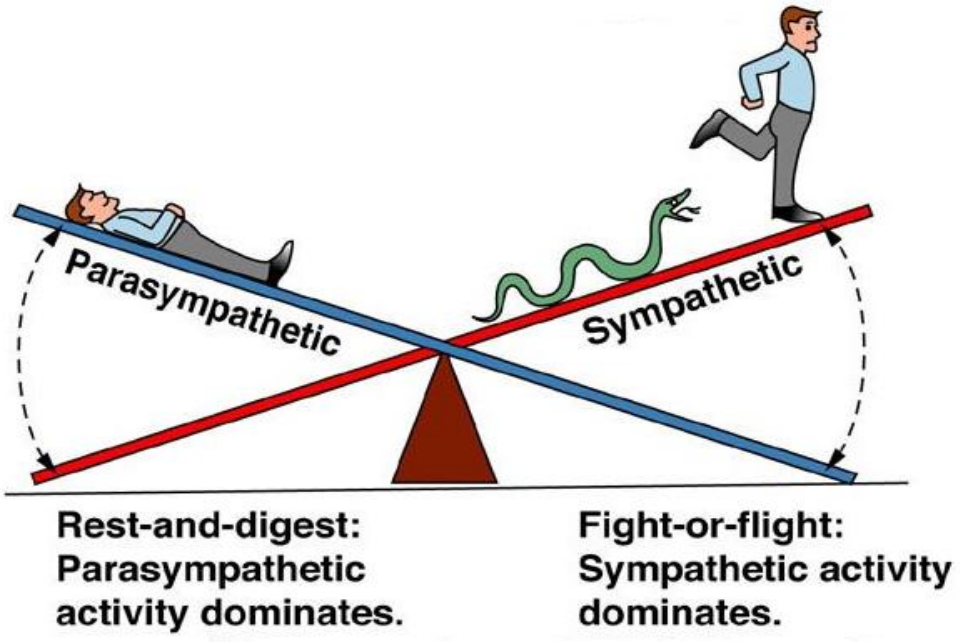


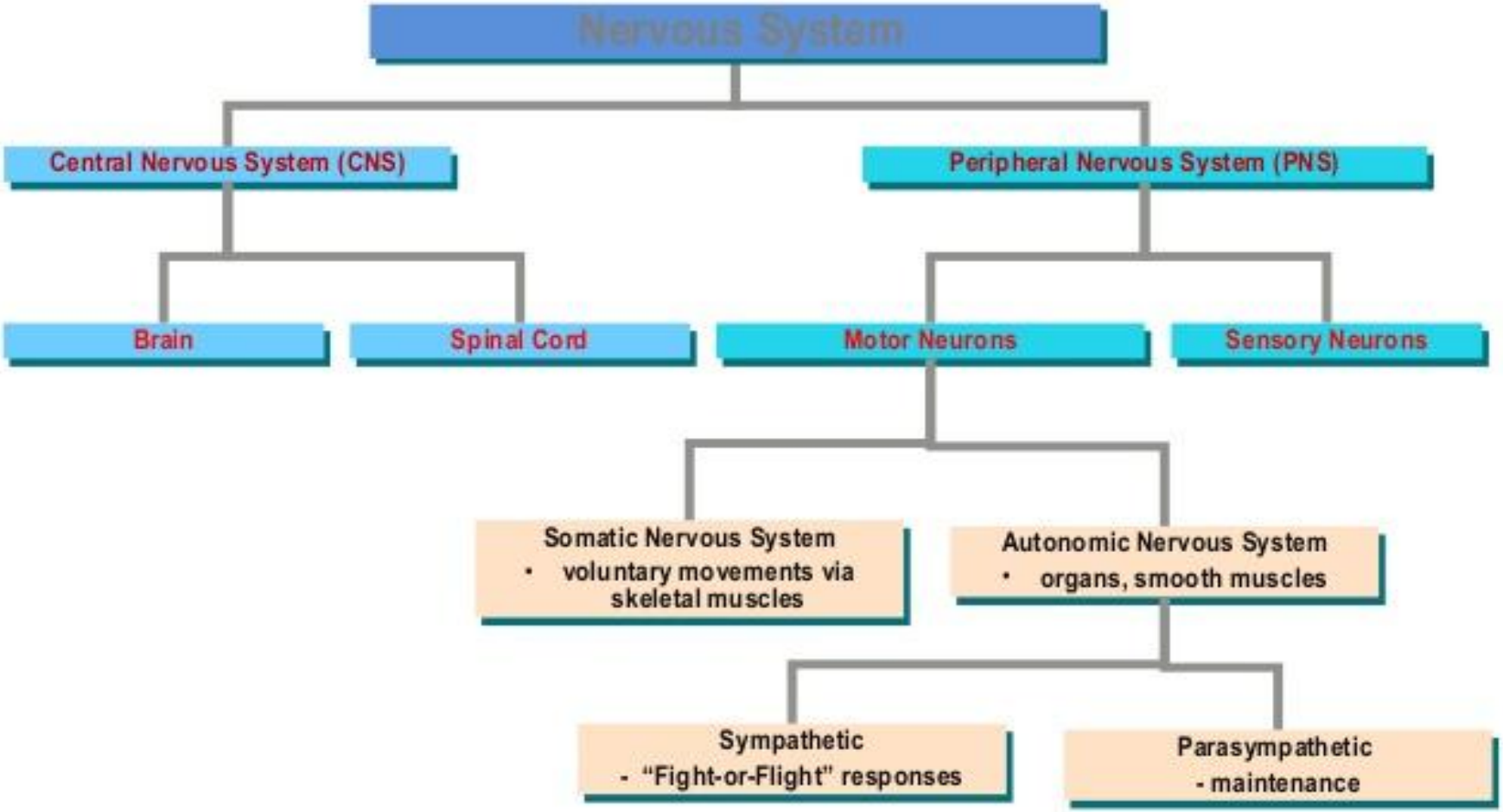
Drugs acting on Autonomic Nervous System

Adrenergic Neurotransmitters:

Biosynthesis and catabolism of catecholamine.

Adrenergic receptors (Alpha & Beta) and their distribution.

Classification:-



The autonomic nervous system regulates certain body processes, such as blood pressure and the rate of breathing. This system works automatically (autonomously), without a person's conscious effort.

The autonomic nervous system is the part of the nervous system that supplies the internal organs, including the blood vessels, stomach, intestine, liver, kidneys, bladder, lungs, pupils, heart, and sweat, salivary, and digestive glands.

The autonomic nervous system controls internal body processes such as the following:

- Blood pressure
- Heart and breathing rates
- Body temperature
- Digestion
- Metabolism (thus affecting body weight)
- The balance of water and electrolytes (such as sodium and calcium)
- The production of body fluids (saliva, sweat, and tears)
- Urination
- Defecation

ANS is composed of

(1) parasympathetic system

Controls body process during ordinary situations.

(2) sympathetic system

Prepares the body for stressful or emergency situations—fight or flight

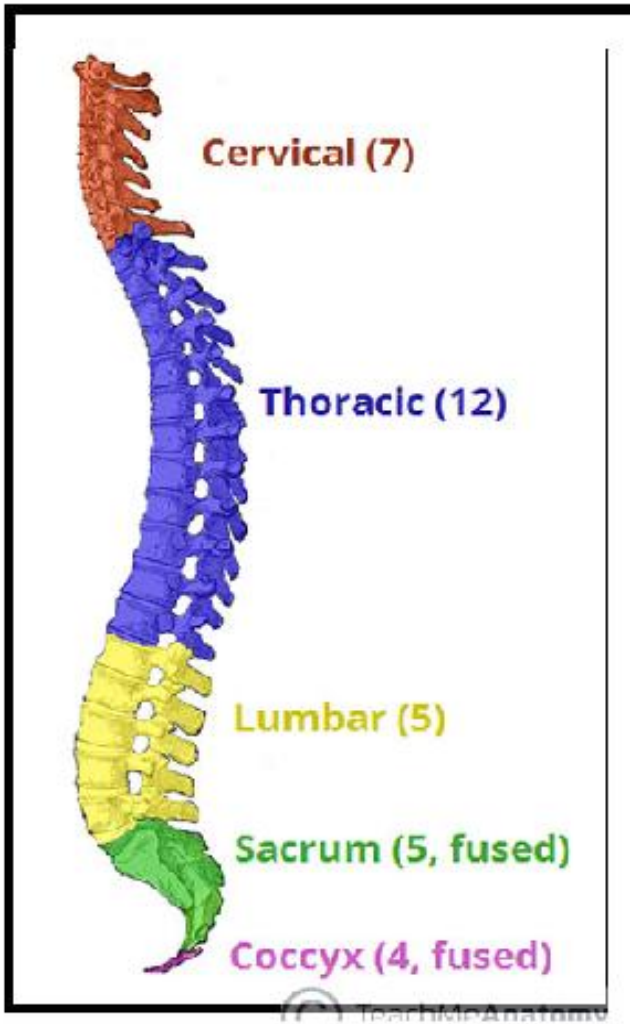
Neurotransmitters

- ❖ Norepinephrine/noradrenaline
- ❖ Acetylcholine

Nerve fibers that secrete **acetylcholine** are called **cholinergic fibers.**

Fibers that secrete **norepinephrine** are called **adrenergic fibers**.

Generally, acetylcholine has parasympathetic (inhibiting) effects and norepinephrine has sympathetic (stimulating) effects.



