Chapter ... 11

SYMPATHOMIMETIC AGENTS

♦ LEARNING OBJECTIVES ♦

After completing this unit, reader should be able to:

- ❖ Know importance of adrenergic receptors.
- ❖ Describe Adrenergic transmission.
- ❖ Describe the pharmacodynamic properties of sympathomimetic drugs.
- ❖ Identify major adverse effects and clinical uses of sympathomimetic drugs.

11.1 SYMPATHETIC NERVOUS SYSTEM

The Sympathetic Nervous System (SNS) is part of the peripheral nervous system and makes up one half of the autonomic nervous system. The SNS is aids in control of the most of the body's internal organs. The SNS is known for allowing the body to function under stress in what is known as the fight or flight response.

There are two types of neurons involved in the transmission of any signal through the sympathetic system: pre-ganglionic and post-ganglionic. The shorter preganglionic neurons originate from the thoracolumbar region of the cord specifically at T1 to L2 and L3, and travel to a ganglion, often one of the paravertebral ganglia, where they synapse with a postganglionic neuron and the long postganglionic neurons extend across most of the body.

Table 11.1: Sympathetic Distribution

Organ	Function
Eye	Pupil dilation
Heart	Increasing heart rate and the force of contraction
Lungs	Dilates the bronchioles
Adrenal Glands	Increases circulating amounts of adrenaline in the blood
Muscles	Increases blood flow to skeletal muscles
Stomach and Intestines	Slows motility through the gut
Skin	Activates sweat glands

At the synapses within the ganglia, preganglionic neurons release acetylcholine, a neurotransmitter that activates nicotinic acetylcholine receptors on postganglionic neurons. In response to this stimulus, the postganglionic neurons release norepinephrine, which

activates adrenergic receptors that are present on the peripheral target tissues. The activation of target tissue receptors causes the effects associated with the sympathetic system.

