Adrenergic Agonists

Adrenergic drugs are medications that stimulate adrenoreceptors in your body. This type of drugs is termed as sympathomimetics whilst the drugs that block the activation of adrenergic receptors are termed sympatholytic (adrenergic antagonists). Some of sympathomimetics can directly activate adrenergic receptors (direct-acting agonists), while others act indirectly by enhancing release or blocking reuptake of norepinephrine (indirect-acting agonists). Adrenergic agonists drugs are used in many life-threatening conditions, including cardiac arrest, shock, asthma attack, or allergic reaction.

Adrenergic neurons release norepinephrine (noradrenaline, NE) as the primary neurotransmitter. These neurons are found in the central nervous system (CNS) and also in the sympathetic nervous system, where they serve as links between ganglia and the effector organs. Adrenergic drugs act on adrenergic receptors, located either presynaptically on the neuron or postsynaptically on the effector organ (figure1).

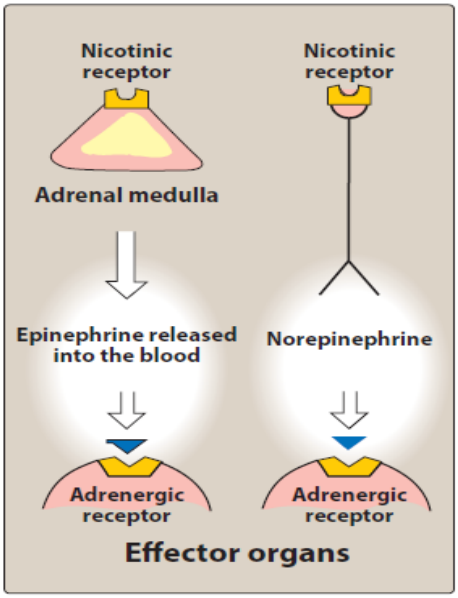


Figure1: Sites of actions of adrenergic agonists.

Neurotransmission at adrenergic neurons

Neurotransmission in adrenergic neurons is very similar to what was described for the cholinergic neurons, except that NE is the neurotransmitter instead of acetylcholine.

Neurotransmission involves the following steps: synthesis, storage, release, and receptor binding of norepinephrine, followed by removal of the neurotransmitter from the synaptic gap.

1- Synthesis of norepinephrine: After transporting the Tyrosine by a carrier to the adrenergic neuron, it will be hydroxylated to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. This is considered the rate-limiting step in the formation of NE. DOPA is then decarboxylated by the enzyme aromatic I-amino acid decarboxylase to form dopamine in the presynaptic neuron (figure 2).

2- Storage of norepinephrine in vesicles

After dopamine synthesis, the amine transporter system transports the dopamine into synaptic vesicles. **This carrier system is blocked by reserpine**. Dopamine is next hydroxylated to form norepinephrine by the enzyme dopamine β-hydroxylase (figure 2).

3- Release of norepinephrine: The release of NE starts after arriving of an action potential at the nerve junction that leads to trigger an influx of calcium ions from the extracellular fluid into the cytoplasm of the neuron. The increase in calcium causes synaptic vesicles to fuse with the cell membrane and to undergo exocytosis to expel their contents into the synapse (figure 2). **Drugs such as guanethidine block this release.**

4- Binding to receptors: Norepinephrine released from the synaptic vesicles diffuses into the synaptic space and binds to postsynaptic receptors on the effector organ or to presynaptic receptors on the nerve ending. Adrenergic receptors use both the cyclic adenosine monophosphate (cAMP) second messenger system and the phosphatidylinositol cycle to transduce the signal into an effect. Norepinephrine also binds to presynaptic receptors (mainly α2 subtype) that modulate the release of the neurotransmitter.

5- Removal of norepinephrine: Norepinephrine may:

1) Diffuse out of the synaptic space and enter the systemic circulation;

2) Be metabolised to inactive metabolites by catechol-O-methyltransferase (COMT) in the synaptic space or

3) Undergo reuptake back into the neuron.

The reuptake by the neuronal membrane involves a sodium-chloride (Na+/Cl-)-dependent norepinephrine transporter (NET) that can be inhibited by tricyclic antidepressants (TCAs), such as imipramine, by serotonin–norepinephrine reuptake inhibitors such as duloxetine, or by cocaine (figure 2). **Reuptake of norepinephrine into the presynaptic neuron is the primary mechanism for termination of its effects.**

6- Potential fates of recaptured norepinephrine: Once norepinephrine re-enters the adrenergic neuron, it may be taken up into synaptic vesicles via the amine transporter system and be sequestered for release by another action potential, or it may persist in a protected pool in the cytoplasm. Alternatively, norepinephrine can be oxidised by monoamine oxidase (MAO) present in neuronal mitochondria (figure 2).

