Al-Mustaqbal University College

Pharmacology I 3rd stage

Adrenergic Agonists

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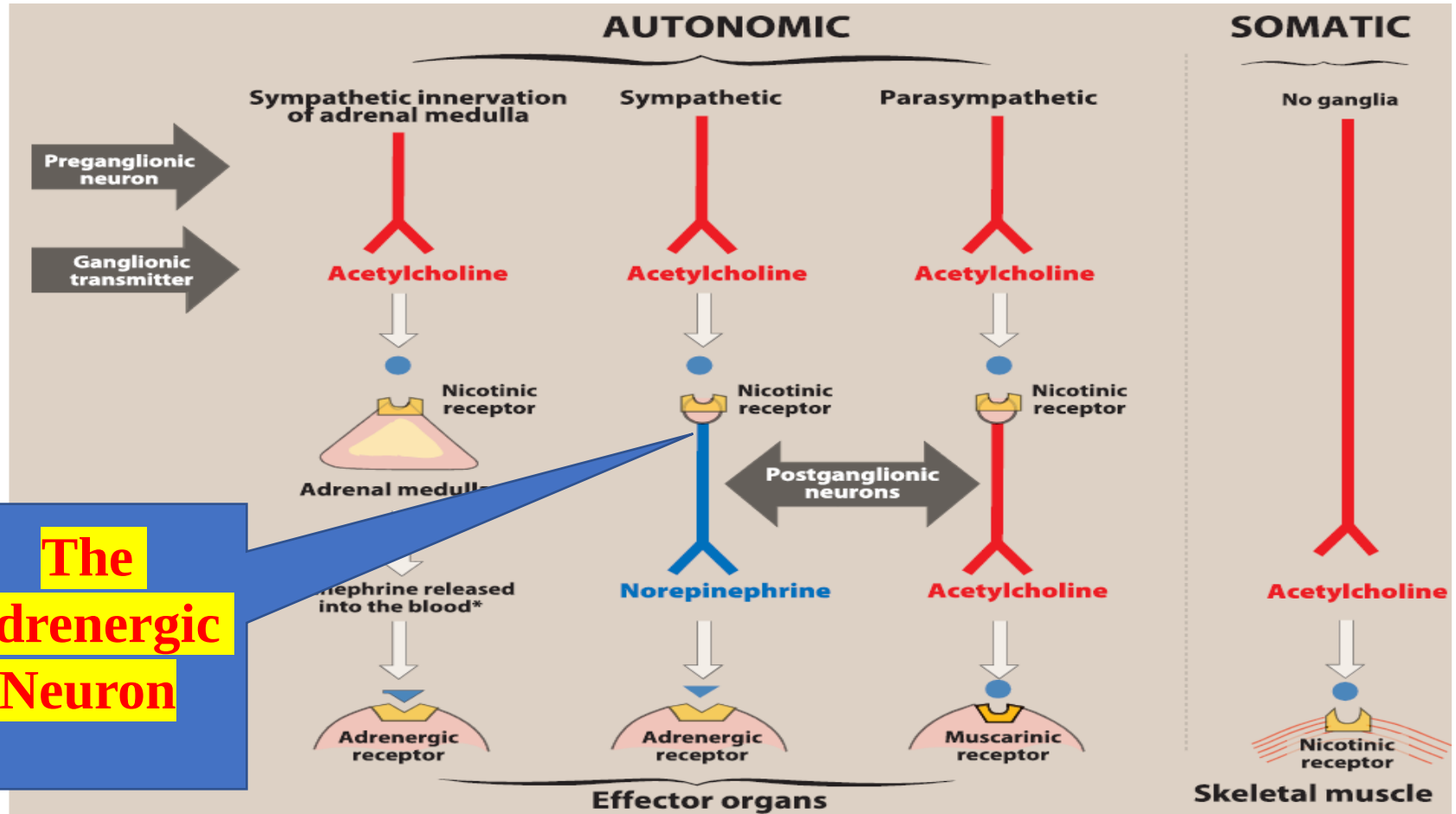
Adrenergic Agonists

The adrenergic drugs affect receptors that are stimulated by norepinephrine (noradrenaline) or epinephrine (adrenaline).



The Adrenergic Neuron

DIRECT-ACTING AGENTS

- *Albuterol* ACCUNEB, PROAIR, VENTOLIN
- *Arformoterol* BROVANA
- *Clonidine* CATAPRES, DURACLON
- *Dobutamine** GENERIC ONLY
- *Dopamine** GENERIC ONLY
- *Epinephrine** ADRENALIN, EPIPEN
- *Fenoldopam* CORLOPAM
- *Formoterol* FORADIL, PERFOROMIST
- *Guanfacine* INTUNIV, TENEX
- *Indacaterol* ARCAPTA
- *Isoproterenol** ISUPREL
- *Metaproterenol* GENERIC ONLY
- *Midodrine* GENERIC ONLY
- *Mirabegron* MYRBETRIQ
- *Norepinephrine** LEVOPHED
- *Oxymetazoline* AFRIN, VISINE
- *Phenylephrine* NEO-SYNEPHRINE, SUDAFED PE
- *Salmeterol* SEREVENT
- *Terbutaline* GENERIC ONLY

INDIRECT-ACTING AGENTS

- *Amphetamine* ADDERALL
- *Cocaine* GENERIC ONLY

DIRECT AND INDIRECT ACTING (mixed action) AGENTS

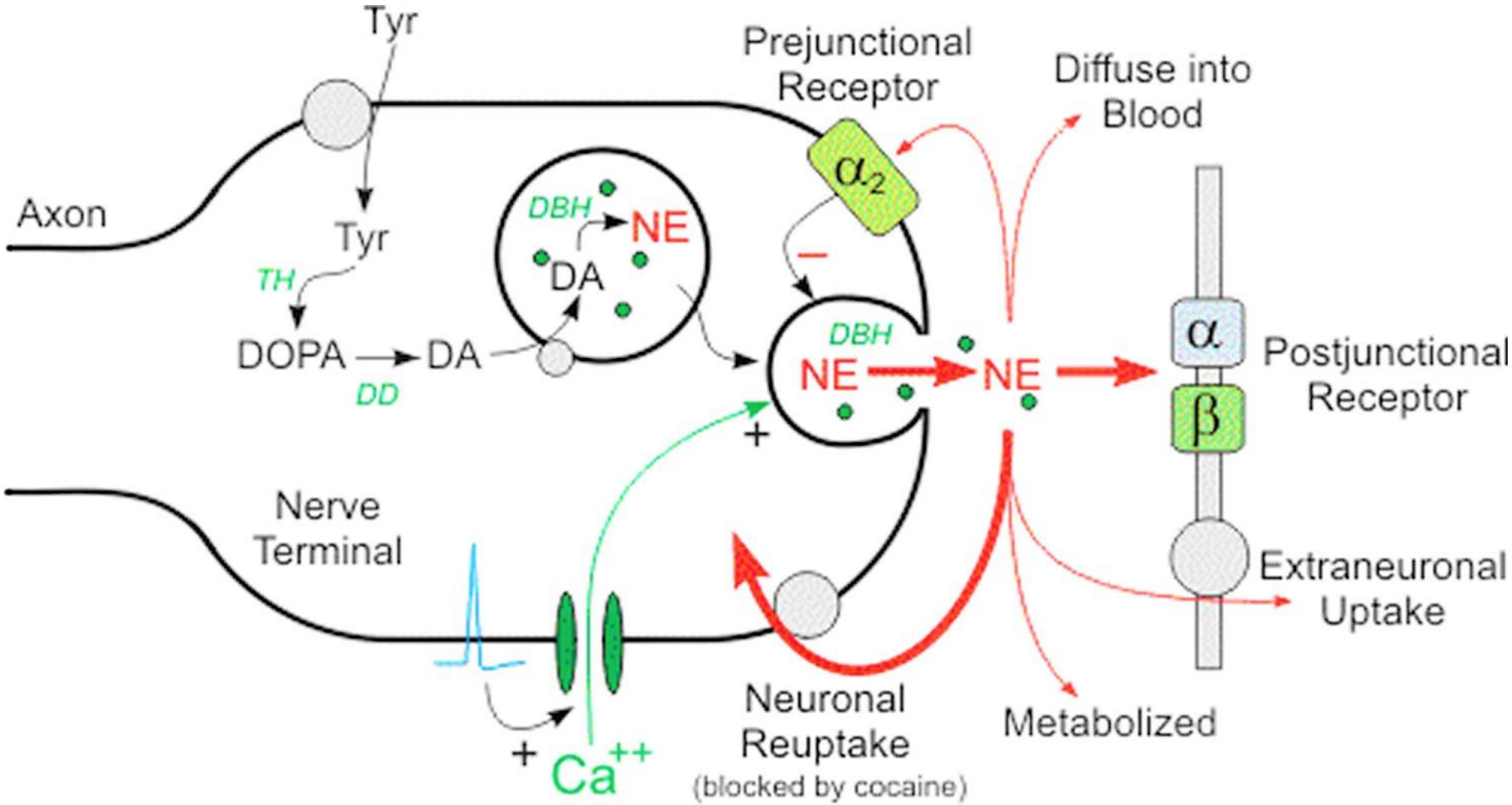
- *Ephedrine* AKOVAZ
- *Pseudoephedrine* SUDAFED