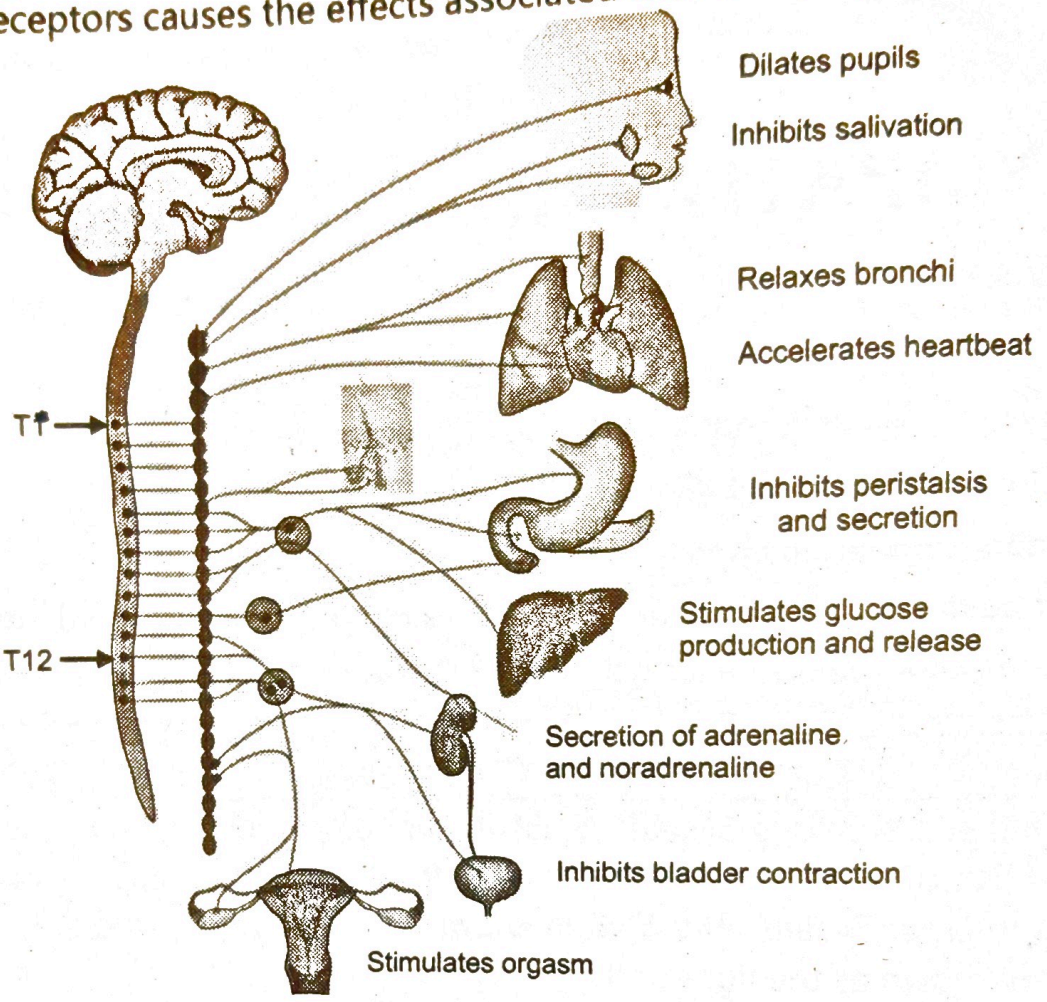
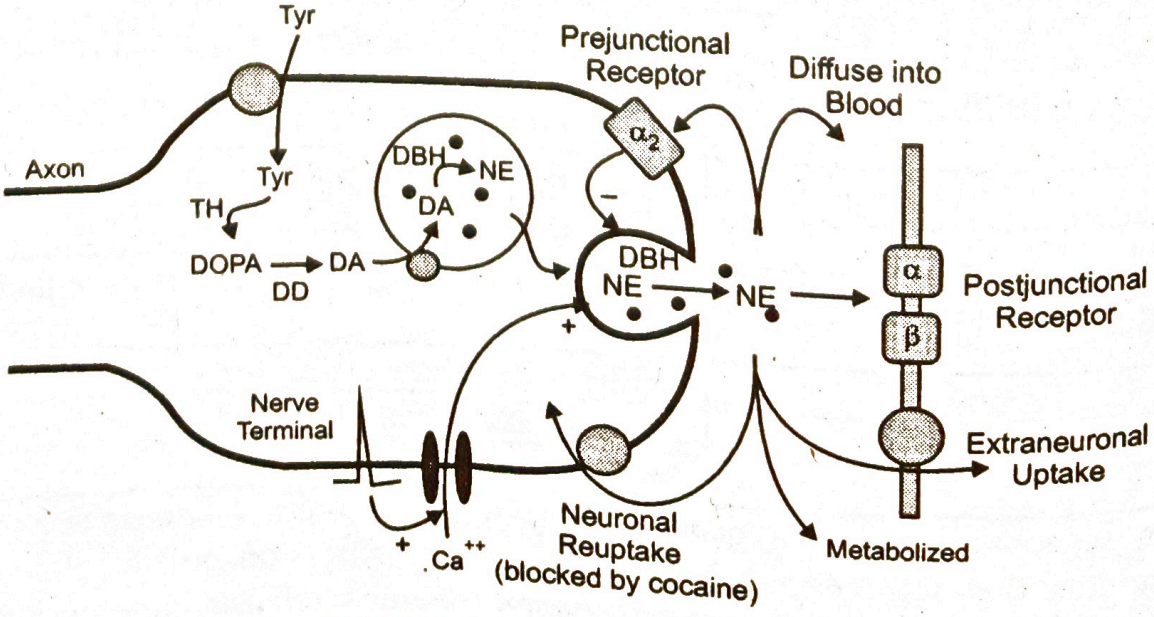


Fig. 11.1: Sympathetic Nervous system

Adrenergic Transmission: Norepinephrine (NE) is the primary neurotransmitter for postganglionic sympathetic adrenergic nerves. It is synthesized inside the nerve axon, stored within vesicles, and then released by the nerve when an action potential travels down the nerve.



Tyr = tyrosine; TH = tyrosine hydroxylase DD = DOPA decarboxylase; DA = dopamine; DBH = dopamine β - hydroxylase; NE = norepinephrine

Fig. 11.2: Adrenergic Transmission

(a) Synthesis of Norepinephrine:

1. The amino acid tyrosine is transported into the sympathetic nerve axon.
2. Tyrosine (Tyr) is converted to DOPA by tyrosine hydroxylase (rate-limiting step for NE synthesis).
3. DOPA is converted to dopamine (DA) by DOPA decarboxylase.
4. Dopamine is transported into vesicles then converted to norepinephrine (NE) by dopamine β-hydroxylase (DBH); transport into the vesicle can be blocked by the drug reserpine.
5. An action potential traveling down the axon depolarizes the membrane and causes calcium to enter the axon.
6. Increased intracellular calcium causes the vesicles to migrate to the axonal membrane and fuse with the membrane, which permits the NE to diffuse out of the vesicle into the extracellular (junctional) space. DBH, and depending on the nerve other secondary neurotransmitters (e.g., ATP), is released along with the NE.
7. The NE binds to the postjunctional receptor and stimulates the effector organ response.

