INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Review Article on Adrenergic Neurotransmitter

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ARTICLE INFO

Published: 30 July 2025
Keywords:
Adrenergic Neurotransmitters, Adrenergic Receptors, Physiological Responses, Signalling Pathways, Gene Expression, Therapeutic Application
DOI:
10.5281/zenodo.16607121

ABSTRACT

This project aims to elucidate the complex interactions between adrenergic neurotransmitters (epinephrine and norepinephrine) and their receptors (alpha-1, alpha-2, beta-1, beta-2, and beta-3) in modulating physiological responses. Using a combination of molecular biology, pharmacological, and physiological approaches, we will: 1. Investigate the expression and function of adrenergic receptors in various tissues (heart, blood vessels, smooth muscle, and immune cells). 2. Examine the effects of adrenergic neurotransmitters on physiological responses (heart rate, blood pressure, energy metabolism, and smooth muscle contraction). 3. Determine the role of adrenergic receptors in regulating signaling pathways and gene expression. 4. Explore the potential therapeutic applications of targeting adrenergic receptors in diseases (hypertension, cardiovascular disease, asthma, and immune disorders). This project will provide new insights into the adrenergic system's mechanisms and its implications for human health and disease. Our findings will contribute to the development of novel therapeutic strategies for adrenergic-related disorders.

INTRODUCTION

Here's a potential introduction to adrenergic neurotransmitters:

Adrenergic neurotransmitters, also known as catecholamine's, are a group of chemical messengers that play a crucial role in regulating various physiological responses in the body. The two primary adrenergic neurotransmitters are:

1. Epinephrine (Adrenaline)
2. Norepinephrine (Noradrenaline)

These neurotransmitters are released by the adrenal glands and sympathetic nerves in response to stress, excitement, or danger. They interact with adrenergic receptors in various tissues, including the heart, blood vessels, smooth muscle, and immune cells, to modulate physiological responses such as:

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

- Heart rate and blood pressure
- Energy metabolism and glucose release
- Smooth muscle contraction and relaxation
- Immune response and inflammation

Adrenergic neurotransmitters are essential for the body's "fight or flight" response, preparing the body to respond to stress or danger. They also play a role in maintaining physiological homeostasis, regulating various bodily functions, and influencing behaviour and mood. Understanding adrenergic neurotransmitters is crucial for developing treatments for various diseases and disorders, such as hypertension, cardiovascular disease, asthma, and attention deficit hyperactivity disorder (ADHD). Adrenergic receptors are a class of G-protein coupled receptors that play a crucial role in mediating the physiological effects of adrenergic neurotransmitters, such as epinephrine (adrenaline) and norepinephrine (noradrenaline). These receptors are widely distributed throughout the body and are found in various tissues, including:

- Heart
- Blood vessels
- Smooth muscle
- Immune cells
- Brain

Adrenergic receptors are divided into two main subfamilies:

1. Alpha-adrenergic receptors (α1, α2).
2. Beta-adrenergic receptors (β1, β2, β3)

Each subfamily has distinct pharmacological and physiological properties, and they play specific roles in regulating various physiological responses, such as:

- Vasoconstriction and vasodilation
J- Heart rate and contractility
- Smooth muscle contraction and relaxation
- Energy metabolism and glucose release
- Immune response and inflammation

Adrenergic receptors are essential for maintaining physiological homeostasis and responding to stress, excitement, or danger. Dysregulation of adrenergic receptors has been implicated in various diseases and disorders, including:

- Hypertension
- Cardiovascular disease
- Asthma
- Attention deficit hyperactivity disorder (ADHD)

Understanding adrenergic receptors is crucial for developing targeted therapies for these diseases and for improving our understanding of the complex physiological processes they regulate. Naturally occur in our body.both agents that activate adrenergic receptors are called sympathomimetics the agents that block the activation of adrenergic receptors are called sympatholytics.

Adrenergic neurotransmitters are 3 types collectively called catecholamines:

1. Noradrenaline (NA)-at postganglionic sympathetic sites (except sweat glands, hair follicles) & in certain areas of brain.

2. Adrenaline (ADR) - secreted by adrenal medulla.

Dopamine(da)- transmitter in basal ganglia, limbic system, ctz, anterior pituitary