Ganglia:

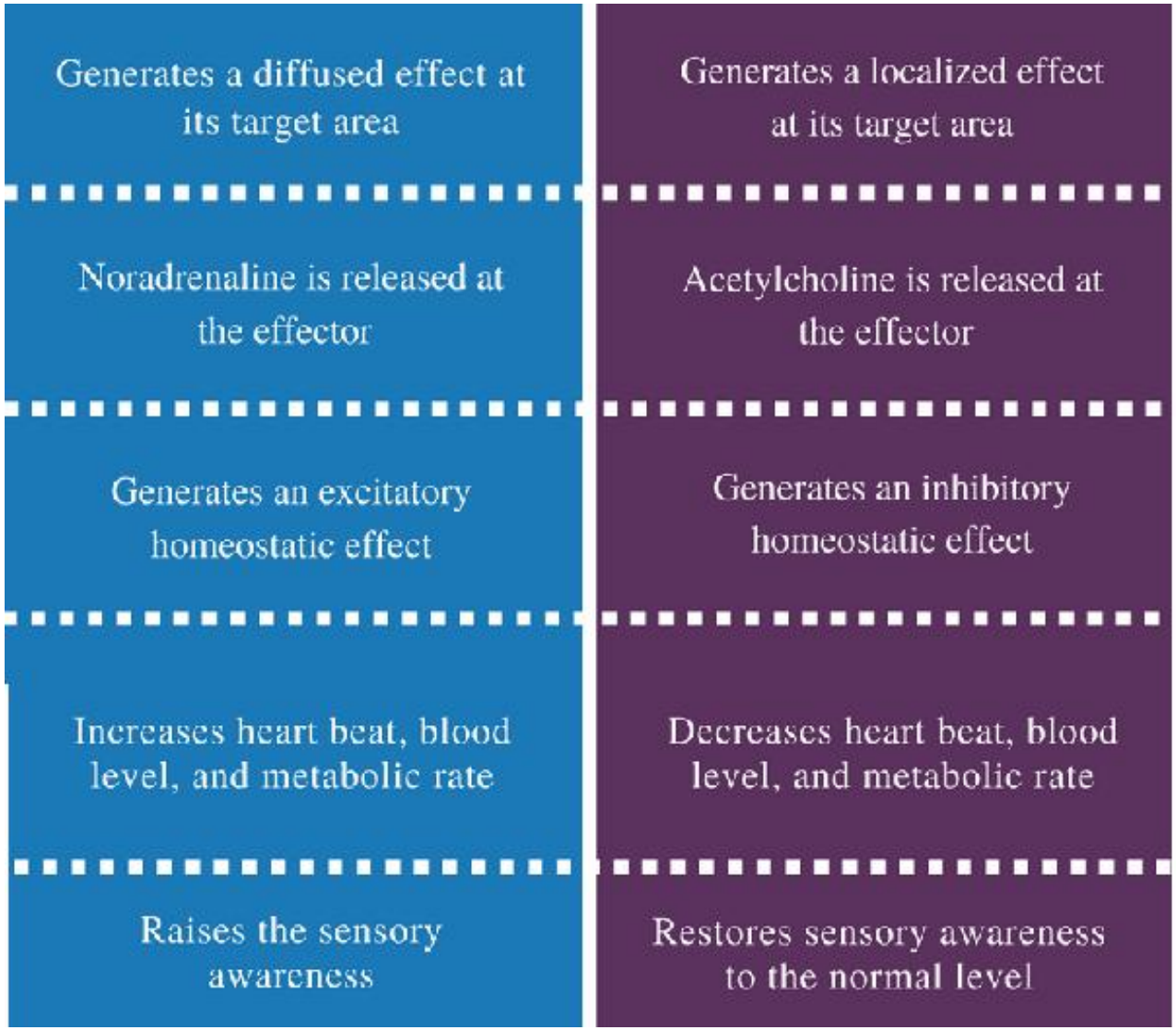
a structure containing a number of nerve cell bodies, typically linked by synapses, and often forming a swelling on a nerve fibre.

Preganglionic neuron – cell body lies within the CNS

Postganglionic fiber (axon) of the ganglionic neuron extends to the visceral organs

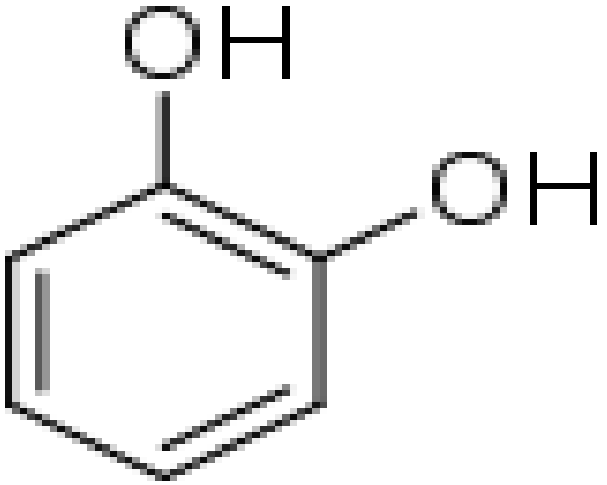
Sympathetic nervous system	Parasympathetic nervous system
Sympathetic nervous system is a part of the autonomic nervous system that serves to accelerate the heart rate, constrict blood vessels, and raise blood pressure	Parasympathetic nervous system is a part of the autonomic nervous system that serves to slow the heart rate, increase intestinal and glandular activity, and relax the sphincter muscles
Originates from cranial, thoracic, and lumbar regions of the central nervous system	Originates from cranial and sacral regions of the central nervous system
Prepares the body for an intense physiological activity	Relaxes the body by inhibiting high energy functions
Action is a quick response	Action is a slow response

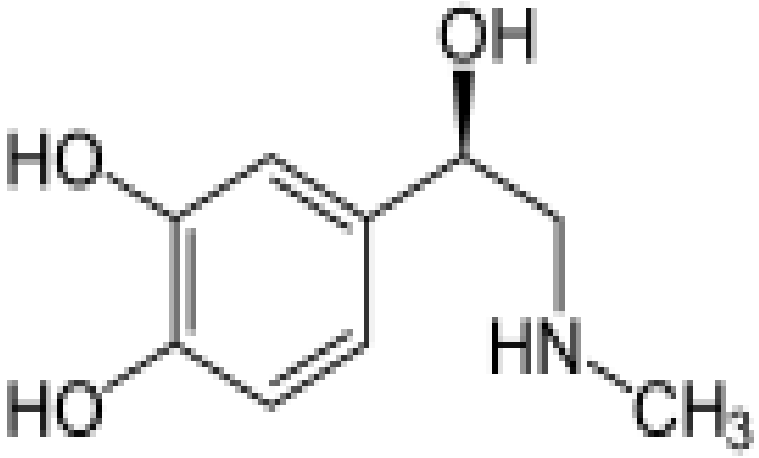
Ganglions are found close to the central nervous system.	Ganglions are found away from the central nervous system but close to the effector
Pre-ganglionic fibers are short	Pre-ganglionic fibers are long
Post-ganglionic fibers are long	Post-ganglionic fibers are short
A large number of post-ganglionic fibers are found	A small number of post-ganglionic fibers are found
Covers a large area in the body	Covers a small area in the body

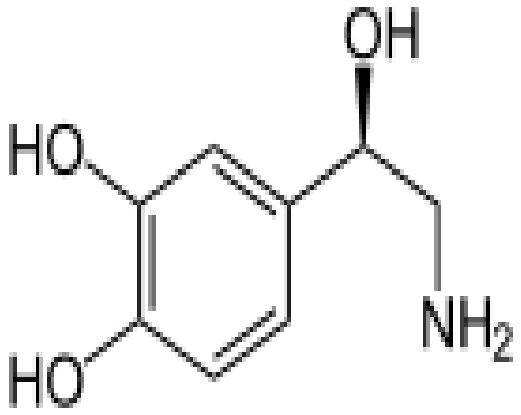

Generates a diffused effect at its target area
Generates a localized effect at its target area
Noradrenaline is released at the effector
Acetylcholine is released at the effector
Generates an excitatory homeostatic effect
Generates an inhibitory homeostatic effect
Increases heart beat, blood level, and metabolic rate
Decreases heart beat, blood level, and metabolic rate
Raises the sensory awareness
Restores sensory awareness to the normal level

Dilates the pupil of the eye	Stimulates the pupil of the eye
Inhibits the saliva secretion	Stimulate the secretion of saliva
Dilates the bronchial tubules	Constricts the bronchial tubules
Releases adrenaline from adrenaline glands	Have no action on the adrenaline gland
Increases the activity of the digestive system	Decreases the activity of the digestive system
Increases the rate of glycogen breakdown	Has no effect on the glycogen breakdown

A **catecholamine** - a monoamine neurotransmitter, an organic compound that has a catechol (benzene with two hydroxyl side groups next to each other) and a side-chain amine.




OH
HO
HO
HN
CH3


OH
HO
HO
NH2

Biosynthesis of norepinephrine takes place within adrenergic neurons near the terminus of the axon and junction with the effector cell.

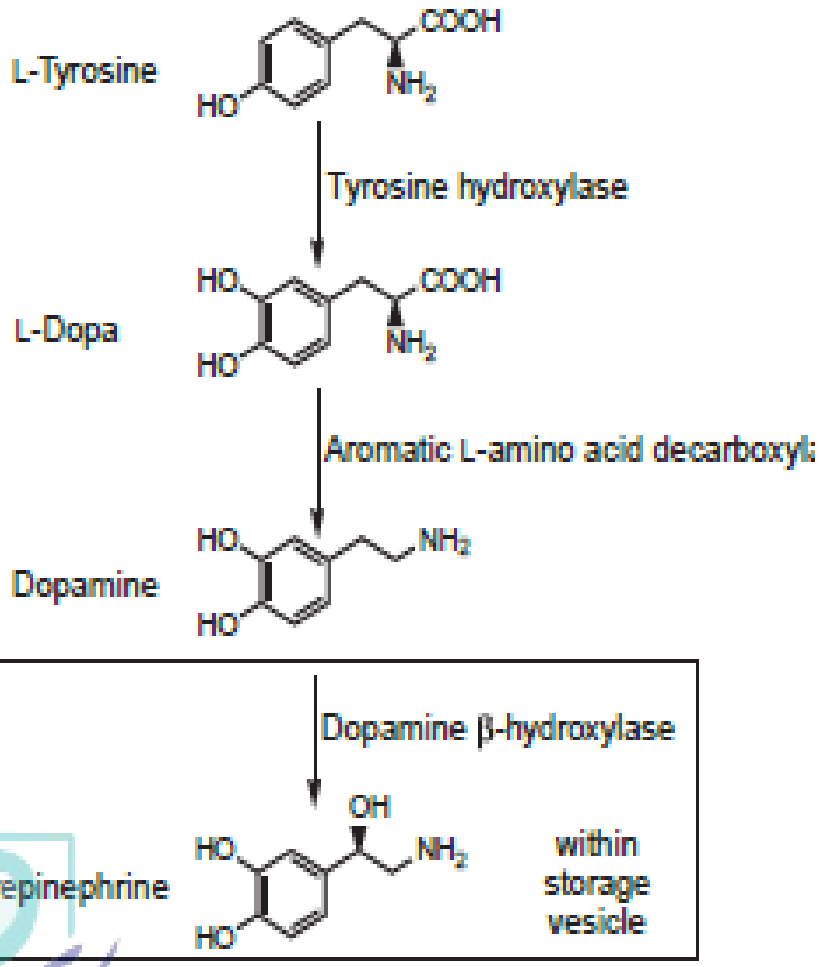
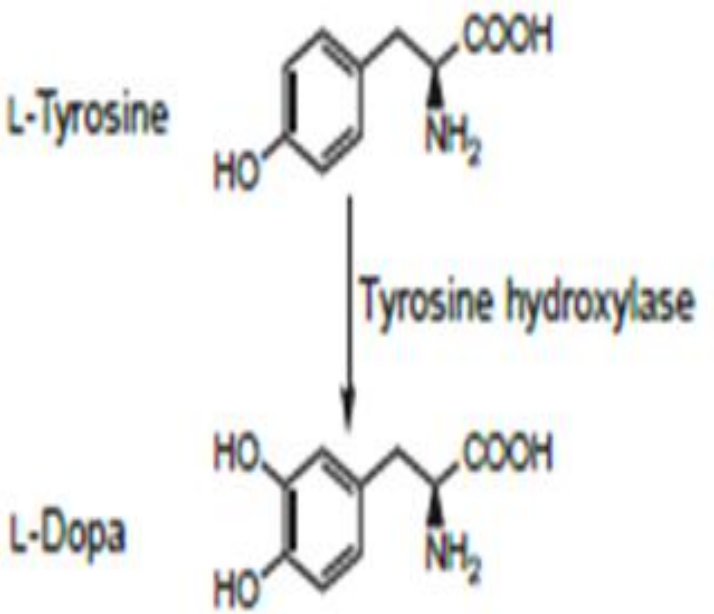


