Pharmacology I

Lecture: **11**

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Adrenergic Agonists

Characteristics of Adrenergic Agonist:

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

A. Catecholamines

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

1. High potency: Catecholamines (with –OH groups in the 3 and 4 positions on the benzene ring) show the highest potency in directly activating α or β receptors.

2. Rapid inactivation: Catecholamines are metabolized by COMT postsynaptically and by MAO intraneuronally, as well as by COMT and MAO in the gut wall, and by MAO in the liver. Thus, catecholamines have only a brief period of action when given parenterally, and they are inactivated (ineffective) when administered orally.

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

B. Non-catecholamines

Compounds lacking the catechol hydroxyl groups have longer half-lives, because they are not inactivated by COMT. These include *phenylephrine*, *ephedrine*, and *amphetamine* (Figure 1). These agents are poor substrates for MAO (an important route of metabolism) and, thus, show a prolonged duration of action. Increased lipid solubility of many of the non-catecholamines (due to lack of polar hydroxyl groups) permits greater access to the CNS.

Mechanism of action of adrenergic agonists:

1. Direct-acting agonists: These drugs act directly on α or β receptors, producing effects similar to those that occur following stimulation of sympathetic nerves or release of epinephrine from the adrenal medulla (Figure 2). Examples of direct-acting agonists include *epinephrine*, *norepinephrine*, *isoproterenol*, 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 (Figure 2).

The norepinephrine then traverses the synapse and binds to α or β receptors. Examples of reuptake inhibitors and agents that cause norepinephrine release include *cocaine* and *amphetamines*, respectively.

3. Mixed-action agonists: *Ephedrine* and its stereoisomer, *pseudoephedrine*, both stimulate adrenoceptors directly and release norepinephrine from the adrenergic neuron (Figure 2).

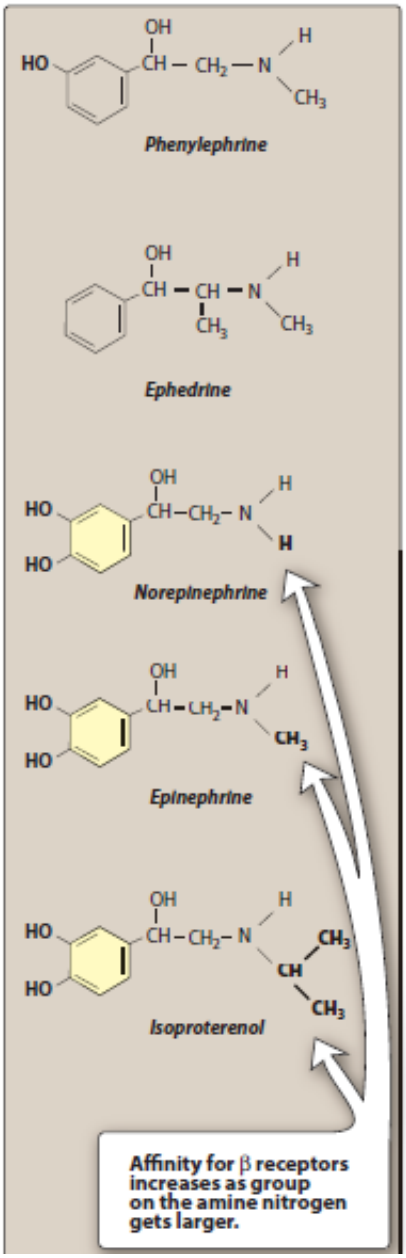

Figure 1: *Structures of several important adrenergic agonists. Drugs containing the catechol ring are shown in yellow.*

Direct-acting agonists:

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

A. Epinephrine

Epinephrine is one of the four catecholamines (*epinephrine*, *norepinephrine*, *dopamine*, and *dobutamine*) commonly used in therapy. The first three are naturally occurring neurotransmitters, and the latter is a synthetic compound. In the adrenal medulla, *norepinephrine* is methylated to yield *epinephrine*, which is stored in chromaffin cells along with *norepinephrine*. On stimulation, the adrenal medulla releases about 80% *epinephrine* and 20% *norepinephrine* directly into the circulation.