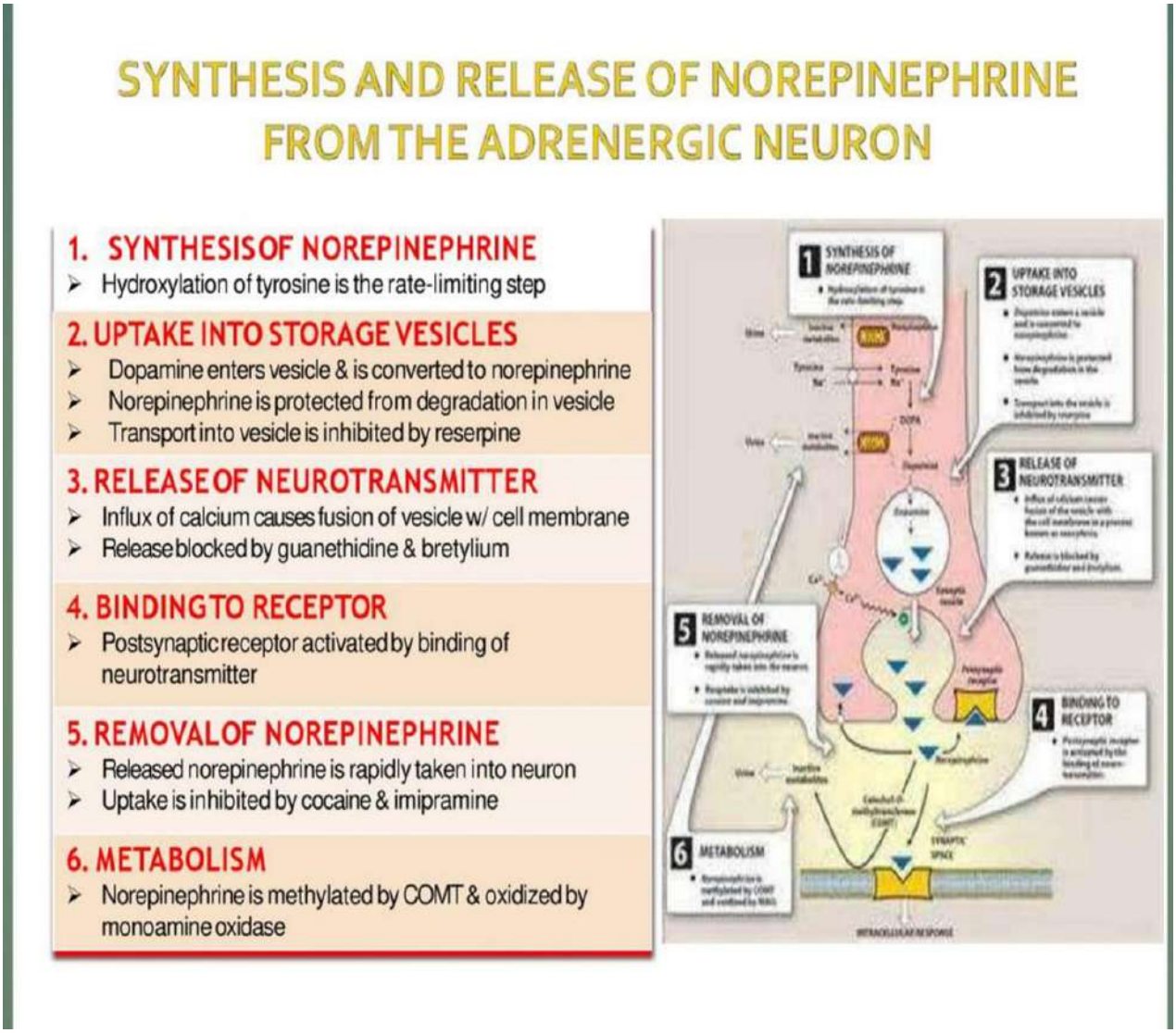
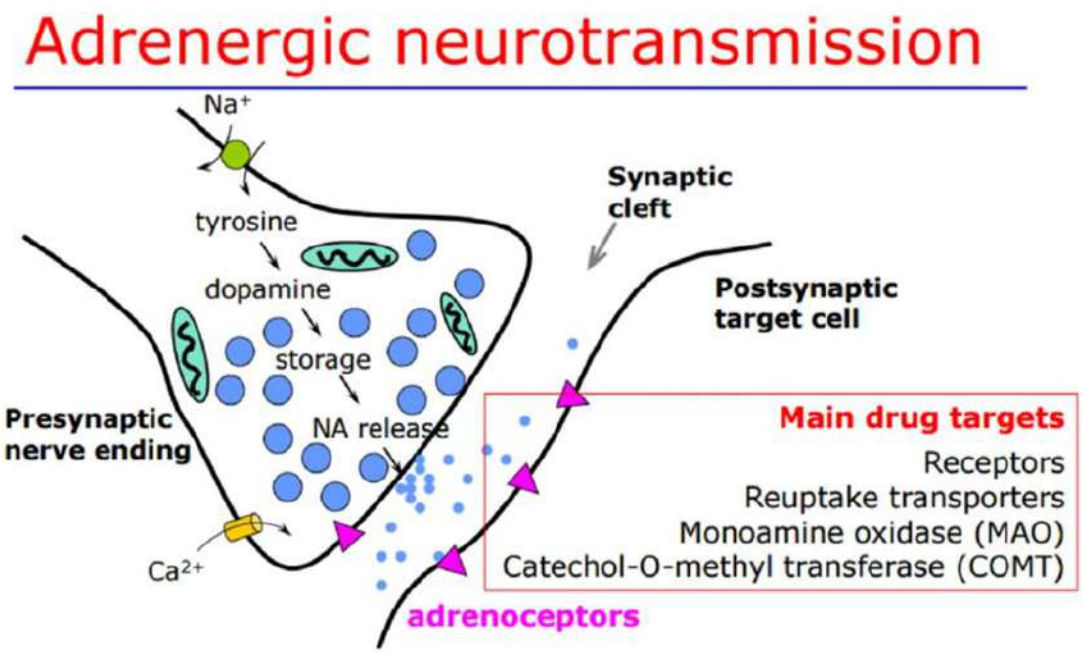


Fig.1.1 Synthesis and release of norepinephrine

Describe the main events in adrenergic neurotransmission and indicate the site of action of named drugs

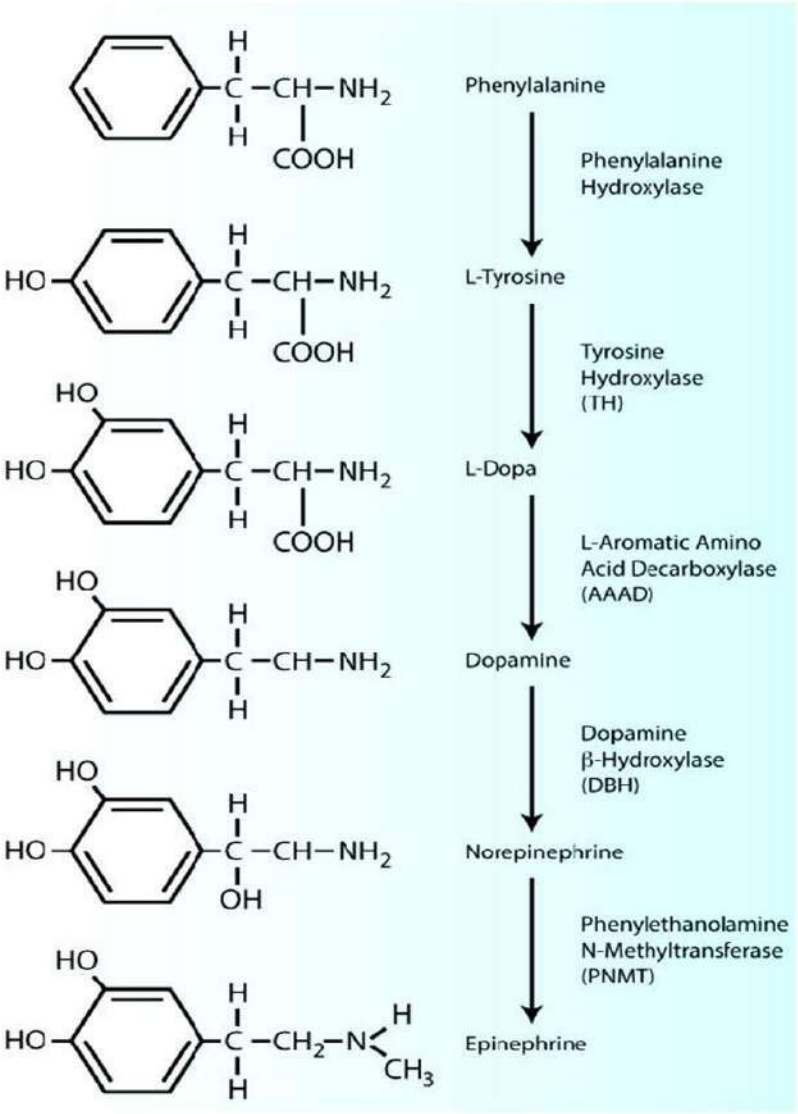
- Neurotransmission takes place at numerous bead-like enlargements called varicosities.
- The process involves 5 steps.
  1. Synthesis
  2. Storage
  3. Release
  4. Receptor binding of noradrenaline
  5. Removal of the neurotransmitter from the synaptic gap.