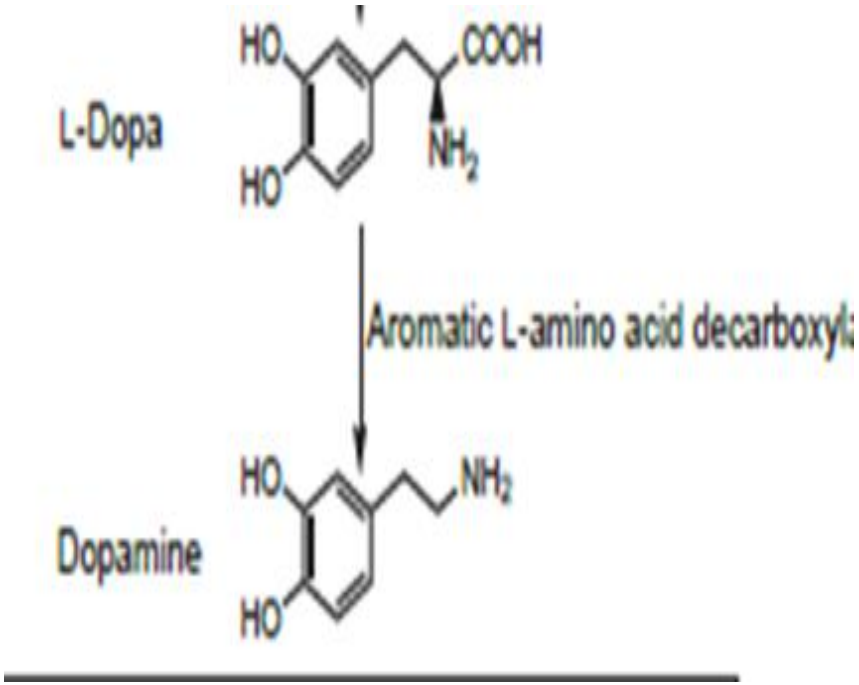
FIGURE 10.7 Biosynthesis of norepinephrine

Active transport of the amino acid l-tyrosine into the adrenergic neuron cell .

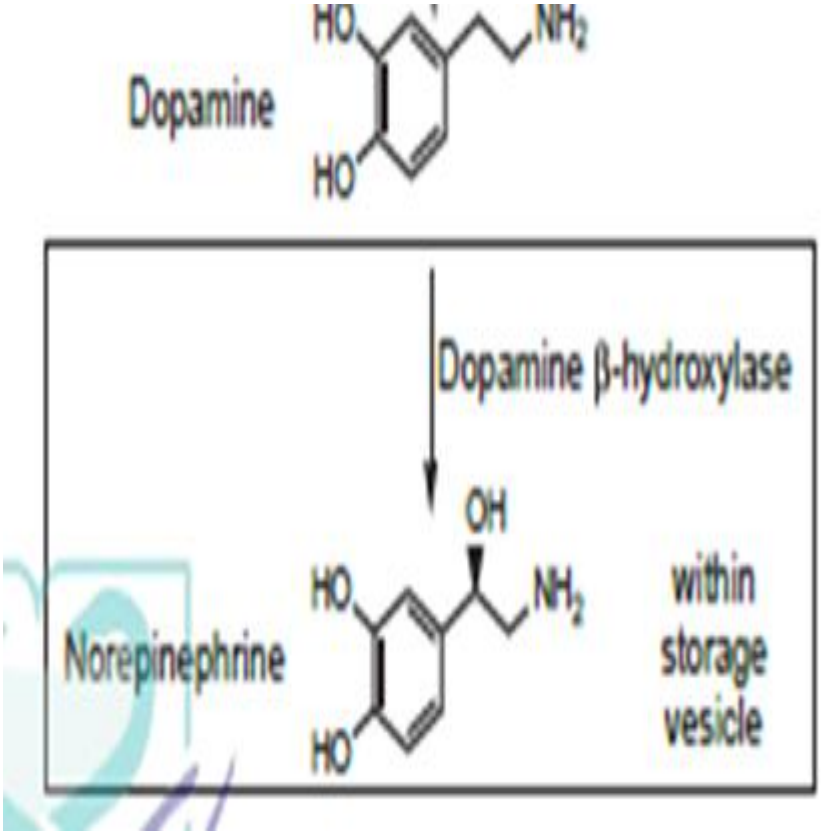
In the first step within the cytoplasm, the enzyme tyrosine hydroxylase (tyrosine-3-monooxygenase) oxidizes the 3’ position of tyrosine to form the catechol amino acid l-dihydroxyphenylalanine (l-DOPA).



The enzyme tyrosine hydroxylase (tyrosine-3-monooxygenase) oxidizes the 3′ position of tyrosine to form the catechol amino acid l-dihydroxyphenylalanine (l-DOPA).



l-DOPA is decarboxylated to dopamine by aromatic l-amino acid decarboxylase, another cytoplasmic enzyme.



The dopamine formed in the into storage vesicles or granules located near the terminus of the adrenergic neuron. The enzyme dopamine β-hydroxylase stereospecifically

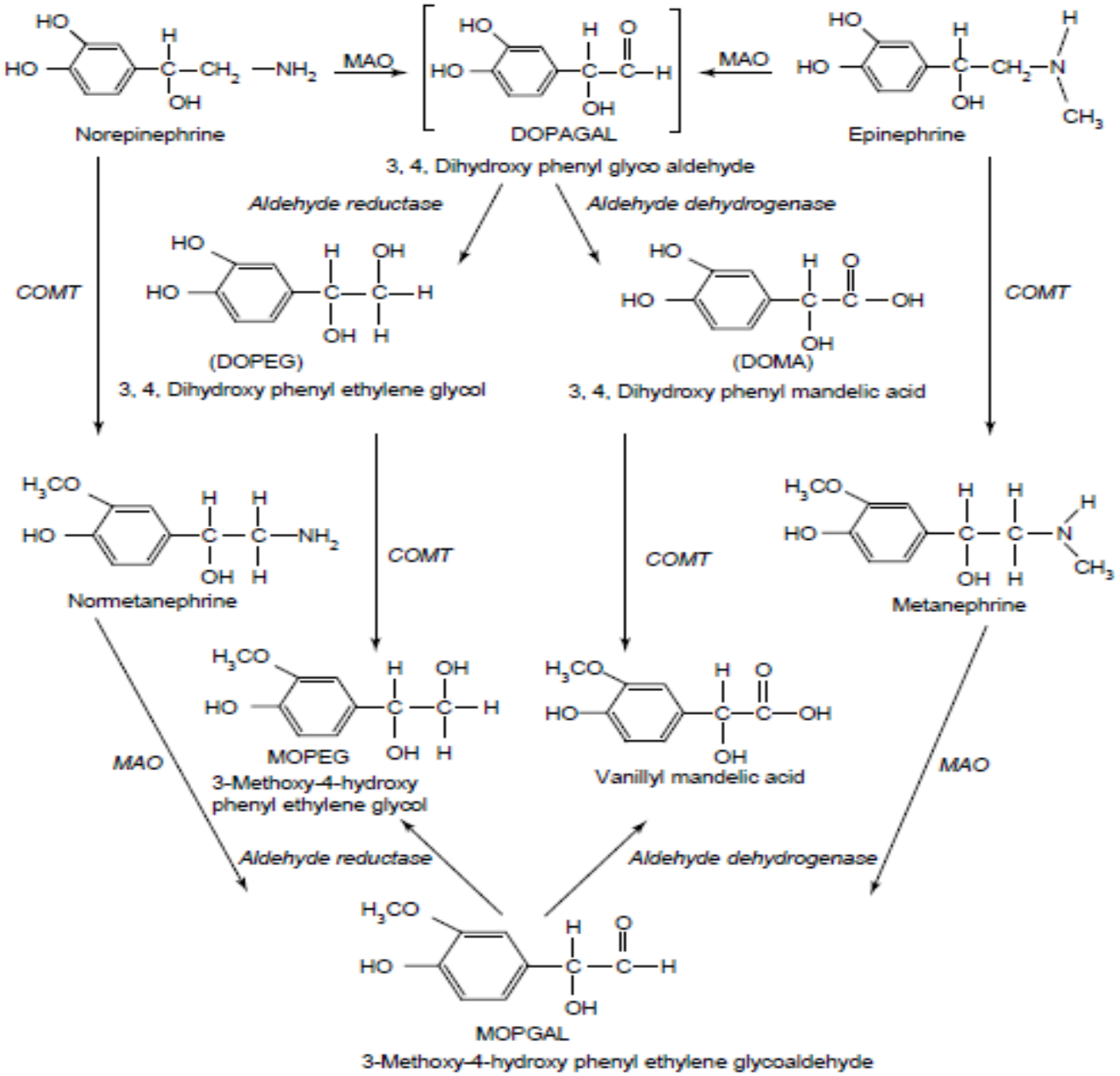
introduces a hydroxyl group in the (*R)* absolute configuration on the carbon atom β to the amino group to generate the neurotransmitter norepinephrine.

