حل اسئلة الكوز

Q) An experiment has been done for a cholinergic drug injected to the rat. How can proof that this drug is selective muscarinic agent??

Decrease in heart rate and blood pressure, miosis and diarrhea, salivation and urination.

Quiz

Ant experiment has been done for a cholinergic drug injected to the rat. How can you proof whether this drug is direct acting cholinergic drugs or indirect acting reversible cholinergic drugs??

If it is direct acting we will seen the following effect:

Salivation, flushing, decreased blood pressure, bradycardia , diarrhea and urination.

But if it is indirect we will seen contraction of skeletal muscle first then paralysis in addition to the above effects.

OR

If it is indirect it will produce effects similar to physostigmine.

If direct we will not seen contraction and paralysis of skeletal muscle.

Pharmacology

Adrenergic drugs

Sympathomimetic drugs

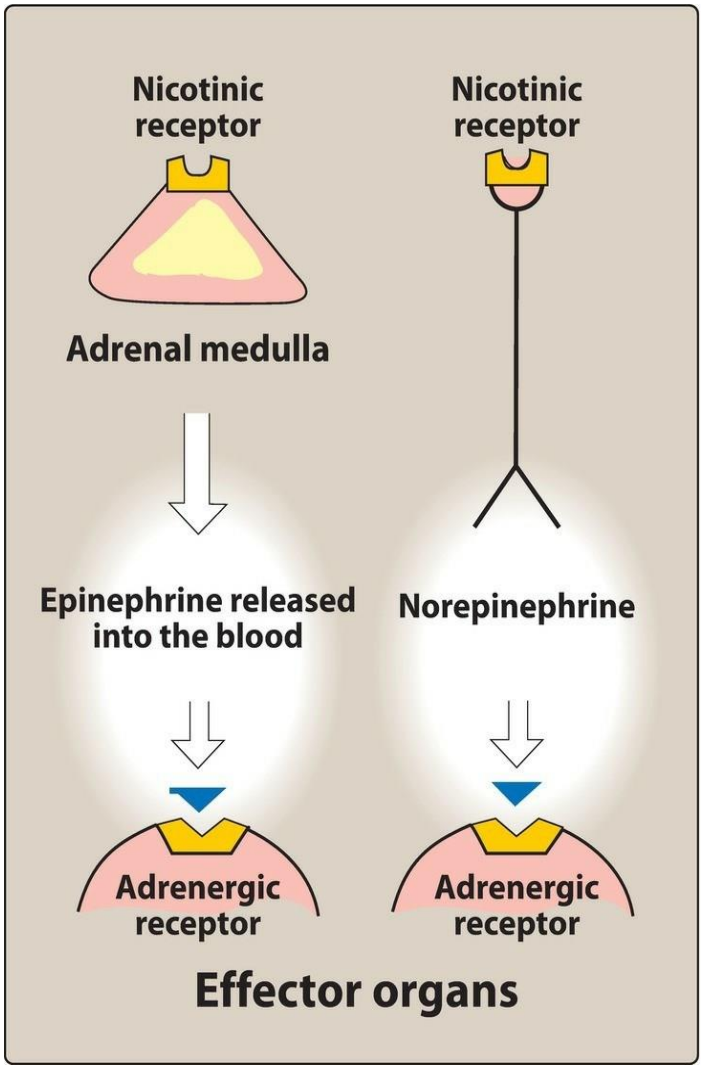
Lec. 6

Introduction

The adrenergic drugs affect receptors that are stimulated by norepinephrine (noradrenaline) or epinephrine (adrenaline). These receptors are known as adrenergic receptors or adrenoceptors. Drugs that activate adrenergic receptors are termed sympathomimetics, and drugs that block activation of adrenergic receptors are termed sympatholytics. Some sympathomimetics directly activate adrenergic receptors (direct-acting agonists), while others act indirectly by enhancing release or blocking reuptake of norepinephrine (indirect-acting agonists).

What is the Adrenergic Neuron??

Adrenergic neurons release norepinephrine as the primary neurotransmitter. These neurons are found in the CNS and 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



Neurotransmission at adrenergic neurons:

1. Neurotransmission in adrenergic neurons involves six steps:
2. Synthesis of norepinephrine
3. Storage of norepinephrine (inhibited by reserpine)
4. Release of norepinephrine (blocked by guanethidine and bretylium)
5. Binding of norepinephrine with receptor (blocked by adrenergic antagonist)
6. Followed by removal of the neurotransmitter from the synaptic gap (inhibited by tricyclic antidepressants, such as imipramine, or by cocaine).
7. Metabolism of norepinephrine.

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. Binding of norepinephrine to receptors triggers a cascade of events within the cell, resulting in the formation of intracellular second messengers that act as links (transducers) in the communication between the neurotransmitter and the action generated within the effector cell. 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 α_2 subtype) that modulate the release of the neurotransmitter.