1. Synthesis of noradrenaline

- Tyrosine is transported by a Na +-linked carrier into the axoplasm of the adrenergic neuron, where it is hydroxylated to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase.
- Tyrosine hydroxylase is inhibited by the end product of the biosynthetic pathway, noradrenaline, and this provides the mechanism for the moment-to-moment regulation of the rate of synthesis; much slower regulation, taking hours or days, occurs by changes in the rate of production of the enzyme.
- This is the rate-limiting step in the formation of noradrenaline.
- DOPA is then decarboxylated by the enzyme dopa decarboxylase (aromatic l-amino acid decarboxylase) to form dopamine in the cytoplasm of the presynaptic neuron.
- Dopa decarboxylase activity is not rate-limiting for noradrenaline synthesis.

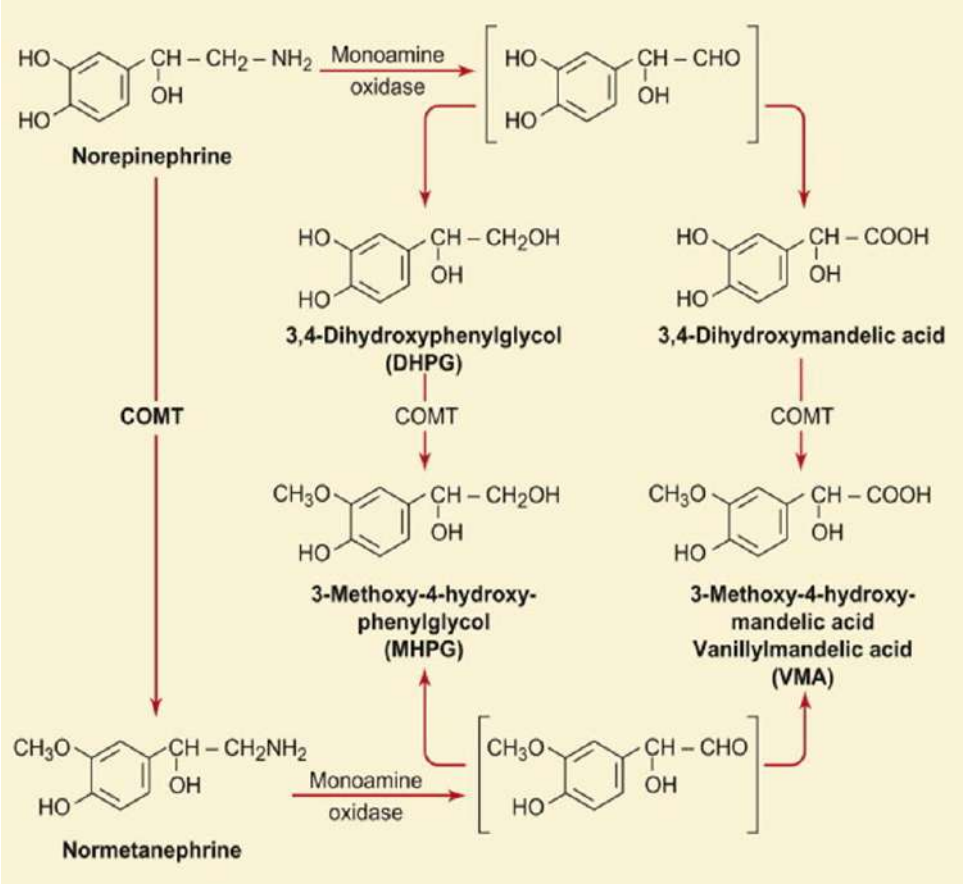
Pathway of catecholamine biosynthesis



1. 2-Biosynthesis of catecholamine

1. The process begins with the amino acid tyrosine, which is taken up from the bloodstream into the nerve terminal.
2. The enzyme tyrosine hydroxylase then converts tyrosine into DOPA (dihydroxyphenylalanine). This is the rate-limiting step, meaning it's the slowest step and thus determines the overall rate of catecholamine synthesis.
3. DOPA is then converted into dopamine by the enzyme DOPA decarboxylase.
4. If the neurotransmitter being produced is norepinephrine, dopamine is then taken up into storage vesicles, where the enzyme dopamine-beta-hydroxylase converts it into norepinephrine.
5. In some neurons, mostly located in the adrenal medulla, norepinephrine can be further converted into epinephrine by the enzyme phenylethanolamine N-methyltransferase.

6. bloodstream into the nerve terminal.



1.3 Catabolism of Catecholamine

Catabolism of Catecholamines

The breakdown, or catabolism, of catecholamines occurs through two main pathways involving specific enzymes:

1.The enzyme monoamine oxidase (MAO) is located in the mitochondria of the nerve terminal and catalyzes the oxidative deamination of the catecholamines. This enzyme breaks down dopamine, norepinephrine, and epinephrine into their respective aldehyde metabolites.

2.The catechol-O-methyltransferase (COMT) enzyme catalyzes the transfer of a methyl group to the catecholamines, creating a methylated metabolite.

The aldehyde metabolites can be further metabolized by aldehyde dehydrogenase to form corresponding acids or by aldehyde reductase to form glycols. For example, certain forms of depression and Parkinson's disease are associated with deficiencies in catecholamine neurotransmitters, while certain forms of mania and schizophrenia are associated with an overactivity of catecholaminergic systems.

Adrenergic Receptors

The adrenergic receptors or adrenoceptors are a class of G protein-coupled receptors that are targets of many catecholamines like norepinephrine (noradrenaline) and epinephrine (adrenaline) produced by the body, but also many medications like beta blockers, beta-2 (β2) agonists and alpha-2 (α2) agonists, which are used

to treat high blood pressure and asthma, for example.