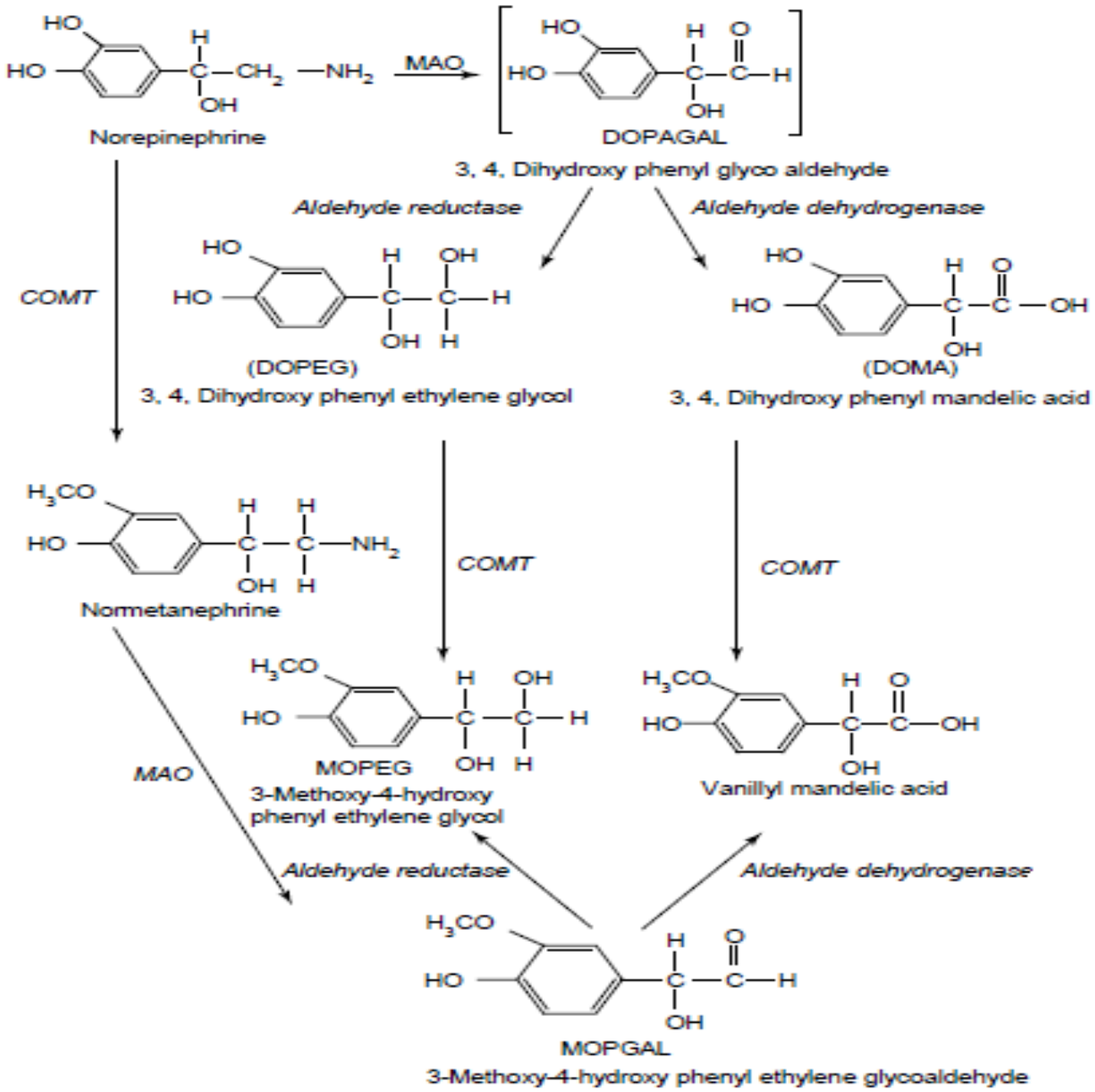
Norepinephrine is stored in the vesicles in a 4:1 complex with adenosine triphosphate (ATP)

When a wave of depolarization reaches the terminus of an adrenergic neuron, it triggers the transient opening of voltage- dependent calcium channels, causing an influx of calcium ions. This influx of calcium ions triggers fusion of the storage vesicles with the neuronal cell membrane, spilling the norepinephrine and other contents of the vesicles into the synapse through Exocytosis.

Norepinephrine to epinephrine-

Enzyme phenylethanolamine-*N methyltransferase.*


Norepinephrine
MAO
DOPAGAL
MAO
Epinephrine
3, 4, Dihydroxy phenyl glyco aldehyde
Aldehyde reductase
Aldehyde dehydrogenase
COMT
COMT
(DOPEG)
3, 4, Dihydroxy phenyl ethylene glycol
(DOMA)
3, 4, Dihydroxy phenyl mandelic acid
Normetanephrine
COMT
COMT
Metanephrine
MAO
MAO
MOPEG
3-Methoxy-4-hydroxy phenyl ethylene glycol
Vanillyl mandelic acid
Aldehyde reductase
Aldehyde dehydrogenase
MOPGAL
3-Methoxy-4-hydroxy phenyl ethylene glycoaldehyde


Norepinephrine
MAO
DOPAGAL
3, 4, Dihydroxy phenyl glyco aldehyde
Aldehyde reductase
Aldehyde dehydrogenase
COMT
(DOPEG)
3, 4, Dihydroxy phenyl ethylene glycol
(DOMA)
3, 4, Dihydroxy phenyl mandelic acid
Normetanephrine
COMT
COMT
MAO
MOPEG
3-Methoxy-4-hydroxy
phenyl ethylene glycol
Vanillyl mandelic acid
Aldehyde reductase
Aldehyde dehydrogenase
MOPGAL
3-Methoxy-4-hydroxy phenyl ethylene glycoaldehyde

Adrenergic receptors

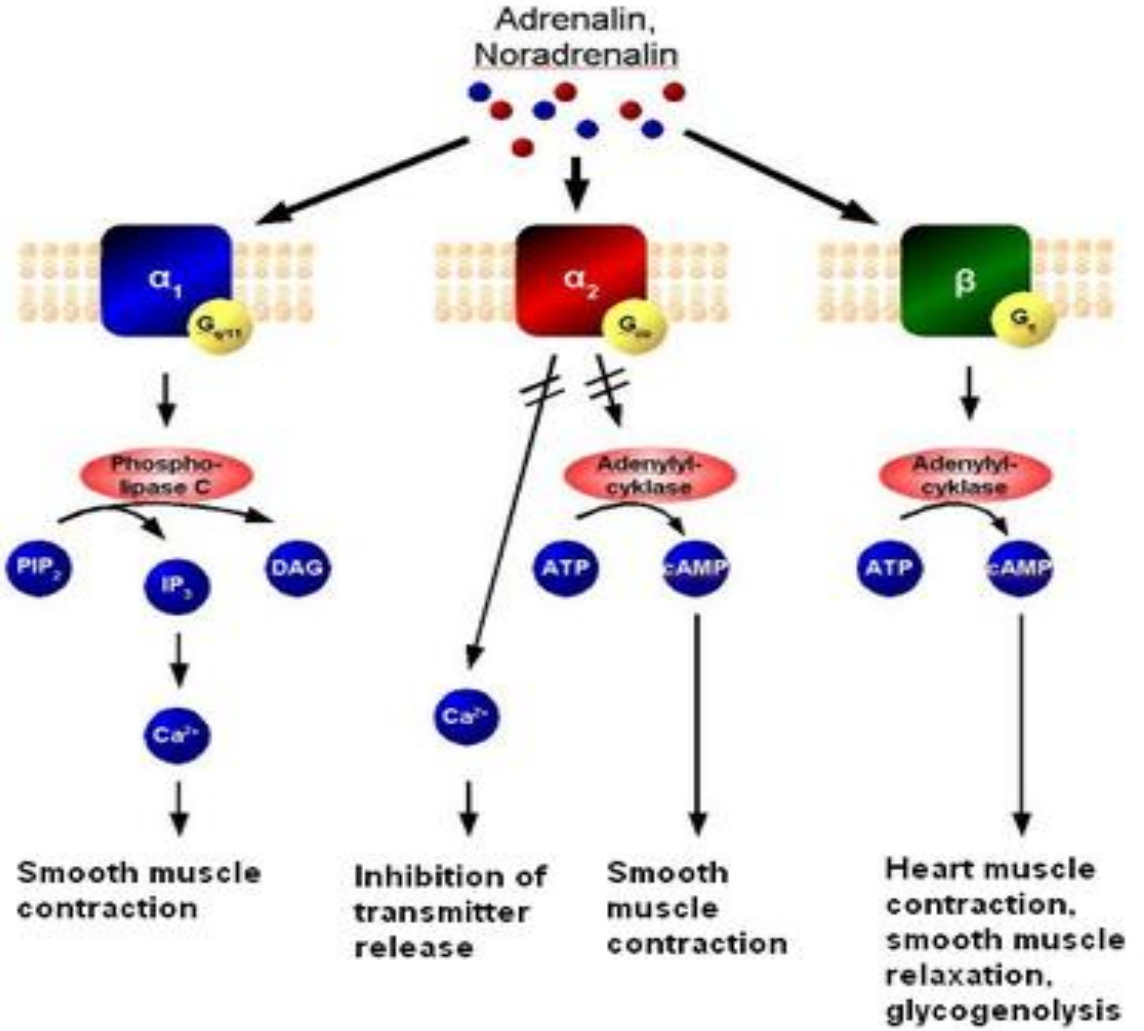
They are membrane bound G-protein coupled receptors and classifi ed as α (alpha) and β (beta) adrenoceptors.