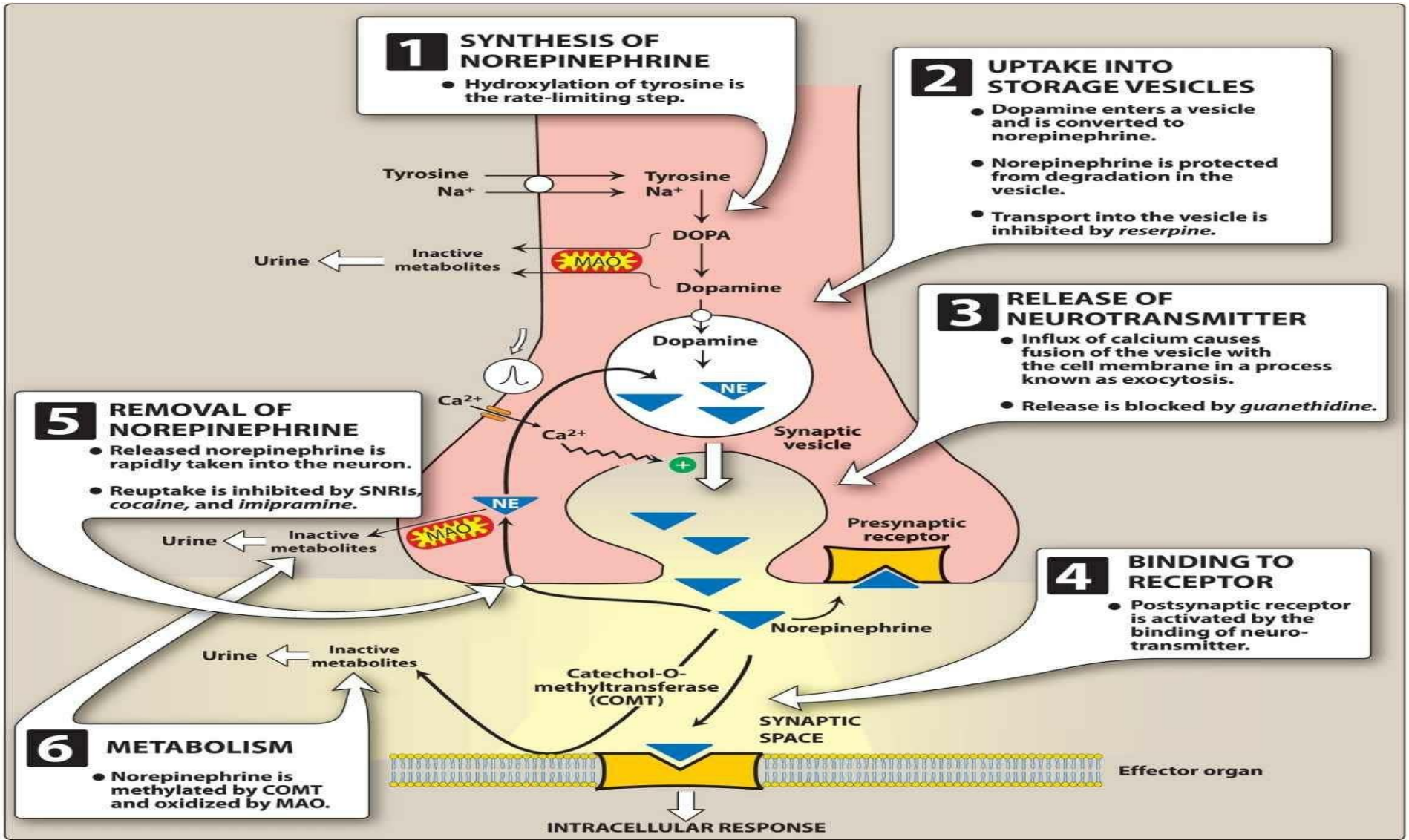
Removal of norepinephrine

Norepinephrine may 1) diffuse out of the synaptic space and enter the systemic circulation, 2) be metabolized 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 that can be inhibited by tricyclic antidepressants (TCAs), such as *imipramine*; by serotonin–norepinephrine reuptake inhibitors such as *duloxetine*; or by *cocaine*. Reuptake of norepinephrine into the presynaptic neuron is the primary mechanism for termination of its effects.

Potential fates of recaptured norepinephrine

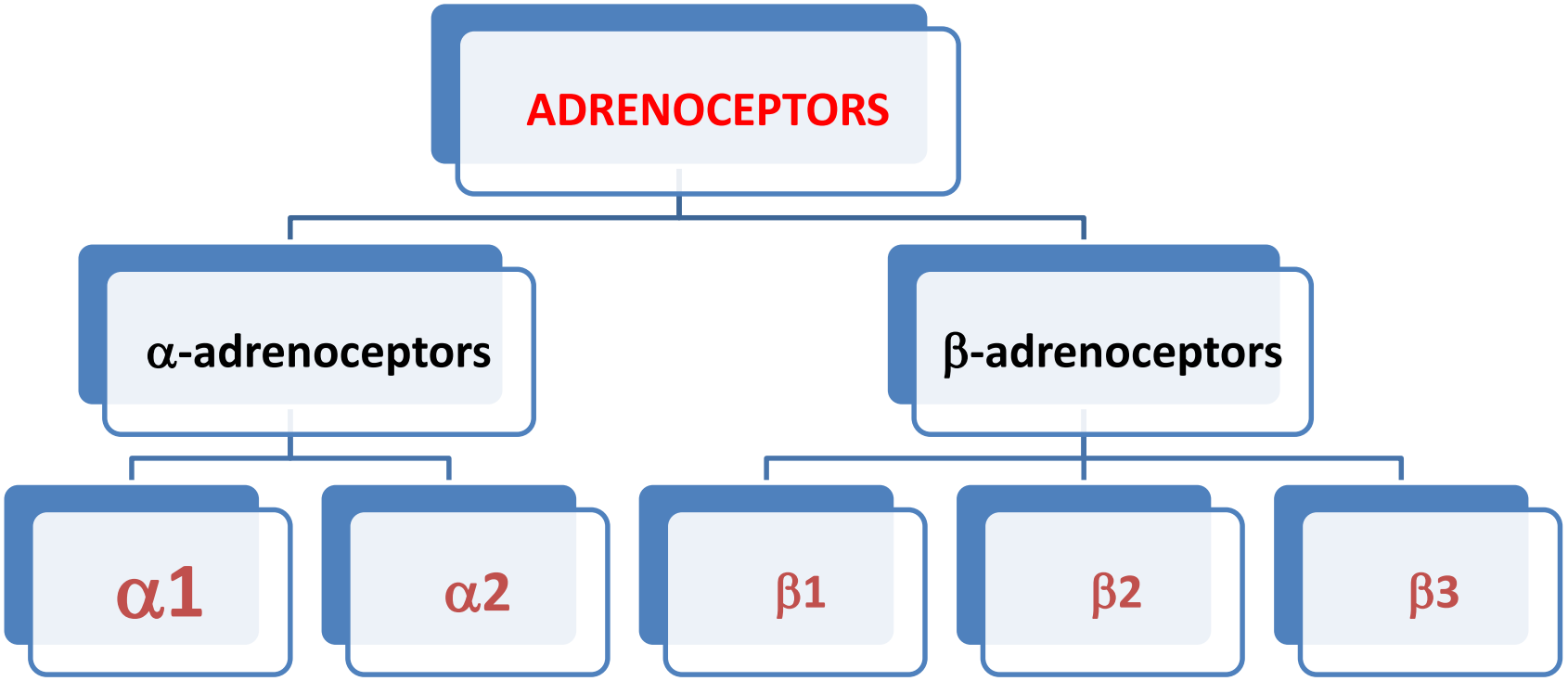
Once norepinephrine reenters the adrenergic neuron, it may be taken up into synaptic vesicles via the amine transporter system and be sequestered for release by another action potential, or it may persist in a protected pool in the cytoplasm. Alternatively, norepinephrine can be oxidized by monoamine oxidase (MAO) present in neuronal mitochondria.

Neurotransmission at adrenergic neurons

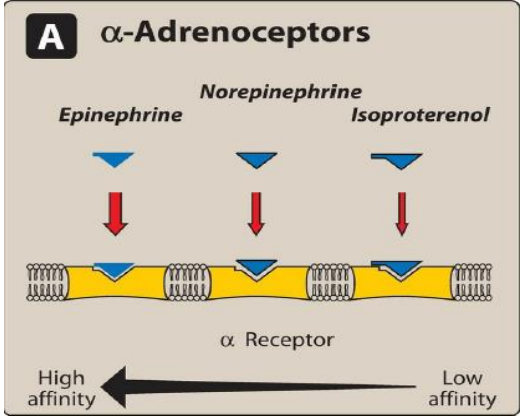


Adrenergic receptors (adrenoceptors)

Two families of receptors, designated α and β were initially identified on the basis of their responses to the adrenergic agonists epinephrine, norepinephrine, and isoproterenol.



α Receptors:



The α-adrenoceptors show a weak response to the synthetic agonist isoproterenol, but they are responsive to the naturally occurring catecholamines epinephrine and norepinephrine.

