INTRODUCTION

The sympathetic system activates and prepares the body for vigorous muscular activity, stress, and emergencies. Adrenergic drugs stimulate the adrenergic nerves directly by mimicking the action of norepinephrine or indirectly by stimulating the release of norepinephrine.

Therapeutically, these drugs are used to combat life-threatening disorders, which include acute attacks of bronchial asthma, shock, cardiac arrest, and allergic reactions. In addition these drugs are used as nasal decongestants and appetite suppressants.

ADRENERGIC NERVE TRANSMISSION

Adrenergic nerves release the neurotransmitters; Norepinephrine (noradrenaline, (NE)), epinephrine (EP), and dopamine (DA). Norepinephrine is released from the nerve ending in response to a nerve impulse or drug (3). NE interacts with alpha and beta-receptor sites at (4). Its receptor action is terminated by recapture and storage in the original nerve ending or inactivated by an enzyme.
The following steps in the synthesis of adrenaline were proposed by Blaschko (1939):

1. Phenylalanine-hydroxylase,
2. Tyrosine-hydroxylase,
3. Aromatic amino-acid decarboxylase,
4. Dopamine-β-hydroxylase,
5. Phenylethanolamine-N-methyl transferase.

Biosynthesis of catecholamines

Five enzymes are involved in the pathway of the biosynthesis of adrenaline. The first enzyme is the iron containing phenylalanine-hydroxylase (also called phenylalanine-4-monoxygenase). The second enzyme, tyrosine-hydroxylase, contains iron, too, and catalyses the conversion of tyrosine to L-β-(3,4-dihydroxyphenyl)-α-alanine (DOPA). After decarboxylation of DOPA to dopamine (aromatic amino-acid decarboxylase) the copper-containing enzyme dopamine-β-hydroxylase converts dopamine to noradrenaline. The final enzyme noradrenaline-N-methyltransferase then methylates noradrenaline to adrenaline.

The noradrenaline formed in the adrenergic nerve endings remain stored in vesicles as its adenosine triphosphate complex. The adrenal medulla also synthesizes and stores noradrenaline and adrenaline.

The neurotransmitters are released by increasing the permeability of nerve terminal membrane to Ca++. The inflow of Ca++ triggers the fusion of vesicle with the cell membrane, resulting in exocytosis.

METABOLISM AND DISTRIBUTION OF THE CATECHOLAMINES

The actions of adrenaline and noradrenaline are terminated by three processes:

1. Re-uptake into the nerve terminal
2. Dilution by diffusion from the junctional cleft and uptake at non-neuronal sites, and
3. Metabolic transformation

Two enzymes namely monoaminooxidase (MAO) and catechol-o-methyl transferase (COMT) are important in the biotransformations of catecholamines. COMT and MAO are distributed widely throughout the body, including the brain the highest concentrations of each are found in the liver and kidney. They differ in their cytosolic locations.
NE released intraneurally is initially deaminated by MAO to 3,4-dihydroxyphenylglycolaldehyde (DOPGAL). The aldehyde group is reduced to glycol by aldehyde reductase, yielding 3,4-dihydroxy-phenylethylene glycol (DOPEG). Aldehyde dehydrogenase converts 3,4-dihydroxyphenyl glycolaldehyde to 3,4-dihydroxy-mandelic acid (DOMA). The final common metabolites formed by the action of COMT are DOMA (3-methoxy-4-hydroxy mandelic acid) is VMA (3-methoxy-4-hydroxymandelic acid).

**ADRENERGIC RECEPTOR SITES**

Adrenergic drugs exert their effects by direct action on adrenergic receptors. There are at least two adrenergic receptor sites (alpha (α) and beta (β)). Norepinephrine activates primarily alpha-receptors and epinephrine activates primarily beta receptors, although it may also activate alpha receptors. Stimulation of alpha receptors is associated with constriction of small blood vessels in the bronchial mucosa and relaxation of smooth muscles of the intestinal tract.
Beta receptor activation relaxes bronchial smooth muscles which cause the bronchi of the lungs to dilate.

In addition beta receptor stimulatory effects cause an increase in the rate and force of heart contractions. As a result increased amounts of blood leave the heart and is diverted from nonactive organs to areas that actively participate in the body’s reaction to stress such as skeletal muscles, brain, and liver.

