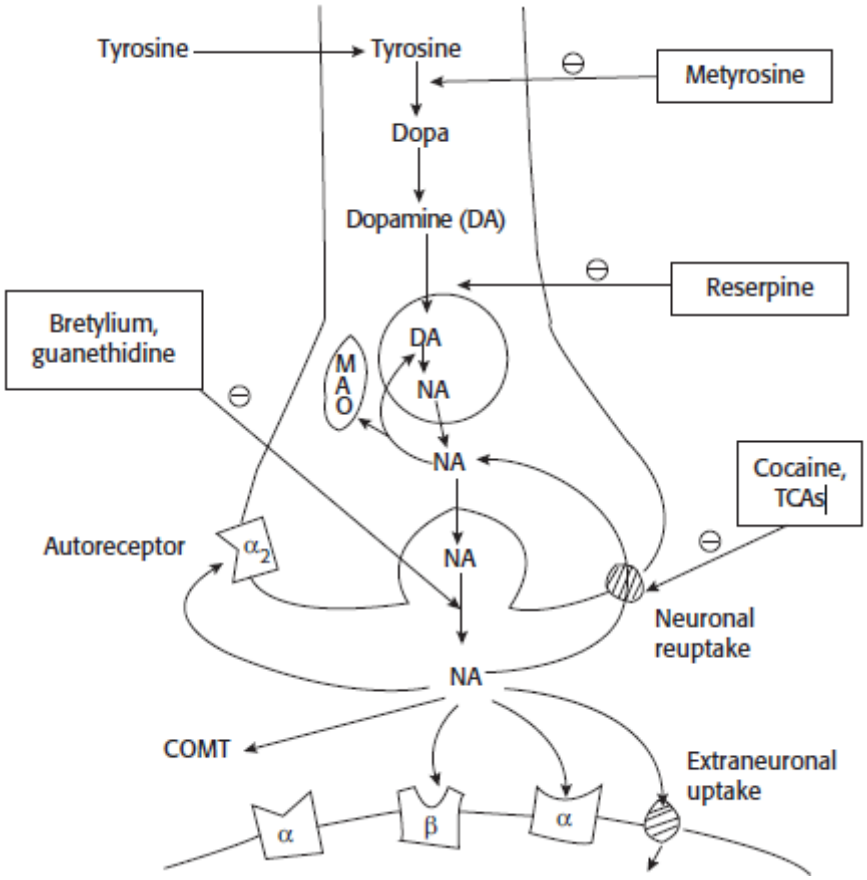
# ADRENERGIC TRANSMISSION

- The transmitter in the sympathetic system is noradrenaline (NA; norepinephrine).
- Nerves that synthesize, store and release NA are called adrenergic (sympathetic) nerves.
- Synthesis of catecholamines begins with the amino acid tyrosine, which is transported into the adrenergic neuron by active transport. In the neuronal cytosol, tyrosine is converted to DOPA and then DOPA is converted to dopamine. Dopamine enters the storage vesicles of the nerve terminal by active transport, where it is converted to NA; the NA formed gets stored in the vesicles. In the adrenal medulla, NA is further converted to adrenaline. Small quantities of NA are released continuously into the synaptic cleft and large quantities during nerve stimulation.




**Three processes are involved in the termination of action of released NA in the synaptic cleft (fate of released NA in the synaptic cleft)**:

Norepinephrine may

1) diffuse out of the synaptic space and enter the systemic circulation,

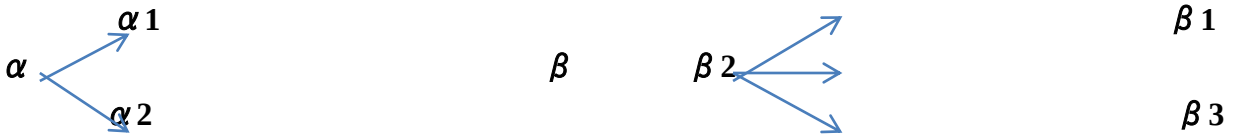
2) be metabolized to inactive metabolites by catechol-O-methyltransferase (COMT) in the synaptic space, or

3) undergo reuptake back into the neuron. Reuptake of norepinephrine into the presynaptic neuron is the primary mechanism for termination of its effects.