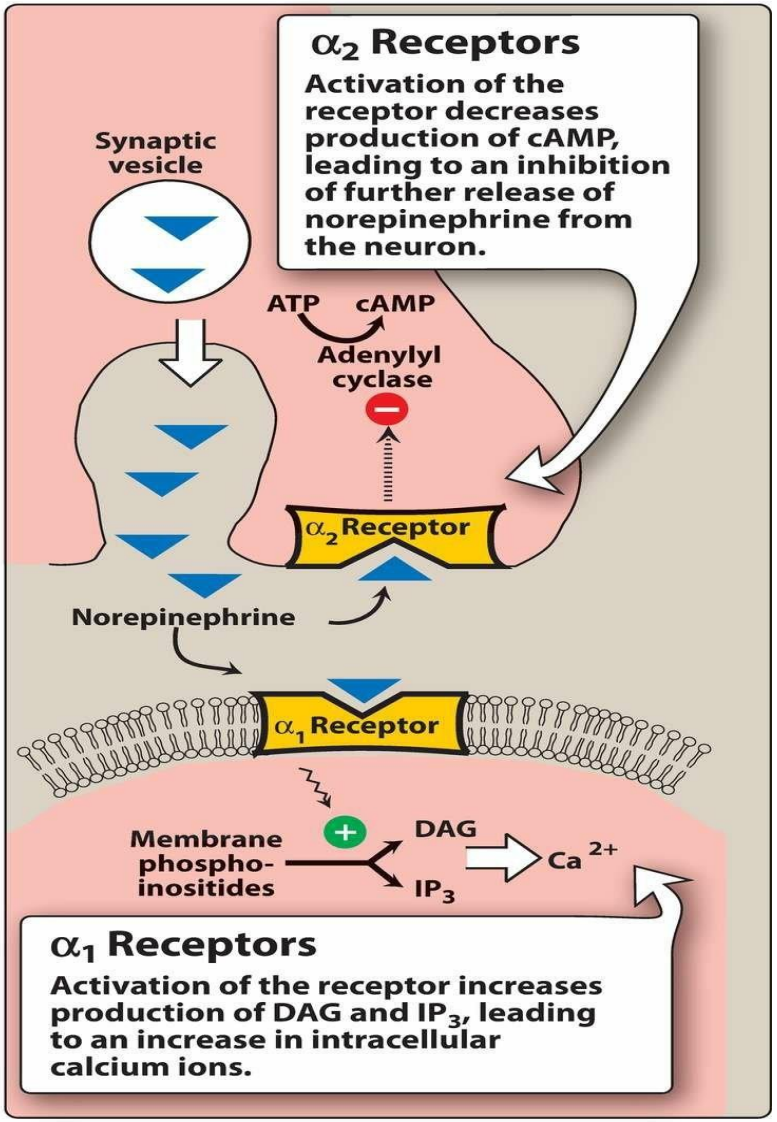
For α receptors, the rank order of potency is

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, 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.

What are the differences between a1 and a2 receptors??

1. a1 present on the postsynaptic membrane While a2 present on the presynaptic membrane.
2. Stimulation of a2 receptors causes feedback inhibition and inhibits further release of norepinephrine from the stimulated adrenergic neuron. By inhibiting further output of norepinephrine from the adrenergic neuron, these receptors are acting as inhibitory autoreceptors



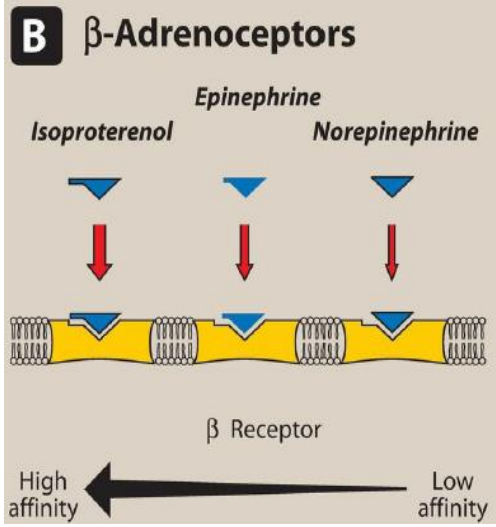
α_2 Receptors

α_2 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 α_1 receptors, the effects of binding at α_2 receptors are mediated by inhibition of adenylyl cyclase and by a fall in the levels of intracellular cAMP.

Further subdivisions

The α_1 and α_2 receptors are further divided into α_{1A}, α_{1B}, α_{1C}, and α_{1D} and into α_{2A}, α_{2B}, and α_{2C}. This extended classification is necessary for understanding the selectivity of some drugs. For example, *tamsulosin* is a selective α_{1A} antagonist that is used to treat benign prostatic hyperplasia. The drug has fewer cardiovascular side effects because it targets α_{1A} subtype receptors found primarily in the urinary tract and prostate gland and does not affect the α_{1B} subtype found in the blood vessels.

β *Receptors*:



β Receptors exhibit a set of responses different from those of the α receptors. These are characterized by a strong response to isoproterenol, with less sensitivity to epinephrine and norepinephrine. 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.

