DRUGS THAT ACT IN THE ANS

Direct-Acting Adrenergic Agonists

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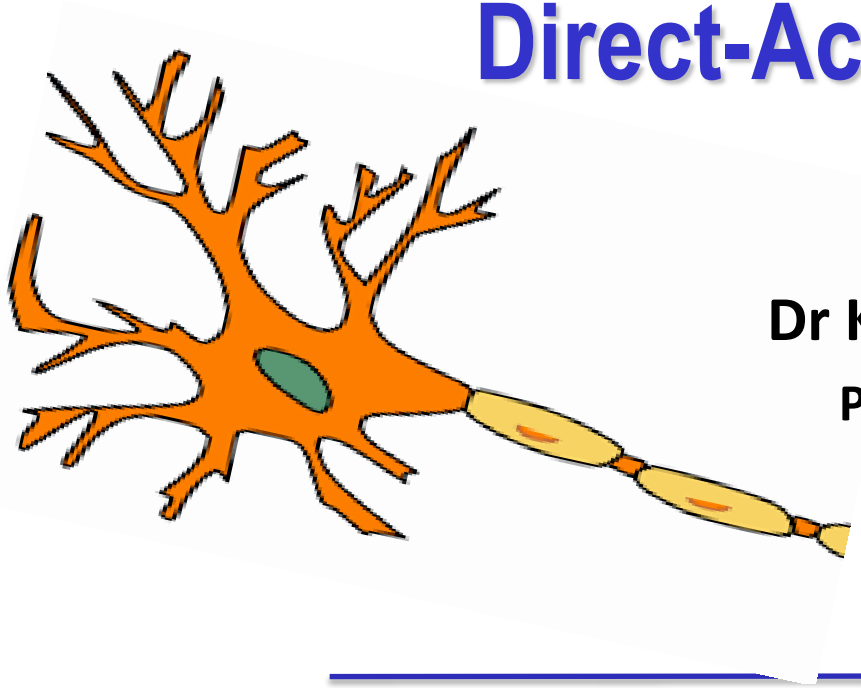

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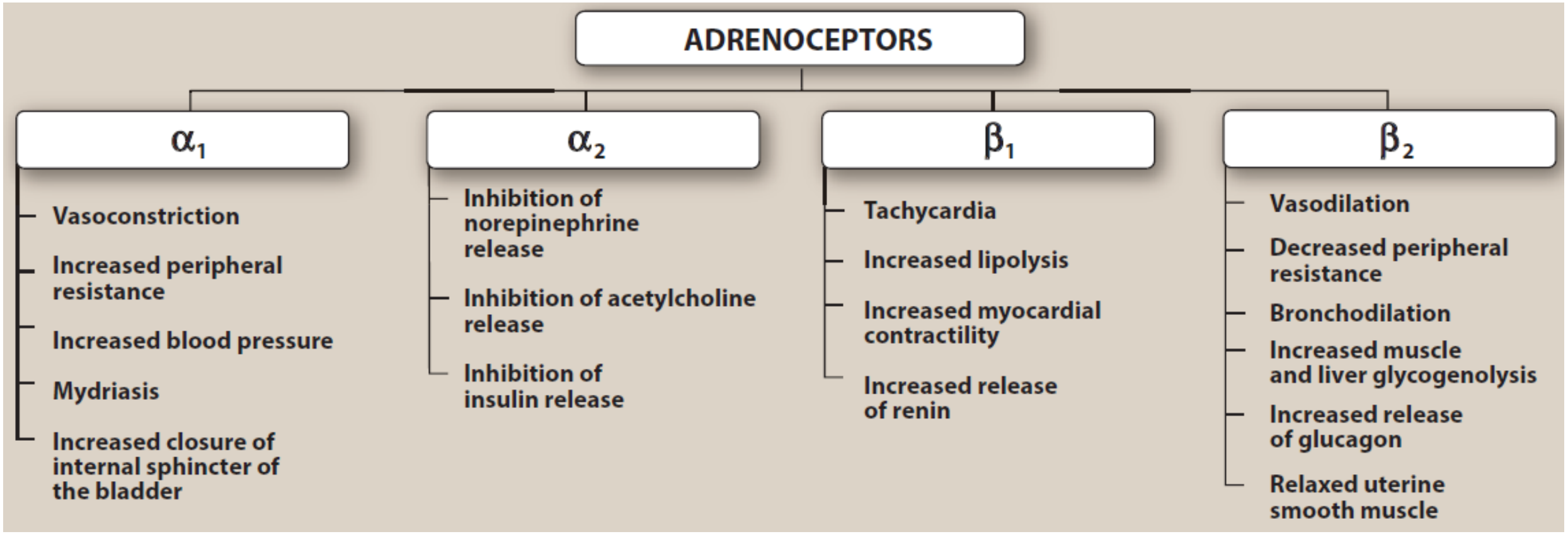