**Adrenergic receptors (adrenoceptors)**

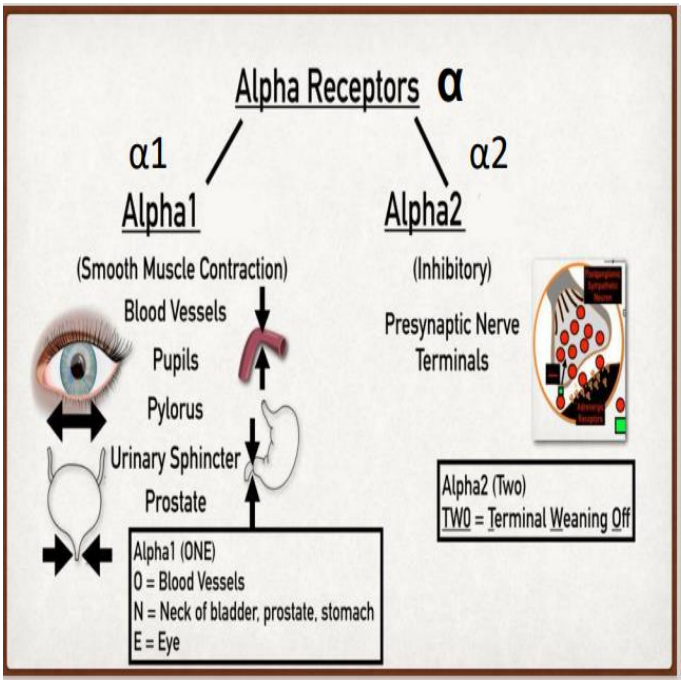
In the sympathetic nervous system, several classes of adrenoceptors can be distinguished pharmacologically. Two main families of receptors, designated $\alpha$ and $\beta$.

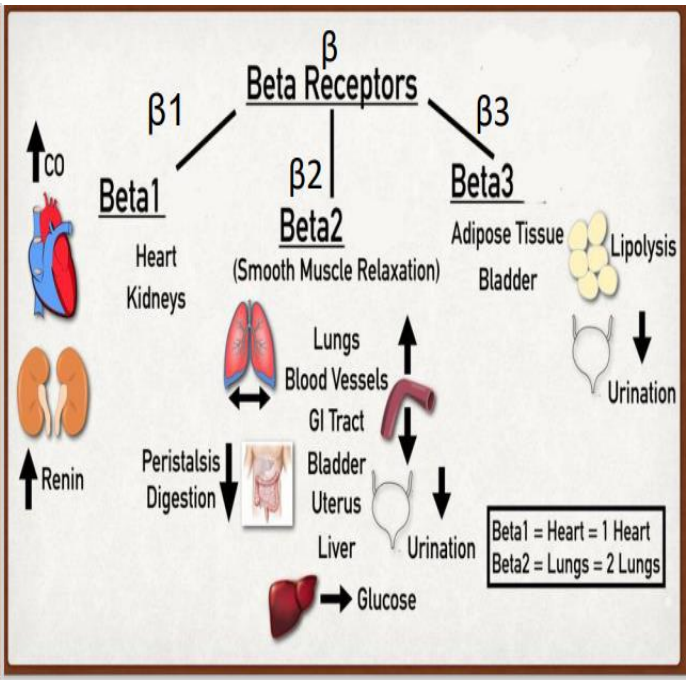
Both the $\alpha$ and $\beta$ receptor types have a number of specific receptor subtypes.




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.