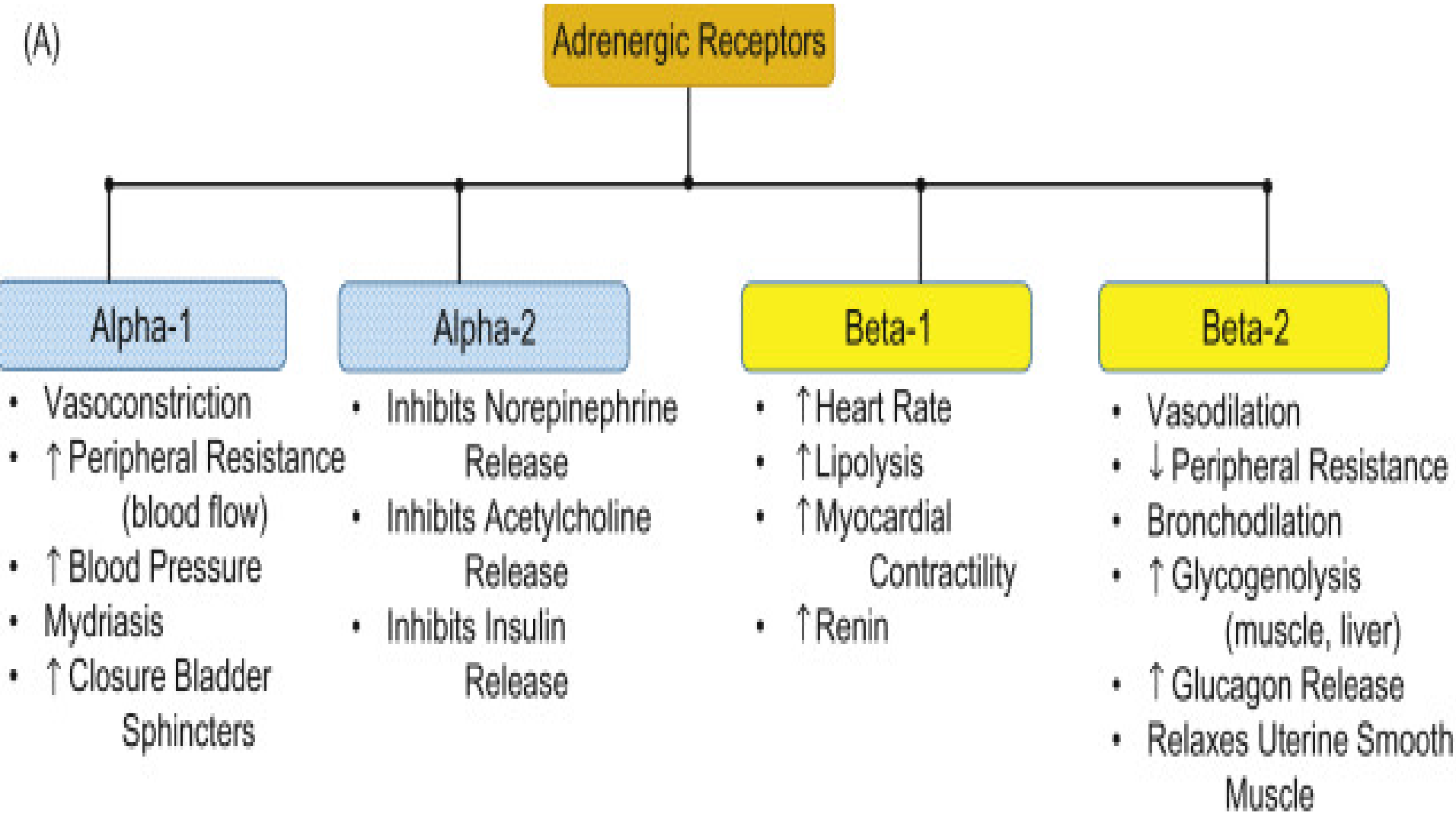
β *Receptors*

The β-adrenoceptors can be subdivided into three major subgroups, β_1, β_2, and β_3, based on their affinities for adrenergic agonists and antagonists. β_1 receptors have approximately equal affinities for *epinephrine* and *norepinephrine*, whereas β_2 receptors have a higher affinity for *epinephrine* than for *norepinephrine*. Thus, tissues with a predominance of β_2 receptors (such as the vasculature of skeletal muscle) are particularly responsive to the effects of circulating epinephrine released by the adrenal medulla. 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.

Distribution of receptors

TISSUE	RECEPTOR TYPE	ACTION
Heart		
• Sinus and AV	β_1	↑ Automaticity
• Conduction pathway	β_1	↑ Conduction velocity, automaticity
• Myofibrils	β_1	↑ Contractility, automaticity
Vascular smooth muscle	β_2	Vasodilation
Bronchial smooth muscle	β_2	Bronchodilation
Kidneys	β_1	↑ Renin release
Liver	β_2, α_1	↑ Glycogenolysis and gluconeogenesis
Adipose tissue	β_1, β_3	↑ Lipolysis
Skeletal muscle	β_2	↑ Increased contractility Potassium uptake; glycogenolysis Dilates arteries to skeletal muscle Tremor
Eye-ciliary muscle	β_2	Relaxation
GI tract	β_2	↓ Motility
Gall bladder	β_2	Relaxation
Urinary bladder detrusor muscle	β_2, β_3	Relaxation
Uterus	β_2	Relaxation

Major effects mediated by α & β adrenoceptors



What is mean, desensitization of the receptors??

Prolonged exposure to the catecholamines reduces the responsiveness of these receptors, a phenomenon known as desensitization.

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) an inability to couple to G-protein, because the receptor has been phosphorylated on the cytoplasmic side.

Location and effect of D1 and D2 receptor

D1: located in the smooth muscle and dilates the renal blood vessel.

D2 found on presynaptic adrenergic neurons, where their activation interferes with *norepinephrine* release.

Classification of Adrenoceptor agonists

1) According to their chemical structure

2) By types of adrenoceptor stimulation

3) By direct or indirect action

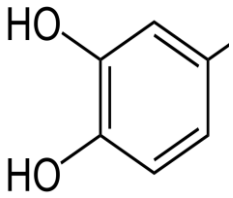
1.Based on chemical structure

Two groups

A) Catecholamines : e.ge.g., ***adrenaline*** (Ad), ***noradrenaline*** (NE), ***isoprenaline*** (ISOP) , ***dopamine*** (DA) , ***dobutamine*** (Dob)

B) Noncatecholamines :e.g., ***amphetamine,***

ephedrine, phenylepohrine (Phe), ***salbutamol*** (Salb).



Catecholamines	Noncatecholamines
Drugs contain catechol nucleus in their chemical structure	Not contain catechol nucleus
show the highest potency in directly activating α or β receptors	Vary in their potency
Rapid inactivation by COMT enzyme postsynaptically and MAO enzyme intraneuronally.	They are not inactivated by COMT and MAO.
Short half life	Prolong half life
Ineffective orally because of poor absorption	Effective orally
Poor penetration into the CNS, nevertheless, drugs have some clinical effects (anxiety, tremor, and headaches) that are attributable to action on the CNS.	greater access to the CNS

2) Based on effects of drugs on receptor types

A. Both alpha & beta agonists

e.g., Adrenaline, noradrenaline, ephedrine, amphetamine

B. Mainly alpha agonists

i) Mainly α_1 agonists

e.g., Phenylphrine.

ii) Mainly α_2 agonist

e.g., clonidine.

C) Mainly Beta agonists

i) Mainly β1 & β2 agonists

e.g., Isoproternol

ii) Mainly β1 agonists

e.g., Dobutamine

iii) Mainly β2 agonists

e.g., Salbutamol

iv) Dopamine agonists

e.g., Dopamine, fenoldopam

3. Based on mechanism of action of adrenergic agonists

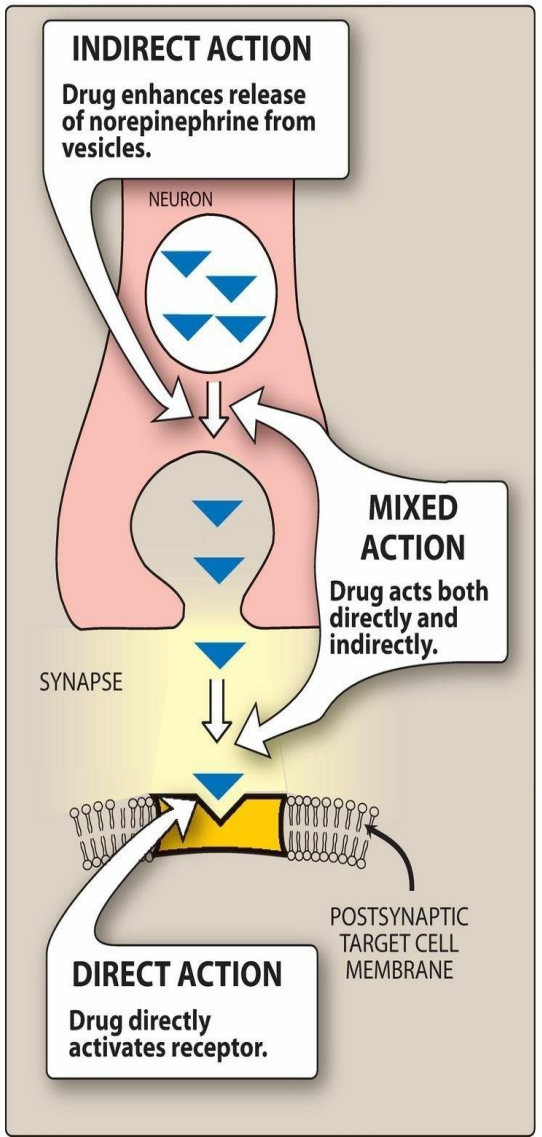
A. Direct acting agonists: Act directly on α or β receptors e.g., Adrenaline, Noradrenaline, Isoproternol, Phenylphrine and salbutamol.