Neurotransmission at Adrenergic neurons

1-Synthesis of Norepinephrine:

Synthesis of norepinephrine: Tyrosine is transported by a carrier into the adrenergic neuron, where it is hydroxylated to (DOPA) by tyrosine hydroxylase. This is the rate-limiting step in the formation of norepinephrine. Then DOPA is decarboxylated by the enzyme amino acid decarboxylase to form dopamine in the presynaptic neuron.

2. Storage of norepinephrine in vesicles: Dopamine is then transported into synaptic vesicles by an amine transporter system. This carrier system is blocked by reserpine. Next, dopamine is hydroxylated to form norepinephrine by the enzyme dopamine β-hydroxylase..

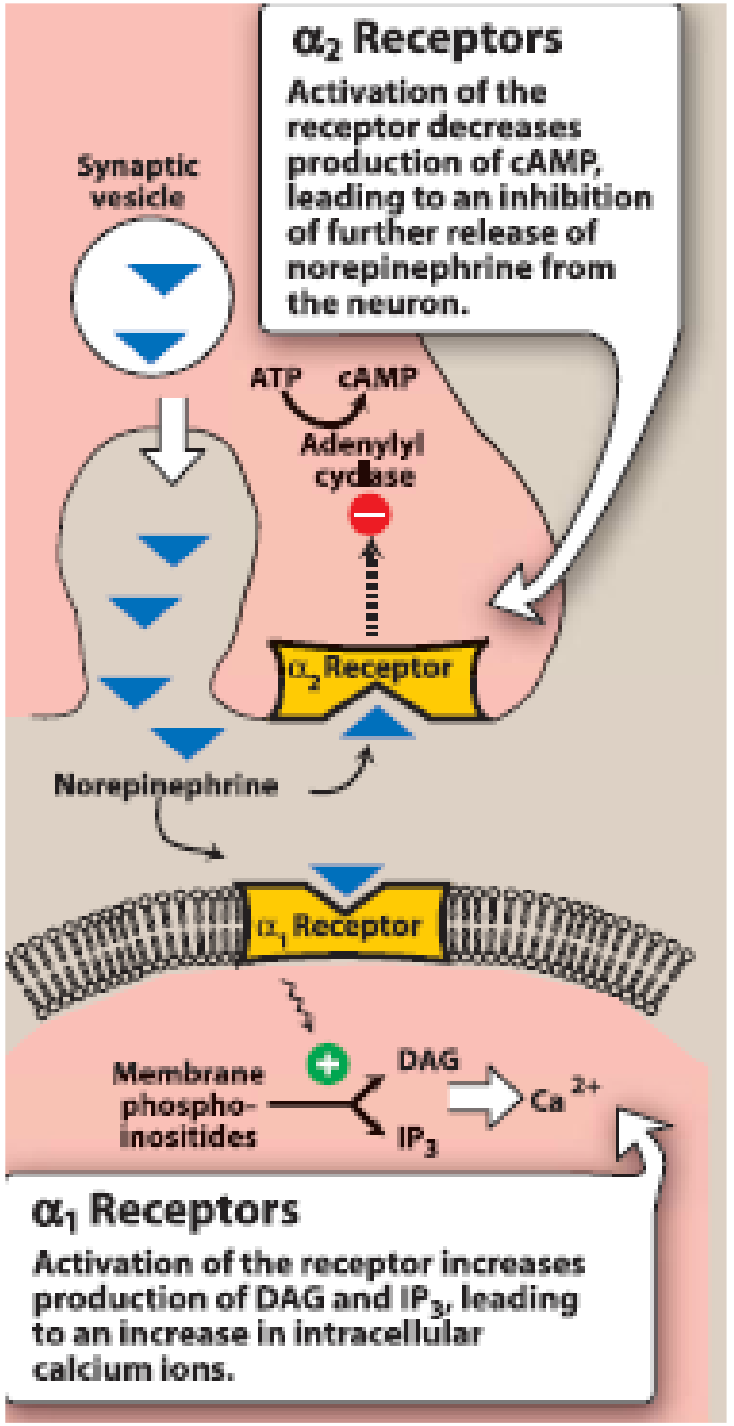


Tyr = tyrosine; TH = tyrosine hydroxylase; DD = DOPA decarboxylase;
DA = dopamine; DBH = dopamine β-hydroxylase; NE = norepinephrine

3. Release of norepinephrine:

An action potential arriving lead to increase calcium ions intracellularly that causes synaptic vesicles to fuse with the cell membrane and to undergo exocytosis and expel their contents into the synapse. Drugs such as guanethidine block this release.

4. Binding to receptors: Norepinephrine released into the synaptic space and binds to presynaptic receptors on the nerve ending(mainly α_2 subtype), or to postsynaptic receptors (mainly G-protein coupled receptor) on the effector organ, resulting in the formation of intracellular second messengers.



5. Removal of norepinephrine:

Norepinephrine may

1) diffuse out of the synaptic space and enter the systemic circulation,
2) metabolized to inactive metabolites by catechol-0-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+/CI-)-dependent norepinephrine transporter that can be inhibited by tricyclic antidepressants (TCAs), such as imipramine; or 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.

6. Potential fates of recaptured norepinephrine (reenters the adrenergic neuron):

1- It may be taken up into synaptic vesicles via the amine transporter system.

2- Norepinephrine can be oxidized by monoamine oxidase (MAO) present in neuronal mitochondria.

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 based on response to the adrenergic agonist's epinephrine, norepinephrine, and isoproterenol.

1. α -Adrenoceptors:

For a receptors, the rank order of potency and affinity is:

epinephrine ≥ norepinephrine >> isoproterenol.

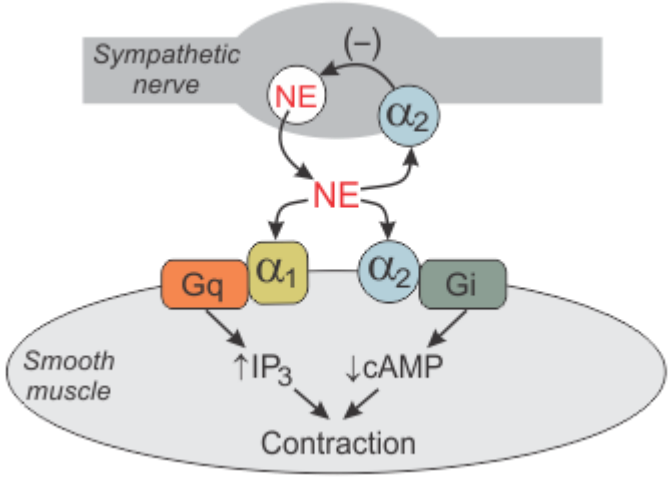
The α -adrenoceptors are divided into two subtypes, α_1 and α_2. based on their affinities for a agonists and antagonists.

For example, α_1 receptors have a higher affinity for phenylephrine than α_2 receptors.