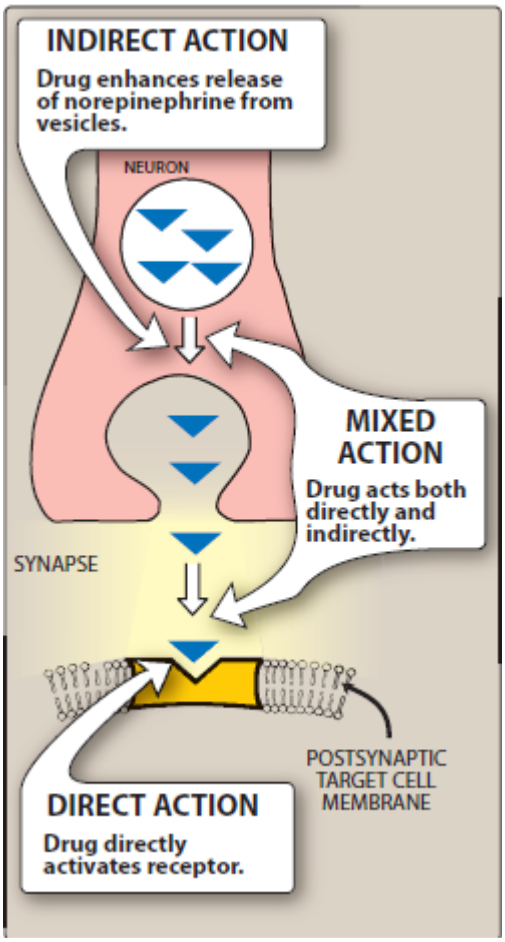

Figure 2: Sites of action of direct-, indirect-, and mixed-acting adrenergic agonists.

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: 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. 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 (Figure 3).

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.

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. However, selective β2 agonists, such as *albuterol*, are favored in the chronic treatment of asthma because of a longer duration of action and minimal cardiac stimulatory effects.

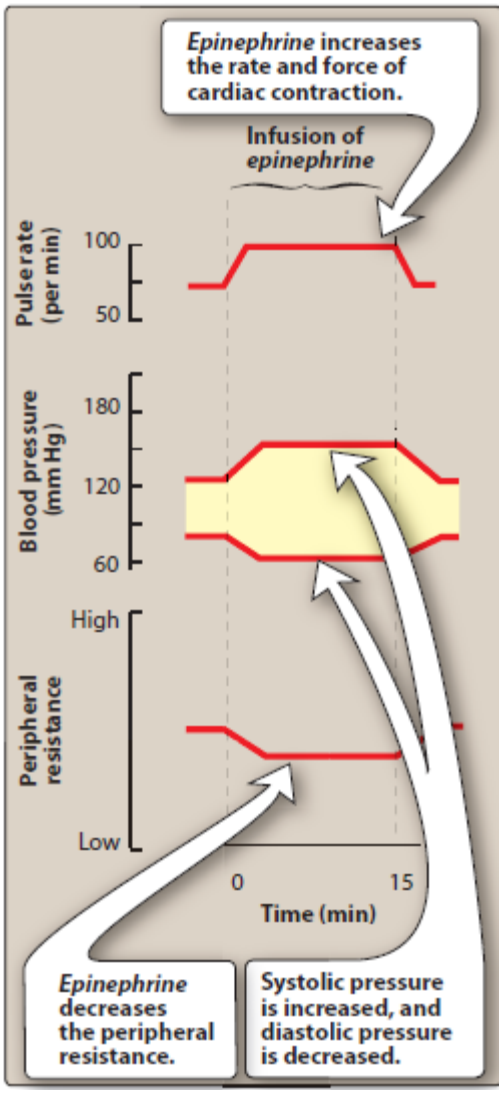

Figure 3: Cardiovascular effects of intravenous infusion of low doses of *epinephrine*.

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*. *Epinephrine* greatly increases the duration of local anesthesia by producing vasoconstriction at the site of injection. This allows the local anesthetic to persist at the injection site before being absorbed into the systemic circulation.

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.

Patients with hyperthyroidism may have an increased production of adrenergic receptors in the vasculature, leading to a hypersensitive response.