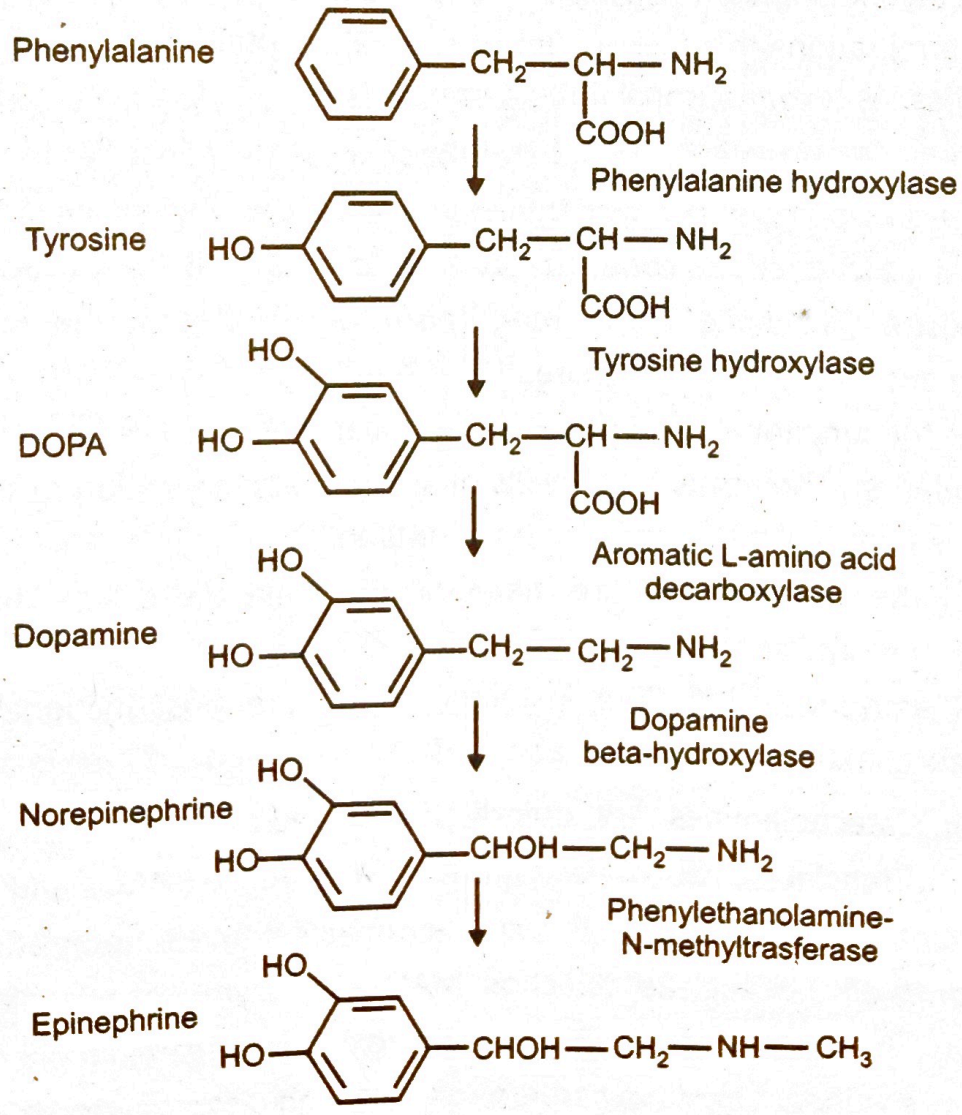


Fig. 11.3: Synthesis of Noradrenaline

(b) Epinephrine synthesis:

Epinephrine is synthesized from norepinephrine within the adrenal medulla, which are small glands associated with the kidneys. Preganglionic fibres of the sympathetic nervous system synapse within the adrenals. Activation of these preganglionic fibres releases acetylcholine, which binds to postjunctional nicotinic receptors in the tissue. This leads to stimulation of NE synthesis within adenomedullary cells, but unlike sympathetic neurons, there is an additional enzyme (phenylethanolamine-N-methyltransferase) that adds a methyl group to the NE molecule to form epinephrine. The epinephrine is released into the blood perfusing the glands and carried throughout the body.

Norepinephrine and Epinephrine Removal and Metabolism: The binding of NE to its receptor depends on the concentration of NE in the vicinity of the receptor. If the nerve stops releasing NE, then the NE concentration in the junctional cleft will decrease and NE will leave the receptor. There are several mechanisms by which the norepinephrine is removed from the intercellular (junctional) space and therefore from the postjunctional receptor:

Reuptake: Catecholamines released by adrenergic terminations are mainly reuptake in the adrenergic terminations themselves, (intraneuronal reuptake or uptake 1) and to a lesser extent by other tissues (extraneuronal uptake or uptake 2).