Conversely, the drug clonidine selectively binds to α_2 receptors and has less effect on α_1 receptors.

a. α_1Receptors: These receptors are present on the postsynaptic membrane of smooth muscle.
Activation of α_1 receptors initiates a series of reactions through the G-protein coupled receptor and 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.



b. α_2 Receptors: These receptors are located primarily on sympathetic presynaptic nerve endings and control the release of norepinephrine(feedback inhibition and inhibits further release of norepinephrine)(as inhibitory autoreceptors) .
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.
[as inhibitory heteroreceptors.]

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.

c. Further subdivisions: The α_1 and a2 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.

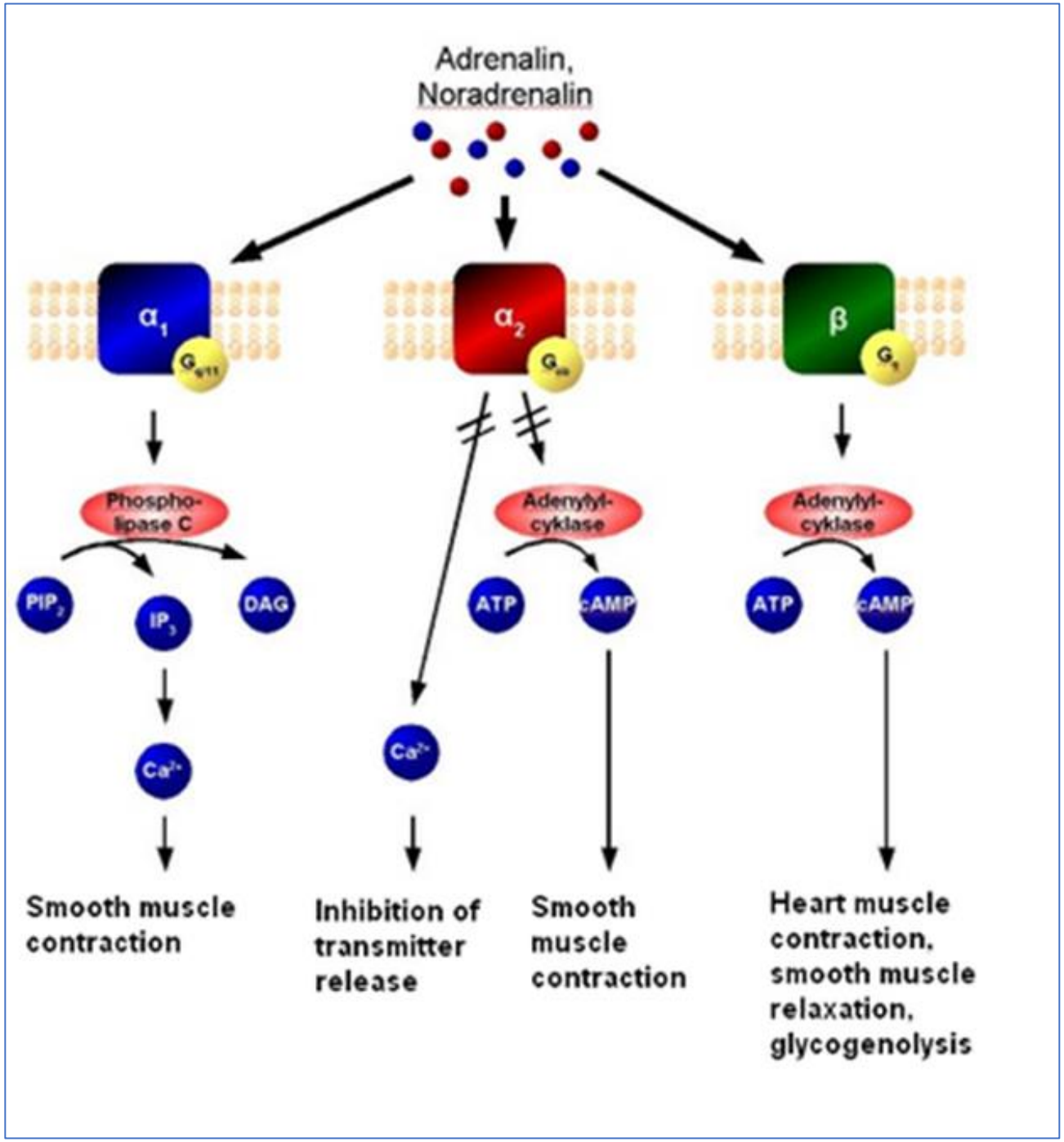
2. β-Adrenoceptors: Responses For β receptors, the rank order of potency is isoproterenol > epinephrine > norepinephrine.

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.

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.