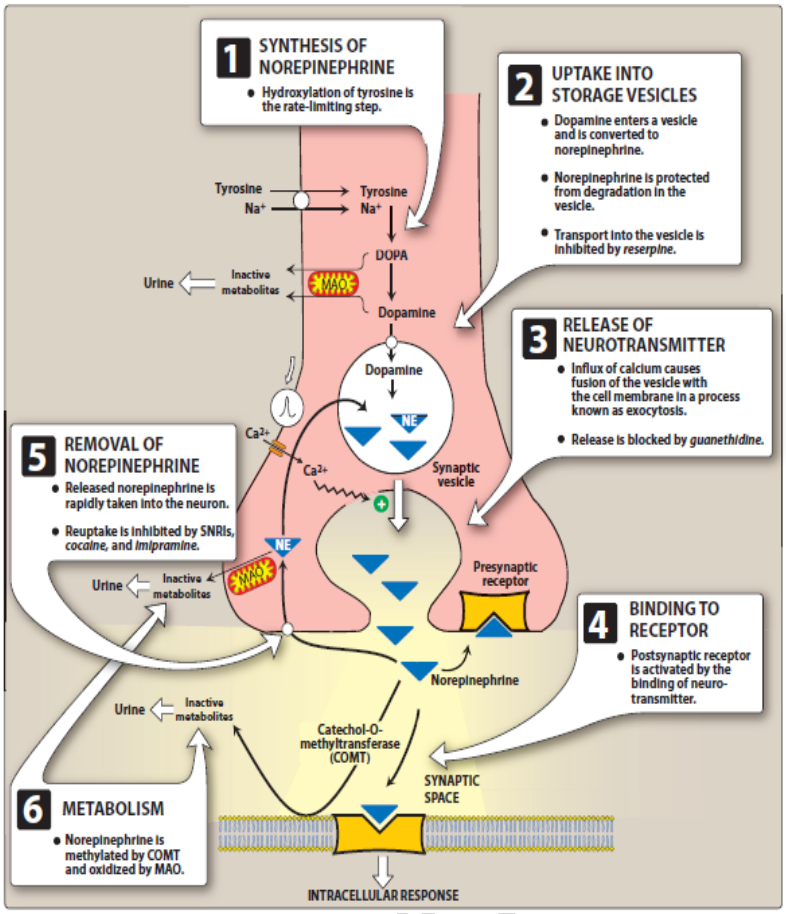


figure 2: Synthesis and release of norepinephrine from the adrenergic neuron. MAO = monoamine oxidase, SNRI = serotonin norepinephrine reuptake inhibitor.

Adrenergic receptors (adrenoceptors)

In the sympathetic nervous system, several classes of adrenoceptors can be distinguished pharmacologically. Two main families of receptors, designated α and β, are classified on the basis of their responses to the adrenergic agonists (epinephrine, norepinephrine, and isoproterenol). Each of these main receptor types has a number of specific receptor subtypes that have been identified.

1- **α-Adrenoceptors:** The α-adrenoceptors show a weak response to the synthetic agonist isoproterenol, but they are responsive to the naturally occurring catecholamines epinephrine and norepinephrine (figure 3). For α-receptors, the rank order of potency and affinity is epinephrine ≥ norepinephrine >> isoproterenol. The α-adrenoceptors are subdivided into two subgroups, α1 and α2, based on their affinities for α agonists and blocking drugs. For example, the α1 receptors have a higher affinity for phenylephrine than α2 receptors. Conversely, the drug clonidine selectively binds to α2 receptors and has less effect on α1 receptors.

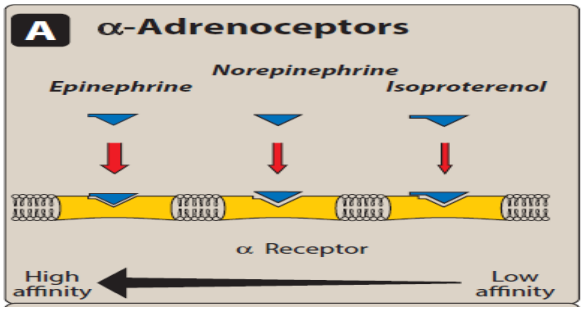


Figure 3: Affinities of α-Adrenoceptors for adrenergic agonists.

a- α1 Receptors: These receptors are present on the postsynaptic membrane of the effector organs and mediate many of the classic effects, originally designated as α-adrenergic, involving constriction of smooth muscle. Activation of α1 receptors initiates a series of reactions through the G protein activation of phospholipase C, ultimately resulting in the generation of second messengers inositol- 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). IP3 initiates the release of Ca2+ from the endoplasmic reticulum into the cytosol, and DAG turns on other proteins within the cell (figure 4).