**Alpha receptor site**

Important features of alpha adrenergic receptor sites in order of preference are:

1. **An anionic site.** The alpha-adrenergic receptor carries a negatively charged group (phosphate). The anionic site binds with the positive ammonium group.

2. One hydrogen bonding area

3. **A flat area.** A non-polar area for the aromatic ring binding.

The alpha receptors fall into two groups;

\[ (i) \ \alpha_1 \text{-Adrenergic receptors.} \] They are found in the smooth muscles of iris, arteries, arterioles and veins.

\[ (ii) \ \alpha_2 \text{-Adrenergic receptors.} \] They mediate the inhibition of adrenergic neurotransmitter release.

**Beta receptor site**

Important features of this receptor site are:

1. **An anionic site.** It is shown that an anionic negative acid group which binds with the positive ammonium group.

2. **Two hydrogen bonding areas.** It is shown as two serine with alcohol (OH) groups form hydrogen bonding with the phenolic—OH groups of the NE.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Receptor subtype</th>
<th>Agonists</th>
<th>Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>beta 1</td>
<td>NE, dobutamine, xamoterol</td>
<td>EP, atenolol, metoprolol</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>beta 1, beta 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular smooth muscle</td>
<td>beta 2</td>
<td>EP, salbutamol, terbutaline, salmeterol</td>
<td>Butoxamine</td>
</tr>
<tr>
<td>Air way smooth muscle</td>
<td>beta 2</td>
<td>Terbutaline, salbutamol, salmeterol and zinterol</td>
<td>Butoxamine</td>
</tr>
<tr>
<td>Smooth muscle contraction</td>
<td>alpha 1</td>
<td>NE, EP, phenylephrine, oxymetazoline</td>
<td>Prazosin, doxazocin</td>
</tr>
<tr>
<td>Inhibition of transmitter release, hypotension, anaesthesia, vasoconstriction</td>
<td>alpha 2</td>
<td>Clenbuterol, alpha-methylnoradrenaline, dexametomidine, and mivazerol, clonidine</td>
<td>Yohimbine, idazoxan, atipamezole, efaroxan, and rauwolscine</td>
</tr>
</tbody>
</table>
3. A flat area. A non-polar area for the aromatic ring.

β-Adrenergic receptors are of three types. They are:

(i) $\beta_1$-Adrenergic receptors. They are found in the myocardium where their stimulation increases the force and rate of myocardial contraction.

(ii) $\beta_2$-Adrenergic receptors. These are found in bronchial and vascular smooth muscles where their stimulation causes smooth muscle dilation or relaxation.

(iii) $\beta_3$-Adrenergic receptors. These receptors are expressed on fat cells and their stimulation causes lipolysis.

CLASSIFICATION OF ADRENERGIC AGONISTS

Adrenergic agonists are sub-divided into 3 classes; direct acting, indirect-acting and dual-acting agonists. These agents act on sympathetic nervous system, activates it.

1. Direct-acting agonists. They bind to and activate $\alpha_1$, $\alpha_2$, $\beta_1$ and $\beta_2$ receptors. Naturally occurring molecules which bind to these receptors include norepinephrine (NE; a neurotransmitter which binds to $\alpha_1$, $\alpha_2$ and $\beta_1$ receptors), epinephrine (EP; a hormone produced in and secreted from the adrenal medulla which binds to $\alpha_1, \alpha_2, \beta_1$ and $\beta_2$ receptors — EP is a non-selective adrenergic agonist) and dopamine (DA; also a neurotransmitter which binds to DA receptors as well as $\alpha_1$, $\alpha_2$ and $\beta_1$ receptors).

2. Indirect acting adrenergic agonists: They (i.e. amphetamines and cocaine) produce NE-like actions by stimulating NE release and preventing its re-uptake and thus its inactivation.

3. Dual-acting adrenergic agonists: These agents (i.e. ephedrine) act as a direct- and an indirect-adrenergic agonists (hence dual-acting). They bind to adrenergic receptors and stimulate NE release.