1. Most (90%) of the NE is transported back into the nerve terminal by a neuronal reuptake transport system. This transporter is blocked by cocaine; therefore, cocaine increases junctional NE concentrations by blocking its reuptake and subsequent metabolism. (This is a major mechanism by which cocaine stimulates cardiac function and raises blood pressure.)
2. Some of the junctional NE diffuses into capillaries and is carried out of the tissue by the circulation. Therefore, high levels of sympathetic activation in the body increase the plasma concentration of NE and its metabolites.
3. Some of the junctional NE are metabolized within the extracellular space before reaching the capillaries.
4. A small amount of NE (5%) is taken up by the postjunctional tissue (termed "extraneuronal uptake") and metabolized.

Metabolism: Catecholamines are quickly inactivated, metabolized by the enzymes catechol-oxymethyltransferase (COMT) and monoamine oxidase (MAO), and by neuronal and extraneuronal reuptakes. COMT, primarily extraneuronal, catalyzes methylation of one of the two oxygen atoms of the nucleus catechol. MAO an enzyme group present inside the neurons, but also in plasma, which catalyzes the oxidative deamination of monoamines: adrenaline, noradrenaline, dopamine, serotonin. COMT inhibitors reinforce and prolong the effects of catecholamines. Inhibitors of monoamine oxidase (MAOI) inhibit this reaction and

the content of monoamines in tissues rises. MAO inhibitors are used as antiparkinsonians and antidepressants. The final product of these pathways is vanillylmandelic acid (VMA).

Vanillymandelic acid along with its precursors normetanephrine and metanephrine, is measured in urine and plasma in the diagnosis of pheochromocytoma, which can cause severe hypertension and cardiac arrhythmias.

11.2 ADRENERGIC RECEPTOR

Adrenergic receptors are membrane bound G-Protein coupled receptors which function primarily by increasing or decreasing the intracellular production of second messengers cAMP or IP3/DAG. In some cases, the activated G-Protein itself operates K^+ or Ca^{+2} channels, or increases prostaglandin production.

In 1948, adrenoceptors were first divided into two major types, α and β, based on their pharmacological characteristics (i.e., rank order of potency of agonists). Subsequently, both α and β types were subdivided into α_1, α_2, β_1 and β_2 subtypes. Based on both pharmacological and molecular evidence, it is now clear that a more useful classification scheme is based on three major types: α_1, α and β - each of which is further divided into at least three subtypes.

Table 11.2: Alpha Adrenergic Receptors and Their Effector Systems

	α_1	α_2
Location	Post-junctional effector organs (Blood vessels of skin and mucous membrane, pilomotor muscle and sweat gland, radial muscles of iris)	Pre-junctional on nerve ending
Effect	Vasoconstriction, increases glandular secretion, radial muscle of iris contraction, GUT relaxation, glycogenolysis	Inhibition of transmitter release, vasoconstriction platelet aggreagation
Effector pathways	Increases Phospholipase C	Inhibition of Adenylcyclase, decreases cAMP
Selective agonist	Phenylephrine, Methoxamine	Clonidine
Selective antagonist	Prazosin	Yohimbine Rawwolscine

- ***Alpha-1 Receptors:*** These are located on postjunctional effector organs and activates Phospholipase C (IP3 + DAG) pathways. Stimulation of postsynaptic alpha-1 receptors

results primarily in vasoconstriction, uterine contractions, platelet aggregation, mydriasis and contraction of the urethral sphincter.

- ***Alpha-2 Receptors*:** Alpha-2 receptors are mainly presynaptic and their stimulation results in a decrease of noradrenaline release. There are however postsynaptic alpha-2 receptors whose stimulation induces platelet aggregation and decreases insulin release *(Adenylcyclase inhibition, K^+ channel opening)*
- ***Beta-1 receptors*:** Beta-1 receptors are postsynaptic and localized primarily in the heart *(Adenylcyclase activation)*. Their stimulation results in a positive inotropic effect (increase of the strength of contractions), positive chronotropic effect (rate acceleration), positive dromotropic effect (conduction acceleration) and positive bathmotropic effect (increase of excitability).
- ***Beta-2 receptors*:** Beta-2 receptors are primarily postsynaptic. Their stimulation induces vasodilation, bronchodilatation, uterus relaxation and cardiac stimulation which is less important than that induced by beta-1 stimulation *(Adenylcyclase activation)*. It is estimated that the distribution of beta receptors in heart is approximately 80% of beta-1 receptors and 20% of beta-2 receptors. The stimulation of beta-2 receptors increases potassium uptake by muscles, which can lead to a decrease of its plasma concentration.
- ***Postsynaptic beta-3 receptors:*** These are present in adipocytes, by activation adenylcyclase, induce cAMP formation, lipolysis and stimulation of mitochondrial respiration with dissipation of heat. Certain obese patients could have a deficiency of beta-3 lipolyticactivity and the use of bêta-3 agonists in the treatment of obesity is considered.