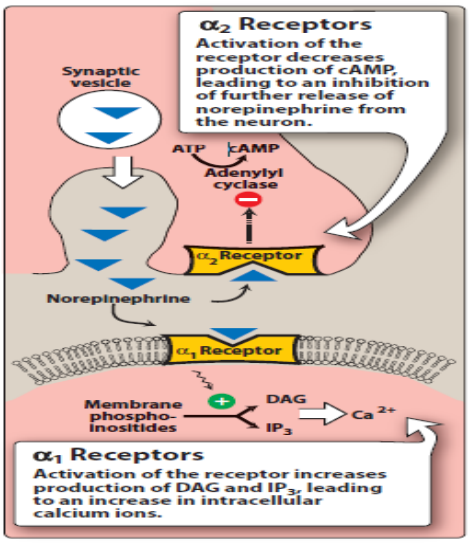


Figure 4: Second messengers mediate the effects of α receptors. DAG = diacylglycerol; IP3 = inositoln trisphosphate; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate.

b- α2 Receptors: These receptors are located primarily on sympathetic presynaptic nerve endings and control the release of norepinephrine. When a sympathetic adrenergic nerve is stimulated, a portion of the released norepinephrine "circles back" and reacts with α2 receptors on the presynaptic membrane (figure 4). Stimulation of α2 receptors causes feedback inhibition and inhibits further release of norepinephrine from the stimulated adrenergic neuron. This inhibitory action serves as a local mechanism for modulating norepinephrine output when there is high sympathetic activity. [Note: In this instance, by inhibiting further output of norepinephrine from the adrenergic neuron, these receptors are acting as

inhibitory autoreceptors.]. α2 receptors are also found on presynaptic parasympathetic neurons. Norepinephrine released from a presynaptic sympathetic neuron can diffuse to and interact with these receptors, inhibiting acetylcholine release. [Note: In these instances, these receptors are behaving as inhibitory heteroreceptors.] This is another mechanism to modulate autonomic activity in a given area. In contrast to α1 receptors, the effects of binding at α2 receptors are mediated by inhibition of adenylyl cyclase and by a fall in the levels of intracellular cAMP.

c- **Further subdivisions:** The α1 and α2 receptors are further divided into α1A, α1B, α1C, and α1D and into α2A, α2B, and α2C. This extended classification is necessary for understanding the selectivity of some drugs. For example, tamsulosin is a selective α1A antagonist that is used to treat benign prostatic hyperplasia. The drug has fewer cardiovascular side effects because it targets α1A subtype receptors found primarily in the urinary tract and prostate gland and does not affect the α1B subtype found in the blood vessels.

2. β-Adrenoceptors: Responses of β receptors differ from those of α receptors and are characterised by a strong response to isoproterenol, with less sensitivity to epinephrine and norepinephrine (figure 5). For β receptors, the rank order of potency is isoproterenol > epinephrine > norepinephrine. The β-adrenoceptors can be subdivided into three major subgroups, β1, β2, and β3, based on their affinities for adrenergic agonists and antagonists. β1 receptors have approximately equal affinities for epinephrine and norepinephrine, whereas β2 receptors have a higher affinity for epinephrine than for norepinephrine. Thus, tissues with a predominance of β2 receptors (such as the vasculature of skeletal muscle) are particularly responsive to the effects of circulating epinephrine released by the adrenal medulla. **β3** receptors are involved in lipolysis and also have effects on the detrusor muscle of the bladder. Binding of a neurotransmitter at any of the three types of β receptors results in activation of adenylyl cyclase and increased concentrations of cAMP within the cell.

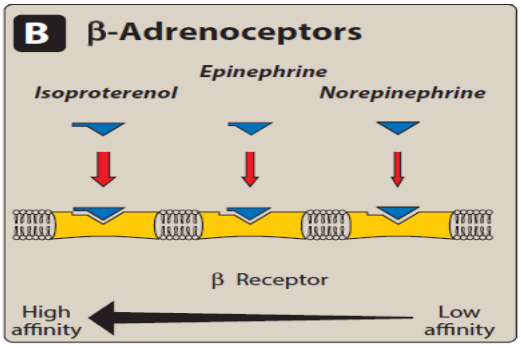


Figure 5: Affinities of ß-Adrenoceptors for adrenergic agonists.

The most prominent effects mediated by the adrenoceptors were summarised in figure 6. As a generalisation, stimulation of α1 receptors characteristically produces vasoconstriction (particularly in skin and abdominal viscera) and an increase in total

peripheral resistance and blood pressure. Stimulation of β1 receptors characteristically causes cardiac stimulation (increase in heart rate and contractility), whereas stimulation of β2 receptors produces vasodilation (in skeletal muscle vascular beds) and smooth muscle relaxation.