Classification

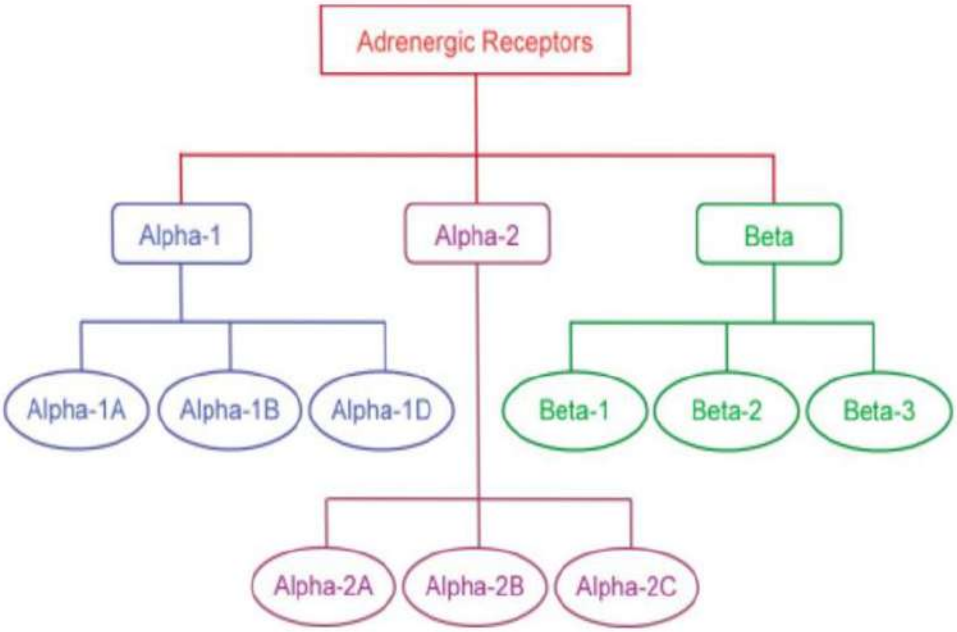


Fig 1.4 Classification of Adrenergic Receptor

Adrenergic receptors (ARs) are a class of G-protein-coupled receptors (GPCRs) that are activated by catecholamines such as epinephrine and norepinephrine (NE). The nine subtypes of ARs (α1A, α1B, α1D, α2A, α2B, α2C, β1, β2, and β3) are distributed in various tissues and organs throughout the body.

Receptor	Major Effector Tissues	Major Functions
$Alpha_1$	SM, sphincters	Contraction (constriction),
$Alpha_2$	Nerve endings	↓ Transmitter release
$Beta_1$	Cardiac muscle, Kidney	↑Heart rate and force, ↑Renin secretion
$Beta_2$	SM including bronchi Liver Skeletal muscle	Relax SM ↑ Gluconeogenesis, glycogenolysis ↑ Glycogenolysis and K+ uptake
$Beta_3$	Adipose	↑ Lipolysis
DA_1	SM especially renal, mesenteric and cardiac	Relax renal vascular SM (higher doses activates β1 and α1 receptors)

Fig.1.5 Receptor and Their Functions

Distribution of Adrenergic Receptor

Receptor type	Tissue location
α1	Arterioles (coronary, visceral, cutaneous), veins, internal sphincters, Iris dilator muscle.
α2	Presynaptic membrane, pancreas, veins, adipose tissue, GIT sphincters, salivary glands.
β1	Heart (SA node, atrial muscle, AV node, ventricles), kidney(JG apparatus), Adipose tissue.
β2	Arterioles(muscular), veins, bronchi (muscles), liver, pancreas, uterus , Iris constrictor muscle.
β3	Adipose tissue, urinary bladder.

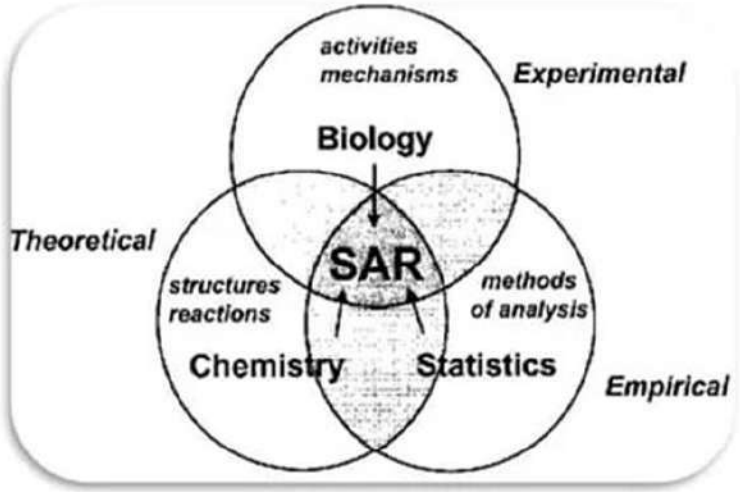
Fig 1.6 Adrenergic Receptor and Their Location

SAR (Structure activity relationship)-

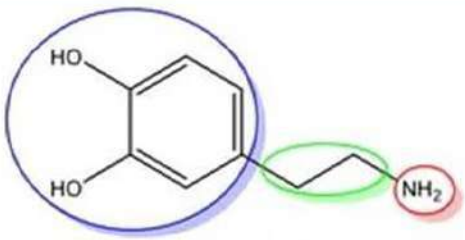
Structure-Activity Relationship (SAR) is an approach designed to find relationships between chemical structure (or structural-related properties) and biological activity of studied compounds. As such it is the concept of linking chemical structure to a chemical property (e.g., water solubility) or biological activity including toxicity.

OR

Structure activity relationship (SAR) is the relationship between the chemical structure of a molecule and its biological activity.



SAR of Sympathomimetic agent



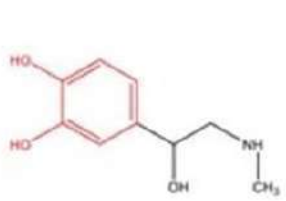
Catechol ring ethylene linkage Amino group terminal

SAR of sympathomimetic agent was studied by 3 different substitutions

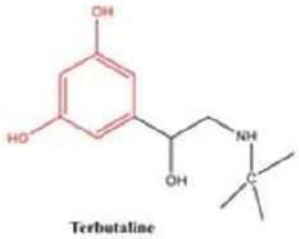
1. Catechol ring substitution
2. Substitution at ethylene linkage
3. Substitution at amino group

1. Catechol ring Substitution

- 3-hydroxy substitution is essential for **α -activity**
- 4-hydroxy substitution is essential for **β-activity**
- 3,4-dihydroxy substitution is required for both **α&β** activity.
- Replacement of catechol ring by resorcinol ring, increases **β_2** selectivity and also Decrease metabolism by COMT and produce longer duration of action.

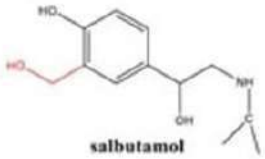


Epinephrine



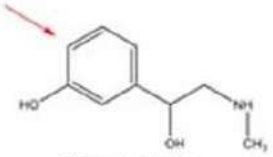
Terbutaline

- Replacement of *m*-hydroxyl of catechol, increases **β_2** selectivity and decreases metabolism by COMT



salbutamol

- Removal of *p*-hydroxyl group of catechol produces **α-**selectivity.



Phenylephrine

2. Substitution at ethylene linkage

- Hydroxy group substitution on the β-carbon is essential for activity.
- Substitution of alkyl groups (methyl or ethyl) at alpha carbon, decreases the metabolism by MAO. And produces longer duration of action.

Example: - Amphetamine (duration of action ↑)

- Ethyl group present at alpha carbon, increasing bulkiness and decrease in activity.

3. Substitution at Amino group

- The nature of amino substituent determines alpha and beta receptor selectivity.
- Substitution of alkyl group on nitrogen increases, activity at alpha receptor is decreases and beta - receptor selectivity is increases.

Example: - isoprenaline (isoproterenol)

- Primary and secondary amines having good adrenergic activity.