CHEMISTRY AND STRUCTURE ACTIVITY RELATIONSHIPS OF ADRENERGIC DRUGS

1. The sympathomimetic drugs may be divided into catechol and non-catechol amines.
2. All catecholamines, possess the catechol nucleus (o-dihydroxybenzene)
3. Noncatecholamines consisting of a benzene ring and an ethylamine side chain. β-phenylethylamine can be viewed as the parent compound, consisting of a benzene ring and an ethylamine side chain.

\[
\beta\text{-Phenylethylamine} \quad \text{Ephedrine (Non-catecholamine)}
\]

4. Separation of the aromatic ring and the amino group by two carbon atom shows the greatest activity.

5. Substitution on the amino group, increasing the size of the alkyl substituent increases β receptor activity, e.g. Isoproterenol.

\[
\text{Isoproterenol}
\]

6. Substitution on the aromatic nucleus, specifically OH groups at the 3 and 4 positions of the ring are required for maximal α and β activity. When one or both of these groups is absent, without other aromatic substitution, the overall potency is reduced. Phenylephrine is thus less potent at both receptors than adrenaline, with β activity almost entirely absent.

7. Hydroxyl (—OH) groups at the 3 and 5 positions, in compounds with large amino substituents, confers β₂ selectivity, e.g. metaproterenol, terbutaline
8. The response of non-catecholamines is largely determined by their ability to release NE, thus their effects are mainly on α and β₁.

9. Phenylethylamines lacking both aromatic —OH groups and the β-OH on the ethyl chain produce almost all of their effects by NA release. Catecholamines have only a brief duration of action, and are ineffective orally, due to degradation by COMT. Agents lacking —OH substitution, especially the compounds with 3-OH, are resistant to COMT and have a longer duration of action and oral effectiveness.

10. Substitution with groups other than —OH, in general, reduces α-adrenergic activity and almost abolishes β-adrenergic activity.

11. Substitution on the β-C atom generally decreases central stimulant action, due to the lower lipid solubility of these agents. However, this also greatly enhances both α and β potency. Thus, ephedrine is less potent than methamphetamine as a CNS stimulant, but is more potent vasoconstrictor and bronchodilator. Absence of the benzene ring reduces the CNS stimulant action, without reducing peripheral effects, when replaced by a saturated, e.g. Cyclopentamine the proportion of α : β activity varies with the compound. However, the absence of benzene confers greater activity and many of these agents are used as nasal decongestants.

12. Optical isomerism is conferred by substitution on either of the ethyl carbon atoms

   Laevorotatory. Substitution at the β-carbon atom produces naturally occurring NE and EP, both of which are over 10 times as potent as their isomers

   Dextrorotatory. Substitution at the α-carbon atom generally confers greater potency in CNS stimulation, e.g. d-amphetamine

**SPECIFIC ADRENERGIC DRUGS**

**A. Direct-acting agonists**

**Adrenaline (Epinephrine)**

**Chemistry.** Adrenaline (C₉H₁₃NO₃) is a catecholamine and belongs to the family of biogenic amines. Chemically it is 1-(3,4-dihydroxyphenyl)-2-methylaminoethanol.

\[
\text{R} = \text{CH}_3 ; \text{Adrenaline}
\]

Epinephrine is prepared by Friedel Craft’s acylation of catechol with chloroaecetyl chloride to give α-haloacetophenone, followed by nucleophilic substitution with methylamine and catalytic reduction.
Adrenaline is available as adrenaline acid tartarate. Adrenaline is a white or creamy white crystalline and odorless powder. It is slightly soluble in water but freely soluble in mineral acids and alkali hydroxides. Adrenaline is insoluble in alcohol, ether and chloroform. It darkens slowly on exposure to air and light.

Adrenaline is a potent stimulator of both $\alpha$ and $\beta$ receptors and, as such, its administration produces effects resembling generalized activation of the sympathetic nervous system particularly prominent are the actions on the heart and vascular smooth muscle. The occurrence of sweating, piloerection and mydriasis depend largely upon the physiological state of the subject.

Adrenaline is one of the most potent vasopressors known, given by IV route, it evokes a characteristic rise in blood pressure. The mechanism of the rise in blood pressure with adrenaline is:

1. Direct myocardial stimulation (positive inotropic effect)
2. An increased heart rate (positive chronotropic effect)
3. Peripheral vasoconstriction

**Absorption, fate and excretion.** Due to rapid oxidation and conjugation in the GIT mucosa and liver adrenaline is ineffective after oral administration. Absorption from subcutaneous tissues occurs slowly due to local vasoconstriction. Adrenaline is rapidly inactivated in the body, despite its stability in blood. The liver is rich in both COMT and MAO, however is not essential in the degradation process. The majority of an administered drug is excreted in the urine as metabolites.