B. Indirect acting agonists: Their actions dependent on release of endogenous norepineprhine.

They have either of **two different mechanisms**:

1. Block the reuptake of *norepinephrine* e.g., cocaine, & tricyclic antidepressants.
2. Cause release of norepinephrine from the cytoplasmic pools or vesicles of the adrenergic neuron. e.g. amphetamine & tyramine

C. Mixed action agonists: stimulate adrenoceptors directly and enhance release of *norepinephrine* from the adrenergic neuron. Eg. **Ephedrine & pseudoephedrine**

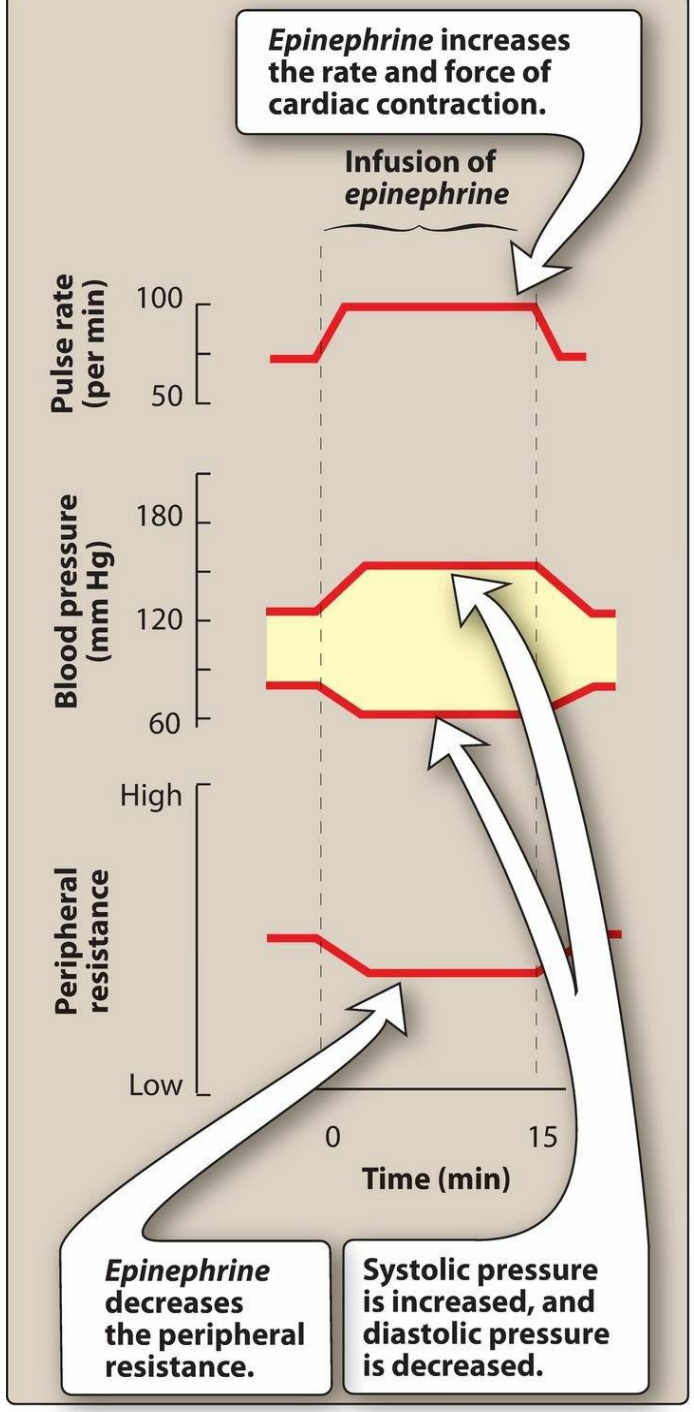


Epinephrine (Adrenaline)

Epinephrine is synthesized from tyrosine in the adrenal medulla and released, along with small quantities of norepinephrine, into the bloodstream. 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 strongest.

Actions:

Cardiovascular: Epinephrine strengthens the contractility of the myocardium (positive inotropic: β1 action) and increases its rate of contraction (positive chronotropic: β1 action). Cardiac output therefore increases. Epinephrine **constricts** arterioles in the skin, mucous membranes, and viscera (α effects), and it **dilates** vessels going to the liver and skeletal muscle (β2 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.



Actions:

Respiratory: Epinephrine causes powerful bronchodilation (β2 action). This action relieves all known allergic- or histamine-induced bronchoconstriction. Epinephrine also inhibits the release of allergy mediators such as histamines from mast cells.

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

Adipose tissue: Epinephrine initiates lipolysis through (stimulate β3). Increased levels of cAMP stimulate a hormone-sensitive lipase, which hydrolyzes triglycerides to free fatty acids and glycerol.

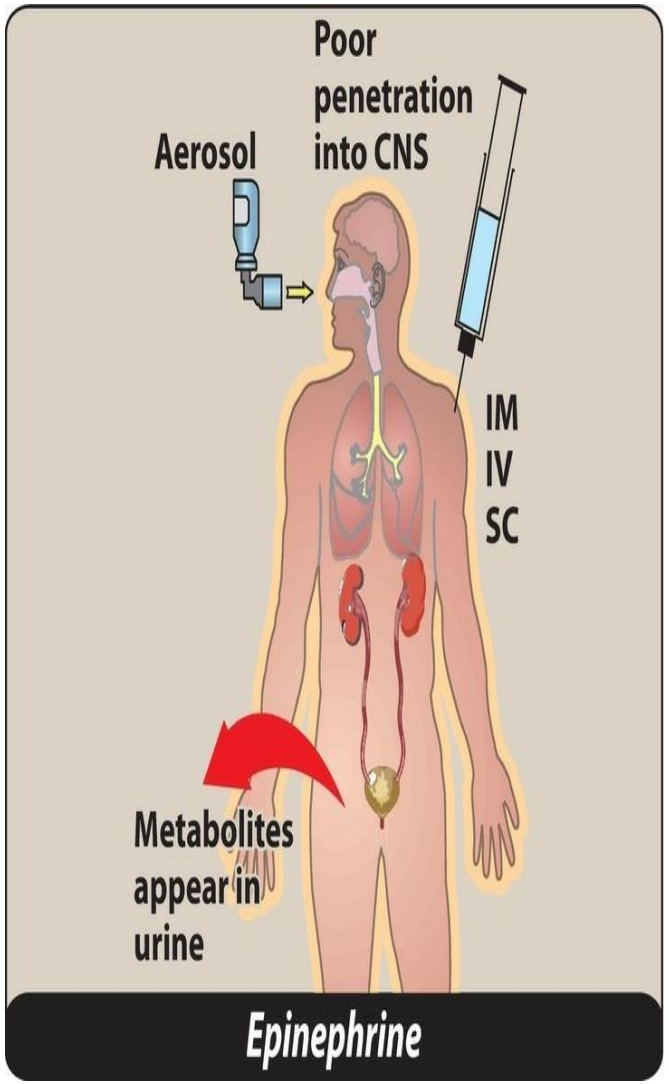
Therapeutic uses

Epinephrine available as injection only and given intravenously, subcutaneously, by inhalation, or topically to the eye and has therapeutic uses.