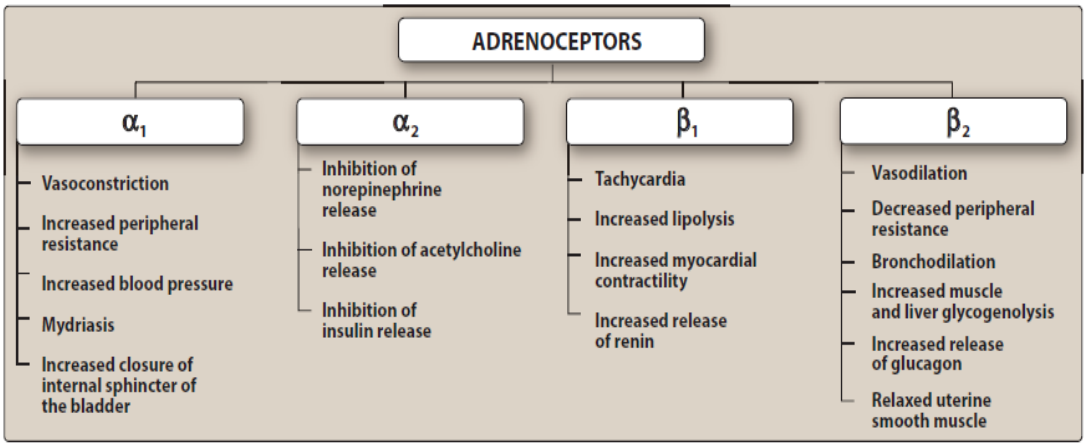


Figure 6: Major effects mediated by α- and β-adrenoceptors.

Desensitisation of receptors: Continuous exposure to the catecholamines reduces the responsiveness of these receptors, a phenomenon known as desensitisation. Three mechanisms have been suggested to explain this phenomenon:

1- Sequestration of the receptors so that they are unavailable for interaction with the ligand.
2- Down-regulation, that is, a disappearance of the receptors either by destruction or by decreased synthesis.
3- And an inability to couple to G protein, because the receptor has been phosphorylated on the cytoplasmic side.

CHARACTERISTICS OF ADRENERGIC AGONISTS

Most of the adrenergic drugs are derivatives of β-phenylethylamine (figure 7). Substitutions on the benzene ring or on the ethylamine side chains produce a variety of compounds with varying abilities to differentiate between α and β receptors and to penetrate the CNS. Two important structural features of these drugs are **1) the number and location of OH substitutions on the benzene ring and 2) the nature of the substituent on the amino nitrogen.**

The nature of the substituent on the amine nitrogen is important in determining β selectivity of the adrenergic agonist. For example, epinephrine, with a –CH3 substituent on the amine nitrogen, is more potent at β receptors than norepinephrine, which has an unsubstituted amine. Similarly, isoproterenol, which has an isopropyl substituent –CH (CH3)2 on the amine nitrogen (figure 7), is a strong β agonist with little α activity (figure 6).

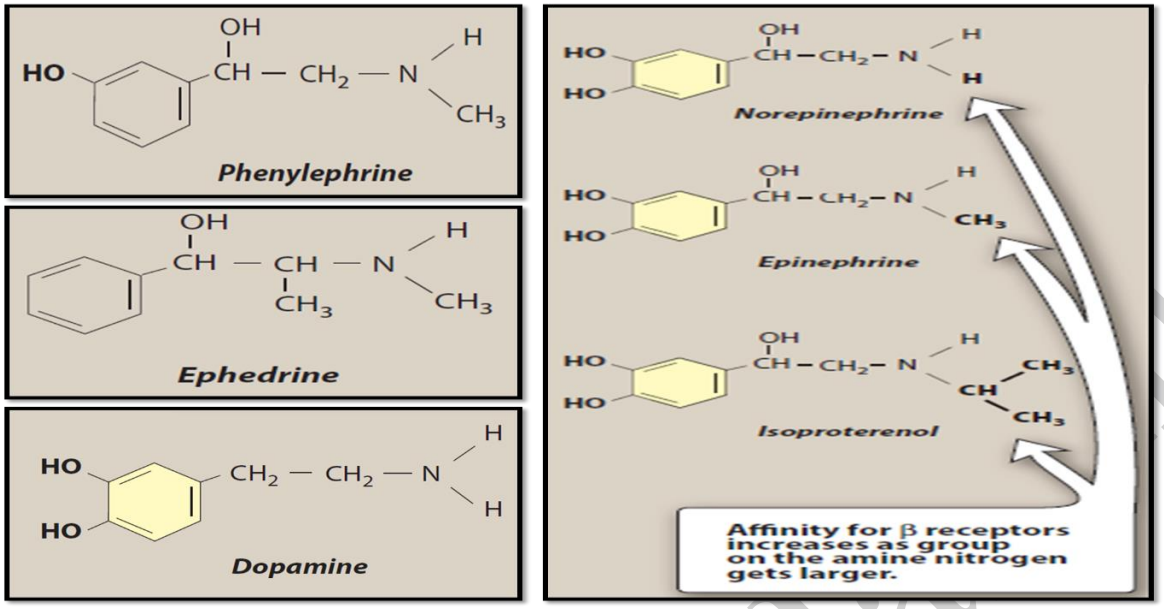


Figure 7: Structures of several important adrenergic agonists. Drugs containing the catechol ring are shown in yellow.