**Uses.** The oral intake of adrenaline has no effect. Therefore it has to be administered parenterally. It is used as sympathomimetic (drugs which support the beating of the heart), broncholytic (drugs which relax the bronchial muscles) and antiasthmatic (drugs against asthma). It is also used to prevent bleedings during surgery or in the case of inner organ bleeding. Because adrenaline leads to constriction of blood vessels, it is administered in combination with local anesthetics. In this combination, anesthetics have a longer lasting effect and can be administered in smaller doses.
Noradrenaline (Norepinephrine)

Chemistry. Norepinephrine, or l-β-[3,4-dihydroxyphenyl]-α-methyl-aminoethanol is the chemical mediator liberated at mammalian post-ganglionic adrenergic nerve terminals. Noradrenaline is available as acid tartarate salt. It is available as odorless, bitter taste, white crystalline powder. It is soluble in water and slightly soluble in alcohol. Noradrenaline should be protected from air and light as it darkens on exposure to air and light.

It differs from adrenaline only by lacking the methyl substitution on the aminoethanol and, as for adrenaline, the l-isomer is pharmacologically active. Noradrenaline constitutes 10-20% of the catecholamine content of the adrenal medulla and as much as 97% in some pheochromocytomas. Norepinephrine bitartrate is a water soluble, crystalline monohydrate salt, which, like adrenaline, it is readily oxidised. It is available for injection as 0.2% bitartrate, which is equivalent to noradrenaline 0.1%. It is usually given as a central i.v. infusion at a concentration of 60 µg/ml.

Pharmacological actions. Both adrenaline and noradrenaline are approximately equipotent at cardiac β₁ receptors. Noradrenaline is a potent agonist for α-receptors but has little action on β₂ receptors. However, noradrenaline is somewhat less potent than adrenaline at most α-receptors.

Dopamine

Chemistry. Dopamine (3,4-dihydroxyphenylethylamine), differs from the other naturally occurring catecholamines, lacking the β-OH group on the ethylamine side chain. It is the metabolic precursor of noradrenaline and adrenaline and is a central neurotransmitter.

Pharmacology. Dopamine is a substrate for both MAO and COMT and is thus ineffective orally. It has minimal effects on the CNS, not crossing the blood brain barrier. Dopamine exerts a positive inotropic effect on the heart, acting at β₁ receptors. Dopamine usually increases the systolic and pulse pressures.

Dosage and administration. Dopamine hydrochloride is a water soluble, crystalline, light and alkali sensitive white powder marketed in solutions of 40, 80 and 160 mg/ml. Dopamine is effective only by i.v. infusion, when it is usually diluted to 0.8 to 1.6 mg/ml. The usual adult dose is 2-5 μg/kg/min.


ISOPROTERENOL (ISOPRENALINE)

Chemistry. Isoproterenol, or dl-β-[3,4-dihydroxyphenyl]-α-isopropylaminoethanol, is a synthetic catecholamine acting almost exclusively at β receptors.
Due to the absence of $\alpha$ adrenergic effects, isoproterenol produces most of its effects in the heart and the smooth muscle of the bronchi, skeletal muscle vasculature, and the GIT in addition, it produces marked metabolic effects in adipose tissue, skeletal muscles and in the liver in some species.

Isoproterenol is available for injection as the water-soluble hydrochloride salt. It is available as a solution for inhalation, 0.25% to 1%, usually diluted 1:5 with normal saline. It is synthesized by following method:

\[
\text{HO} - \text{C} - \text{CH}_2\text{Cl} + (\text{CH}_3)_2\text{CH} - \text{NH}_2 \rightarrow \text{HO} - \text{C} - \text{CH}_2\text{NH} - \text{CH} - \text{CH}_3
\]

4-Chloroacetylcatechol Isopropylamine

\[
\text{HO} - \text{C} - \text{CH}_2\text{NH} - \text{CH} - \text{CH}_3 \xrightarrow{\text{H}_2/\text{catalyst}} \text{HO} - \text{C} - \text{CH}_2\text{NH} - \text{CH} - \text{CH}_3
\]

Isoproterenol

**Phenylephrine**

**Chemistry.** Chemically it is 1-(3-hydroxyphenyl)-2-methylaminoethanol. Phenylephrine differs from adrenaline only by lacking the 4-OH group on the benzene ring and subsequently is resistant to COMT and has predominantly $\alpha$-agonist effects.

\[
\text{HO} - \text{C} - \text{CH}_2\text{NH} - \text{CH}_3
\]

Phenylephrine
Phenylephrine is prepared by condensation of 3-chloroacetylphenol with methylamine followed by catalytic reduction.