Table 11.3: Beta Adrenergic Receptors and their Effector Systems

	β_1	β_2	β_3
Location	Heart, JG cells of Kidney	Bronchi, blood vessels, uterus, GIT, urinary tract	Adipose tissue
Effect	Increase Heart Rate, Cardiac out and force of contraction	Bronchodilations, vasodilation, uterine contraction	Lipolysis
Effector pathways	Increases Adenylcyclase, Opens L-type Ca^{2+} channels	Increases Adenylcyclase	Increases Adenylcyclase
Selective agonist	Dobutamine	Salbutamol, Terbutaline	α-Methyl propranolol
Selective antagonist	Metoprolol, Atenolol	BRL 37344	

Sympathomimetics: Sympathomimetics are a substance that mimic or modify the actions of endogenous catecholamines of the system. It is also called as adrenergic agents. Direct agonists directly activate adrenoceptors, while indirect agonists enhance the actions of endogenous catecholamines. α, β, and dopamine (D) receptors are stimulated in various target tissues such as the eyes, heart, and vascular smooth muscle. The clinical indications for sympathomimetics are broad and include asthma, heart failure, shock, and anaphylaxis. Side effects include hypertension, sinus tachycardia, and skeletal muscle tremor.

Most of the actions of catecholamines and sympathomimetic agents can be classified into seven broad types:

1. A peripheral excitatory action on certain types of smooth muscle, such as those in blood vessels supplying skin, kidney and mucous membrane, and on gland cells, such as those in salivary and sweat glands.
2. A peripheral inhibitory action on certain other types of smooth muscle, such as those in the wall of the gut, in the bronchial tree and in blood vessels supplying skeletal muscle.
3. A cardiac excitatory action, responsible for an increase in heart rate and force of contraction.
4. Metabolic actions, such as an increase in rate of glycogenolysis in liver and muscle and liberation of free fatty acids from adipose tissue.
5. Endocrine actions, such as modulation of the secretion of insulin, renin and pituitary hormones.
6. Central nervous system actions, such as respiratory stimulation and with some of the drugs an increase in wakefulness and psychomotor activity and a reduction in appetite.
7. Presynaptic actions that result in either inhibition or facilitation of the release of neurotransmitter such as norepinephrine and acetylcholine.

11.2.1 Classification of Adrenergic Agents

Adrenergic agents classified on the basis of actions are as follows:

(A) Direct acting Sympathomimetics:

They act directly as agonists on adrenergic receptor. E.g. Adrenaline, noradrenaline, isoprenaline, pheynylephrine, methoxamine, xylometazoline, salbutamol etc.

(a) Alpha agonist:

(i) Non-selective: Epinephrine, Norepinephrine.

(ii) Selective:

1. **Alpha-1 agonist:** Phenylephrine.
2. **Alpha-2 agonist:** Clonidine, Guafacine, Guanabenz, Detomidine, Romifidine, Medetomidine.

(b) Beta agonists:

(i) **Non-selective:** Isoproterenol, Epinephrine.

(ii) **Selective:**

1. **Beta-1 agonist:** Dobutamine.
2. **Beta-2 agonist:** Terbutaline, Salbutamol, Mitaproterenol, Ritodrine.

(B) Indirect Acting Sympathomimetics:

These act on adrenergic neurons to release noradrenaline which then act on adrenoceptors. E.g. Tyramine.

(C) Mixed Acting Sympathomimetics:

They act directly as well as indirectly. E.g. Ephedrine, amphetamine, mephentermine.

These drugs can also be divided according to their chemical structures into two broad groups:

(a) **Catecholamines:** Catecholamines are the drugs which have catechol nucleus in their structures. Compounds with OH substitution in the 3 and 4 positions of the benzene ring. E.g. Epinephrine, Norepinephrine, Dopamine, Isoprenaline.

(b) **Non-catecholamines:** Compounds which lack the hydroxyl group (OH). E.g. Phenylephrine, Ephedrine, Amphetamine, Methamophetamine, Metaramiol, Tyramine.

Catecholamines: The catecholamines include the sympathetic Neurohumoral transmitters noradrenaline and dopamine, adrenaline, isoprenaline.

Adrenaline (Epinephrine):

Epinephrine (adrenaline) acts strongly on both α and β adrenoceptors. Its pharmacological effects depend on the concentration and the type and number of available receptors; generally, it has more affinity for β receptors. So, at lower concentration, β effect predominates. But if the number of α receptor is more in an organ (e.g., blood vessels), higher concentration of epinephrine will produce α-mediated action.