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.

B. Norepinephrine

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

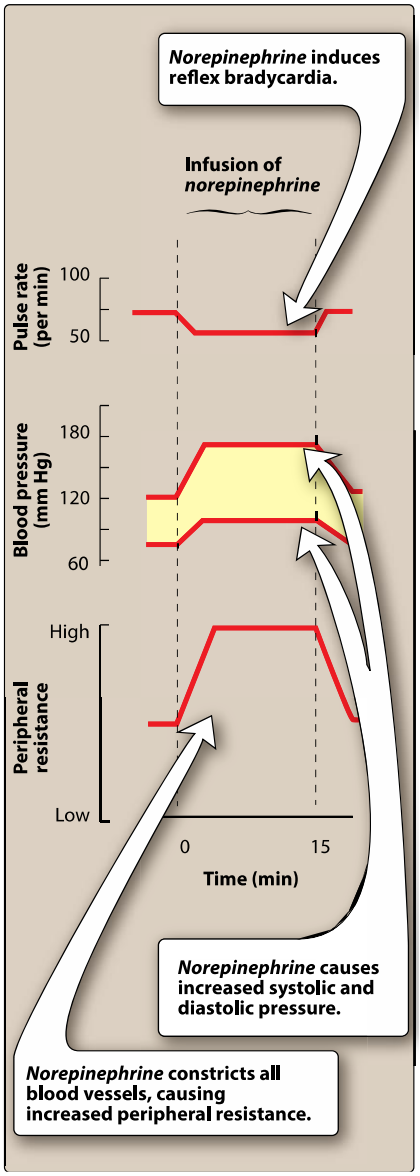

Figure 4: Cardiovascular effects of intravenous infusion of *norepinephrine*.

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 (Figure 4). [Note: *Norepinephrine* causes greater vasoconstriction than *epinephrine*, because it does not induce compensatory vasodilation via β2 receptors on blood vessels supplying skeletal muscles. The weak β2 activity of *norepinephrine* also explains why it is not useful in the treatment of asthma or anaphylaxis.]

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 (Figure 4). 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, because it increases vascular resistance and, therefore, increases blood pressure. It has no other clinically significant uses.