Properties. Phenylephrine is available as hydrochloride salt. It is white, odorless, bitter taste, crystalline powder. It is soluble in water, alcohol, and glycerol. It should be stored in airtight container to protect from light because it is decomposed by light.

Uses. Phenylephrine is a selective $\alpha_1$-receptor agonist. Oral absorption is not reliable and so it is given parenterally or topically as eye or nasal drops. Phenylephrine predominantly acts on peripheral arterioles resulting in a rise in systolic and diastolic pressures accompanied by a marked reflex bradycardia. Phenylephrine is used as a nasal decongestant, mydriatic, and as a vasopressor agent.

Dobutamine

Chemistry. Dobutamine is a synthetic catecholamine derivative. It resembles dopamine chemically, but possesses a bulky aromatic residue on the amino group despite the absence of a $\beta$-OH group. Dobutamine is a racemic mixture of two enantiomeric forms. The (+) isomer has potent $\beta$-agonist actions. The (–) isomer has potent $\alpha_1$-agonistic and poor $\beta$-agonistic actions.

Properties. Dobutamine is a white color, sparingly water soluble powder. It is a selective $\beta_1$-receptor agonist and has only slight indirect actions. It increases cardiac output without any effect on heart rate and blood pressure. It may activate $\alpha_1$-receptor in higher dose.

Uses. Dobutamine is used in patients of heart failure associated with myocardial infarction, open heart surgery and cardiomyopathy.

SELECTIVE $\beta_2$-ADRENERGIC STIMULANTS

Because of their relative selectivity, these agents relax the smooth muscle of the bronchi, uterus and blood vessels. Generally they have far less action on the heart than isoproterenol and other agents. Increased $\beta_2$-agonist activity is conferred by the substitution of increasing bulky lipophilic groups on the amino group of isoproterenol.
Changing the hydroxyl group (—OH) substitutions on phenyl group of isoproterenol from 3, 4 to 3, 5 results in metaproterenol, which retains its $\beta_2$-agonistic actions but has reduced $\beta_1$-agonistic activity. Further the shift of the —OH group produces resistance to MAO and prolongs the duration of action. Such agents include,

(a) Salbutamol  
(b) Terbutaline  
(c) Ritodrine  
(d) Metaproterenol  
(e) Nylidrin  
(f) Isoetharine.

Most of these drugs are administered orally or by inhalation.

**Terbutaline**

**Chemistry.** Terbutaline is a non-catecholamine, therefore is resistant to COMT. Chemically terbutaline is N-tert-butyl-N-[2-(3,5-dihydroxyphenyl)-2-hydroxymethyl] amine which is available as sulphate salt.
Terbutaline is prepared by reduction of 2-(tert-buty lamino)-3′, 5′-dihydroxyacetophenone by catalytic hydrogenation:

\[
\text{C} - \text{CH}_2 - \text{N} - \text{C} - \text{CH}_3 \quad \xrightarrow{\text{H}_2/\text{Ni}} \quad \text{C} - \text{CH}_2 - \text{N} - \text{C} - \text{CH}_3
\]

**Properties.** Terbutaline is a white, odorless, bitter taste crystalline powder. It is soluble in water, slightly soluble in alcohol and practically insoluble in ether and chloroform. It should be protected from light.

**Isoetharine.** Isoetharine is 3,4-dihydroxy-α-[1-(isopropylamino)propyl]benzyl alcohol. It is available as its methane sulphonate salt. It occurs as white, odorless, bitter taste, water soluble solid.

\[
\text{HO} \quad \text{C} - \text{CH}_2 - \text{N} - \text{C} - \text{CH}_3 \quad \text{OH}
\]

**Uses.** Isoetharine has β2-agonistic properties and is used as a bronchodilator.

**Nylidrin**

Nylidrin occurs as hydrochloride. It is sparingly soluble in water and slightly soluble in alcohol. Practically insoluble in ether, chloroform and benzene.