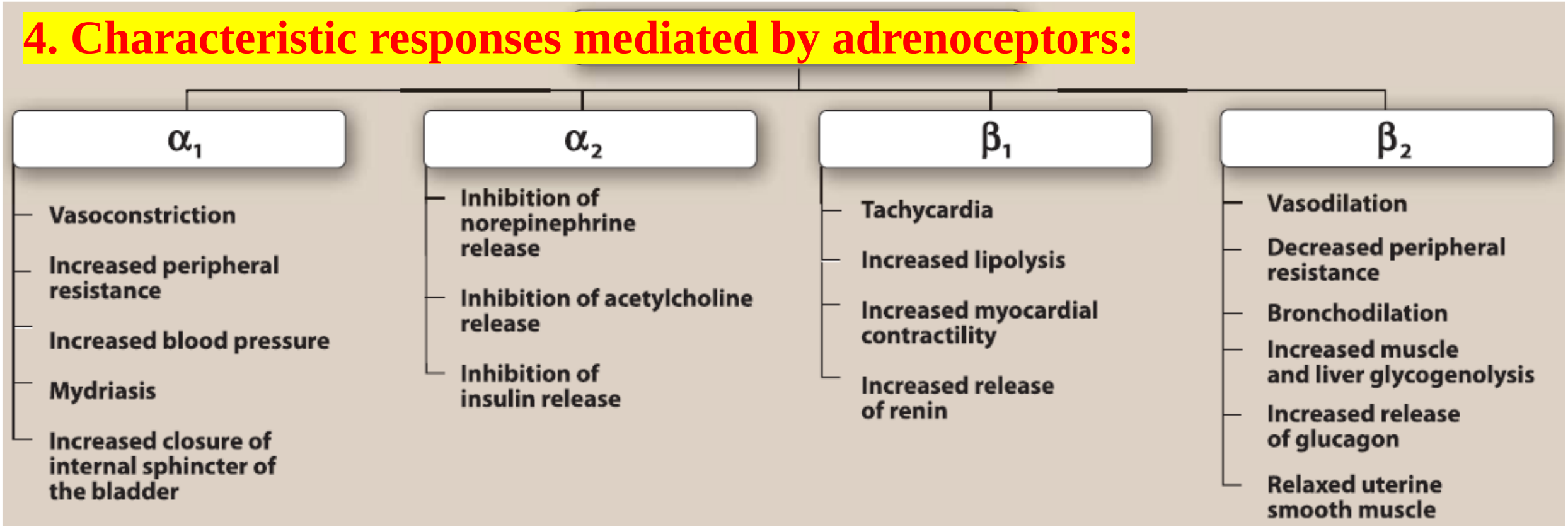


3. Distribution of receptors: Adrenergically innervated organs and tissues usually have a predominant type of receptor.

For example,

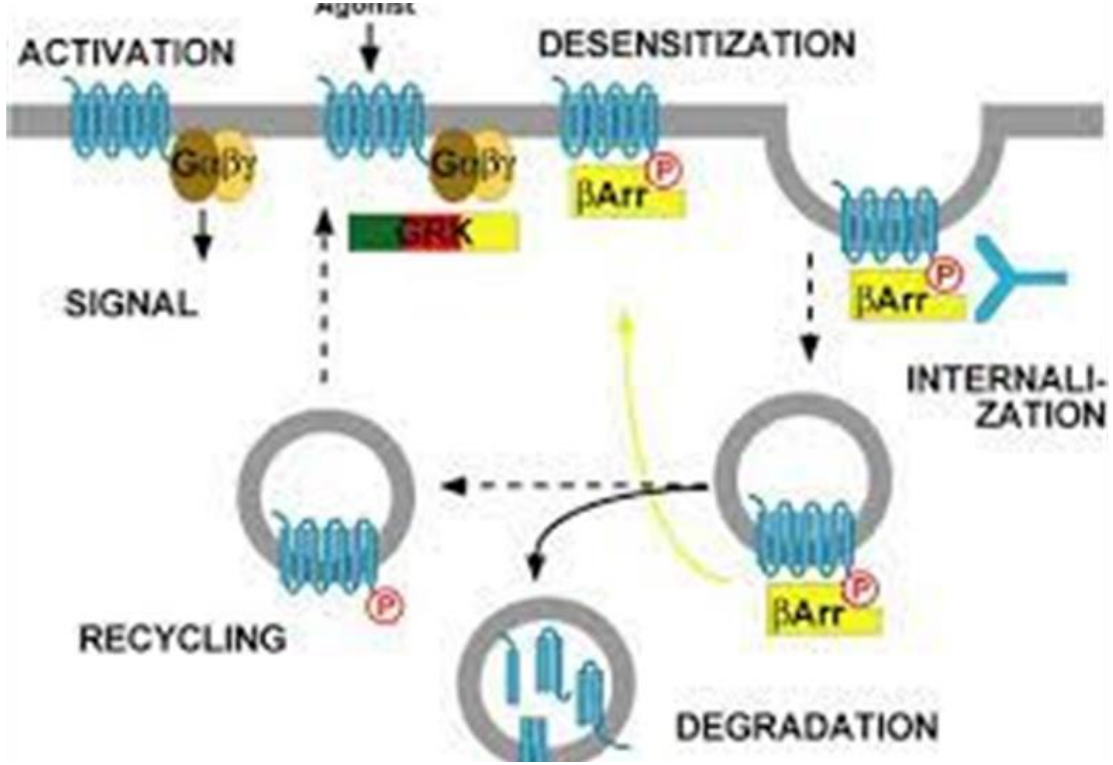
- Vasculature of skeletal muscle β_2 receptors.
- Heart contains predominantly β_1 receptors.

4. Characteristic responses mediated by adrenoceptors:



5. Desensitization of 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; and
3) an inability to couple to G-protein, because the receptor has been phosphorylated on the cytoplasmic side.

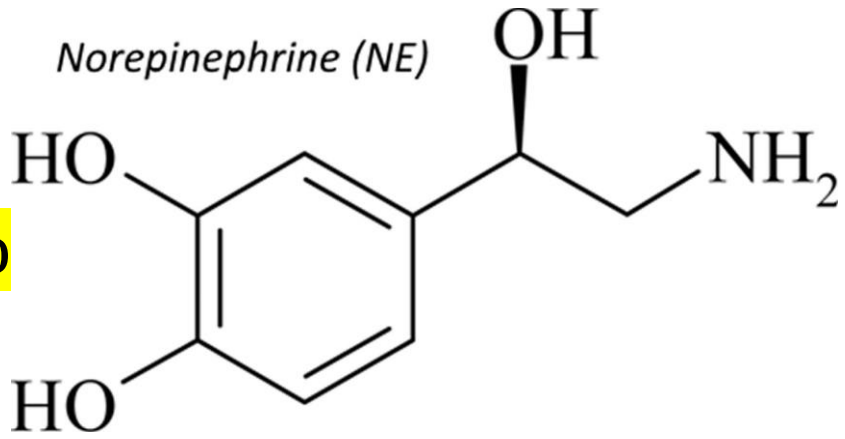


CHARACTERISTICS OF ADRENERGIC AGONISTS

Most adrenergic drugs are derivatives of p-phenylethylamine.
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.

A. Catecholamines

Sympathomimetic amines that contain the 3,4-dihydroxybenzene group
(such as epinephrine, norepinephrine, isoprotereno and dopamine) are called catecholamines.



Catecholamines compounds share the following properties:

1. High potency in directly activating α or β receptors.

2. Rapid inactivation: Catecholamines are metabolized by COMT postsynaptically and by MAO intraneuronally, 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.

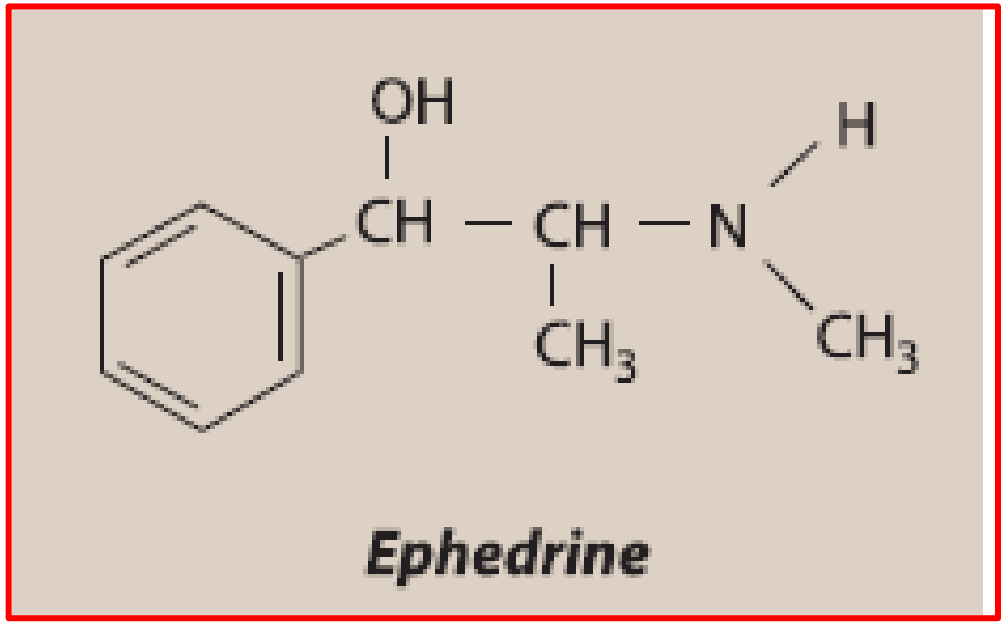
3. Poor penetration into the CNS: Catecholamines are polar and, therefore, do not readily penetrate into the CNS. Nevertheless, most catecholamines have some clinical effects (anxiety, tremor, and headaches) that are attributable to action on the CNS.

B. Noncatecholamines

Compounds lacking the catechol hydroxyl groups, because they are not inactivated by COMT and are poor substrates for MAO, thus, have longer half-lives.

Increased lipid solubility of (due to lack of polar hydroxyl groups) permits greater access to the CNS.