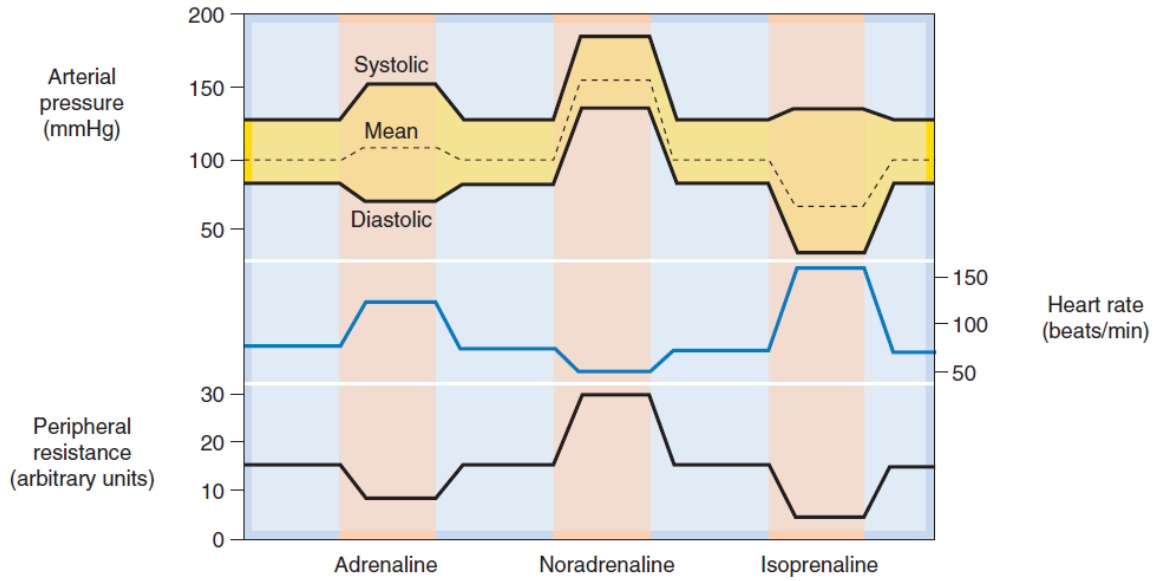

Figure 4: *Schematic representation of the cardiovascular effects of intravenous infusions of adrenaline, noradrenaline and isoprenaline in humans. Noradrenaline (predominantly α agonist) causes vasoconstriction and increased systolic and diastolic pressure, with a reflex bradycardia. Isoprenaline (β agonist) is a vasodilator, but strongly increases cardiac force and rate. Mean arterial pressure falls. Adrenaline combines both actions.*

C. Isoproterenol

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

Isoproterenol produces intense stimulation of the heart, increasing heart rate, contractility, and cardiac output (Figure 4). 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 (Figure 4). *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*.

D. Dopamine

Dopamine [DOE-pa-meen], 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.

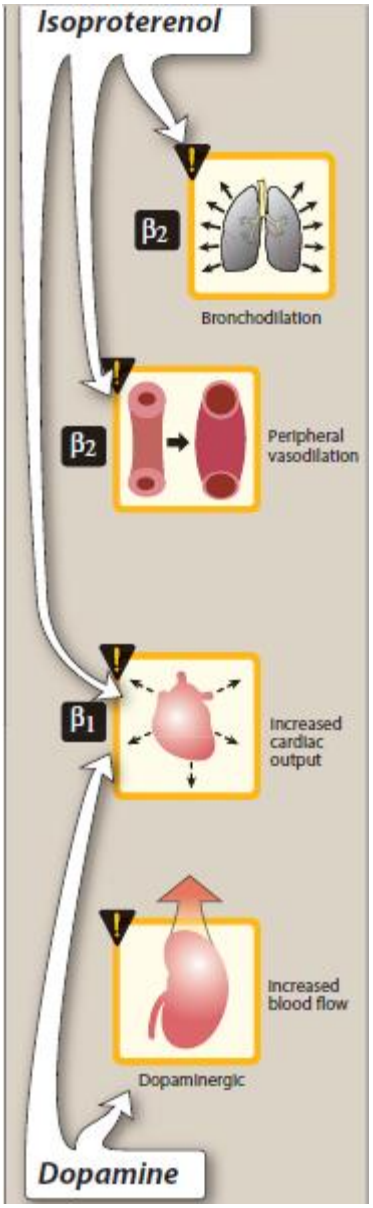

Figure 5: Clinically important actions of *isoproterenol* and *dopamine*.

1. Actions:

a. Cardiovascular: *Dopamine* exerts a stimulatory effect on the β1 receptors of the heart, having both positive inotropic and chronotropic effects (Figure 6.13). 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 (Figure 6.13). 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.

E. Fenoldopam

Fenoldopam is an agonist of peripheral dopamine D1 receptors. It is used as rapid-acting vasodilators to treat sever 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 half-life after IV infusion. Headache, flushing, dizziness, nausea, vomiting, and tachycardia (due to vasodilation) may be observed with this agent.

F. Dobutamine

Dobutamine is a synthetic, direct-acting catecholamine that is a β_1 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. The drug increases cardiac output and does not significantly elevate oxygen demands of the myocardium, a major advantage over other sympathomimetic drugs.

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. Rebound congestion and dependence are observed with long-term use.

H. Phenylephrine

Phenylephrine is a direct-acting, synthetic adrenergic drug that 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. 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* is also used in ophthalmic solutions for mydriasis.

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 β_2 agonists used primarily as bronchodilators and administered by a metered-dose inhaler. *Albuterol* is the short-acting β_2 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.

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

K. Salmeterol and formoterol

Salmeterol and *formoterol* are long acting β agonists (LABAs) that are β_2 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. These agents are not recommended as monotherapy, but are highly efficacious when combined with a corticosteroid. *Salmeterol* and *formoterol* are the agents of choice for treating nocturnal asthma in symptomatic patients taking other asthma medications.

L. Mirabegron

Mirabegron is a β_3 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.