1. **Bronchospasm:** in in the emergency treatment of acute asthma and anaphylactic shock, epinephrine is the drug of choice (given subcutaneously).
2. **Anaphylactic shock:** Epinephrine is the drug of choice for the treatment of Type I hypersensitivity reactions in response to allergens.
3. **Cardiac arrest:** Epinephrine may be used to restore cardiac rhythm.
4. **Anesthetics:** Epinephrine usually mixed with local anesthetic increase the duration of the local anesthesia by producing vasoconstriction at the site of injection. It can also be used topically to vasoconstricts mucous membranes to control oozing of capillary blood.
5. **Intraocular surgery:** Epinephrine is used in the induction and maintenance of mydriasis during intraocular surgery

Pharmacokinetics of Epinephrine

1. *Has* a rapid onset but a brief duration of action (due to rapid degradation).
2. In anaphylaxis given I.M (nterior thigh) due to rapid absorption.
3. In emergencies, *epinephrine* is given intravenously (IV) for the most rapid onset of action. It may also be given subcutaneously, by endotracheal tube, or by inhalation
4. It is rapidly metabolized by MAO and COMT, and the metabolites metanephrine and vanillylmandelic acid are excreted in urine.



Side effects and drug-drug interaction of Epinephrine

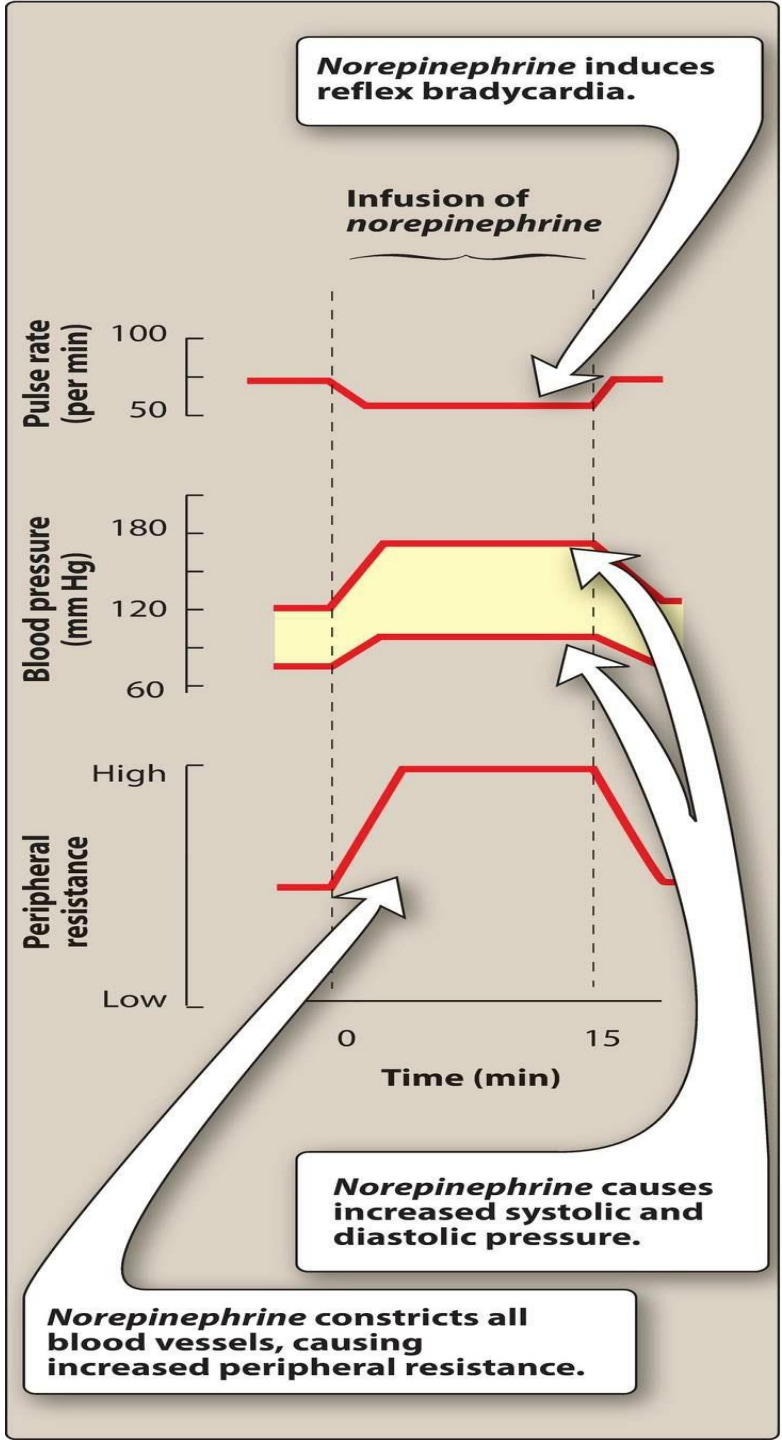
1. Anxiety, fear, tension, headache, and tremor.
2. Cardiac arrhythmias, particularly if the patient is receiving *digoxin*.
3. Pulmonary edema due to increased afterload caused by vasoconstrictive properties of the drug.
4. Patients with hyperthyroidism may have an increased production of adrenergic receptors in the vasculature, leading to an enhanced response to *epinephrine*, and the dose must be reduced in these individuals.
5. Inhalation anesthetics also sensitize the heart to the effects of *epinephrine*, which may lead to tachycardia.
6. *Epinephrine* increases the release of endogenous stores of glucose. In diabetic patients, dosages of *insulin* may have to be increased.
7. Nonselective β-blockers prevent vasodilatory effects of *epinephrine* on β2 receptors, leaving α receptor stimulation unopposed. This may lead to increased peripheral resistance and increased blood pressure.

Norepinephrine

It stimulate all types of adrenergic receptors because NE act as neuromediator of adrenergic nerves. When it given in therapeutic doses to humans, the α-adrenergic receptor is most affected.

Cardiovascular actions:

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



Baroreceptor reflex:

In isolated cardiac tissue, norepinephrine stimulates cardiac contractility; however, in vivo (i.e inside the body), little if any cardiac stimulation is noted. This is due to the increased blood pressure that induces a reflex rise in vagal activity by stimulating the baroreceptors. This reflex bradycardia 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.

Explain why? Epinephrine cause tachycardia while norepinephrine cause bradycardia.

Effect of atropine pretreatment:

If atropine, which blocks the transmission of vagal effects, is given before norepinephrine, then norepinephrine stimulation of the heart is evident as tachycardia.

Therapeutic uses:

Norepinphrine available as injection and given by intravenous infusion to treat cardiogenic shock, because it increases vascular resistance and, therefore, increases blood pressure. However, metaraminol is favored, because it does not reduce blood flow to the kidney, as does norepinephrine.

Adverse effects:

Headache and anexeity and may cause blanching and sloughing of skin along injected vein (due to extreme vasoconstriction). it can cause tissue necrosis. It should not be administered in peripheral veins, if possible. Impaired circulation from norepinephrine may be treated with the a receptor antagonist phentolamine.