Sympathomimetic agents

- Adrenergic drugs/ agents are medication that stimulate certain nerves in human body. They do this either by mimicking the action of the NTS or by stimulating their release.
- These drugs are used in many life-threatening conditions including **cardiac arrest, shock, asthma attack, allergic reaction.**
- Sympathomimetic agents are that partially or completely mimic the action of Norepinephrine (NE) and epinephrine (EPI).
- They are also called as sympathomimetic drugs / adrenomimetic drugs / adrenergic agonist / adrenoreceptor agonist.
- Adrenergic drugs stimulate alpha, beta adrenergic receptor and dopaminergic receptors in various target tissue like eyes, heart and vascular smooth muscles.

Classification of sympathomimetics agents

Classification is divided into two different bases

1. Chemical classification
2. Based on the mechanism of action

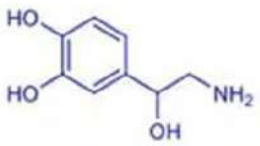
1. Chemical classification

Catecholamines	Non-catecholamines
Norepinephrine, Epinephrine, Dopamine, Dobutamine, isoproterenol	**Phenylephrine, hydroxy-amphetamine, Ephedrine, salbutamol, naphazoline, terbutaline** etc.

2. Based on the mechanism of action

Direct Acting drugs	Indirect Acting drugs	Mixed action drugs
Nor-epinephrine, Epinephrine, Phenylephrine*, Dopamine, Methyldopa, Clonidine, Dobutamine, Isoproterenol, Terbutaline, Salbutamol*, Bitolterol, Naphazoline, Oxymetazoline Xylometazoline	Hydroxy amphetamine, Pseudoephedrine, Propylhexedrine.	Ephedrine, Metaraminol

1. **NOREPINEPHRINE (Noradrenaline, Nephridine)**

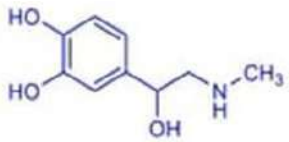


4-(2-amino-1-hydroxyethyl)benzene-1,2-diol
1-(3,4-dihydroxyphenyl)-2-amino ethanol

- **MOA: -** it is act by being released into the synaptic cleft, where it is acts on adrenergic receptor (alpha receptor-potent activity)
- **Metabolism:** Norepinephrine rapidly metabolized by both COMT and MAO, resulting in poor oral bioavailability and short duration of action (1 or 2 minutes even when given intravenously).
- **Therapeutic uses:**

  It is used to counteract various **hypotensive crises**, because it is an activity **raises blood pressure** and as an adjunct treatment in **cardiac arrest** because its **Beta- activity stimulates the heart**. It has limited clinical application caused by non-selective nature of its activities.
- **Adverse effect: -**
  - Blurred vision
  - Dizziness
  - Irregular heartbeat
  - Fainting

2. **EPINEPHRINE (Adrenaline): - (3,4-duhydroxyphenyl-N-methyl-2-ethanol)**



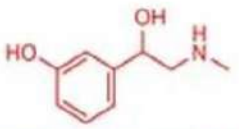
4-(1-hydroxy-2-(methylamino)ethyl)benzene-1,2-diol

- **Mechanism of action: -** It binds with adrenergic receptors which results in metabolic changes when its alpha-adrenergic receptors.
- **Metabolism:**

  The metabolic action of epinephrine leads to formation of 35 - adenosine monophosphate (C-AMP), which is the energy controlling reaction in effector cells.
- **Uses: -** It is much more widely used clinically than NE. Epinephrine is us following conditions bronchial asthma, hypersensitivity reactions, heart block cardiac arrest, control of bleeding frequently added to local anaesthetic like lignocaine.
- **Adverse reactions: -**
- The most common ill effects of epinephrine are
  - Anxiety
  - Tachycardia
  - Palpitation
  - tremors restlessness
  - headache
  - acute pulmonary oedema etc.

3. PHENYLEPHRINE

Phenylephrine differs from adrenaline only by lacking the 4th OH group on the benzene ring



3-(1-hydroxy-2-(methylamino)ethyl)phenol

Mechanism of action: -

- It is selective direct acting as alpha- receptor agonist.
- No effect on beta receptor.
- It is potent vasoconstrictor but less potent than epinephrine.
- Activation of alpha receptor causes the vasoconstriction of arterioles.

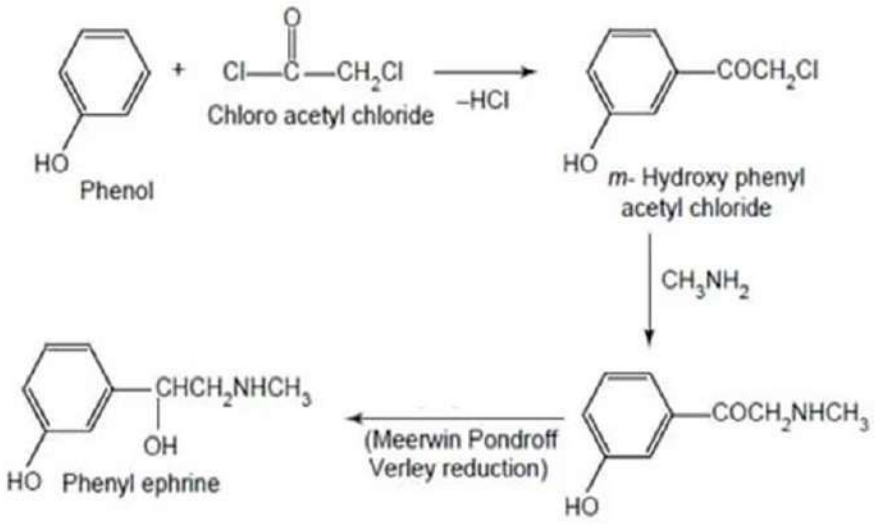
Metabolism: - Metabolized by MAO (Monoaminoxidase) and it lacks catechol moiety hence not metabolized by COMT

Uses: - It finds its main use in the relief of nasal congestion and as a mydriatic. It is also used to prolong the action of local anaesthetics.

Adverse Reactions: skin rash, itching, dizziness, light headedness, high BP

Synthesis: -

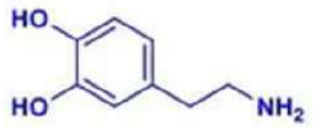
From: Phenol



4. DOPAMINE (Domin, Dopacard)

❖ **Mechanism of action:** Dopamine is naturally occurring catecholamine and has a neuro transmitter function in CNS. It exerts alpha adrenergic vasoconstrictor activity. Through beta adrenoreceptor

stimulation dopamine increases myocardial contractility. Thus, dopamine is a catecholamine which is unique in having a mixed action.



dopamine

4-(2-aminoethyl)benzene-1,2-diol

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

OR

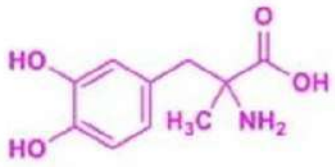
Dopamine exerts the CVS effects by interacting with D1-dopaminergic receptors especially in the renal, mesenteric, and coronary beds. At high concentrations, dopamine acts on β1 adrenergic receptors and causes positive ionotropic effects.