Mechanism of Action: Adrenaline produces their action by direct combination with receptors located on the cell membrane. The outcome of this drug receptor combination is either an increase (excitation) or a decrease (inhibition) in the tissue activity. α-receptor stimulation is believed to be mainly responsible for excitatory effects of the catecholamines and they can be completely blocked by ergotoxine; Beta receptor stimulation usually produces inhibitory effects and these are not blocked by ergotoxine.

11.2.2 Pharmacological Action

Cardiovascular system:

(a) **On Blood Vessels:** Epinephrine mainly acts on small arterioles and precapillary sphinctors. It also exerts its action, to some extent, on veins and large arteries. It causes constriction of cutaneous, renal, pulmonary, arterial and venous, and other visceral blood vessels because of the presence of predominant α receptors.

Epinephrine dilates blood vessels of skeletal muscles (at low doses), coronary and liver and this is mediated by powerful β_2 receptors. At higher dose, it causes vasoconstriction in skeletal muscle.

(b) **On Heart:** The direct β_1 receptor mediated actions of epinephrine are positive chronotropic (increased heart rate) and ionotropic (increased force of contraction) effect on heart, increased cardiac output, myocardial contractility, coronary blood flow and so oxygen consumption by heart. The conduction velocity through A-V node, bundle of His, parkinje fibre, atrias and ventricular fibres is increased by epinephrine to cause the above responses.

(c) **On Blood Pressure (B.P):** At lower concentration slow I.V. infusion or S.C. injection of epinephrine causes fall in peripheral resistance because vascular β_2 receptors are more sensitive than α receptors. Higher dose or rapid I.V. infusion produces marked increase in systolic as well as diastolic B.P. (as the number of a receptors are more than β_2 receptors in blood vessels), which is followed by a fall in the mean B.P. (because when the epinephrine concentration is reduced by degradation, rest of the amount remain attached on more sensitive β_2 receptors). This is called as biphasic response of epinephrine on blood pressure.

Dale's Reversal Phenomenon or Epinephrine Reversal: Scientist Dale first recorded that the contractile effect of epinephrine on blood vessel was reversed by the presence of an α receptor blocker, ergot. Epinephrine causes increase, which is followed by decrease, in B.P. The drug is having more affinity for β_2 receptors than α receptors. The rise, in B.P. is mediated by α-receptors as these are more in number than more powerful and sensitive β2 receptors in blood vessels. Here though the β_2 receptors are also occupied by the drug, their effect is suppressed by the activation of large number of α receptors. As the concentration of epinephrine is decreased by metabolism or elimination, it dissociates first from the less sensitive α receptors. So, at later stage, the number of activated β_2 receptors remains more than the activated α-receptors which causes decrease in B.P. The presence of α receptor blocker like phenoxybenzamine or ergotamine renders the blockade of α receptors on blood vessels and inhibits the rising phase of the epinephrine-induced B.P. But the β_2 receptors-mediated action (fall in B.P.) predominates even at higher concentration of the drug as their suppressors (α receptors) are blocked. As the effect of epinephrine is reversed by the presence of α blockers and this was first observed by Dale, the phenomenon is called as Dale's reversal phenomenon.

Effects on Smooth Muscle:

(a) **GIT:** The GIT smooth muscle is relaxed by epinephrine. This effect is mediated by both α_1 and β_2 receptors on effector cells.

(b) **Bronchial smooth muscle relaxes:** (β_2 receptors activation → cAMP ↑).

Respiration: Besides being a bronchodilator adrenaline is a weak stimulant of respiration. Given intravenously in man can induce apnoea partly by stimulation the baroreceptors and partly by a direct central action. Adrenaline particularly in aerosol form, constricts the pulmonary vessel and relieves bronchial congestion this results in an increase in the vital capacity.

Uterus: On the uterus, its action varies according to the species, stage of gestation and sexual cycle. In cat, epinephrine relaxes (via. β_2 receptors) non-gravid uterus but contracts (via. α_1 receptors) gravid uterus. In rabbits, both gravid and non-gravid uterus is contracted by epinephrine. In rats, both uterus are relaxed. The non-pregnant uterus of human is contracted and pregnant one is relaxed (at term) by the drug.

Species	Non-pregnant	Pregnant
Rat	Relaxation	Relaxation
Rabbit	Contraction	Contraction
Cat	Relaxation	Contraction
Human	Contraction	Relaxation

Urinary Bladder: Epinephrine relaxes detrusor muscle (β_2 receptors) and contracts the trigone and sphinctor muscles (α receptors) of the bladder.

Effect on Metabolism: Epinephrine stimulates glycogenolysis (β_2 mediated) in liver and muscle, causes inhibition of insulin secretion (α mediated) and increases free fatty acids in blood (β_1 mediated $\rightarrow$ activation of triglyceride lipase $\rightarrow$ breakdown of triglycerides into free fatty acids and glycerol).