Catecholamines

Sympathomimetic amines that contain the 3,4-dihydroxybenzene group (such as epinephrine, norepinephrine, isoproterenol, and dopamine) are called catecholamines. These compounds share the following properties:

1. **High potency:** Catecholamines (with –OH groups in the 3 and 4 positions on the benzene ring) show the highest potency in directly activating α or β receptors.
2. **Rapid inactivation:** Catecholamines are metabolised by COMT postsynaptically and by MAO intraneuronally, as well as by COMT and MAO in the gut wall, and by MAO in the liver. Thus, catecholamines have only a brief period of action when given parenterally, and they are inactivated (ineffective) when administered orally.
3. **Poor penetration into the CNS:** Catecholamines are polar and, therefore, do not readily penetrate into the CNS. Nevertheless, most catecholamines have some clinical effects (anxiety, tremor, and headaches) that are attributable to action on the CNS.

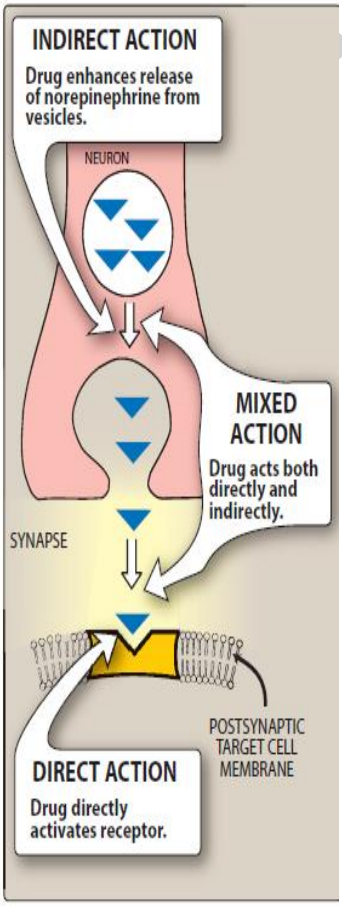
Noncatecholamines

Compounds lacking the catechol hydroxyl groups have longer half-lives, because they are not inactivated by COMT. These include phenylephrine, ephedrine, and amphetamine (figure 7). These agents are poor substrates for MAO (an important route of metabolism) and, thus, show a prolonged duration of action. Increased lipid solubility of many of the noncatecholamines (due to lack of polar hydroxyl groups) permits greater access to the CNS.

Adrenergic agonists classification:

Adrenergic agonists can be classified according to their mechanism of action to three types as demonstrated in table 1.

Table 1: Summary about the adrenergic agonist compounds.

Adrenergic agonists				
Type	**Stimulated receptors**	**Effect**	**Examples**	**Summary**
Direct-acting agonists	α **or** β	Producing effects similar to those that occur following stimulation of sympathetic nerves OR release of epinephrine from the adrenal medulla	Epinephrine, norepinephrine, isoproterenol, and phenylephrine.	
Indirect-acting agonists	α **or** β	These agents may block the reuptake of norepinephrine or cause the release of norepinephrine from the cytoplasmic pools or vesicles of the adrenergic neuron	Examples of reuptake inhibitors and agents that cause norepinephrine release include cocaine and amphetamines, respectively.	
Mixed-action agonists	α **or** β	They do not only release stored norepinephrine from nerve endings but also directly stimulate both α and β receptors.	Ephedrine and pseudoephedrine	

DIRECT-ACTING ADRENERGIC AGONISTS

Direct-acting agonists bind to adrenergic receptors on effector organs without interacting with the presynaptic neuron. As a group, these agents are widely used clinically.

Epinephrine

Epinephrine is one of the four catecholamines (epinephrine, norepinephrine, dopamine, and dobutamine) commonly used in therapy. The first three are naturally occurring neurotransmitters, and the latter is a synthetic compound. In the adrenal

medulla, norepinephrine is methylated to yield epinephrine, which is stored in chromaffin cells along with norepinephrine. On stimulation, the adrenal medulla releases about 80% epinephrine and 20% norepinephrine directly into the circulation. Epinephrine interacts with both α and β receptors. At low doses, β effects (vasodilation) on the vascular system predominate, whereas at high doses, α effects (vasoconstriction) are the strongest.

Epinephrine actions:

A- Cardiovascular: The major actions of epinephrine are on the cardiovascular system as It strengthens the contractility of the myocardium (positive inotrope: β_1 action) and increases its rate of contraction (positive chronotrope: β_1 **action**) hence cardiac output increases.

2- It activates β_1 **receptors** on the kidney to cause renin release. Renin is an enzyme involved in the production of angiotensin II, a potent vasoconstrictor.

3- Epinephrine constricts arterioles in the skin, mucous membranes, and viscera (α **effects),** and it dilates vessels going to the liver and skeletal muscle (β_2 **effects**). Renal blood flow is decreased. Therefore, the cumulative effect is an increase in systolic blood pressure, coupled with a slight decrease in diastolic pressure due to β_2 receptor–mediated vasodilation in the skeletal muscle vascular bed (figure 8).