There are two main groups of adrenoreceptors, α and β, with 9 subtypes in total:

α are divided to α_1 (a G_q coupled receptor) and α_2 (a G_i coupled receptor)

- α_1 has 3 subtypes: α_{1A}, α_{1B} and α_{1D}
- α_2 has 3 subtypes: α_{2A}, α_{2B} and α_{2C}

β are divided to β_1, β_2 and β_3. All 3 are coupled to $G_s$proteins, but β_2 and β_3 also couple to G_i


Adrenalin,
Noradrenalin
α1
α2
β
Phospho-
lipase C
PIP2
IP3
DAG
Ca2+
Adenylyl-
cyklase
ATP
cAMP
Adenylyl-
cyklase
ATP
cAMP
Ca2+
Smooth muscle
contraction
Inhibition of
transmitter
release
Smooth
muscle
contraction
Heart muscle
contraction,
smooth muscle
relaxation,
glycogenolysis

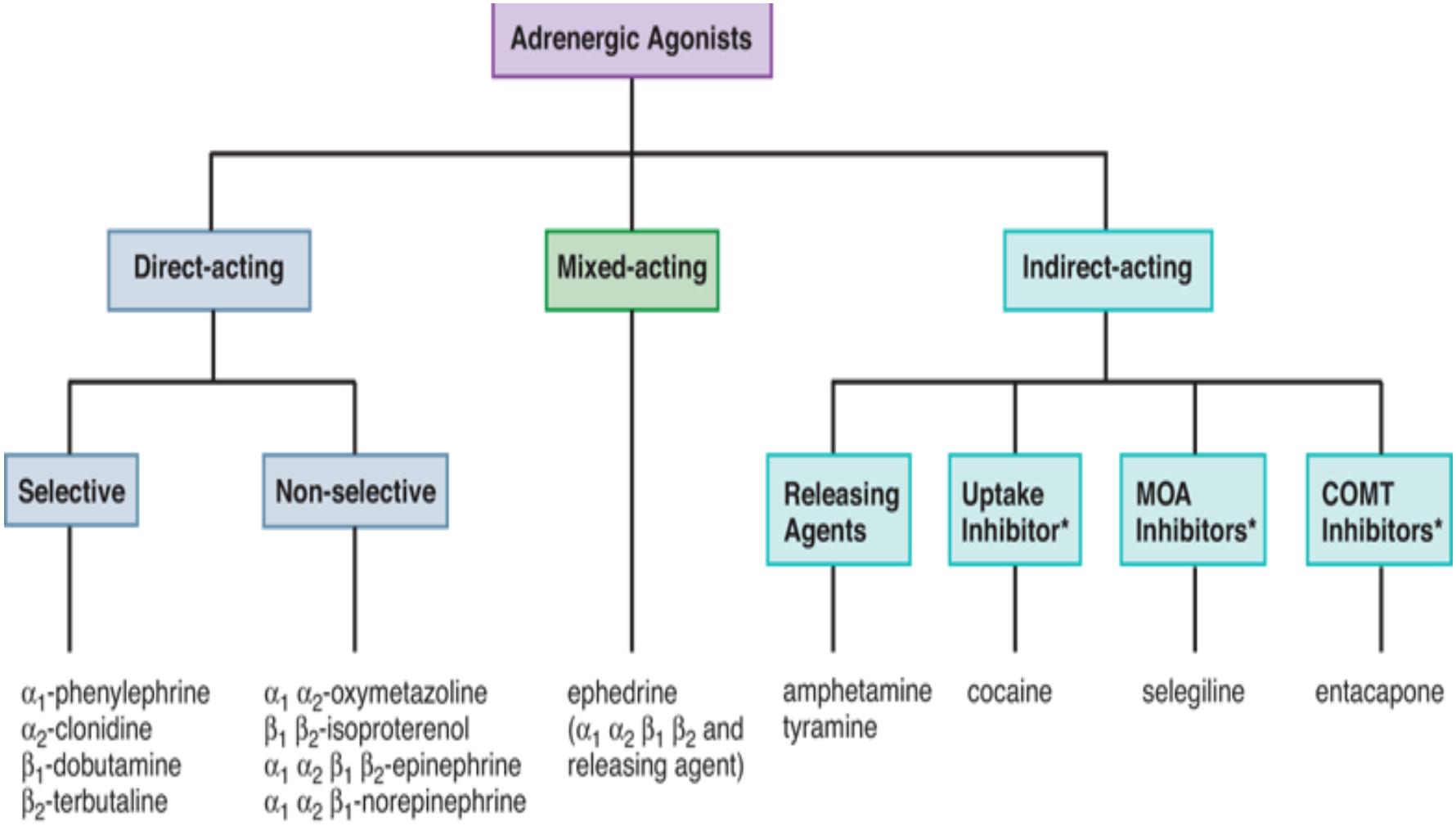
- β1, causes increase in the force and rate of contraction.
- β2 receptor stimulates bronchodilation.
- β3 stimulation causes lipolysis.

Receptor Type	Tissue Distribution	Physiological Effects	Agonist
α1	Vascular Smooth Muscles, Visceral smooth Muscles	Smooth muscle contractions, Gluconeogenesis, Vasoconstriction	Norepinephrine, Phenylephrine, Methoxamine
α2	Pre-synaptic terminals, pancreas, platelets, Ciliary epithelium, Salivary Glands	Inhibits release of Neurotransmitter	Clonidine, Monoxidine
β1	Heart, Kidney, some pre-synaptic terminals	Increase heart rate and Renin secretion	Isoproterenol, Norepinephrine, Dobutamine
β2	Visceral smooth muscles, Bronchioles, Liver, Skeletal Muscles	Vasodilation, Bronchodilation, Inhibits insulin secretion	Isoproterenol, Salbutamol, Salmeterol, Albuterol, Formoterol, Terbutaline, Levalbuterol
β3	Adipose Tissue	Increase lipolysis	Isoproterenol, Amibegron, Solabegron

Sympathomimetic agents

Stimulants which mimic the effects of agonists of the sympathetic nervous system such as the catecholamines.[epinephrine(adrenaline), norepinephrine (noradrenaline), dopamine, etc.].

Some of these predominantly act on the **adrenergic alpha-receptors** (e.g. noradrenaline (norepinephrine), while others act on the **adrenergic beta-receptors** (e.g. isoproterenol).


Adrenergic Agonists
Direct-acting
Mixed-acting
Indirect-acting
Selective
Non-selective
Releasing Agents
Uptake Inhibitor*
MOA Inhibitors*
COMT Inhibitors*
α1-phenylephrine
α2-clonidine
β1-dobutamine
β2-terbutaline
α1 α2-oxymetazoline
β1 β2-isoproterenol
α1 α2 β1 β2-epinephrine
α1 α2 β1-norepinephrine
ephedrine
(α1 α2 β1 β2 and releasing agent)
amphetamine
tyramine
cocaine
selegiline
entacapone

Direct-acting adrenergic agonists

They bind to and activate α1, α2, β1, and β2 receptors.

NE (α1, α2, and β1 receptors), Epinephrine (α1, α2, β1, and β2 receptors), and Dopamine (α1, α2, and β1 receptors).

Examples of drugs: xylometazoline, phenylephrine, methoxamine.

Indirect-acting adrenergic agonists

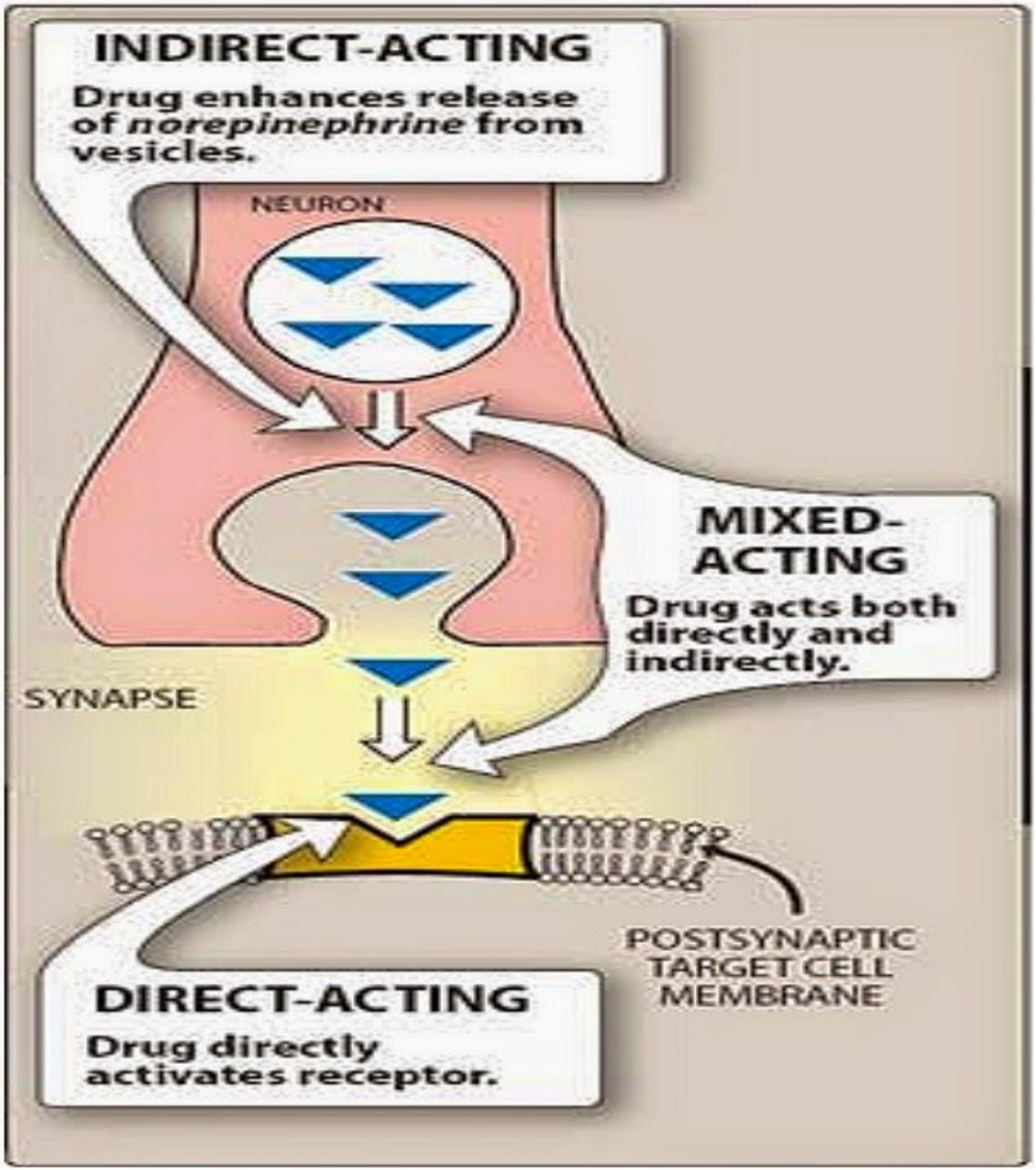
Increase availability of neurotransmiters.

1. Displacement of stores catecholamines: (Tyramine, amphetamine)
2. Inhibition of reuptake (Cocaine, TCA)
3. Blocking metabolizing enzymes (MAO- Selegiline, COMT- entacapone)

Dual-acting/Mixed acting adrenergic agonists

These agents act as direct and indirect adrenergic agonists (hence, dual-acting). They bind to adrenergic receptors and stimulate NE release.

Examples: Ephedrine, Amphetamine, Mephenteramine.

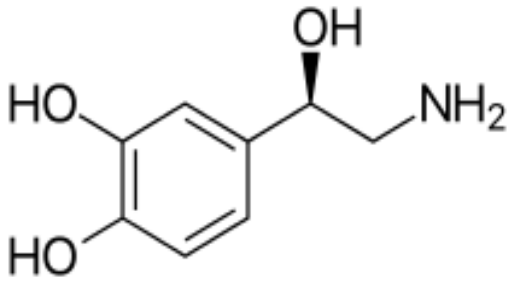

INDIRECT-ACTING
Drug enhances release of *norepinephrine* from vesicles.
NEURON
MIXED-ACTING
Drug acts both directly and indirectly.
SYNAPSE
POSTSYNAPTIC TARGET CELL MEMBRANE
DIRECT-ACTING
Drug directly activates receptor.