Major effects mediated by α- and β-adrenoceptors.

Direct-Acting Adrenergic Agonists/ A. Epinephrine

Epinephrine is one of the four **catecholamines (epinephrine, norepinephrine, dopamine, and dobutamine)** commonly used in therapy.

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.

Direct-Acting Adrenergic Agonists/ A. Epinephrine/ 1. Actions:

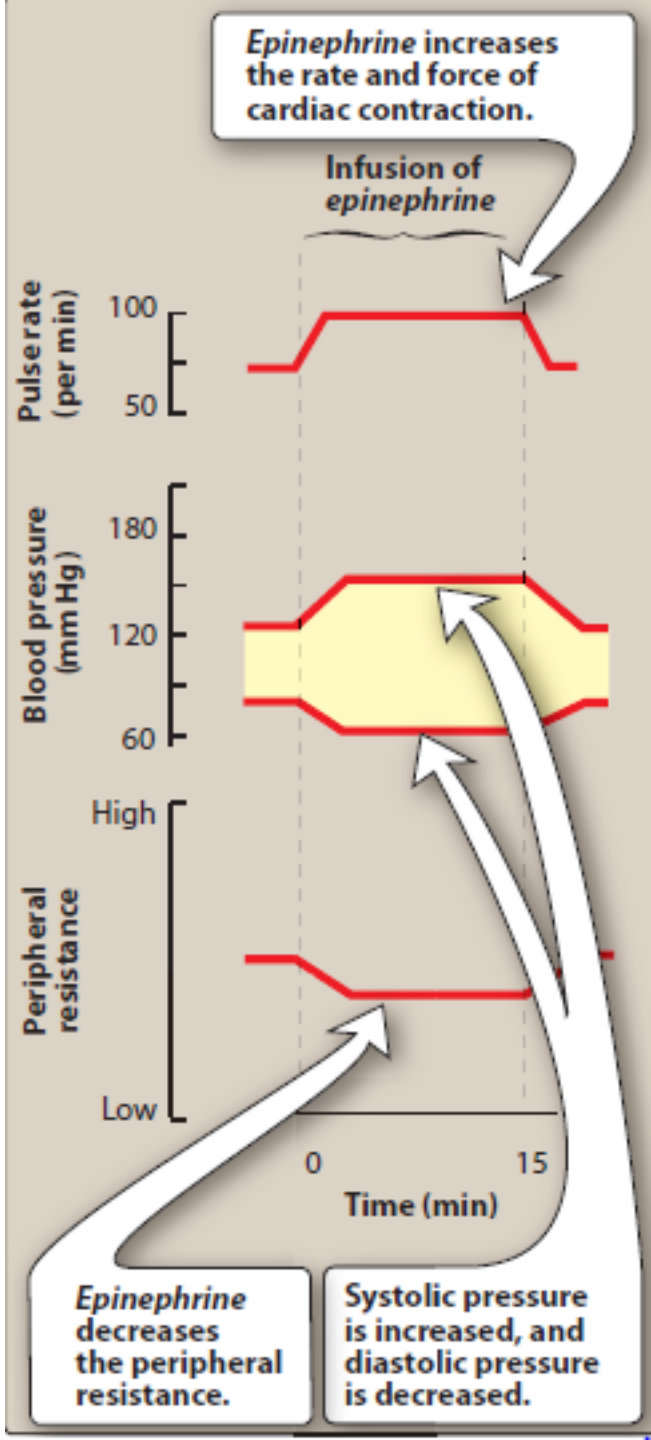
a. Cardiovascular: The major actions of epinephrine are on the cardiovascular system.