These include phenylephrine, ephedrine, and amphetamine

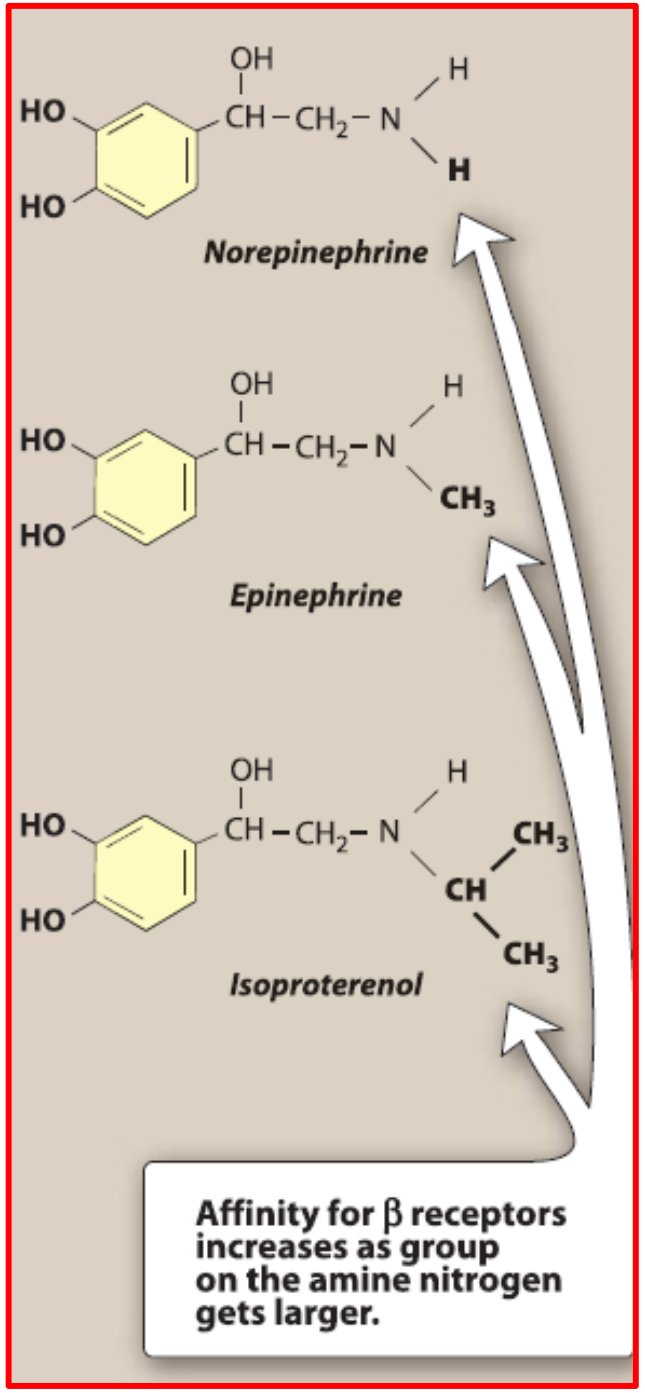


Ephedrine

C. Substitutions on the amine 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, is more potent at β receptors than norepinephrine. Similarly, isoproterenol, is a strong β agonist with little α activity



D. Mechanism of action of adrenergic agonists

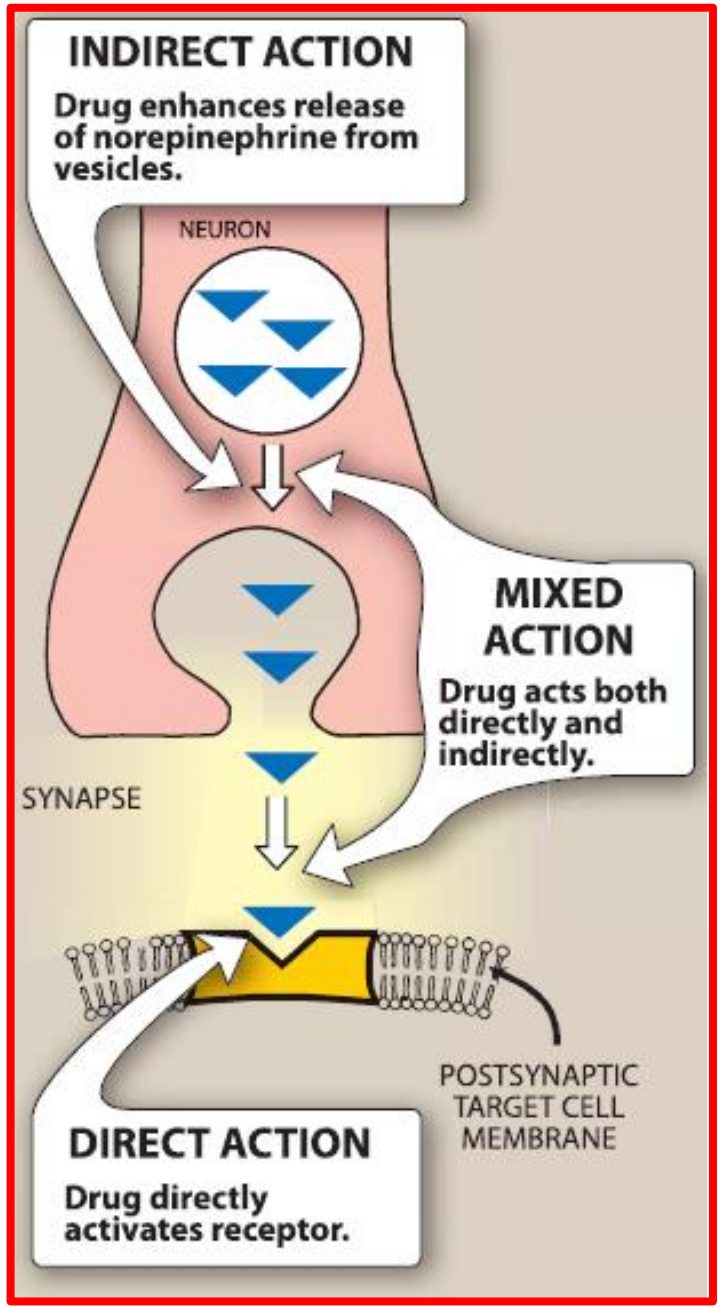
1. Direct-acting agonists: These drugs act directly on α or β receptors.

Examples of direct-acting agonists include epinephrine, norepinephrine, isoproterenol, dopamine, and phenylephrine.

2. Indirect-acting agonists: 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 amphetamine, respectively.

3. Mixed-action agonists: Ephedrine and its stereoisomer, pseudoephedrine, both stimulate adrenoceptors directly and enhance release of norepinephrine from the adrenergic neuron.



I--DIRECT-ACTING ADRENERGIC AGONISTS

Direct-acting agonists bind to adrenergic receptors on effector organs

A. Epinephrine [ep-i-NEF-rin]

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.

1. Actions

a. Cardiovascular:

Epinephrine strengthens the contractility of the myocardium (positive inotrope: β_1 action) and increases its rate of contraction (positive chronotrope: β_1 action). Therefore, cardiac output increases. These effects increase oxygen demands on the myocardium.

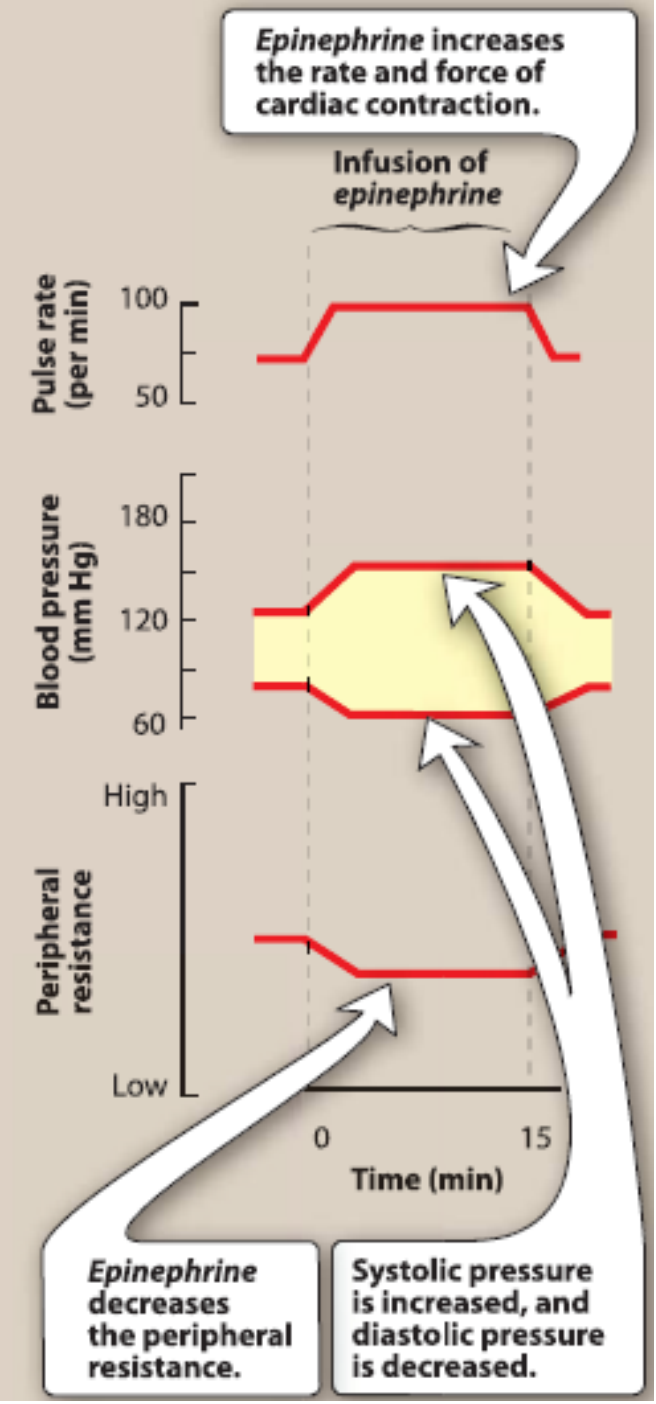
Epinephrine activates β_1 receptors on the kidney to cause renin release. Renin is an enzyme involved in the production of angiotensin II, a potent vasoconstrictor.