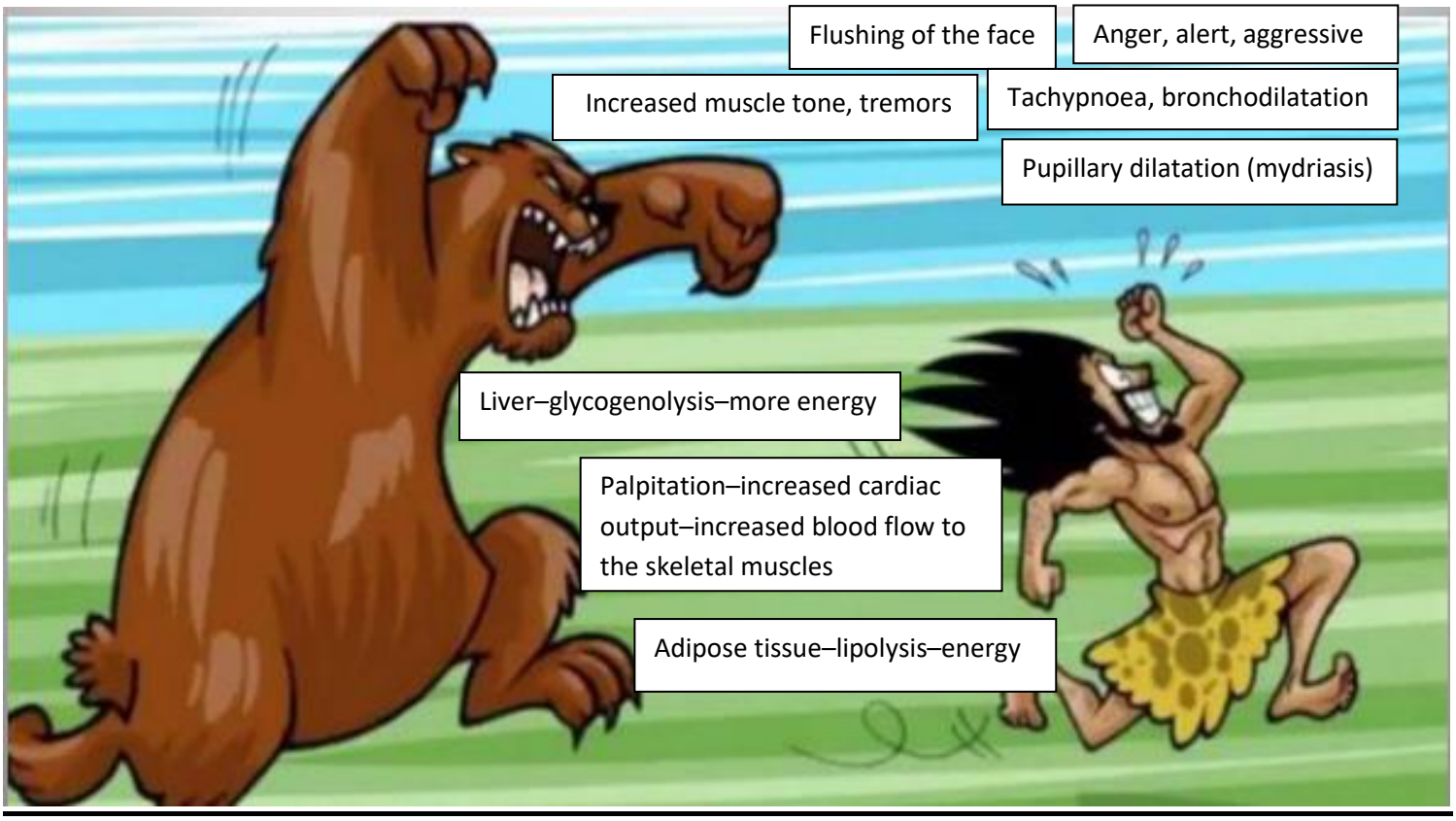
- Stimulation of α1 receptors characteristically produces vasoconstriction (particularly in skin and abdominal viscera) and an increase in total peripheral resistance and blood pressure.
- Stimulation of β1 receptors characteristically causes cardiac stimulation (increase in heart rate and contractility)
- Stimulation of β2 receptors produces vasodilation (in skeletal muscle vascular beds) and smooth muscle relaxation.
- β3 Receptors are involved in lipolysis (along with β1), and also have effects on the detrusor muscle of the bladder.