\[
\text{HO} - \text{C} - \text{CH}_2 - \text{N} - \text{C} - \text{CH}_2 - \text{CH}_2 - \text{C}_6\text{H}_5
\]

Nylidrin is synthesized from \( p \)-hydroxyephedrine by following steps;

1. \( p \)-Hydroxyephedrine is condensed with 4-phenyl-2-butanone to get schiff base.
2. The schiff base is reduced to yield Nylidrin

\[
\text{HO--CH--N--C--CH}_2--\text{CH}_2--\text{C}_6\text{H}_5}
\]

\[\xrightarrow{H_2/Ni} \]

Nylidrin

**Uses.** Vasodilator (peripheral).

**Ritodrine**

Ritodrine occurs as Ritodrine hydrochloride. Ritodrine hydrochloride is water soluble, odorless, white colored crystalline compound.

\[
\text{OH}
\]

\[
\text{H--C--CH--NH--CH}_2--\text{CH}_2--\text{C}_6\text{H}_5}
\]

Ritodrine

**Uses.** Ritodrine is a short acting $\beta_2$-stimulant and is used parenterally for delaying premature delivery of foetus.

**Metaproterenol**

Metaproterenol occurs as sulphate salt. It is odorless, bitter taste, water-soluble crystalline solid. It is photosensitive compound hence should be protected from light and air.

\[
\text{OH}
\]

\[
\text{H--NCH(\text{CH}_3)}_2
\]

**Uses.** Metaproterenol possesses strong $\beta_2$-agonistic properties. It is used in the treatment of bronchial asthma.

**SELECTIVE $\alpha$-ADRENERGIC STIMULANTS**

Some adrenergic drugs have selective action on $\alpha$-adrenergic receptors. Ex: Phenylephrine and methoxamine.

**Methoxamine**

Methoxamine is available as hydrochloride. It is white, crystalline, odorless, water soluble solid.
Methoxamine is a parenteral vasopressor and selective for \( \alpha_1 \)-receptors and so have few cardiac stimulatory properties. Because it is not substrate for COMT, its duration of action is significantly longer than that of norepinephrine, but primary use is limited to treat hypotension during surgery or shock.

**Uses.** Methoxamine is also used to treat supraventricular tachycardia.

**INDIRECTLY ACTING ADRENERGIC DRUGS**

This class is comprised of non-catecholamines. Most of these drugs retain phenylethylamine skeleton.

\[
\begin{align*}
\text{R} & \quad \text{CH}_3 \\
\text{β} & \quad \text{α} \\
\text{α} & \quad \text{NH} - \text{R'} \\
\text{R} & = \text{H or OH} \\
\text{R'} & = \text{H or CH}_3 \text{ or heterocyclic ring}
\end{align*}
\]

These compounds are resistant to COMT and MAO enzymes due to lack of phenolic hydroxyl groups and presence of \( \alpha \)-methyl groups. These compounds pass more readily through blood brain barrier because of increased lipophilicity.

**Amphetamine**

**Chemistry.** Amphetamine is an indirect-acting sympathomimetic amine and its action depends on the release of norepinephrine from adrenergic nerves. It is synthesized by reductive amination of phenylacetone with ammonia and hydrogen.

\[
\text{Phenylacetone} \xrightarrow{\text{NH}_3, \text{H}_2/\text{Ni}} \text{Amphetamine}
\]

**Properties.** Amphetamine is bitter taste, slightly water miscible, mobile liquid. Amphetamine occurs as sulphate salt, which is slightly bitter taste, water soluble solid.

**Uses.** Amphetamine is one of the most potent sympathomimetic. CNS stimulant effects are thought to be due to stimulation of the cortex. The d-isomer is 3-4 times more potent than the \( l \)-isomer. Amphetamine causes increased wakefulness, elevated mood, increased initiative, self-confidence and ability to concentrate. In addition to these effects it also has anorexigic action and can be used in the treatment of obesity.

**Hydroxyamphetamine**

Hydroxyamphetamine occurs as hydrobromide salt. Hydroxyamphetamine hydrobromide is water soluble, white crystalline compound.
Hydroxyamphetamine is synthesized by reducing \( p \)-methoxybenzyl methyl ketoxime followed by hydrolysis of methoxy group with HI.

\[
\begin{align*}
\text{Cyclopentanone} & \quad \text{Knovenagel reaction} \quad \text{Decarboxylation} \\
\text{CH}_2\text{C} = \text{CH}_3 & \quad \text{OH} & \quad \text{CH}_2\text{C} = \text{CH}_3 \\
\text{N-OH} & \quad \text{NH}_2 & \quad \text{NH}_2 \\
\text{OCH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

Hydroxyamphetamine possesses \( \alpha \)-receptor stimulant activity but lacks CNS activity. It is a powerful vasoconstrictor.