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_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	Relaxation	Cholinergic receptors
Uterus	β_2	Relaxation	Oxytocin

CATECHOLAMINES

- Rapid onset of action
- Brief duration of action
- Not administered orally
- Do not penetrate the blood-brain barrier

NONCATECHOL-AMINES

Compared to catecholamines:

- Longer duration of action
- All can be administered orally or via inhalation

DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
Epinephrine	α_1, α_2 β_1, β_2	Acute asthma Anaphylactic shock In local anesthetics to increase duration of action
Norepinephrine	α_1, α_2 β_1	Treatment of shock
Isoproterenol	β_1, β_2	As a cardiac stimulant
Dopamine	Dopaminergic α_1, β_1	Treatment of shock Treatment of congestive heart failure Raise blood pressure
Dobutamine	β_1	Treatment of acute heart failure
Oxymetazoline	α_1	As a nasal decongestant
Phenylephrine	α_1	As a nasal decongestant Raise blood pressure Treatment of paroxysmal supraventricular tachycardia
Clonidine	α_2	Treatment of hypertension
Albuterol *Terbutaline*	β_2	Treatment of bronchospasm (short acting)
Salmeterol *Formoterol*	β_2	Treatment of bronchospasm (long acting)
Amphetamine	α, β, CNS	As a CNS stimulant in treatment of children with attention deficit syndrome, narcolepsy, and for appetite control
Ephedrine *Pseudoephedrine*	α, β, CNS	As a nasal decongestant Raise blood pressure

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.

A. Amphetamine

The marked central stimulatory action of *amphetamine* is often mistaken by drug abusers as its only action. However, the drug 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. Thus, *amphetamine* is an indirect-acting adrenergic drug. The actions and therapeutic uses of *amphetamine* and its derivatives are discussed under stimulants of the CNS.

B. Tyramine

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 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.

C. Cocaine

Cocaine is unique among local anesthetics in having the ability to block the sodium-chloride (Na+/Cl-)-dependent norepinephrine transporter required for cellular uptake of norepinephrine into the adrenergic neuron. Consequently, norepinephrine accumulates in the synaptic space, resulting in enhanced sympathetic activity and potentiation of the actions of epinephrine and norepinephrine. Therefore, small doses of the catecholamines produce greatly magnified effects in an individual taking *cocaine*. In addition, the duration

of action of epinephrine and norepinephrine is increased. Like *amphetamines*, it can increase blood pressure by α1 agonist actions and β stimulatory effects.

MIXED-ACTION ADRENERGIC AGONISTS

Ephedrine and *pseudoephedrine* are mixed-action adrenergic agents. They not only release stored norepinephrine from nerve endings but also directly stimulate both α and β receptors. Thus, a wide variety of adrenergic actions ensue that are similar to those of *epinephrine*, although less potent.

Ephedrine and *pseudoephedrine* are not catechols and are poor substrates for COMT and MAO. Therefore, these drugs have a long duration of action. *Ephedrine* and *pseudoephedrine* have excellent absorption orally and penetrate into the CNS, but *pseudoephedrine* has fewer CNS effects. *Ephedrine* is eliminated largely unchanged in urine, and *pseudoephedrine* undergoes incomplete hepatic metabolism before elimination in urine. *Ephedrine* raises systolic and diastolic blood pressures by vasoconstriction and cardiac stimulation and can be used to treat hypotension. *Ephedrine* produces bronchodilation, but it is less potent and slower acting than *epinephrine* or *isoproterenol*. It was previously used to prevent asthma attacks but has been replaced by more effective medications. *Ephedrine* produces a mild stimulation of the CNS. This increases alertness, decreases fatigue, and prevents sleep. It also improves athletic performance. [Note: The clinical use of *ephedrine* is declining because of the availability of better, more potent agents that cause fewer adverse effects. *Ephedrine*-containing herbal supplements (mainly ephedra-containing products) have been banned by the U.S. Food and Drug Administration because of life-threatening cardiovascular reactions.] *Pseudoephedrine* is primarily used orally to treat nasal and sinus congestion. *Pseudoephedrine* has been illegally used to produce *methamphetamine*.