# Adrenergic agonists (Sympathomimetics):

The sympathomimetic drugs mimic the effects of sympathetic nerve stimulation.




## 1. Direct-acting agonists:

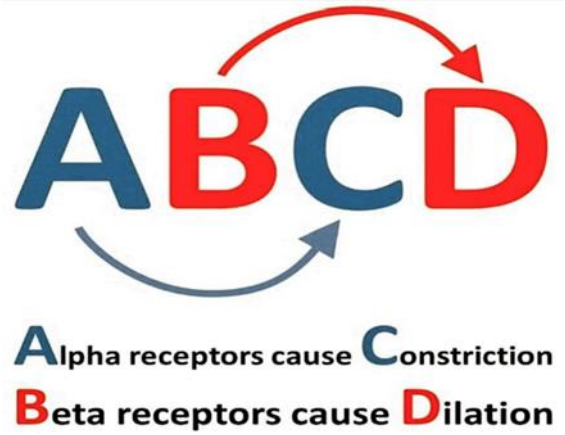
***Epinephrine:*** It is a catecholamine, which is secreted mainly by adrenal medulla. Adrenaline is a direct acting nonselective adrenergic agonist. Epinephrine (adrenaline) acts on α1, α2, β1, β2 and β3 receptors. Actions of epinephrine are:

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). 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 β2 receptor–mediated vasodilation in the skeletal muscle vascular bed.

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 histamine 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 β3 receptors of adipose tissue.

**Therapeutic uses of epinephrine (ABCDE)**

1. Anaphylactic shock: epinephrine is the life-saving drug in anaphylactic shock.

It rapidly reverses the manifestations of severe allergic reactions when given IM.

2. Bronchial asthma: Adrenaline is a powerful bronchodilator and has rapid onset but short duration of action. It is useful for acute attack. Its use has declined because of its dangerous cardiac-stimulant effect. It is given subcutaneously. It can be given by nebulization (as inhalation).

3. Cardiac resuscitation: In the treatment of cardiac arrest due to drowning or electrocution, epinephrine is injected IV along with other supportive measures such as external cardiac massage, as a part of advanced life support.

4. Prolongs the Duration of local anesthesia: epinephrine by its vasoconstrictor effect (α1) delays the systemic absorption of local anesthetic and prolongs the duration of local anesthesia and promotes local hemostasis.

5. Controls Epistaxis and other capillary oozing: Epinephrine is used as a local haemostatic to control bleeding following tooth extraction and during surgical procedures in nose, throat, larynx, etc. because of its vasoconstrictor effect.

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

**Adverse effects of epinephrine:**

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 due to increased afterload caused by vasoconstrictive properties of the drug. 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. 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. 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.

**Routs of administration:**
SC ( slow absorption).
IM (rapid absorption).
IV ( in emergency: rapid onset of action).
Inhalation (in bronchial asthma).
Intracardiac IC ( in resuscitation).

IV and IC routes are very dangerous (must be diluted to 1:10000).

**Contraindications:**
1. Severe hypertension .
2. Cardiac disease.
3. Thyrotoxicosis.

***Norepinephrine:*** when administered in therapeutic doses, the α- adrenergic receptor is most affected.
**Effects:**
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 bronchospasm or anaphylaxis.]
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.
**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.
**Pharmacokinetics:**
Norepinephrine is given IV for rapid onset of action. It is rapidly metabolized by MAO and COMT.
**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:*** Isoproterenol is a direct-acting synthetic catecholamine that stimulates both β1- and β2-adrenergic receptors. Its nonselectivity is a disadvantage and the reason why it is rarely used therapeutically. Its action on α receptors is insignificant. Isoproterenol produces intense stimulation of the heart (β1 effect), 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 mean arterial and diastolic blood pressures. Isoproterenol is also a potent bronchodilator (β2 effect). The adverse effects of isoproterenol are similar to the β receptor–related side effects of epinephrine.