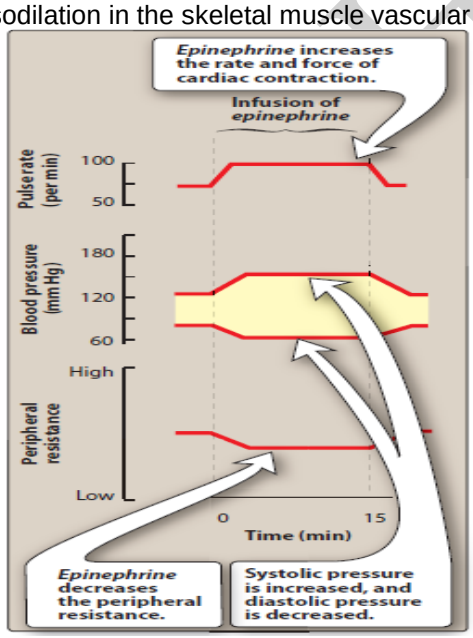


Figure 8: Cardiovascular effects of intravenous infusion of low doses of epinephrine.

B- Respiratory: Epinephrine causes powerful bronchodilation by acting directly on bronchial smooth muscle (**β2 action**). It also inhibits the release of allergy mediators such as histamines from mast cells.

C- Hyperglycemia: Epinephrine has a significant hyperglycaemic effect because of increased glycogenolysis in the liver (**β2 effect**), increased release of glucagon (**β2 effect**), and a decreased release of insulin (**α2 effect**).

D. Lipolysis: Epinephrine initiates lipolysis through agonist activity on the **β receptors of adipose tissue**. Increased levels of cAMP stimulate a hormone-sensitive lipase, which hydrolyses triglycerides to free fatty acids and glycerol.

Therapeutic uses:

1- Epinephrine is the drug of choice in treating the acute asthma and anaphylactic shock (type I hypersensitivity reactions (including anaphylaxis) in response to allergens) as it is considered a lifesaving drug in these two life threating conditions. Within a few minutes after subcutaneous administration, respiratory function greatly improves. However, selective **β2 agonists**, such as albuterol, are favoured in the chronic treatment of asthma because of a longer duration of action and minimal cardiac stimulatory effects.
2- **Treating Cardiac arrest**
3- **In anaesthesia:** Local anaesthetic solutions may contain low concentrations (for example, 1:100,000 parts) of epinephrine, which can greatly increase the duration of local anaesthesia by producing vasoconstriction at the site of injection.

Pharmacokinetics:

Main pharmacokinetics aspects were summarised in figure 9.

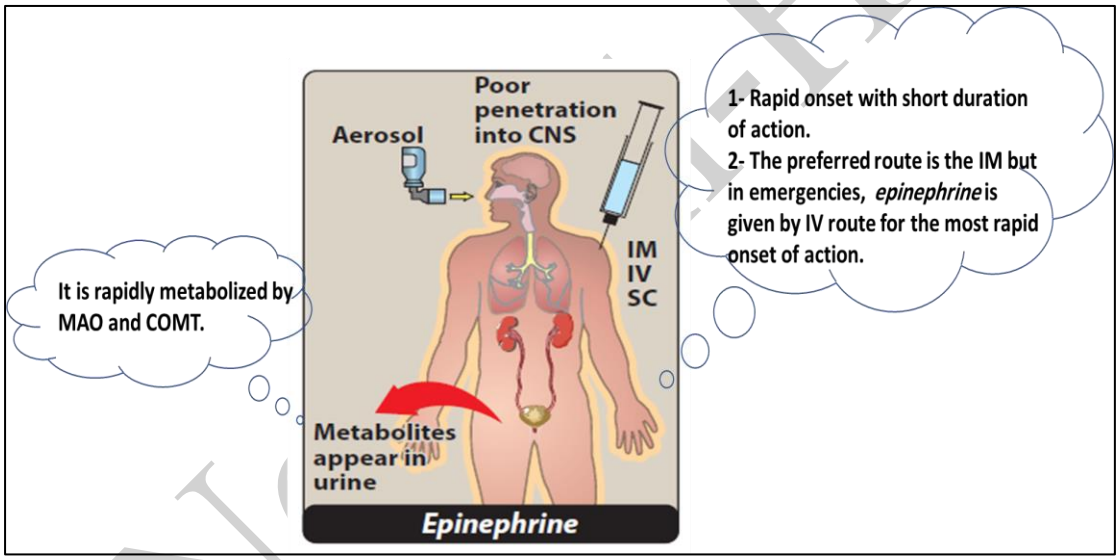


Figure 9: Pharmacokinetics of epinephrine. CNS = central nervous system.

Adverse effects:

1- It can cause anxiety, fear, tension and headache
2- It can trigger cardiac arrhythmias, particularly if the patient is receiving digoxin.
3- It can induce pulmonary oedema.
4- It can lead to tachycardia.
5- It can cause Hyperglycaemia and increment in blood pressure.

Norepinephrine

Because norepinephrine is the neurotransmitter of adrenergic nerves, it should, theoretically, stimulate all types of adrenergic receptors. However, when administered **in therapeutic doses, the α-adrenergic receptor is most affected.**

A- Cardiovascular actions:

1- **Vasoconstriction:** Norepinephrine causes a rise in peripheral resistance due to intense vasoconstriction of most vascular beds, including the kidney (α1 effect). Both systolic and diastolic blood pressures increase. [Note: Norepinephrine causes greater vasoconstriction than epinephrine, because it does not induce compensatory vasodilation via **β2** receptors on blood vessels supplying skeletal muscles. The weak β2 activity of norepinephrine also explains why it is not useful in the treatment of asthma or anaphylaxis.]