- **Metabolism:** Dopamine rapidly metabolized by COMT and MAO. The end products are different than those of adrenaline and noradrenaline. They are excreted in urine.
- **Uses: -**
  - treatment of shock resulting from trauma, surgery, and myocardial infarction
  - treatment of congestive heart failure, renal and liver failure.
  - also, dopamine causes the release of norepinephrine
- **Adverse Reactions:**
  - nausea,
  - vomiting,
  - tachycardia
  - ectopic beats
  - Occasionally hypertension may develop.

5. METHYLDOPA

Differs structurally from L-DOPA only in the presence of a alpha - methyl group.

- **Mechanism of action:** It is originally synthesized as an **L-Aromatic Amino Acid Decarboxylase** (AADC) inhibitor. However, it's mechanism of action is not caused by inhibition of AADC but rather by its metabolism in CNS to its active metabolite alpha-methyl norepinephrine.

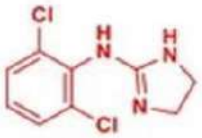


2-amino-3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid

- Given orally or intravenously
- **Metabolism:** - Methyldopa converted to alpha-methyl dopamine by the enzyme AADC which further converted to a- methyl norepinephrine by the enzyme dopamine B hydroxylase.
- **Uses: -** It finds its main use in the relief of nasal congestion and as a mydriatic. It is also used to prolong the action of local anaesthetics.
- **Adverse Reactions:** mild and transient sedation, dry mouth, reduce, Parkinsonism, hyperprolactinemia

6. CLONIDINE

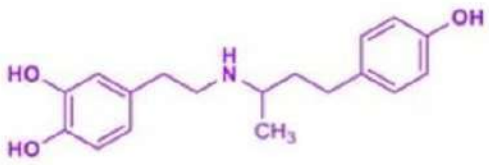
Alpha 2 selective agonist



Clonidine
N-(2,6-dichlorophenyl)-4,5-dihydro-1*H*-imidazol-2-amine

- **MOA:** - Clonidine can briefly exhibit vasoconstrictive activity as a result of stimulation of peripheral alpha-adrenergic receptors. hypotension (intravenous administration causes transient hypertension with prolonged hypotension; oral causes hypotension only)
- Can be given orally or as transdermal patch
- **Metabolism: -** half of the absorbed portion of an orally administered dose will be metabolized by the liver into inactive metabolites, other half being excreted unchanged by the kidneys.
- **Uses:** - main use is as antihypertensive; other uses are in treatment of substance addiction, in the relief of vasomotor symptoms of the menopause and in anaesthesia
- **Side effects –** dry mouth, sedation is very common; less so are sexual dysfunction and serious bradycardia. Patches can cause contact dermatitis.

7. DOBUTAMINE



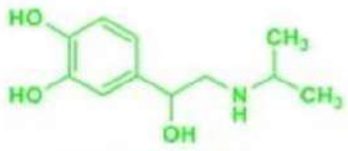
4-(2-((4-(4-hydroxyphenyl)butan-2-yl)amino)ethyl)benzene-1,2-diol

- β selective agonist
- Dobutamine is a catecholamine that is 4-(3-aminobutyl) phenol in which one of the hydrogens attached to the nitrogen is substituted by a 2-(3,4-dihydroxyphenyl) ethyl group.
- **Mechanism of action:** Dobutamine is synthetic direct acting sympathomimetics and is potent agonist of Beta-adrenoreceptor.
- **Effects** – more inotropic than chronotropic, increases stroke volume and cardiac output
- Given intravenously
- **Metabolism:** Dobutamine is metabolized by COMT and conjugation but not by MAO.
- **Uses:** congestive heart failure, acute myocardial infarction and before cardiac surgery
- **Side effects** – tachycardia, hypertension, angina pain, arrhythmia, nausea, and headache.

8. ISOPROTERENOL (ISOPRENALINE)

It is synthetic catecholamine derived from noradrenalin by substitution of an isopropyl group on the nitrogen atom of aliphatic side chain.

- **Mechanism of action:** The pharmacological actions of isoprenaline are due to its powerful beta stimulant activity and it has almost no action on alpha receptors
- **Metabolism:** It is metabolized by COMT, sulphate and glucuronide conjugation
- Can be inhaled or given orally
- **Uses** – to increase heart rate in bradycardia or heart blocks
- **Side effects** – palpitations, sinus tachycardia, ischemia, arrhythmias, flushing, headache, dizziness and sweating occasionally occurs.

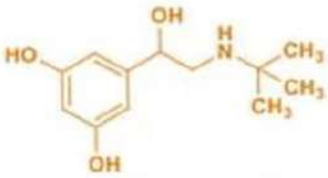


isoproterenol

4-(1-hydroxy-2-(isopropylamino)ethyl)benzene-1,2-diol

9. TERBUTALINE

- **MOA:** - β2 selective agonist, shows bronchodilatation (relaxation of bronchial muscles)
- **Metabolism:** - Terbutaline resistant to metabolism by either COMT or MAO. Instead, its metabolism primarily involves glucuronide conjugation.

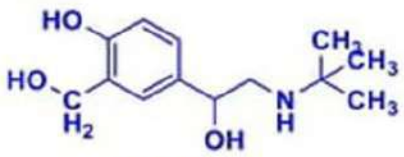


5-(2-(*tert*-butylamino)-1-hydroxyethyl)benzene-1,3-diol

- Given orally, subcutaneously, and as inhalant
- **Uses** - acute bronchospasm, asthma, COPD and for status asthmaticus; also used to treat uterine contractions.
- **A/E:** - Dizziness, headache, drowsiness, palpitations, rapid heart rate, shortness of breath, chest discomfort, nausea, vomiting.

10. SALBUTAMOL

Strong β2 adrenergic activity



salbutamol

1-(4-hydroxy-3-hydroxymethyl phenyl)-1-hydroxy-2-tert butylamino ethane

MOA: - stimulate β2 adrenergic receptor which are predominant receptor in bronchial smooth muscle.