***Dopamine:***

Dopamine occurs naturally in the CNS in, 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.

**Effects:**

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.

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.

**Therapeutic uses:**

Dopamine can be used for cardiogenic and septic shock. 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. It enhances perfusion to the kidney and splanchnic areas. Increased blood flow to the kidney enhances the glomerular filtration rate and causes diuresis. By contrast, norepinephrine can diminish blood supply to the kidney and may reduce renal function. 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.

***Fenoldopam:*** It is used as a rapid-acting vasodilator to treat severe hypertension in hospitalized patients, acting on coronary arteries, kidney arterioles, and mesenteric arteries.

***Dobutamine:*** is a synthetic, direct-acting catecholamine that is primarily a β1 receptor agonist. 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.

***Oxymetazoline:*** stimulates both α1- and α2-adrenergic receptors. Oxymetazoline is found in many over-the-counter 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. Local irritation and sneezing may occur with intranasal administration. Use for greater than 3 days is not recommended, as rebound congestion and dependence may occur.

***Phenylephrine:*** binds primarily to α1 receptors.
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, making it useful in the treatment of paroxysmal supraventricular tachycardia. 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. Phenylephrine has replaced pseudoephedrine in many oral decongestants, since pseudoephedrine has been misused to make methamphetamine. Phenylephrine is also used in ophthalmic solutions for mydriasis.

***Clonidine:*** is an α2 agonist used for the treatment of hypertension. It can also be used to 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. 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 discontinuation must be avoided to prevent rebound hypertension.

***Albuterol, metaproterenol, and terbutaline***: are short-acting β2 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 β2 receptors than metaproterenol.
Injectable terbutaline is used off-label as a uterine relaxant to suppress premature labor, and use for this indication should not exceed 72 hours.
When these drugs are administered orally, they may cause tachycardia or arrhythmia (due to β1 receptor activation), especially in patients with underlying cardiac disease. Monoamine oxidase inhibitors (MAOIs) also increase the risk of adverse cardiovascular effects, and concomitant use should be avoided.

***Salmeterol, formoterol, and indacaterol***: are long-acting β2 selective agonists (LABAs) used for the management of respiratory disorders such as asthma and chronic obstructive pulmonary disease. 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 . 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:*** 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.

## 2. Indirect-Acting Adrenergic Agonists

Indirect-acting adrenergic agonists 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.

***Amphetamine:***

- It stimulates the CNS. It can also increase blood pressure significantly by α1 agonist action on the vasculature, as well as β1 stimulatory effects on the heart.
- Its actions are mediated primarily through an increase in nonvesicular release of catecholamines such as dopamine and norepinephrine from nerve terminals.
- Amphetamine is used in the treatment of attention deficit hyperactivity disorder (ADHD) in which some children are hyperkinetic and lack the ability to be involved in any activity for longer than a few minutes.
- It is also used in narcolepsy (a relatively rare sleep disorder characterized by uncontrollable bouts of sleepiness during the day) and in appetite suppression.
- Factors that limit the therapeutic usefulness of amphetamine include psychological and physiologic dependence.

***Tyramine:***

- It 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 by-product 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:***

- It has the ability to block the sodium–chloride 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.
- Like amphetamines, it can increase blood pressure by α1 agonist actions and β stimulatory effects.

## 3. Mixed-Action Adrenergic Agonists:

***Ephedrine*** and ***pseudoephedrine***:

- They are not catecholamines and are poor substrates for COMT and MAO. Therefore, these drugs have a long duration of action.
- Ephedrine and pseudoephedrine have excellent absorption after oral administration and penetrate the CNS.
- Ephedrine raises systolic and diastolic blood pressures by vasoconstriction and cardiac stimulation and it is indicated in anesthesia-induced hypotension.
- Oral pseudoephedrine is primarily used to treat nasal and sinus congestion.