2- **Baroreceptor reflex:** Norepinephrine increases blood pressure, and this stimulates the baroreceptors, inducing a rise in vagal activity. The increased vagal activity produces a reflex bradycardia, which is sufficient to counteract the local actions of norepinephrine on the heart, although the reflex compensation does not affect the positive inotropic effects of the drug. When atropine, which blocks the transmission of vagal effects, is given before norepinephrine, stimulation of the heart by norepinephrine is evident as tachycardia.

Therapeutic uses: Norepinephrine is used to treat **shock**, because it increases vascular resistance and, therefore, increases blood pressure. It has no other clinically significant uses.

Pharmacokinetics: Norepinephrine is given IV for rapid onset of action. The duration of action is 1 to 2 minutes, following the end of the infusion. It is rapidly metabolised by MAO and COMT, and inactive metabolites are excreted in the urine.

Adverse effects: These are similar to epinephrine. In addition, norepinephrine is a potent vasoconstrictor and may cause blanching and sloughing of skin along an injected vein. If extravasation (leakage of drug from the vessel into tissues surrounding the injection site) occurs, it can cause tissue necrosis. It should not be administered in peripheral veins, if possible. Impaired circulation from norepinephrine may be treated with the α receptor antagonist phentolamine.

Isoproterenol: It is a direct-acting synthetic catecholamine that stimulates both β1- and β2-adrenergic receptors. Because of its nonselectivity, it is rarely used therapeutically. Its action on α receptors is insignificant. Isoproterenol produces intense stimulation of the heart, increasing heart rate, contractility, and cardiac output. It is as active as epinephrine in this action. Moreover, it is a potent bronchodilator (β2 effect). The use of isoproterenol has largely been replaced with other drugs, but it may be useful in atrioventricular (AV) block. The adverse effects of isoproterenol are similar to those of epinephrine.

Dopamine

It is the immediate metabolic precursor of norepinephrine, occurs naturally in the CNS. Dopamine can activate α- and β-adrenergic receptors but this depends on the dopamine dose, for example: At higher doses, it causes vasoconstriction by activating α1 receptors, whereas at lower doses, it stimulates β1 cardiac receptors. In addition, D1 and D2 dopaminergic receptors, distinct from the α- and β-adrenergic receptors, occur in the peripheral mesenteric and renal vascular beds, where binding of dopamine produces vasodilation. D2 receptors are also found on presynaptic adrenergic neurons, where their activation interferes with norepinephrine release.

Actions

a. Cardiovascular: Dopamine exerts a stimulatory effect on the β1 receptors of the heart, having both positive inotropic and chronotropic effects. At very high doses, dopamine activates α1 receptors on the vasculature, resulting in vasoconstriction.

b. Renal and visceral: Dopamine dilates renal and splanchnic arterioles by activating dopaminergic receptors, thereby increasing blood flow to the kidneys and other viscera.

Therapeutic uses: Dopamine is the drug of choice for cardiogenic and septic shock and is given by continuous infusion. It raises blood pressure by stimulating the β1 receptors on the heart to increase cardiac output and α1 receptors on blood vessels to increase total peripheral resistance. In addition, it enhances perfusion to the kidney and splanchnic areas. Increased blood flow to the kidney enhances the glomerular filtration rate and causes diuresis. In this regard, dopamine is far superior to norepinephrine, which diminishes blood supply to the kidney and may cause renal shutdown. It is also used to treat hypotension and severe heart failure.

Adverse effects: An overdose of dopamine produces the same effects as sympathetic stimulation. Dopamine is rapidly metabolised by MAO or COMT, and its adverse effects (nausea, hypertension, and arrhythmias) are, therefore, short-lived.

There are more adrenergic agonist drugs that can be used in different medical situation to save peoples' life. The most important ones are summarised in table 2.

Table 2: A summary about the direct-acting adrenergic agonists drugs.