**Uses.** Hydroxyamphetamine is used in the following conditions:
(a) Narcolepsy (sudden attack of sleep in completely inappropriate situations)
(b) Hyperkinetic syndrome in children
(c) As an anorexiant in the treatment of obesity

**Propylhexedrine**
Propylhexedrine is 1-cyclohexyl-2-methylaminopropane, which occurs as racemic mixture. Propylhexedrine is prepared from methamphetamine by reduction.

**Properties.** It is an oily liquid having amine odor and boils at 205°C. It is slightly soluble in water and miscible with alcohol, chloroform, and ether.

\[
\begin{align*}
\text{CH}_2\text{CH} - \text{NH} - \text{CH}_3 & \quad \text{CH}_2\text{CH} - \text{NH} - \text{CH}_3 \\
\text{Methamphetamine} & \quad \text{Propylhexedrine}
\end{align*}
\]

**Uses.** Propylhexedrine is used as 1) Nasal decongestant 2) adrenergic agent (vasoconstrictor)

**Cyclopentamine**
Cyclopentamine is a non-catecholamine possessing indirectly acting adrenergic agonistic activity.

Cyclopentamine is prepared from cyclopentanone by following sequential steps:
(a) Cyclopentanone is condensed with cyanoacetic acid by Knovenagel reaction, followed by decarboxylation to get an unsaturated nitrile.
ADRENERGIC DRUGS

$$\text{Cyclopentanone} + \text{Cyanoacetic acid} \rightarrow \text{Cyclopentanone} + \text{Cyanoacetic acid} \rightarrow \text{Cyclopentanone} + \text{Cyanoacetic acid} \rightarrow \text{Cyclopentanone} + \text{Cyanoacetic acid} \rightarrow$$

(b) The unsaturated nitrile is reduced to get 2-cyclopentylmethyl nitrile

(c) 2-cyclopentyl methyl nitrile is allowed to react with methyl magnesium bromide to afford a methyl ketone which on reductive amination with methylamine yields cyclopentamine.

Naphazoline

Naphazoline is 2-(1-naphthylmethyl)-2-imidazoline. It is prepared by strong heating of 1-naphthaleneacetonitrile with ethylenediamine monochloride at 200°C.

**Uses.** Naphazoline is direct acting sympathomimetic drug, which has only α-agonistic activity. It is used topically as nasal decongestant.

Tetrahydrozoline

Tetrahydrozoline occurs as hydrochloride.
Properties. It is freely soluble in water, and alcohol but very slightly soluble in chloroform and practically insoluble in ether. It melts at 256°C.

Tetrahydrozoline is prepared by the following reaction:

1. 4-Keto-1, 2, 3, 4-tetrahydro-1-naphthoic acid amide is reduced by catalytic hydrogenation followed by condensation with ethylenediamine yields tetrahydrozoline.

Uses. 1. Adrenergic (vasoconstrictor); 2. Nasal decongestant.

Xylometazoline

Xylometazoline occurs as hydrochloride which is 2-(4-tert-butyl)-2, 6-dimethylbenzyl)-2-imidazoline.

Uses. Xylometazoline is a sympathomimetic decongestant. It is a sympathomimetic with marked alpha-adrenergic action. It acts as a vasoconstrictor when applied topically to mucus membrane and thus reduces swelling and congestion.
**Oxymetazoline**

Oxymetazoline occurs as hydrochloride which is 6-tert-butyl-3-(2-imidazolin-2-ylmethyl)-2,4-dimethylphenolmonohydrochloride.

![Chemical Structure of Oxymetazoline]

**Uses.** Oxymetazoline is direct acting sympathomimetic drug. It is used topically as nasal decongestant.

**ADRENERGIC DRUGS WITH MIXED ACTION**

These drugs act both directly with the receptor sites and partly by the release of endogeneous norepinephrine.