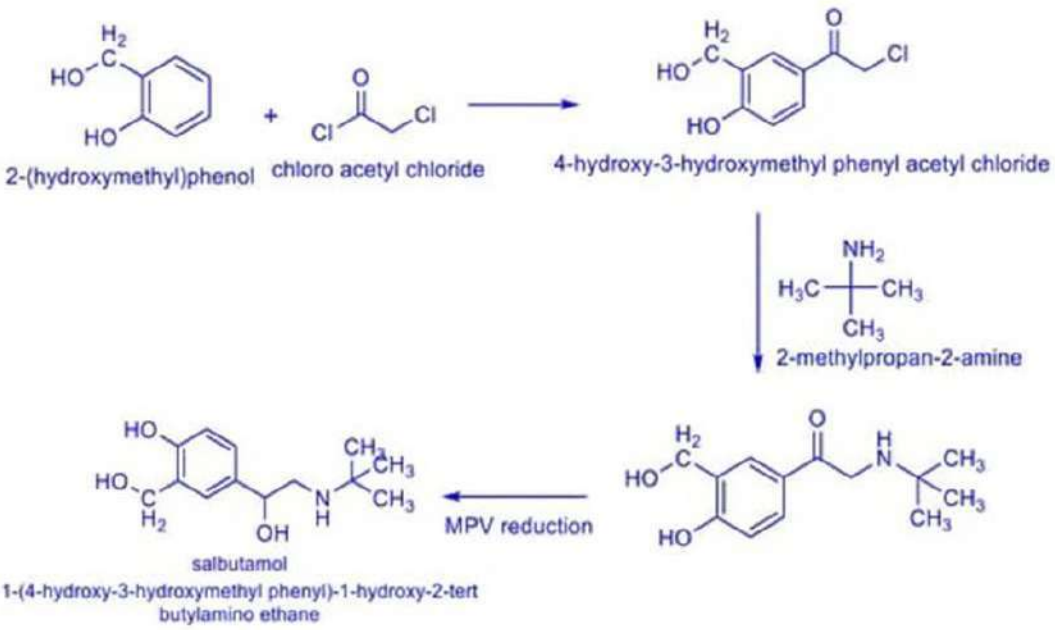
Beta 2 receptor smooth muscle > activates adenylyl cyclase > increase cAMP > smooth muscle relaxation > bronchodilation

Metabolism: - hydrolysed by esterase enzyme in tissue and also conjugatively metabolized to salbutamol-4-O-sulfate and by oxidative deamination.

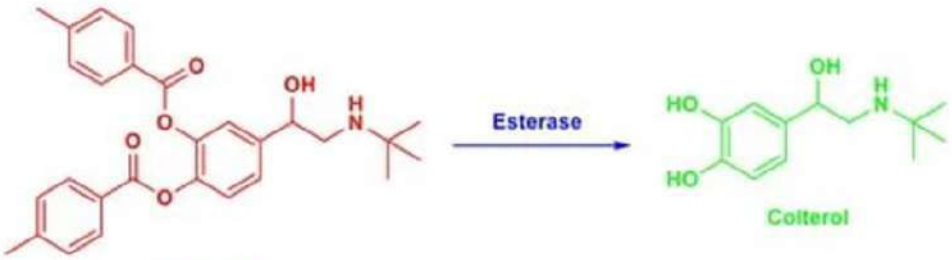
USE: - mainly used in COPD, Asthma.

A/E: - Headache, palpitation, trembling.

Synthesis of salbutamol: -



11. BITOLTEROL



Bitolterol

4-(2-(*tert*-butylamino)-1-hydroxyethyl)-1,2-phenylene bis(4-methylbenzoate)

Mechanism of action: -

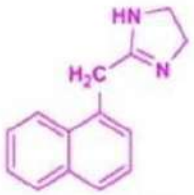
Bitolterol is a type of Beta 2 adrenergic agonist. When Beta adrenergic receptor are activated its activation results in relaxation of smooth muscle in the lung and dilation and opening of the airways which make airflow easy through the tubes.

Metabolism: - It is prodrug of colterol in which catechol hydroxyl groups converted to 4-methyl benzoic acid ester. **This ester is cleaved by esterase to colterol which is metabolise by COMT**

Uses: It is used for the relief of bronchospasm in condition like **COPD and asthma**

A/E: - Cough, dry Mouth, high Blood Pressure, irritation of the larger a passage of the lungs, mouth irritation, taste problems, temporary redness of neck.

12. NAPHAZOLINE



2-(naphthalen-1-ylmethyl)-4,5-dihydro-1*H*-imidazole

2-(1-naphthlene methyl) imidazoline

MOA: -

It stimulates alpha adrenergic receptor in the arterioles of the conjunctiva and the nasal mucosa to produce vasoconstriction.

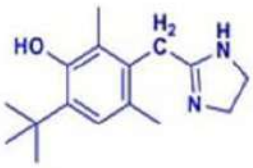
Metabolism: - metabolism of naphazoline under hepatic metabolism but most of the fraction of drug in unchanged form is excreted from the urine.

Uses: - it is a decongestant used to relieve

- Redness, puffiness, and itchy/watering eyes due to cold, allergies and eye irritation.

A/E: - Nose irritation, dry mouth, slow down the nervous system which lead unconsciousness.

13. OXYMETAZOLINE



6-(*tert*-butyl)-3-((4,5-dihydro-1*H*-imidazol-2-yl)methyl)-2,4-dimethylphenol

3-((4,5-Dihydro imidazol-2-yl)methyl)-6-(tert-butyl)-2,4-dimethyl phenol

MOA: - it acts on α-adrenergic receptor in the arterioles of nasal mucosa. In produces constriction, resulting in decrease blood flow and decreased nasal congestion.

Metabolism: - metabolised by liver enzymes to produce mono hydrogenated metabolite that excreted from urine.

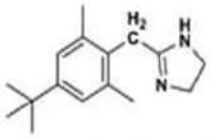
Uses: - as a nasal decongestant. Relieve nasal discomfort caused by cold, allergies and hay fever.

A/E: - drowsiness, dizziness, high BP, headache

14. XYLOMETAZOLINE

MOA: - binds with α-adrenergic receptor to cause vasoconstriction of nasal blood vessels.

Metabolism: - metabolised by some hepatic enzymes and most of the portion excreted from urine in unchanged form.



2-(4-(*tert*-butyl)-2,6-dimethylbenzyl)-4,5-dihydro-1*H*-imidazole
3-[(4,5-Dihydro imidazol-2-yl)methyl]-6-(tert-butyl)-2,4-dimethyl benzene

Uses: - as a nasal decongestant. Relieve nasal discomfort caused by cold, allergies and hay fever.

A/E: - temporary burning and dryness in the nose, sneezing, stinging.

INDIRECT ACTING AGENTS

Indirect acting sympathomimetics act by releasing endogenous NE. They also enter the nerve ending by the way of the active uptake process and displace NE from its storage granules.

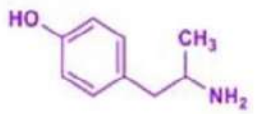
15. HYDROXYAMPHETAMINE (Phenyl-iso-propylamines)

It is an effective indirect acting sympathomimetic drug. The presence alpha-methyl group increases effectiveness of indirect acting agents. It differs from Amphetamine in the presence of *p*-OH group and so it has little or no CNS stimulating action

MOA: - it causes the release of NE from adrenergic nerve terminals > resulting in mydriasis (Dilation of pupils)

Metabolism: - it is metabolised in Liver by COMT and excreted through kidney.