Alternatives to phentolamine include intradermal terbutaline and topical nitroglycerin.

Isoproterenol

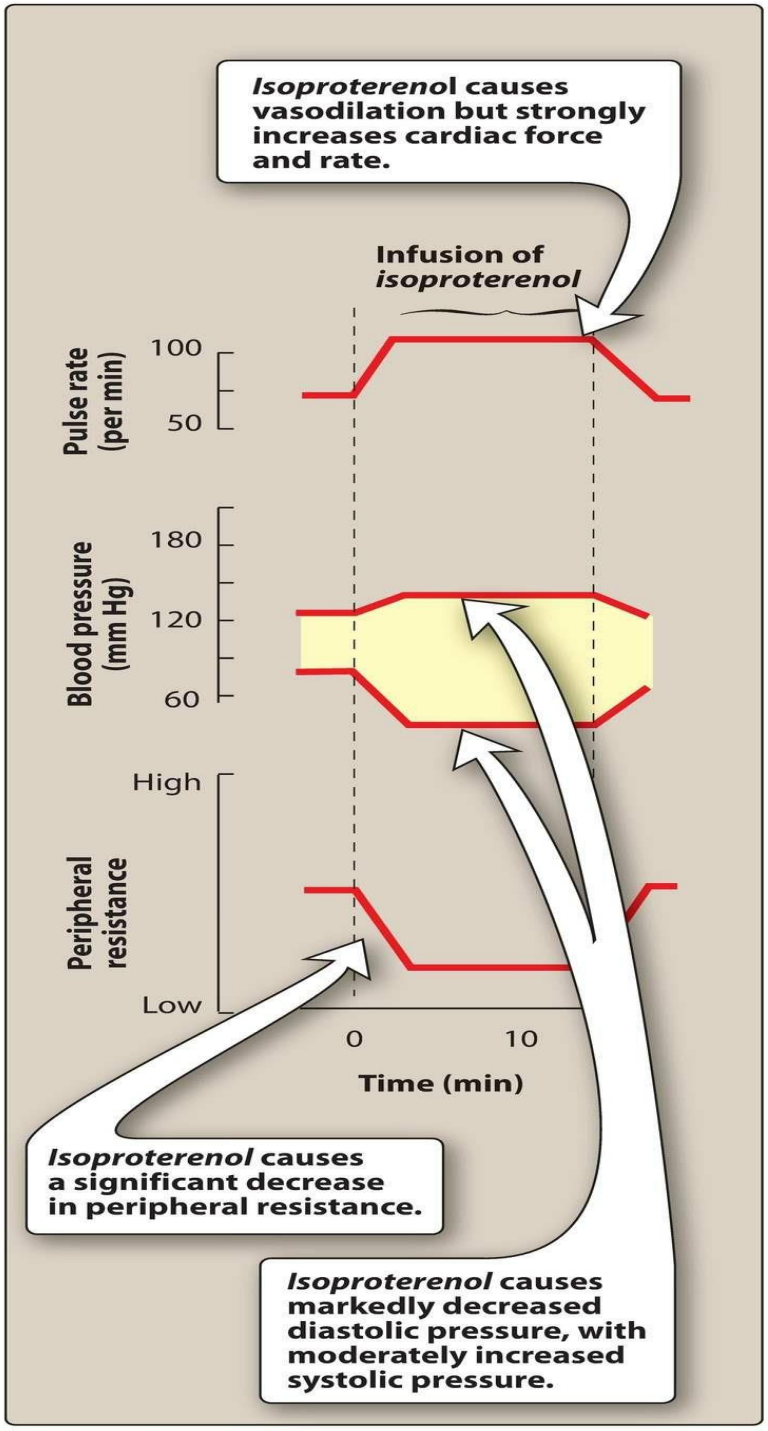
Isoproterenol is a direct-acting synthetic catecholamine that predominantly stimulates both β1- and β2-adrenergic receptors. Its nonselectivity is one of its drawbacks and the reason why it is rarely used therapeutically. Its action on α receptors is insignificant.

Actions:

Cardiovascular: Isoproterenol produces intense stimulation of the heart to increase its rate and force of contraction, causing increased cardiac output . Isoproterenol also dilates the arterioles of skeletal muscle (β2 effect), resulting in decreased peripheral resistance. It **may increase systolic blood pressure** slightly, but it **greatly reduces mean arterial and diastolic blood** pressure.

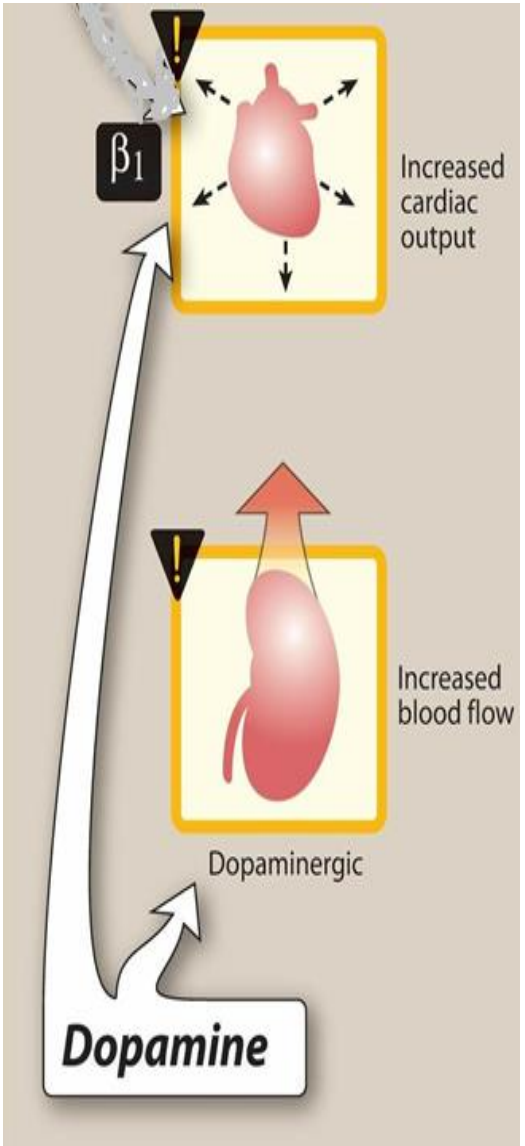
Pulmonary: A profound and rapid bronchodilation is produced by the drug (β2 action).

Side effects: same as epinphrine



Dopamine

Dopamine, the immediate metabolic precursor of norepinephrine, occurs naturally in the CNS in the basal ganglia, where it functions as a neurotransmitter, as well as in the adrenal medulla. Dopamine can activate α- and β-adrenergic receptors. In addition to that, dopamine stimulates both D1 and D2 dopaminergic receptors which 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:

- **Cardiovascular**: Dopamine stimulates β1 receptors of the heart, having both inotropic and chronotropic effects. At very high doses, dopamine activates a1 receptors on the vasculature, resulting in vasoconstriction.
- **Renal and visceral**: Dopamine dilates renal and splanchnic arterioles by activating D1 receptor, thus increasing blood flow to the kidneys and other viscera.
- *Therapeutic uses:* Dopamine given as infusion in treatment of cardiogenic shock and septic shock. also used to treat hypotension, severe heart failure, and bradycardia unresponsive to other treatments.