Effect on Eye: Mydriasis occurs due to contraction of radial muscles (α_1 receptors) of iris by epinephrine. The intraoccular pressure falls, specially in wide angle glaucoma, due to relaxation of ciliary muscle (β_2 receptors).

Effect on Skeletal Muscle: Epinephrine does not directly excite skeletal muscle but facilitates neuromuscular transmission through the activation of α and β_2 receptors of somatic Moto neurons releasing Ach rapidly. The twitch tension of white muscle (fast contracting fibres) is increased. Whereas that of red muscle (slow fibres) is reduced. Other β_2 agonists (e.g. salbutamol) may also act similarly.

Effect on CNS: Being polar compound, epinephrine cannot enter into the CNS, but restlessness, apprehension, headache and tremor may occur due to its secondary to some peripheral effects on CNS, skeletal muscles, and intermediary metabolism.

Absorption, fate and Excretion: Catecholamines are not administered orally because of their rapid inactivation in the gut and the liver. On inhalation of adrenaline or isoprenaline aerosols, small quantities may be absorbed in the systemic circulation.

Adrenaline is metabolized by Catechol-O-Methyl transferase (COMT) located extracellular and Monoamine oxidase (MAO) situated inside the mitochondria of the adrenergic neuron. A small quantity of catecholamines is excreted unchanged.

Adverse Reaction: These are mostly cardiovascular and are due to extension of the pharmacological actions. Adrenaline, given subcutaneously, may produce palpitation and tremors. Adrenaline rapidly injected, intravenously, may cause a sudden marked increase in blood pressure

Preparation: Adrenaline injection 0.5 or 1 ml. ampoules containing 1 : 1000 adrenaline. Adrenaline inhalation is a non-sterile 1 : 1000 solution of adrenaline tartrate. Adrenaline injection (BAIF, 180 pg/0.1 ml).D ógs - 0.1 to 0.3 ml, I.V. injection.

Other Adrenergic Drugs:

Norepinephrine (Levarterenol): It is pharmacologically equipotent to epinephrine in respect of its action on β_1-receptors, but very less potent on β_2 receptors. Norepinephrine is

a potent agonist of α receptors. However, it is less potent than epinephrine on these (α) receptors.

Isoproterenol (Isoprenaline): Like epinephrine and norepinephrine, isoproterenol is also ineffective orally. It acts most entirely on β receptors and has very little effect on α receptors. It increases the heart rate and force of contraction (β_1 mediated), reduces blood pressure (β_2 mediated), relaxes smooth muscle (β_2, mainly bronchial and GIT) and stimulates insulin secretion (β_2 mediated).

Pharmacological actions: Its main actions are on the heart, skeletal muscle vasculature and smooth muscles.

- It stimulates the heart and causes tachycardia.
- It lowers the peripheral vascular resistance in skeletal, renal and mesenteric vascular beds and produces a fall mainly in the diastolic pressure. This fall in blood pressure is antagonized by its powerful cardiac stimulant action.
- The systolic blood pressure may be raised or shows only a negligible fall while the diastolic blood pressure usually reduced.
- Therapeutic doses do not affect the pulmonary arterial pressure.
- It relaxes the smooth muscles particularly those of bronchi and gastrointestinal tract.

Absorption, fate and excretion: Isoprenaline is inconsistently absorbed on sublingual or oral administration. Absorption is quicker after intramuscular injection and by inhalation. It is rapidly inactivated by uptake into tissue and metabolised by COMT. Hence, its action is short lasting, given orally it is less effective.

Adverse reactions: It can cause palpitation, tachycardia, arrhythmias, angina pain, headache and flushing. Combined isoprenaline adrenaline administration in bronchial asthma may prove fatal. The incidence of toxic manifestations is less with inhalation than after sublingual administration.

Preparation and dosage:

- Isoprenaline tablet contains 10 mg of isoprenaline sulphate.
  Dose: 5 to 20 mg sublingually.
- Isoprenaline hydrochloride for inhalation is available as 1 : 100 and 1 : 200 solution in normal saline. Dose 0.5 ml of 1 : 200 solutions.

Dopamine: Dopamine, a sympathomimetic amine vasopressor, is the naturally occurring immediate precursor of norepinephrine. Dopamine hydrochloride is a white to off-white crystalline powder, which may have a slight odor of hydrochloric acid. It is freely soluble in water and soluble in alcohol. Dopamine HCl is sensitive to alkalies, iron salts, and oxidizing agents. Dopamine HCl is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarction, trauma, endotoxic septicaemia, open-heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Dobutamine: A derivative of dopamine, but not a D_1 or D_2 receptor agonist. Though it acts on both α and β adrenergic receptors, the only prominent action of clinically employed doses is increases in force of cardiac contraction and output, without significant change in heart rate, peripheral resistance and blood pressure. As such it has been considered to be a

relatively selective β_1 agonist. It is used as an inotropic agent in pump failure accompanying myocardial infarction, cardiac surgery and for short term management of severe congestive heart failure.