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). These combined effects result in a decrease in renal blood flow. 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.

b. Respiratory: Epinephrine causes powerful bronchodilation by acting directly on bronchial smooth muscle (β_2 action). It also inhibits the release of allergy mediators such as histamine from mast cells.

c. Hyperglycemia: Epinephrine has a significant hyperglycemic effect because of increased glycogenolysis in the liver (β_2 effect), increased release of glucagon (β2 effect), and a decreased release of insulin (α_2 effect).

d. Lipolysis: Epinephrine initiates by hydrolyzes triglycerides to free fatty acids and glycerol. through agonist activity on the β receptors of adipose tissue.



2. Therapeutic uses

a. Bronchospasm: Epinephrine is bronchodilator.

b. Anaphylactic shock: Epinephrine is the drug of choice for the treatment of type I hypersensitivity reactions. Within a few minutes after subcutaneous administration, respiratory function greatly improves.

c. Cardiac arrest: Epinephrine may be used to restore cardiac rhythm in patients with cardiac arrest.

d. Local anesthesia: Epinephrine greatly increases the duration of local anesthesia by producing vasoconstriction at the site of injection.

e. Intraocular surgery: Epinephrine is used in the induction and maintenance of mydriasis during intraocular surgery.

3. Pharmacokinetics: Epinephrine has a rapid onset but a brief duration of action (due to rapid degradation).

The preferred route for anaphylaxis in the outpatient setting is intramuscular (anterior thigh) due to rapid absorption.
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.

It is rapidly metabolized by MAO and COMT, and the metabolites metanephrine and vanillylmandelic acid are excreted in urine.

4. Adverse effects: Epinephrine can produce adverse CNS effects that include anxiety, fear, tension, headache, and tremor.

cardiac arrhythmias.

pulmonary edema.

dose must be reduced in Patients with hyperthyroidism.

Epinephrine increases the release of endogenous stores of glucose. In diabetic patients, dosages of insulin may have to be increased.

Nonselective β -blockers prevent vasodilatory effects of epinephrine on β_2 receptors, leaving a receptor stimulation unopposed. This may lead to increased peripheral resistance and increased blood pressure.

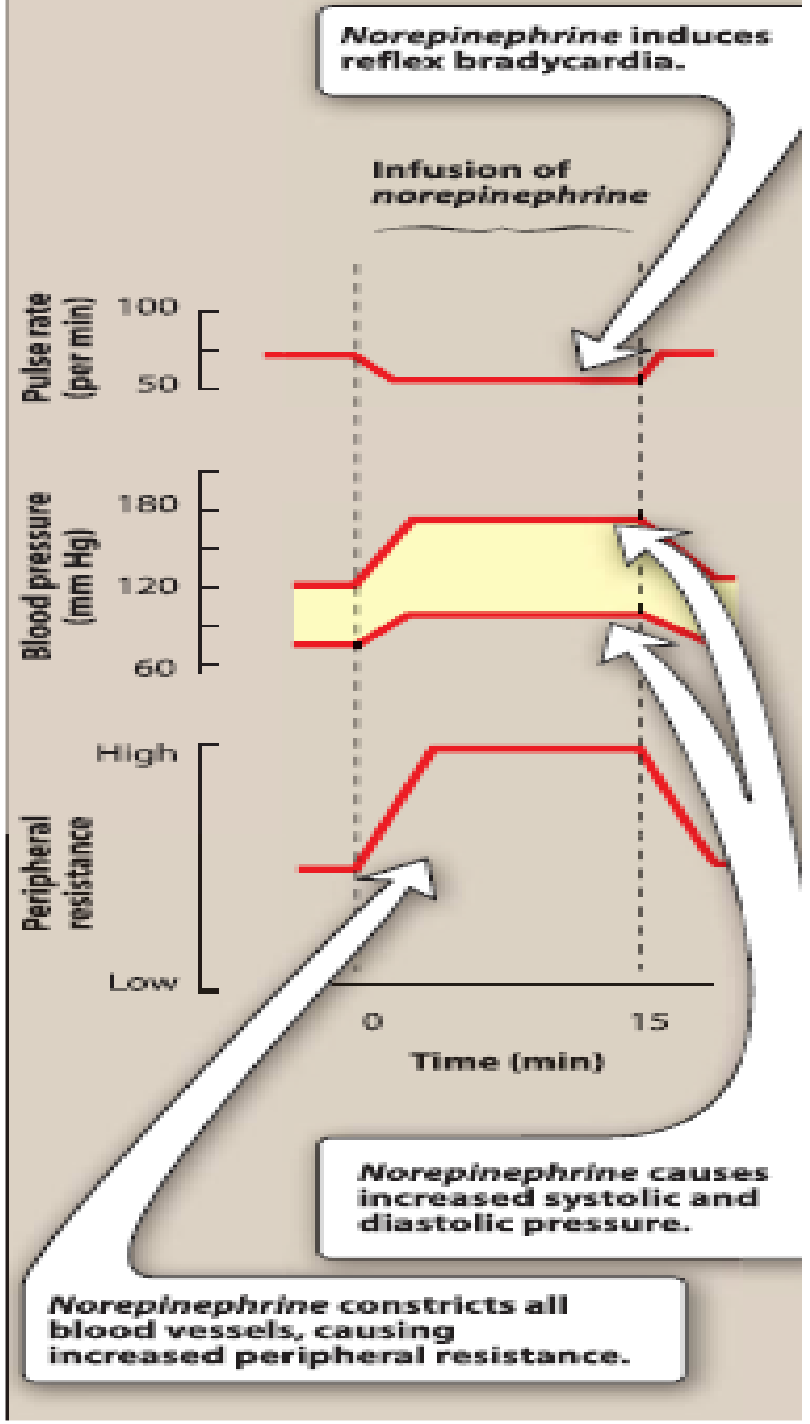
B. Norepinephrine [nor-ep-ih-NEF-rin]

when administered in therapeutic doses, the α - adrenergic receptor is most affected.

1. Cardiovascular actions

a. Vasoconstriction: Norepinephrine causes a rise in peripheral resistance due to intense vasoconstriction of most vascular beds, including the kidney (α_1 effect). Both systolic and diastolic blood pressures increase.

The weak β_2 activity of norepinephrine explains why it is not useful in the treatment of bronchospasm or anaphylaxis.



b. 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.

2. Therapeutic uses: Norepinephrine is used to treat shock (for example, septic shock), because it increases vascular resistance and, therefore, increases blood pressure. It has no other clinically significant uses.

3. 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 metabolized by MAO and COMT, and inactive metabolites are excreted in the urine.

4. 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), it can cause tissue necrosis.

Impaired circulation from norepinephrine may be treated with the α receptor antagonist phentolamine. Alternatives to phentolamine include intradermal terbutaline and topical nitroglycerin.

C. Isoproterenol [eye-soe-proe-TER-e-nole] is a direct-acting synthetic catecholamine that stimulates both β_1 and β_2 -adrenergic receptors.

Its nonselectivity is a disadvantage and the reason why it is rarely used therapeutically.