(explain why dopamine use in the above cases?)

- *Adverse effects*

Dopamine is rapidly metabolized by MAO or COMT, and its adverse effects (nausea, hypertension, and arrhythmias) are, therefore, short lived.

Fenoldopam (D1 receptor agonist)

- *Fenoldopam* is an agonist of peripheral *dopamine* D1 receptors.
- It is used as a rapid-acting vasodilator to treat severe hypertension in hospitalized patients, acting on coronary arteries, kidney arterioles, and mesenteric arteries.
- 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 occur with this agent.

Dobutamine (β1-receptor agonist)

- **Actions**: Dobutamine is a synthetic, direct-acting catecholamine that is a β1-receptor agonist. It increases cardiac rate and cardiac output with few vascular effects (has minor β2 and α1 effects).
- **Therapeutic uses:** Dobutamine is used to increase cardiac output in congestive heart failure.
- **Its Side effects** similar to epinephrine and Tolerance may develop with prolonged use.

Oxymetazoline

- Oxymetazoline is a direct-acting synthetic adrenergic agonist that stimulates both a1- and a2-adrenergic receptors.
- **Uses:** It is primarily used locally in the eye or the nose as a vasoconstrictor.
- **Side effects**: Oxymetazoline is absorbed in the systemic circulation and may produce nervousness, headaches, and trouble sleeping. When administered in the nose, burning of the nasal mucosa and sneezing may occur. **Rebound congestion is observed with long-term use that is why it should not be used more than 3 days.**

Phenylephrine

- Phenylephrine is a direct-acting, synthetic adrenergic drug that binds primarily to a receptors and favors a1 over a2 .
- Phenylephrine is a vasoconstrictor that raises **both systolic and diastolic blood pressures**.
- It has no effect on the heart itself but rather induces reflex bradycardia when given parenterally.
- Uses: It used topically as nasal decongestant and in ophthalmic solution for mydriasis. Also as injection to increase blood pressure (treatment of hypotension) and useful in the treatment of paroxysmal supraventricular tachycardia. Also can be used orally as decongestant and replaced pseudoephedrine.
- **Side effects:** Large doses can cause hypertensive headache and cardiac irregularities

Midodrine (selective α_1 agonist)

- *Midodrine*, a prodrug, is metabolized to the pharmacologically active desglymidodrine.
- It is a selective α_1 agonist, which acts in the periphery to increase arterial and venous tone. *Used in* treatment of orthostatic hypotension.
- To avoid supine hypertension, doses within 4 hours of bedtime are not recommended.

Clonidine

(α2 agonist)

Clonidine acts centrally on **α2** to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery.

Uses: used for the treatment of essential hypertension; minimize symptoms of withdrawal from opiates, tobacco smoking, and benzodiazepines. Both clonidine and the α2 agonist guanfacine may be used in the management of attention deficit hyperactivity disorder.

Side effects: lethargy, sedation, constipation, and xerostomia. Abrupt discontinuation must be avoided to prevent rebound hypertension.

Note: Clonidine also has efficacy in the treatment of diarrhea in diabetics with autonomic neuropathy, perhaps due to its ability to enhance salt and water absorption from the intestines.

Uses of Clonidine :

1. Essential hypertension
2. Minimize the symptoms that accompany withdrawal from opiates, alcohol or benzodiazepines.
3. Have efficacy in the treatment of diarrhea in diabetics with autonomic neuropathy, perhaps due to its ability to enhance salt and water absorption from the intestines.
4. Facilitate cessation of cigarette smoking.
5. Diminish menopausal hot flushes
6. Both clonidine and the a2 agonist guanfacine may be used in the management of attention deficit hyperactivity disorder.

Selective β2- agonist

Albuterol(salbutamol) and terbutaline: are short-acting β2 agonists used primarily as bronchodilators in treatment of asthma. Side effect is tremor and tolerance.

Salmeterol and formoterol Are β2-adrenergic selective, long-acting bronchodilators (LABAs).

They are the agents of choice for treating asthma. However, LABAs are not recommended as monotherapy for the treatment of asthma, because they have been shown to increase the risk of asthma-related deaths; however, these agents are highly efficacious when combined with an asthma controller medication such as an inhaled corticosteroid

Mirabegron
β3 agonist

- *Mirabegron* is a β3 agonist that relaxes the detrusor smooth muscle and increases bladder capacity.
- It is used for patients with overactive bladder.
- *Mirabegron* may increase blood pressure and should not be used in patients with uncontrolled hypertension.
- It increases levels of *digoxin* and inhibits the CYP2D6 isozyme, which may enhance the effects of other medications metabolized by this pathway (for example, *metoprolol*).

Indirect-Acting Adrenergic Agonists

Indirect-acting adrenergic agonists cause norepinephrine release from presynaptic terminals or inhibit the uptake of norepinephrine . They potentiate the effects of norepinephrine produced endogenously, but these agents do not directly affect postsynaptic receptors.

Amphetamine

- It is CNS stimulant drugs.
- Consider as drug abuse.
- Increase blood pressure significantly by α1 agonist action on the vasculature, as well as β1 stimulatory effects on the heart.
- Act by increase the release of dopamine and norepinephrine from nerve terminals.
- Uses: in treatment of narcolepsy and attention deficit hyperactivity syndrome in children.

Tyramine (It is not drug)

- *Tyramine* is not a clinically useful drug, but it is important because it is found in fermented foods, such as aged cheese and Chianti wine. It is a normal byproduct of tyrosine metabolism. Normally, it is oxidized by MAO in the gastrointestinal tract, but if the patient is taking MAOIs, it can precipitate serious vasopressor episodes.
- Like *amphetamines*, *tyramine* can enter the nerve terminal and displace stored norepinephrine. The released catecholamine then acts on adrenoceptors.

Cocaine

Cocaine is unique among local anesthetics in having the ability to block the Na+/K+-activated ATPase (required for cellular uptake of norepinephrine) on the cell membrane of the adrenergic neuron.

Consequently, norepinephrine accumulates in the synaptic space, resulting in enhancement of sympathetic activity and potentiation of the actions of epinephrine and norepinephrine. Like amphetamines, it can increase blood pressure by α-agonist actions and β-stimulatory effects.

Mixed-Action Adrenergic Agonists

Mixed-action drugs induce the release of norepinephrine from presynaptic terminals, and they activate adrenergic receptors on the postsynaptic membrane. For example Ephedrine and pseudoephedrine.

Ephedrine and pseudoephedrine

- These drugs are mixed-action adrenergic agents.
- They not only release stored norepinephrine from nerve endings but also directly stimulate both α and βreceptors.
- Ephedrine produces a mild stimulation of the CNS. This increases alertness, decreases fatigue, and prevents sleep. It also improves athletic performance.
- Pseudoephedrine is primarily used to treat nasal and sinus congestion.

Dipivefrine

It is a prodrug of epinephrine and when applied over the cornea penetrates it and is then hydrolyzed to epinephrine by the esterase, it has long duration of action and is used to treat open-angle glaucoma . It is available as a 0.1% ophthalmic solution.


THANKYOU