Activity	Drugs	
Alpha agonist	NE Naphazoline, oxymetazoline, xylometazoline	Epinephrine, Dopamine
Alpha 1 agonist	Phenylephrine	
Alpha 2 agonist	Methyl dopa, clonidine	
Beta agonist	Isoproterenol	
Beta 1	NE, Dobutamine	
Beta 2	Bitolterol, salbutamol, terbutaline	

Direct acting adrenergics

- Nor-epinephrine, Epinephrine, Phenylephrine*, Dopamine,
- Methyldopa, Clonidine, Dobutamine, Isoproterenol, Terbutaline, Salbutamol*, Bitolterol, Naphazoline, Oxymetazoline and Xylometazoline.

Nor epinephrine



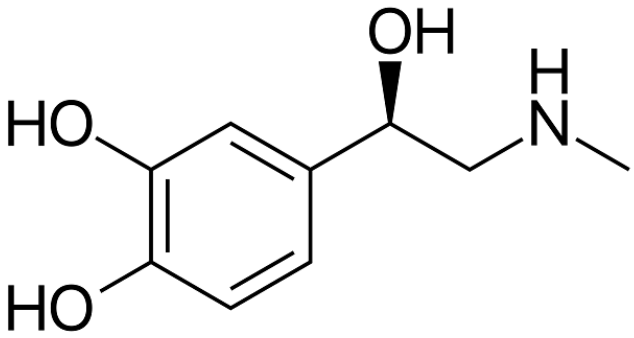
IUPAC Name: (R)-4-(2-amino-1-hydroxyethyl)benzene-1,2-diol

Stimulate α1 and α2 receptors , β1 receptors.

Uses: Increase in BP

In cardiac arrest (+ inortropic effect)

Epinephrine



IUPAC Name: 4-[(1R)-2-Amino- hydroxyethyl]benzene-1,2-diol

(R)-Epinephrine is 12 times more active than S form.

Stimulate α and β receptors.

Uses: **Vasoconstrictor and cardiac stimulant.**

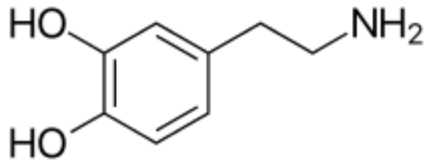
Bronchodialator, inhibits release of allergic mediators.

Increased glycogenolysis in liver, decreased release of insulin

Lipolysis

Used in anaphylactic shock (bronchospasm, angioedema, severe hypotension)

Dopamine

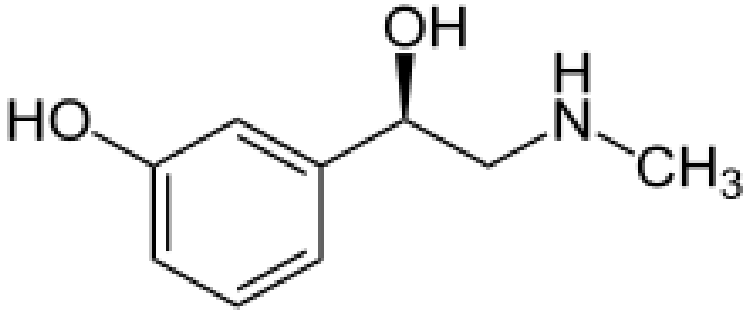


IUPAC name: 4-(2-Aminoethyl)benzene-1,2-diol

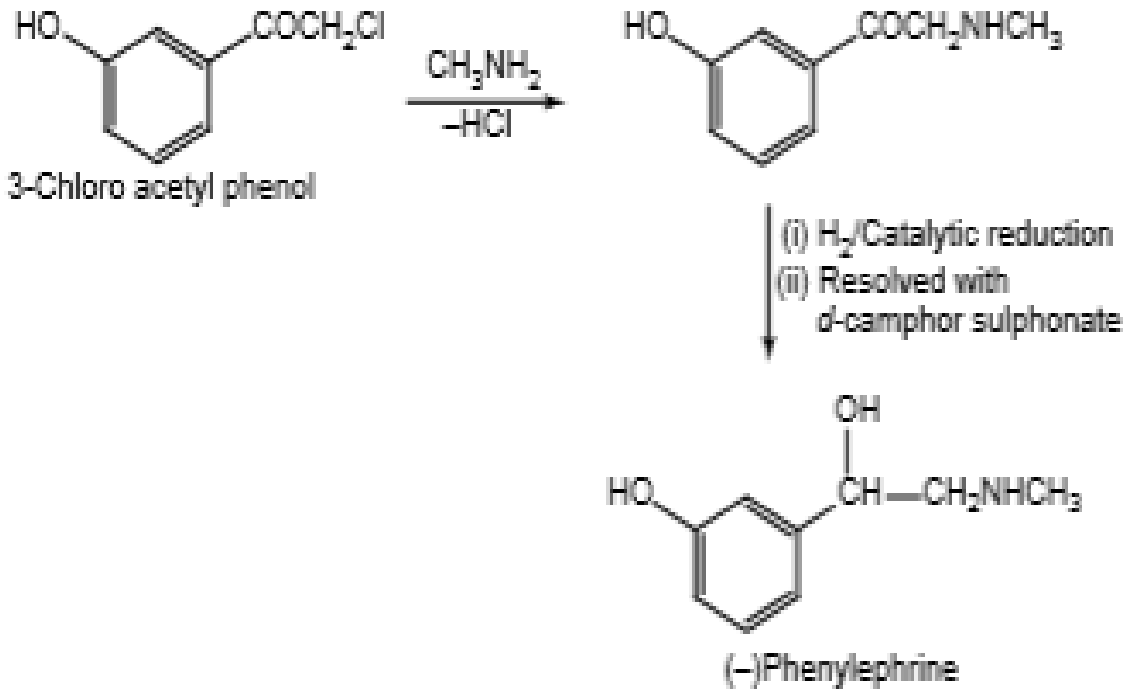
Uses: stimulant drug in the treatment of severe low blood pressure, slow heart rate, and cardiac arrest. (especially in treating these in newborn infants).

correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarction, trauma, open-heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Phenylephrine



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



α1 receptor agonist

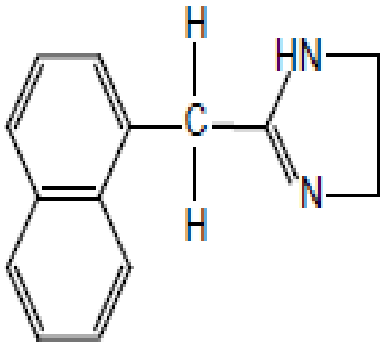
Uses- Vasoconstrictor

Mydraitic agent

Nasal decongestant

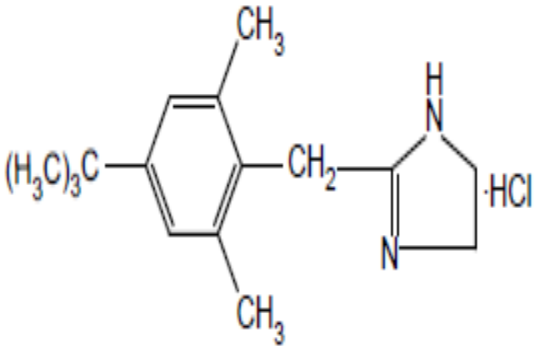
- Methyldopa, Clonidine, Dobutamine, Isoproterenol, Terbutaline,
- Salbutamol*, Bitolterol, Naphazoline, Oxymetazoline and Xylometazoline.

Naphazoline

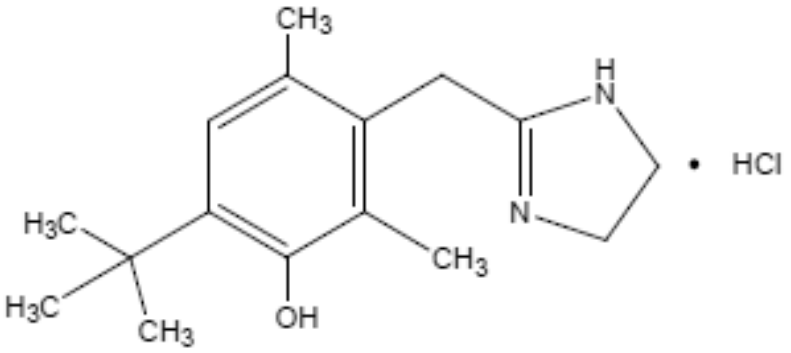


2-(1-Naphthyl methyl)-2-imidazoline

Xylometazoline



Xylometazoline



Oxymetazoline

USES

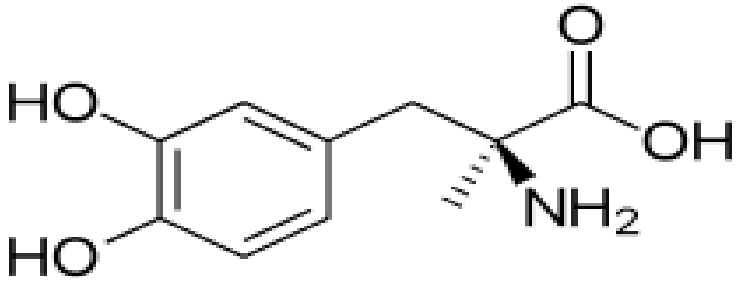
DECONGESTANTS

Naphazoline- alpha receptor agonist. ocular congestion relief

Xylometazoline - Nasal

Oxymetazoline - Nasal

Methyl dopa

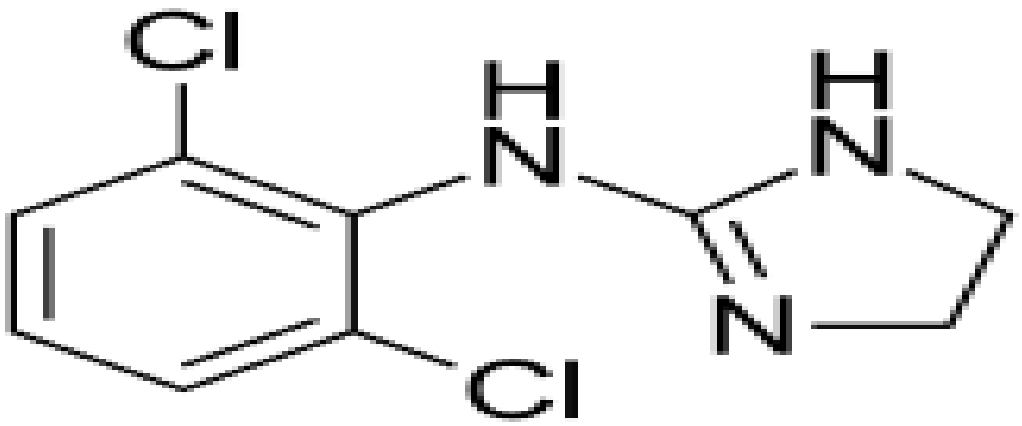


(*S*)-2-amino-3-(3,4-dihydroxyphenyl)-2-methyl-propanoic acid

Mechanism of action: alpha-2 Adrenergic Agonist

- Hypertension (or high blood pressure)
- Gestational hypertension (or pregnancy-induced hypertension) and pre-eclampsia