Use: - it is used to dilate the pupil for diagnosis of eye examination and surgery. (Ophthalmic preparation)



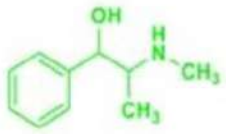
hydroxyamphetamine
4-(2-aminopropyl)phenol
4-hydroxy-α-methyl phenylethylamine

A/E: - blur vision, headache, temporary stinging, change in colour vision.

16. PSEUDOEPHEDRINE

MOA: - it releases the NE and NE bind with α-adrenergic receptor in the arterioles of nasal mucosa. In produces constriction and decreased nasal congestion.

Metabolism: - it is metabolised in Liver by COMT and excreted through kidney.



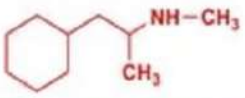
2-(methylamino)-1-phenyl-1-propanol
2-(methylamino)-1-phenylpropan-1-ol

Uses: - as a nasal decongestant. Relieve nasal discomfort caused by cold, allergies and hay fever.

A/E: - Feeling sick, headache, dry mouth, high BP

17. PROPYLHEXEDRINE

MOA: - it is causing the release of NE and shows the nasal decongestion action



1-cyclohexyl-*N*-methylpropan-2-amine

Metabolism: - It converts into propylhexedrine metabolite nor propylhexedrine and excreted through kidney.

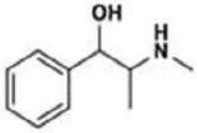
Uses: - It's major use is for local vasoconstrictive on nasal mucosa in the symptomatic relief of nasal congestion caused by the common cold, allergic rhinitis or sinusitis

A/E: - Burning, stinging, sneezing.

AGENTS WITH MIXED MECHANISM

18. EPHEDRINE

Ephedrine is one of the examples of phenylethylamine considered to have mixed mechanism of action usually have no hydroxyl on aromatic ring but do have a ß-hydroxyl group.



EPHEDRINE

2-(methylamino)-1-phenylpropan-1-ol

Mechanism of action: The drug acts on both alpha and Beta receptors. It is the classic example of a sympathomimetic with a mixed mechanism of action.

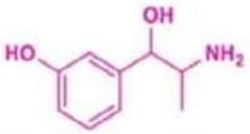
Metabolism: The drug is not metabolized by either MAO or COMT. Rather it is P- hydroxylated and N-demethylated by cytochrome, P450 mixed function oxidases.

Uses: Ephedrine and its salts are used orally intravenously and topically a variety of conditions such as allergic disorders cold, hypotensive conditions and narcolepsy.

A/E: - Arrhythmia, anxiety, tachycardia, headache, hypertension, acute pulmonary oedema.

19. METARAMINOL

MOA: - it stimulates α1 receptor to cause peripheral vasoconstriction and increases the blood pressure.



3-(2-amino-1-hydroxypropyl)phenol

Metabolism: metabolise by intestinal glucuronidation, sulphation and MAO

Uses: - It is used in spinal anaesthesia, acute hypotension.

A/E: - headache, nausea, vomiting, dizziness, anxiety.

RESULT:

***Key Findings: *** 1. *Expression and distribution*: Adrenergic neurotransmitters (epinephrine and norepinephrine) are expressed in various tissues, including the heart, blood vessels, smooth muscle, and immune cells.

2. *Receptor subtypes*: Alpha-1, alpha-2, beta-1, beta-2, and beta-3 adrenergic receptor subtypes are present in different tissues, with distinct pharmacological and physiological properties.

3. *Physiological effects*: Adrenergic neurotransmitters regulate heart rate, blood pressure, energy metabolism, smooth muscle contraction, and immune response.

4. *Pathophysiological implications*: Dysregulation of the adrenergic system contributes to cardiovascular disease, hypertension, asthma, and attention deficit hyperactivity disorder (ADHD).

***Major Outcomes: ***

1. *Elucidation of adrenergic receptor signalling pathways*: Identified key signalling pathways involved in adrenergic receptor activation and regulation.

2. *Development of novel therapeutic strategies*: Proposed new approaches for treating adrenergic-related disorders, including targeted receptor agonists/antagonists and gene therapy.

3. *Improved understanding of adrenergic system regulation*: Revealed complex interactions between adrenergic neurotransmitters, receptors, and other physiological systems.

DISCUSSION:

Neurotransmitters are released from synaptic vesicles into the synaptic cleft where they are able to interact with neurotransmitter receptors on the target cell. The neurotransmitter's effect on the target cell is determined by the receptor it binds to. Many neurotransmitters are synthesized from simple and plentiful precursors such as amino acids, which are readily available and often require a small number of biosynthetic steps for conversion. Neurotransmitters are essential to the function of complex neural systems. The exact number of unique neurotransmitters in humans is unknown, but more than 100 have been identified.[2] Common neurotransmitters include glutamate, GABA, acetylcholine, glycine and norepinephrine.

CONCLUSION:

Neurotransmitters are excitatory or inhibitory or, in some cases, have both types of functions. Excitatory neurotransmitters trigger depolarization, which increases the likelihood of a response. Inhibitory neurotransmitters trigger hyperpolarization, which decreases the likelihood of a response.

Summery:

Neurotransmitters are endogenous substances that are released from neurons, act on receptor sites that are typically present on membranes of postsynaptic cells, and produce a functional change in the properties of the target cell. Over the years there has been general agreement that several criteria should be met before a substance can be designated a neurotransmitter. First, a neurotransmitter must be synthesized by and released from neurons. In many cases, this means that the presynaptic neuron should contain a transmitter and the appropriate enzymes required for synthesis of that neurotransmitter. However, synthesis in the nerve terminal is not an absolute

requirement. For example, peptide transmitters are synthesized in the cell body and transported to distant sites, where they are released (see Chapter 10). Second, the substance should be released from nerve terminals in a chemically or pharmacologically identifiable form. Thus, one should be able to isolate the transmitter and characterize its structure using biochemical or other techniques. Third, a neurotransmitter should reproduce at the postsynaptic cell the specific events (such as changes in membrane properties) that are seen after stimulation of the presynaptic neuron; the concentrations that approximate those seen after release of the neurotransmitter by nerve stimulation should mimic the effects of presynaptic stimulation. Fourth, the effects of a putative neurotransmitter should be blocked by known competitive antagonists of the transmitter in a dose-dependent manner. In addition, treatments that inhibit synthesis of the candidate transmitter should block the effects of presynaptic stimulation. Fifth, there should be appropriate active mechanisms to terminate the action of the putative neurotransmitter. Such mechanisms can include enzymatic degradation and reuptake of the substance into the presynaptic neuron or glial cells through specific transporter molecules.

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HOW TO CITE: Ankita Joshi*, Samiksha Auti, Gaikwad Vaishnavi, Zine Snehal, Mule Asmita, Jadhav Bhakti, Review article on Adrenergic Neurotransmitter, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 7, 4116-4137. https://doi.org/10.5281/zenodo.16607121