Epinephrine strengthens the contractility of the myocardium (**positive inotrope**: β1 action) and increases its rate of contraction (**positive chronotrope**: β1 action). Therefore, cardiac output increases.

These effects increase oxygen demands on the myocardium.

Epinephrine activates β1 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 (β2 effects). Renal blood flow is decreased.



Direct-Acting Adrenergic Agonists/ A. Epinephrine/ 1. Actions:

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 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).

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 hydrolyzes triglycerides to free fatty acids and glycerol.

Direct-Acting Adrenergic Agonists/ A. Epinephrine/ 2. Therapeutic uses:

a. **Bronchospasm:** Epinephrine is the primary drug used in the **emergency** treatment of respiratory conditions when **bronchoconstriction** has resulted in diminished respiratory function.

Thus, in treatment of acute asthma and anaphylactic shock, epinephrine is the drug of choice and can be life saving in this setting.

Within a few minutes after subcutaneous administration, respiratory function greatly improves.

Direct-Acting Adrenergic Agonists/ A. Epinephrine/ 2. Therapeutic uses:

b. Anaphylactic shock: Epinephrine is the drug of choice for the treatment of type I hypersensitivity reactions (including anaphylaxis) in response to allergens.

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

d. Anesthetics: Local anesthetic solutions may contain low concentrations (for example, 1:100,000 parts) of epinephrine.

Very weak solutions of epinephrine can also be applied topically to vasoconstrict mucous membranes and control oozing of capillary blood.

Direct-Acting Adrenergic Agonists/ A. Epinephrine/ 4. Adverse effects:

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

It can trigger **cardiac** arrhythmias, particularly if the patient is receiving digoxin.

Epinephrine can also induce **pulmonary** edema.

Epinephrine may have enhanced cardiovascular actions in patients with **hyperthyroidism**, and the dose must be reduced in these individuals.

Inhalation anesthetics also sensitize the heart to the effects of epinephrine, which may lead to tachycardia.

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

Direct-Acting Adrenergic Agonists/ B. Norepinephrine/ Actions:

1. Cardiovascular actions:

a. 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.

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.

Direct-Acting Adrenergic Agonists/ B. Norepinephrine

2. 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.

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 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.