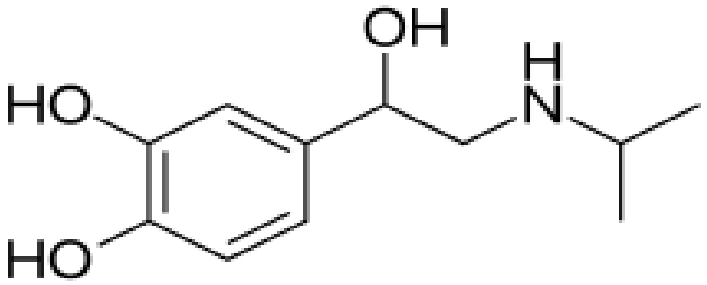
clonidine



***N*-(2,6-Dichlorophenyl)-4,5--1*H*-imidazol-2-amine**

Adrenergic alpha2-Agonist.
Treat high blood pressure

Isoproterenol/isoprenaline



(*RS*)-4-[1-hydroxy(isopropylamino)ethyl]benzene-1,2-diol

MOA: beta-1 and beta-2 adrenergic receptor agonist resulting in the following: Increased heart rate. Increased heart contractility. Relaxation of bronchial, gastrointestinal, and uterine smooth muscle.

It is used to treat heart block and episodes of Adams-Stokes syndrome, in emergencies for cardiac arrest until electric shock can be administered,

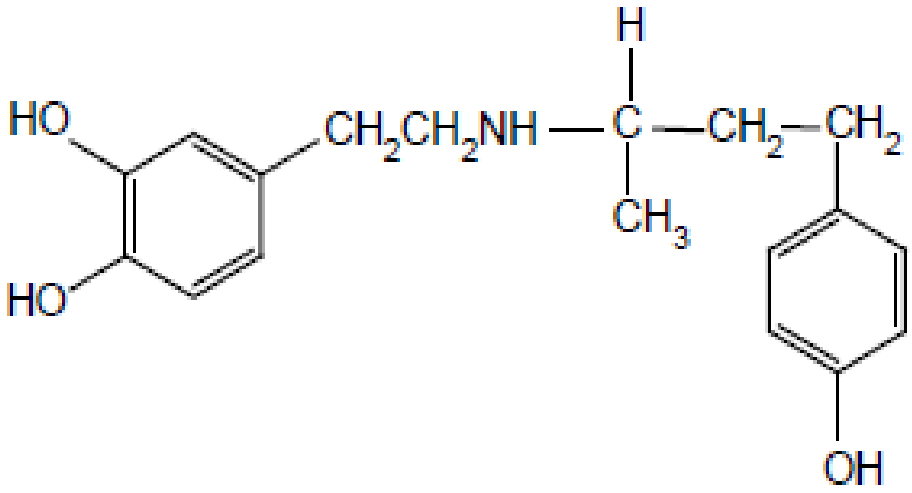
for bronchospasm occurring during anesthesia,

and as an adjunct in the treatment of hypovolemic shock, septic shock,

low cardiac output (hypoperfusion) states,

congestive heart failure, and cardiogenic shock.

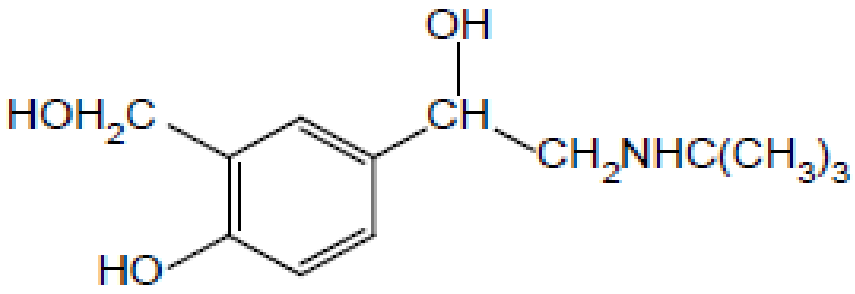
Dobutamine (Cardiject, Dotamin, Kardia)



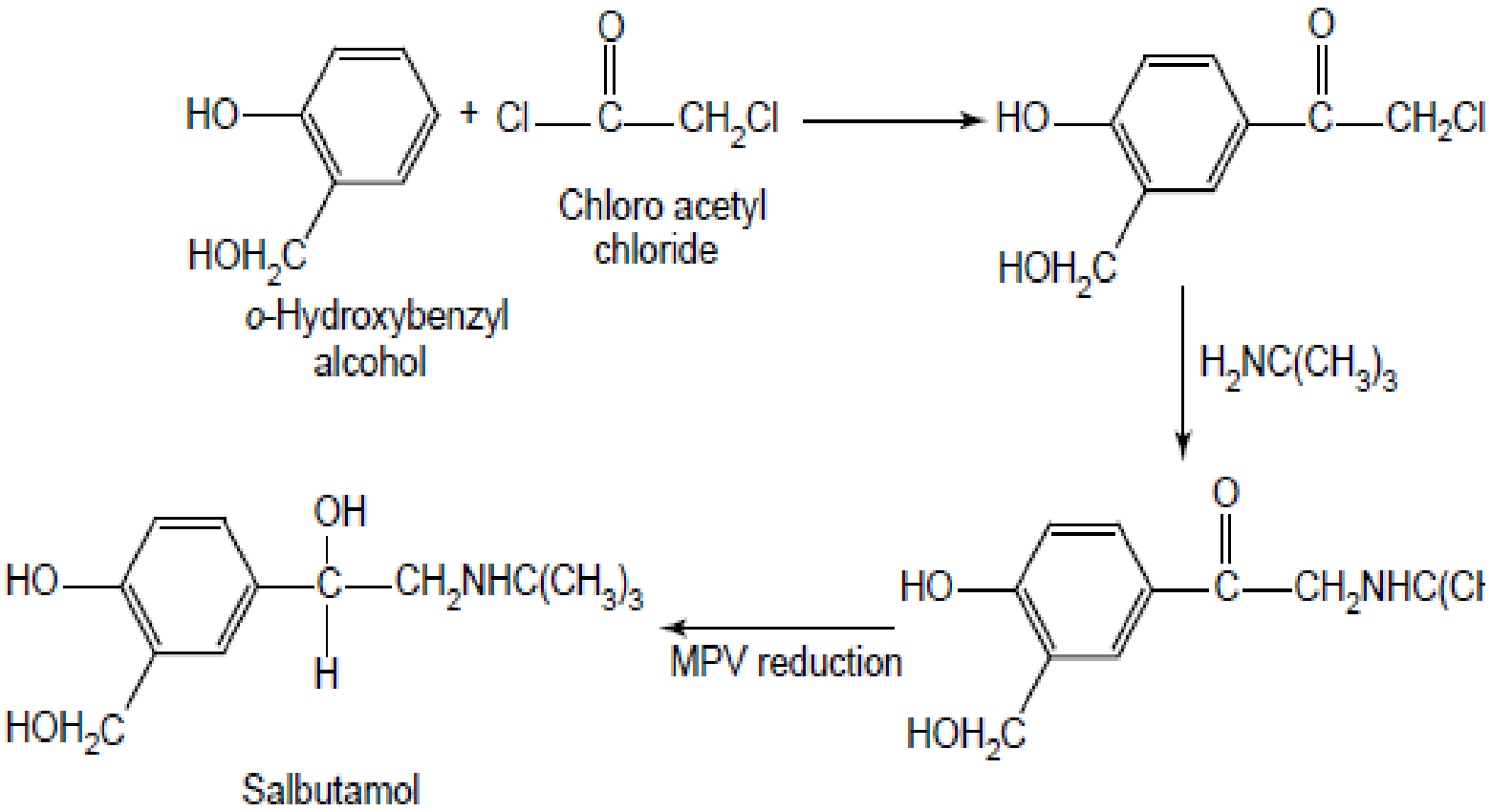
(*RS*)-4-(2-{[4-(4-hydroxyphenyl)butan-2-yl]amino}ethyl)benzene-1,2-diol

Dobutamine directly stimulates beta-1 receptors of the heart to increase myocardial contractility and stroke volume, resulting in increased cardiac output.It enhances the automaticity of SA node.