Therapeutic classification of Adrenergic Drugs:

(a) **Adrenergic drugs used for raising blood pressure** E.g. Noradrenaline, Phenylephrine, Ephedrine, Methoxamine, Dopamine, Mephentermine.

(b) **Those used for their inotropic actions of the heart:** E.g. Dopamine, Dobutamine, Isoprenaline, Adrenaline.

(c) **Those used for CNS stimulation:** E.g. Amphetamine, Methamphetamine, Dexamphetamine.

(d) **Those used for bronchodilations:** E.g. Adrenaline, Terbutaline, Isoprenaline, Salmeterol, Salbutamol, Formoterol etc.

(e) **Those used as Nasal decongestants** E.g. Phenylephrine, Naphazoline, Xylometazoline, Pseudoephedrine, Oxymetazoline, Phenylpropanolamine.

(f) **Those used for suppressing the appetite.** E.g. Fenfluramine, Phenteramine, Dexfenfluramine.

(g) **Those used in allergic reactions:** E.g. Adrenaline, Ephedrine.

(h) **Uterine relaxant and vasodilators:** E.g. Ritodrine, Salbutamol, Terbutaline.

11.3 NON-CATECHOLAMINES

The sympathomimetic amines devoid of the catechol nucleus comprise compounds like ephedrine, amphetamine and other vasopressors as well as smooth muscle relaxing compounds.

1. They release noradrenaline and/or dopamine from the sympathetic neurones. This indirect action produces effects mainly resembling those of externally administered noradrenaline.
2. They act as partial agonists of noradrenaline and are capable of directly stimulating the adrenergic alpha and/or beta receptors. This explains the relaxation of the bronchial smooth muscle by ephedrine, of uterine smooth muscle by nylidrin, and stimulation of the myocardium by mephentermine.

They are effective orally. Compared to catecholamines, they have longer duration of actions as they are relatively resistant to the action MAO. They cross the blood brain barrier and therefore have significant CNS effects.

Ephedrine: Ephedrine is an alkaloid obtained from plants of the genus ephedra.

Adrenergic drugs are divided into catecholamines and non-catecholamines. The difference between catecholamine and non-catecholamines is follows:

Table 11.4: The difference between catecholamine and non-catecholamines

Catecholamines	Non-catecholamines
1. Contain hydroxyl groups at positions 3 and 4 on the benzene ring.	1. Lack one or both hydroxyl groups on benzene ring.
2. Mainly have direct action. Few compounds may have mixed action (like dopamine).	2. Mainly have indirect or mixed actions and few may have direct action (like phenylephrine).
3. Have high affinity for α and/or β receptors.	3. Have moderate to poor affinity for adrenoceptors.
4. Usually have shorter half-life because of their rapid metabolism	4. Have moderate to longer half-life as these are degraded slowly.
5. Metabolised mainly by MAO or COMT.	5. Poor substrates for MAO and resistant to COMT.
6. Usually not effective by oral route and are given parenterally.	6. Most of the drugs are effective orally.
7. Being polar drugs, poorly penetrate the CNS and hence have minimal effect on CNS.	7. Easily pass blood brain barrier and produce significant CNS effects.
8. Effects are produced even after adrenergic denervation.	8. Loose activity following adrenergic denervation.
9. No development of tolerance.	9. Tolerance develops following repeated administration.

Table 11.5: Clinical Uses of Adrenergic Drugs

Therapeutic Uses	Drug
Cardiovascular System: • Cardiac arrest. • Cardiogenic shock. • Heart block (A-V block).	Adrenaline. Dobutamine, Dopamine. Isoproterenol.
Anaphylactic reactions or type I hypersensitivity.	Adrenaline.
Miscellaneous uses • Local anaesthetic to prolong the action. • Bronchial asthma. • As decongestant (allergic rhinitis). • Ophthalmic use (to dilate pupil).	Adrenaline (vasoconstrictor agent). Epinephrine, Isoproterenol, Salbutamol. Epinephrine. Ephedrine, Phenylephrine.

QUESTIONS

1. What are adrenergic agents?
2. Write the biosynthetic pathways for synthesis of epinephrine.
3. Enlist the adrenoceptor with their location.
4. Write the therapeutic uses of adrenaline.
5. Classify sympathomimetic agents.
6. Write the pharmacological account of adrenaline.
7. Write the dales vasomotor reversal phenomena.
8. Write the neither pharmacological account of nor epinephrine.

***