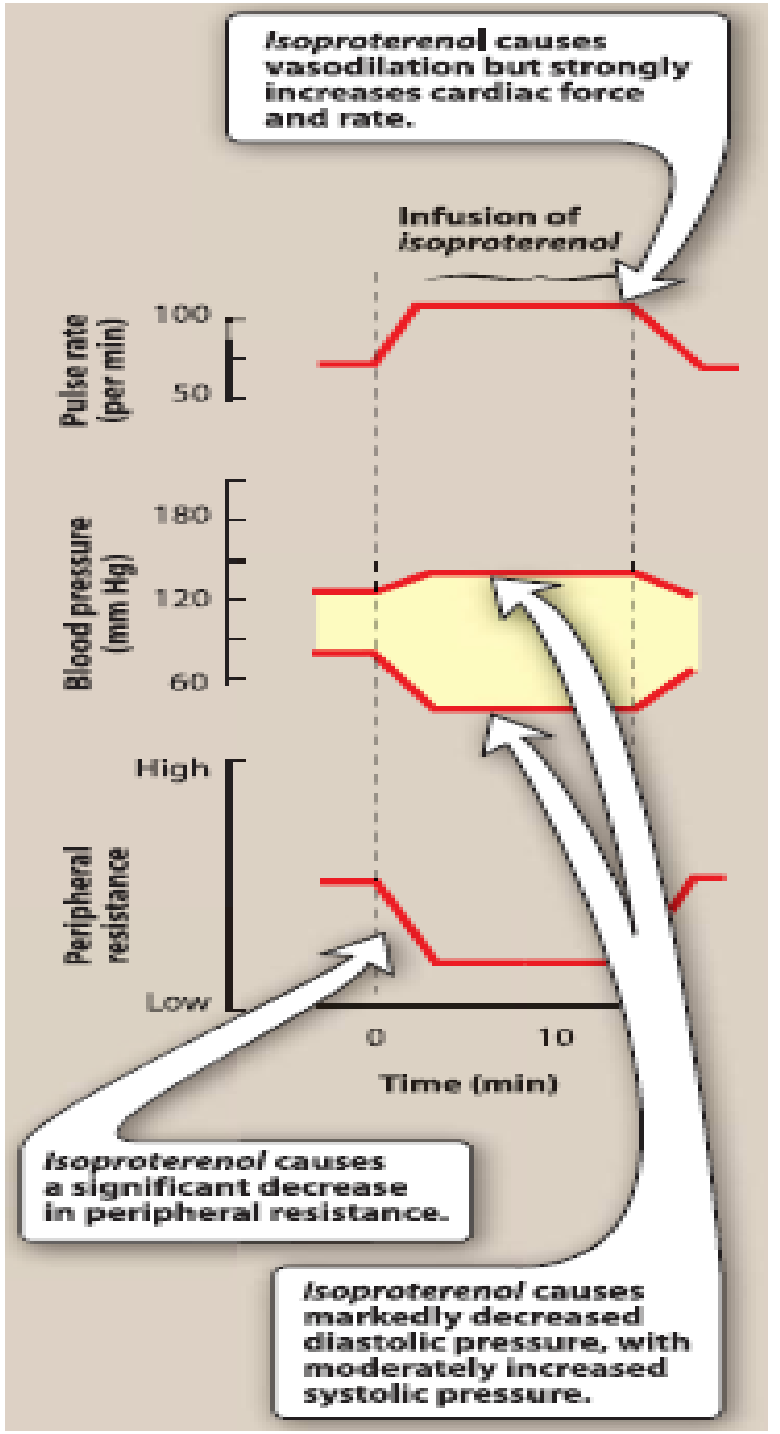
Its action on heart (β_1 effect), increasing heart rate, contractility, and cardiac output.

Isoproterenol also dilates the arterioles of skeletal muscle (β_2 effect), resulting in decreased peripheral resistance and reduces mean arterial and diastolic blood pressures.

It increases systolic blood pressure slightly.

Isoproterenol is also a potent bronchodilator (β_2 effect).

The adverse effects of isoproterenol are similar to the β receptor-related side effects of epinephrine.

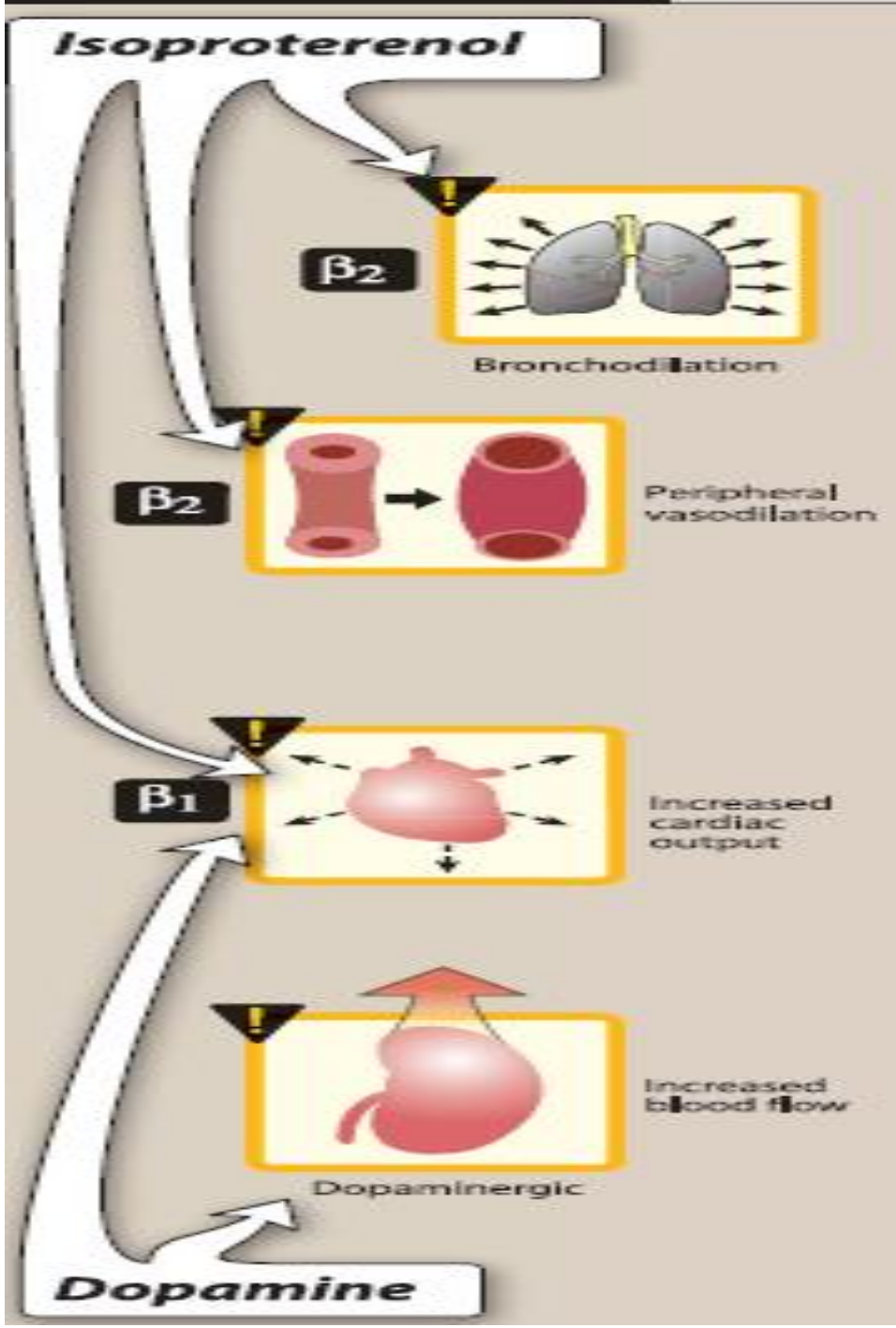


D. Dopamine [DOE-pa-meen], the immediate metabolic precursor of norepinephrine, and neurotransmitter in the CNS, as well as in the adrenal medulla.

Dopamine can activate α- and β-adrenergic receptors.

1. Actions

a. Cardiovascular: At higher doses, it causes vasoconstriction by activating α_1 receptors, whereas at lower doses, it stimulates β_1, cardiac receptors. having both positive inotropic and chronotropic effects



b. Renal and visceral: D_1 and D_2 dopaminergic receptors, occur in the peripheral mesenteric and renal vascular beds, where binding of dopamine produces vasodilation. Thereby increasing blood flow to the kidneys and other viscera.
in the past, low-dose ("renal-dose") dopamine was often used in the prevention or treatment of acute renal failure.