Salbutamol (Synonym: Albuterol, Asthalin, Salbid)



(*RS*)-4-[2-(*tert*-Butylamino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol

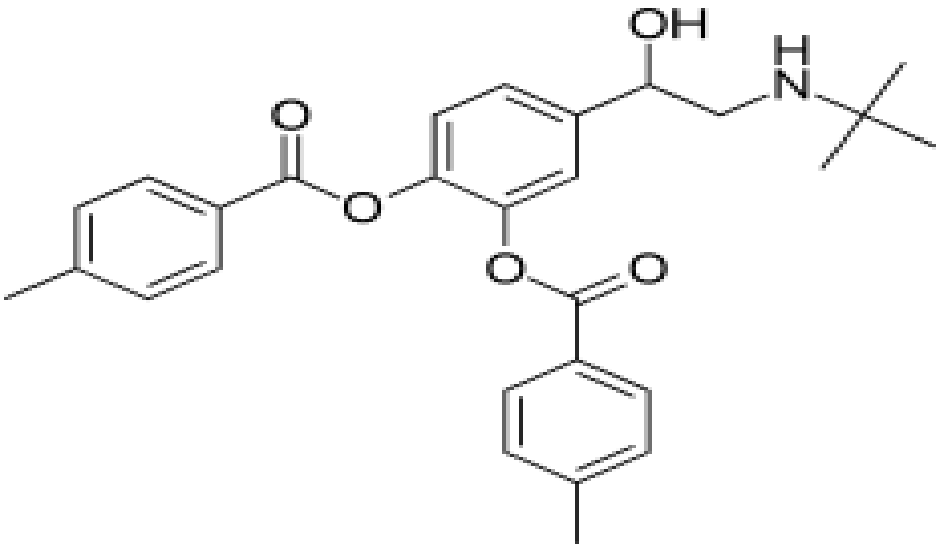

HO
HOH2C
o-Hydroxybenzyl alcohol
+ Cl
O
C
CH2Cl
Chloro acetyl chloride
H2NC(CH3)3
MPV reduction
OH
H
CH2NHC(CH3)3
Salbutamol

The **Meerwein–Ponndorf–Verley (MPV) reduction** in organic chemistry is the **reduction of ketones and aldehydes to their corresponding alcohols utilizing aluminium alkoxide catalysis in the presence of a alcohol.**

Uses

- It 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.**

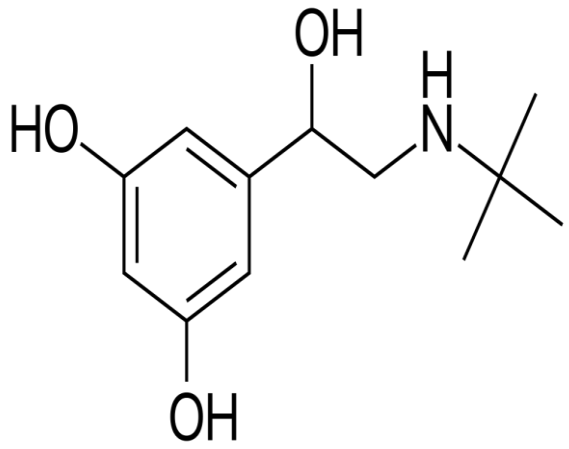
Bitolterol



(*RS*)-[4-(1-Hydroxy-2-*tert*-butylamino-ethyl)-2-(4-methylbenzoyl)oxy-phenyl] 4-methylbenzoate

short-acting β_2 adrenergic receptor agonist used for the relief of bronchospasm in conditions such as asthma and COPD .

Terbutaline



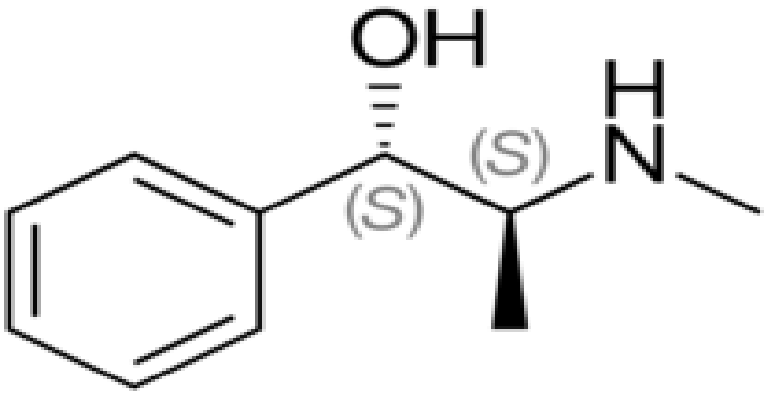
(*RS*)-5-[2-(*tert*-Butylamino)-1-hydroxyethyl]benzene-1,3-diol

- **Terbutaline** is a selective b_2-receptor agonist that produces relaxation of smooth muscle found principally in bronchial, vascular and uterine tissues.

- Uses: Terbutaline is used as a fast-acting bronchodilator (often used as a short-term asthma treatment)

Indirect acting agents: Hydroxyamphetamine, Pseudoephedrine, propylhexidrine

Pseudoephedrine



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

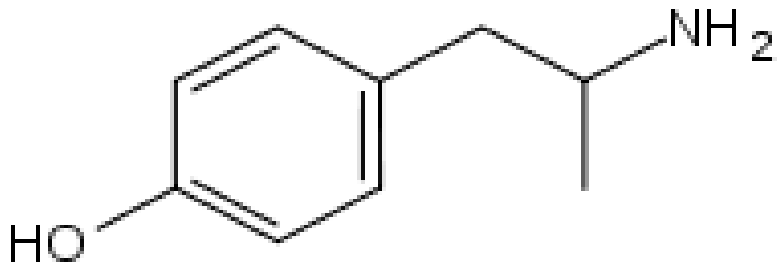
Pseudoephedrine is an agonist of α- and β-adrenoceptors.

Promotes release of stored norephinephrine into the neuronal synapse.

Widely used as a nasal decongestant

used in the illicit manufacture of the widely abused drug methamphetamine. For this reason, sale of pseudoephedrine over-the-counter products is becoming increasingly restricted.

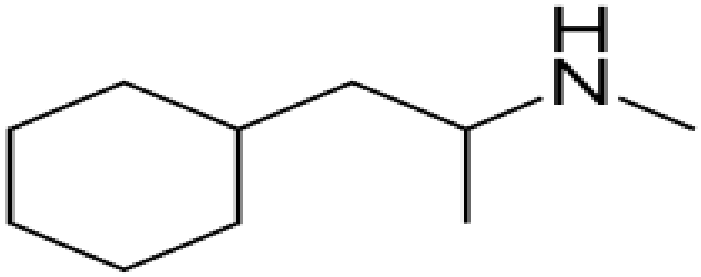
Hydroxyamphetamine



4-(2-aminopropyl)phenol

stimulates the release of norepinephrine from postganglionic adrenergic nerves resulting in the stimulation of both alpha and beta adrenergic receptors. Local alpha stimulatory effects include dilation of the pupil, increased flow of aqueous humor, and vasoconstriction; whereas beta stimulatory effects include relaxation of the ciliary muscle and a decreased production in aqueous humor.

Propylhexidrine



(±)-1-cyclohexyl-*N*-methylpropan-2-amine

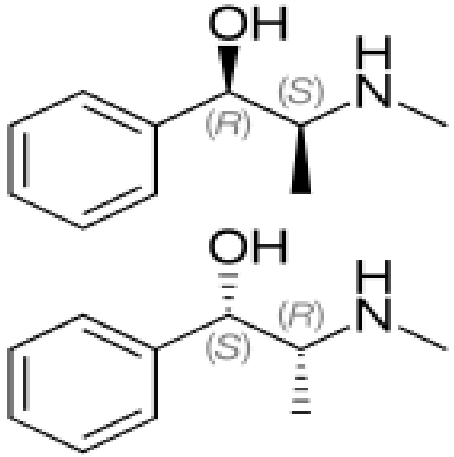
Propylhexedrine binds to and activates alpha-adrenergic receptors in the mucosa of the respiratory tract, thereby mimicking the actions of norepinephrine and epinephrine. This results in vasoconstriction and reduces swelling and inflammation of the mucous membrane lining, therefore relieving nasal and sinus congestion.

Propylhexidrine causes the norepinephrine, dopamine, and serotonin (5HT) transporters to reverse their direction of flow.

Agents with mixed mechanism

Ephedrine, Metaraminol.

Ephedrine



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

Enhances release of norepinephrine

Uses:

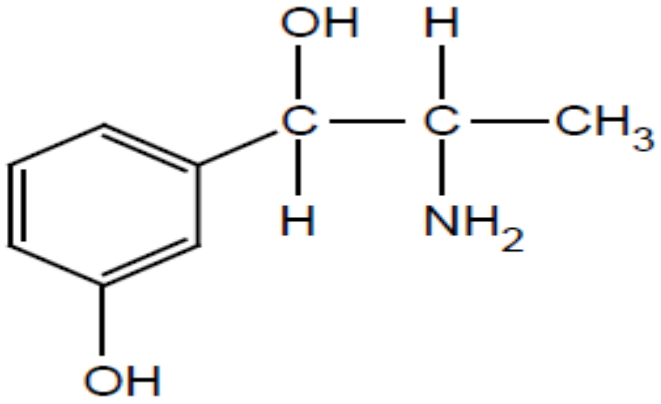
Allergic disorders

Nasal decongestant

Hypotension conditions

Narcolepsy

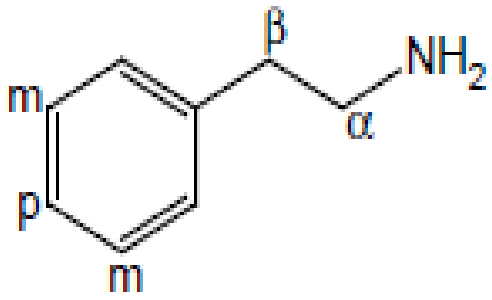
Metaraminol.



(1*R*,2*S*)-3-[-2-amino-1-hydroxy-propyl]phenol

Alpha 1 recepor agonist

acute hypotensive states, such as anaphylactic shock or shock secondary to myocardial infarction and trauma.



β–Phenyl ethylamine

I. Phenyl ring substitution

1. Substitution on the meta and para postions and on the amino, α, and β positions of the ethylamine side chain influences the mechanism of sympathomimetic action and the receptor selectivity of the drug.

2. Maximal activity is seen in β-phenyl ethylamine derivatives, containing **hydroxyl groups in the meta and para positions** of the aromatic ring (catechol) and a **β-hydroxyl group of the correct stereochemical configuration** on the ethylamine portion of the molecule.

3. Catechol moeity can be replaced with other substituted phenyl moieties to provide selective adrenergic agonism.

- Replacement of the ***catechol*** function of isoproterenol with the ***resorcinol*** structure gives the drug metaproterenol, which is a selective β2-receptor agonist.

4. noradrenaline: 3, 4-dihydroxy benzene ring Active at both α and β receptors.

But poor oral activity (metabolized by COMT), the change in substitution pattern 3, 5-dihydroxy as in metaproterenol gives good oral activity.

It also provides selectivity for β2 receptors.

II. Substitution at nitrogen

1. Amino group: important for direct agonistic activity. It should be separated from the aromatic ring by two carbon atoms.
2. As the bulk of the nitrogen substituent increases, α-receptor agonistic activity decreases and β-receptor activity increases.

NE that is an effective β1-receptor agonist is also a potent α-agonist, while epinephrine is a potent agonist at α, β1, and β2 receptors.

3. N-tertiary butyl group enhances β2 selectivity.

4. Primary and secondary amines are more potent direct-acting agonists than 3° or 4° amines.

III. Substitution on the carbon side chain

1. Methyl or ethyl substitution on the α-carbon of the ethylamine side chain reduces direct receptor agonist activity at both α and β receptors.
2. α-alkyl group increases the duration of action of the phenylethylamine agonist by making the compound resistant to metabolic deamination by MAO.

3. Another effect of α-substitution is the introduction of a chiral centre, which has pronounced effects on the stereo-chemical requirements for activity.