**Ephedrine**

**Introduction.** Occurs naturally in many plants, being the principal alkaloid of *Ma Huang* which has been used in China for over 2000 years. It has agonist activity at both α and β-receptors. It contain two asymmetric carbon atoms, four compounds are available only racemic and L-ephedrine are clinically in use. Ephedrine differs from adrenaline mainly by its,

1. effectiveness after oral administration
2. longer duration of action
3. more pronounced central actions
4. much lower potency

It produces a sharp rise in systolic, diastolic and pulse pressures, with a reflex bradycardia, similar to adrenaline but lasting for 10 times as long.

**Structural elucidation of ephedrine**

(i) The molecular formula of ephedrine is $C_{10}H_{15}NO$.

(ii) **Basic structure.** Ephedrine on oxidation gives benzoic acid. Therefore the structure of ephedrine contains a benzene ring with only one side chain.

![Chemical Structure of Ephedrine and Oxidation]

(iii) **Nature of nitrogen.** Ephedrine on reaction with nitrous acid gives N-nitrosoamine hence nitrogen atom in ephedrine is $2^\text{th}$ amine.
(iv) **Nature of Oxygen.** Ephedrine on reaction with benzoyl chloride gives dibenzoyl derivative. This shows that ephedrine contains one hydroxyl group.

\[
\text{Alcohol} + \text{Benzoylchloride} \rightarrow \text{A benzoyl derivative}
\]

\[
\text{C}_{10}H_{15}NO + 2\text{C}_6H_5COCl \rightarrow \text{C}_{10}H_{13}N(COOC_6H_5)_2
\]

(v) **Hydramine fission.** Ephedrine on heating with hydrochloric acid gives methylamine and propiophenone. These products are formed by hydramine fission of ephedrine.

\[
\text{Ephedrine} \xrightarrow{\text{HCl}} \text{Methylamine} + \text{Propiophenone}
\]

(vi) The following structure was proposed for ephedrine which was able to undergo hydramine fission

\[
\text{Proposed structure of ephedrine}
\]

(vii) **Evidence for proposed structure.** The above proposed structure yield 1,2-methylphenyl ethylene oxide on Hofmann's exhaustive methylatin method:

\[
\text{Quaternary ammonium hydroxide of ephedrine}
\]

(viii) **Stereochemistry.** The proposed structure contains two chiral centres, hence even after the removal of hydroxyl group by a hydrogen atom the obtained product is optically active. The naturally available ephedrine too is optically active. The naturally isolated ephedrine [(–) ephedrine] gives deoxy ephedrine (by replacement of –OH group by hydrogen atom), which is still optically active. Since ephedrine molecule contains two dissimilar chiral centres hence 4 optically active isomers are possible.
Uses. Ephedrine is mainly used as a bronchodilator in asthma. It is used to treat narcolepsy and depressive state. It is also used as nasal decongestant, mydriatic and in certain allergic disorders.

Metaraminol

Chemistry. Chemically metaraminol is 3-hydroxyphenylisopropanolamine. Metaraminol is an isomer of phenylephrine.

\[
\begin{align*}
\text{HO—HO} & \quad —\text{C—C—CH}_3 \\
& \quad \text{CH}_3 \\
\text{1R, 2S-Metaraminol}
\end{align*}
\]

Metaraminol is synthesized from m-hydroxy benzaldehyde by a selective condensation with nitroethane using tetrabutylammonium fluoride in tetrahydrofuran as a catalyst, followed by a reduction with Raney nickel in formic acid.

\[
\begin{align*}
\text{HO—C—NO}_2 + \text{CH}_2—\text{CH}_3 & \quad \xrightarrow{(i) \text{Tetrabutylammonium fluoride}} \quad \text{HO—C—CH}_3 \\
& \quad \text{H} \\
& \quad \text{NH}_2 \\
\text{Metaraminol}
\end{align*}
\]

Uses. Metaraminol is used for its pressor action for maintaining blood pressure during anesthesia, haemorrhage and other hypotensive states.

Mephentermine

Mephentermine is another general adrenergic agonist with both direct and indirect activity. Mephentermine's therapeutic utility is as a parenteral vasopressor used to treat hypotension induced by spinal anesthesia or other drugs.

\[
\begin{align*}
\text{CH}_3 \\
\text{H}_2\text{C—C—NHCH}_3 \\
\text{CH}_2 \\
\end{align*}
\]