D_2 receptors are also found on presynaptic adrenergic neurons, where their activation interferes with norepinephrine release.

2. Therapeutic uses:

1- Cardiogenic and septic shock. (It raises blood pressure through activate α- and β-adrenergic receptors).

2- It enhances perfusion to the kidney and splanchnic areas, as enhances the glomerular filtration rate and causes diuresis.

By contrast, norepinephrine can diminish blood supply to the kidney and may reduce renal function.

3- Dopamine is also used to treat hypotension, severe heart failure, and bradycardia unresponsive to other treatments.

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

E- Fenoldopam [fen-OL-de-pam] is an agonist of peripheral dopamine D_1 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.

Fenoldopam is a racemic mixture, and the R-isomer is the active component. It undergoes extensive first-pass metabolism and has a 10-minute elimination halflife after IV infusion.

Headache, flushing, dizziness, nausea, vomiting, and tachycardia {due to vasodilation) may occur with this agent.

F- Dobutamine [doe-BYOO-ta-meen] is a synthetic, direct-acting catecholamine that is primarily a β_1 receptor agonist with minor β_2 and α_1 effects.

It increases heart rate and cardiac output with few vascular effects.

Dobutamine is used to increase cardiac output in acute heart failure, as well as for inotropic support after cardiac surgery.

The drug increases cardiac output and does not elevate oxygen demands of the myocardium as much as other sympathomimetic drugs.

Dobutamine should be used with caution in atrial fibrillation, because it increases atrioventricular {AV) conduction.

Other adverse effects are similar to epinephrine. Tolerance may develop with prolonged use.

G. Oxymetazoline [OX-ee-mee-TAZ-ih-leen] is a direct synthetic α_1 - and α_2 - adrenergic receptors agonist.

Oxymetazoline is found in many nasal decongestants, or in ophthalmic drops.

Oxymetazoline directly stimulates a receptors on blood vessels supplying the nasal mucosa and conjunctiva, thereby producing vasoconstriction and decreasing congestion.

Side effects:
1- It is absorbed in the systemic circulation and may produce nervousness, headaches, and trouble sleeping.
2- Local irritation and sneezing may occur with intranasal administration.
3- Use for greater than 3 days is not recommended, as rebound congestion and dependence may occur.

Phenylephrine [fen-iii-EF-reen] is a direct-acting, α_1 receptors agonist.

Phenylephrine is a vasoconstrictor that raises both systolic and diastolic blood pressures. And causes reflex bradycardia.

1- Uses treatment of paroxysmal supraventricular tachycardia.
2- Treatment of hypotension in hospitalized or surgical patients (especially those with a rapid heart rate).
3- Nasal decongestant. And replaced pseudoephedrine in many oral decongestants
4- in ophthalmic solutions for mydriasis.

Large doses can cause hypertensive headache and cardiac irregularities.

I. Midodrine

Midodrine, a prodrug, is metabolized to desglymidodrine. It is a selective α_1 agonist.
Midodrine is indicated for the treatment of orthostatic hypotension.

The drug should be given three times daily, with doses at 3- or 4-hour intervals.

To avoid supine hypertension, doses within 4 hours of bedtime are not recommended.

J. Clonidine [KLOE-ni-deen] is an α_2 agonist.

Uses:

1- Treatment of hypertension.

2- It can minimize symptoms of withdrawal from opiates, tobacco smoking, and benzodiazepines.

3- management of attention deficit hyperactivity disorder.

Clonidine acts centrally on presynaptic α_2 receptors to produce inhibition of sympathetic outflow to the periphery.

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

K. Albuterol [ai-BYOO-ter-ole], metaproterenol [MET-a-proe-TER-enol], and terbutaline [ter-BYOO-te-leen] are short-acting β_2 agonists (SABAs) used primarily as bronchodilators and administered by a metered-dose inhaler.

Albuterol is the SABA of choice for the management of acute asthma symptoms, because it is more selective for β_2 receptors than metaproterenol.

side effects

1- common one is tremor, but patients tend to develop tolerance to this effect.

2- restlessness, apprehension, and anxiety, tachycardia or arrhythmia (due to β_1 receptor activation).

Monoamine oxidase inhibitors (MAOis) also increase the risk of adverse cardiovascular effects, and concomitant use should be avoided.

L. Salmeterol [sal-ME-ter-ole], formoterol [for-MOH-ter-ole], and indacatero/[IN-daKA- ter-ol] are long-acting β_2 selective agonists (LABAs)

Uses:
Asthma and chronic obstructive pulmonary disease.
A single dose an inhaled dose provides bronchodilation over 12 hours, compared with less than 3 hours for albuterol.

Unlike formoterol, however, salmeterol has a somewhat delayed onset of action.
LA Bas are not recommended as monotherapy for the treatment of asthma, because they have been shown to increase the risk of asthmarelated deaths; however, these agents are highly efficacious when combined with an asthma controller medication such as an inhaled corticosteroid.

M. Mirabegron [mir-a-BEG-ron] is a β_3 agonist that relaxes the detrusor smooth muscle and increases bladder capacity. It is used for patients with overactive bladder.

Mirabegron is contraindicated for uncontrolled hypertension.
It is enzyme inhibitor increases levels of digoxin and metoprolol.

II--Indirect-acting Adrenergic Agonists

Indirect-acting adrenergic agonists cause the release, inhibit the reuptake, or inhibit the degradation of epinephrine or norepinephrine.

A. Amphetamine.
B. Tyramine.
C. Cocaine.

A. Amphetamine [am-FET-ameen]

However, the drug can also increase blood pressure significantly by α_1 agonist action on the vasculature, as well as β_1 stimulatory effects on the heart.

It increases release of catecholamines such as dopamine and norepinephrine from nerve terminals.

Thus, amphetamine is an indirect-acting adrenergic drug.

B. Tyramine [TIE-ra-meen] is not a clinically useful drug

It is found in fermented foods, such as aged cheese and wine.
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.

C. Cocaine [koe-KANE] blocks the sodium-chloride (Na+/CI-)--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.

In addition, the duration of action of epinephrine and norepinephrine is increased. Like amphetamines, it can increase blood pressure by α_1 agonist actions and β stimulatory effects.

III-- Mixed-action Adrenergic Agonists

Ephedrine [eh-FED-rin] and pseudoephedrine [soo-doe-eh-FED-rin]
They enhance release of stored norepinephrine from nerve endings and directly stimulate both a and p receptors. So, they have adrenergic actions like those of epinephrine, although less potent.

Ephedrine and pseudoephedrine are poor substrates for COMT and MAO. They have a long duration of action. And good absorption after oral administration and penetrate the CNS, but pseudoephedrine has fewer CNS effects.

Ephedrine raises systolic and diastolic blood pressures.
Ephedrine produces a mild stimulation of the CNS, 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.

Oral pseudoephedrine is primarily used 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.

TISSUE	RECEPTOR TYPE	ACTION	OPPOSING ACTIONS
Heart			
• Sinus and AV	β_1	↑ Automaticity	Cholinergic receptors
• Conduction pathway	β_1	↑ Conduction velocity, automaticity	Cholinergic receptors
• Myofibrils	β_1	↑ Contractility, automaticity	
Vascular smooth muscle	β_2	Vasodilation	α-Adrenergic receptors
Bronchial smooth muscle	β_2	Bronchodilation	Cholinergic receptors
Kidneys	β_1	↑ Renin release	α_1-Adrenergic receptors
Liver	β_2, α_1	↑ Glycogenolysis and gluconeogenesis	—
Adipose tissue	β_1, β_3	↑ Lipolysis	α_2-Adrenergic receptors

Skeletal muscle	β_2	↑ Increased contractility Potassium uptake; glycogenolysis Dilates arteries to skeletal muscle Tremor	—
Eye-ciliary muscle	β_2	Relaxation	Cholinergic receptors
GI tract	β_2	↓ Motility	Cholinergic receptors
Gall bladder	β_2	Relaxation	Cholinergic receptors
Urinary bladder detrusor muscle	β_2, β_3	Relaxation	Cholinergic receptors
Uterus	β_2	Relaxation	Oxytocin

References

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Thank you