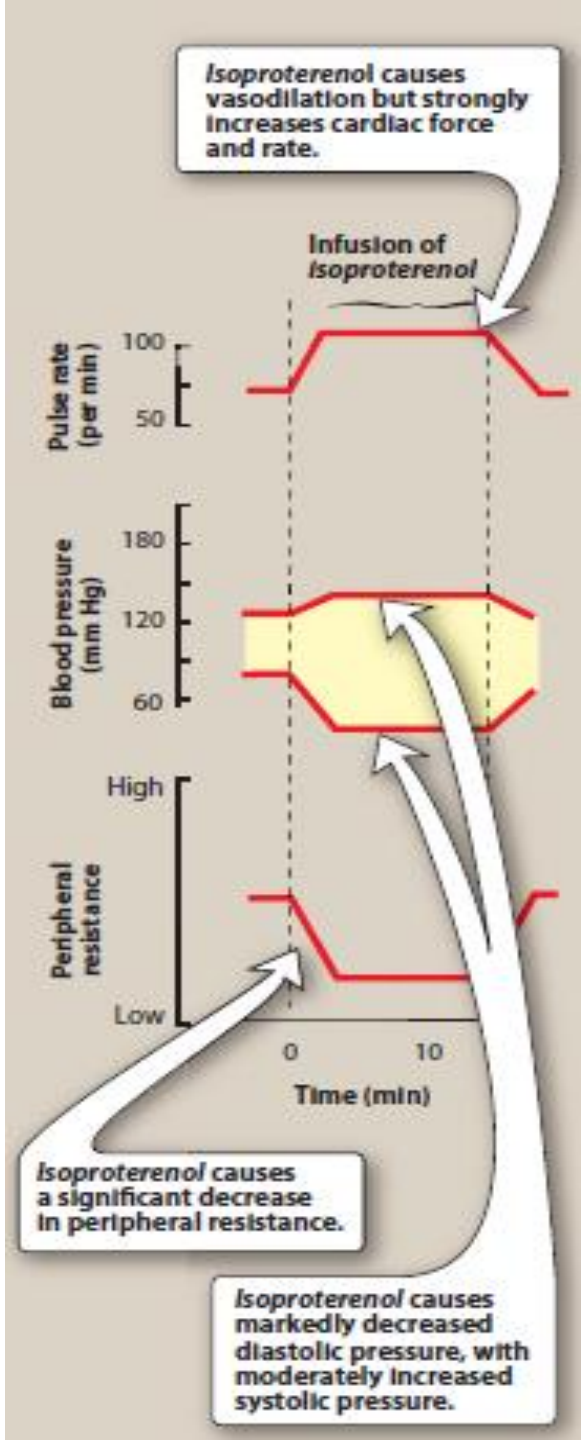
Direct-Acting Adrenergic Agonists/ C. Isoproterenol

Isoproterenol is a direct-acting synthetic catecholamine that stimulates both **β1- and β2**-adrenergic receptors.

Isoproterenol produces intense stimulation of the heart, increasing heart rate, contractility, and cardiac output.

It is as active as epinephrine in this action. Isoproterenol also dilates the arterioles of **skeletal muscle (β2 effect),** resulting in decreased peripheral resistance.

Because of its cardiac stimulatory action, it may **increase systolic blood** pressure slightly, but it greatly **reduces diastolic blood** pressures.



C. Isoproterenol

Isoproterenol 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.

Direct-Acting Adrenergic Agonists/ D. 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. 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.

Direct-Acting Adrenergic Agonists/ D. Dopamine

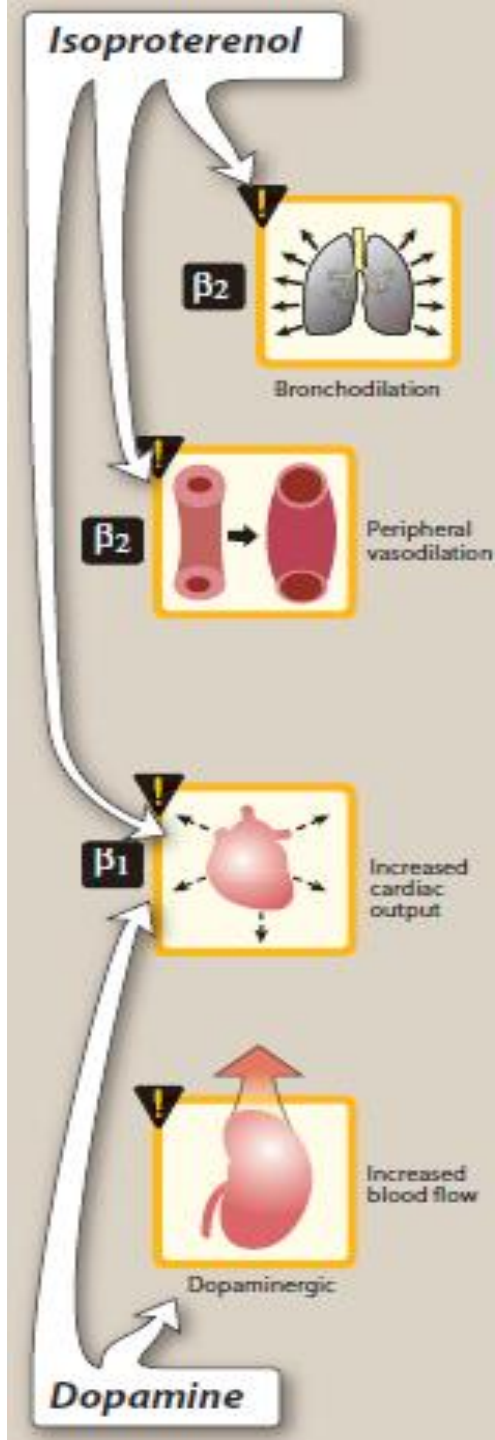
1. Actions:

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.

These receptors are not affected by α- or β-blocking drugs. Therefore, dopamine is clinically useful in the treatment of **shock**, in which significant increases in sympathetic activity might compromise renal function.



2. 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, as described above.

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.

3. 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

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 may be observed with this agent.**

F. Dobutamine

Dobutamine is a synthetic, direct-acting **catecholamine** that is a **β1 receptor** agonist. It increases cardiac rate and 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.

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

Other adverse effects are similar to epinephrine.

Tolerance may develop with prolonged use.

G. Oxymetazoline

Oxymetazoline is a direct-acting synthetic adrenergic agonist that stimulates both **α1- and α2-adrenergic receptors.**

Oxymetazoline 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.

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

It is absorbed in the systemic circulation regardless of the route of administration and may produce nervousness, headaches, and trouble sleeping.

Local irritation and sneezing may occur with intranasal administration.

H. Phenylephrine

Phenylephrine is a direct-acting, synthetic adrenergic drug that binds primarily to **α1 receptors.**

It has no effect on the heart itself but, rather, induces **reflex bradycardia** when given parenterally.

The drug is used to treat hypotension in hospitalized or surgical patients (especially those with a rapid heart rate).

Large doses can cause hypertensive headache and cardiac irregularities.

Phenylephrine acts as a nasal decongestant when applied topically or taken orally.

I. Clonidine

Clonidine is an **α2 agonist** that is used for the treatment of hypertension.

It can also be used to minimize the symptoms that accompany withdrawal from opiates, tobacco smoking, and benzodiazepines.

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

The most common side effects of clonidine are lethargy, sedation, constipation, and xerostomia.

Abrupt discontinuance must be avoided to prevent **rebound hypertension**.

J. Albuterol and terbutaline

Albuterol and terbutaline are **short-acting β2 agonists** used primarily as **bronchodilators** and administered by a metered-dose inhaler.

Albuterol is the short-acting β2 agonist of choice for the management of acute **asthma** symptoms.

Terbutaline is also used off-label as a uterine relaxant to **suppress premature labor**.

One of the most common side effects of these agents is **tremor**, but patients tend to develop tolerance to this effect.

Other side effects include restlessness, apprehension, and anxiety. When these drugs are administered orally, they may cause **tachycardia** or arrhythmia (due to **β1 receptor** activation), especially in patients with underlying cardiac disease.

K. Salmeterol and formoterol

Salmeterol and formoterol are **long acting β agonists (LABAs) that are β2** selective.

A single dose by a metered-dose inhalation device, such as a dry powder inhaler, provides sustained **bronchodilation** over 12 hours, compared with less than 3 hours for albuterol.

Unlike formoterol, however, salmeterol has a somewhat delayed onset of action.

Salmeterol and formoterol are the agents of choice for treating nocturnal asthma in symptomatic patients taking other asthma medications.

L. Mirabegron

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 also **inhibits the CYP2D6 isozyme**, which may enhance the effects of other medications metabolized by this pathway (for example, **metoprolol**).