Adrenergic agonist drugs	Activated adreno receptors	Actions, therapeutic uses and adverse effects
Fenoldopam	D1	*It is used as a rapid-acting vasodilator to treat severe hypertension in hospitalised patients. *It undergoes extensive first-pass metabolism and has a 10-minute elimination half-life after IV infusion. *Headache, flushing, dizziness, nausea, vomiting, and tachycardia (due to vasodilation) may be observed as side effects.
Dobutamine	**ß$_1$**	*It is a synthetic, direct-acting catecholamine. *It increases cardiac rate and output in acute heart failure with few vascular effects. *The drug does not significantly elevate oxygen demands of the myocardium, a major advantage over other sympathomimetic drugs. *It should be used with caution in atrial fibrillation *Other adverse effects are similar to epinephrine. *Tolerance may develop with prolonged use.
Oxymetazoline	α1- and α2	*It is found in many over-the-counter short-term nasal spray decongestants, as well as in ophthalmic drops for the relief of redness of the eyes associated with swimming, colds, and contact lenses. *It may produce nervousness, headaches, and trouble sleeping as it can be systemically absorbed. *Rebound congestion and dependence are observed with long-term use.
Phenylephrine	α1	*It is a vasoconstrictor that raises both systolic and diastolic blood pressures. *It is used to treat hypotension in hospitalised or surgical patients (especially those with a rapid heart rate). *Large doses can cause hypertensive headache and cardiac irregularities. *It acts as a nasal decongestant when applied topically or taken orally. Phenylephrine has replaced pseudoephedrine in many oral decongestants, since pseudoephedrine has been misused to make methamphetamine. *It is also used in ophthalmic solutions for mydriasis.
Clonidine	α2	*It is used for the treatment of hypertension. *It can be used to minimise the symptoms that accompany withdrawal from opiates. *The side effects of clonidine are lethargy, sedation, constipation, and xerostomia. *Abrupt discontinuance must be avoided to prevent rebound hypertension.
Albuterol and terbutaline	β2	*They are used primarily as bronchodilators and administered by a metered-dose inhaler. *Some side effects include restlessness, and anxiety. When these drugs are administeredorally, they may cause tachycardia or arrhythmia.
Salmeterol and formoterol	β2	*A single dose provides sustained bronchodilation over 12 hours, compared with less than 3 hours for albuterol. *Agents of choice for treating nocturnal asthma in symptomatic patients taking other asthma medications.
Mirabegron	β3	*It is used for treating of overactive bladder. *It may increase blood pressure and should not be used in patients with uncontrolled hypertension.

INDIRECT-ACTING ADRENERGIC AGONISTS

Indirect-acting adrenergic agonists (IAAA) cause the release, inhibit the reuptake, or inhibit the degradation of epinephrine or norepinephrine. They potentiate the effects of epinephrine or norepinephrine produced endogenously, but do not directly affect postsynaptic receptors.

Indirect-acting adrenergic agonists properties were summarised in table 3.

Table 3: Properties of indirect-acting adrenergic agonists.

IAAA	Receptor specificity	Features
Amphetamine	**ß$_1$, α$_1$ and CNS**	*Its actions are mediated primarily through an increase in nonvesicular release of catecholamines such as dopamine and norepinephrine from nerve terminals. *It can increase blood pressure significantly by α_1 agonist action on the vasculature, as well as β_1 stimulatory effects on the heart. *It can be abused by addicts.
Tyramine	Adrenoreceptors	* Tyramine can enter the nerve terminal and displace stored norepinephrine. The released catecholamine then acts on adrenoceptors. *It is important because it is found in fermented foods, such as aged cheese. *Normally, it is oxidized by MAO in the gastrointestinal tract, but, if the patient is taking MAOIs, it can precipitate serious vasopressor episodes. *Not used clinically.
Cocaine	α_1 agonist actions and β	*It can be abused by addicts. *It can block the sodium-chloride (Na_+/Cl)-dependent norepinephrine transporter required for cellular uptake of norepinephrine into the adrenergic neuron. Consequently, norepinephrine accumulates in the synaptic space, resulting in enhanced sympathetic activity and potentiation of the actions of epinephrine and norepinephrine. *It can increase the blood pressure.

Mixed- Acting Agonists:

Ephedrine and pseudoephedrine are mixed-action adrenergic agents. They not only release stored norepinephrine from nerve endings but also directly stimulate both α and β receptors. Thus, a wide variety of adrenergic actions ensue that are similar to those of epinephrine, although less potent. Ephedrine and pseudoephedrine are not catechols and are poor substrates for COMT and MAO. Therefore, these drugs have a long duration of action.

Ephedrine and pseudoephedrine have excellent absorption orally and penetrate into the CNS, but pseudoephedrine has fewer CNS effects. Ephedrine is eliminated largely unchanged in urine, and pseudoephedrine undergoes incomplete hepatic metabolism before elimination in urine. Ephedrine raises systolic and diastolic blood

pressures by vasoconstriction and cardiac stimulation and can be used to treat hypotension. Ephedrine produces bronchodilation, but it is less potent and slower acting than epinephrine or isoproterenol. It was previously used to prevent asthma attacks but has been replaced by more effective medications. Ephedrine produces a mild stimulation of the CNS. This increases alertness, decreases fatigue, and prevents sleep. It also improves athletic performance. [Note: The clinical use of ephedrine is declining because of the availability of better, more potent agents that cause fewer adverse effects. Ephedrine-containing herbal supplements (mainly ephedra-containing products) have been banned by the U.S. Food and Drug Administration because of lifethreatening cardiovascular reactions.]

Pseudoephedrine is primarily used orally to treat nasal and sinus congestion. Pseudoephedrine has been illegally used to produce methamphetamine. Therefore, products containing pseudoephedrine have certain restrictions and must be kept behind the sales counter in the United States.