Adrenergic Agonists
THE ADRENERGIC NEURON

• Adrenergic neurons release norepinephrine as the primary neurotransmitter.
• These neurons are found in the central nervous system (CNS) and also 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.
1. SYNTHESIS OF NOREPINEPHRINE
   - Hydroxylation of tyrosine is the rate-limiting step.

2. UPTAKE INTO STORAGE VESICLES
   - Dopamine enters a vesicle and is converted to norepinephrine.
   - Norepinephrine is protected from degradation in the vesicle.
   - Transport into the vesicle is inhibited by reserpine.

3. RELEASE OF NEUROTRANSMITTER
   - Influx of calcium causes fusion of the vesicle with the cell membrane in a process known as exocytosis.
   - Release is blocked by guanethidine.

4. BINDING TO RECEPTOR
   - Postsynaptic receptor is activated by the binding of neurotransmitter.

5. REMOVAL OF NOREPINEPHRINE
   - Released norepinephrine is rapidly taken into the neuron.
   - Reuptake is inhibited by SNRIs, cocaine, and imipramine.

6. METABOLISM
   - Norepinephrine is methylated by COMT and oxidized by MAO.

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**Diagram Elements:**
- Tyrosine
- Dopamine
- DOPA
- Norepinephrine (NE)
- Synaptic vesicle
- Presynaptic receptor
- Catechol-O-methyltransferase (COMT)
- Synaptic space
- MAO
- SNRIs
- Urine
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 on the basis of their responses to the adrenergic agonists epinephrine, norepinephrine, and isoproterenol.

• Each of these main receptor types has a number of specific receptor subtypes that have been identified.

• Alterations in the primary structure of the receptors influence their affinity for various agents.
**α₂ Receptors**
Activation of the receptor decreases production of cAMP, leading to an inhibition of further release of norepinephrine from the neuron.

**α₁ Receptors**
Activation of the receptor increases production of DAG and IP₃, leading to an increase in intracellular calcium ions.
A. α-Adrenoceptors

Epinephrine   Norepinephrine   Isoproterenol

↓↓↓

↓↓↓

↓↓↓

α Receptor

High affinity  Low affinity

B. β-Adrenoceptors

Isoproterenol   Epinephrine   Norepinephrine

↓↓↓

↓↓↓

↓↓↓

β Receptor

High affinity  Low affinity
Distribution of receptors:

• Adrenergically innervated organs and tissues usually have a predominant type of receptor.
• For example, tissues such as the vasculature of skeletal muscle have both $\alpha_1$ and $\beta_2$ receptors, but the $\beta_2$ receptors predominate.
• Other tissues may have one type of receptor almost exclusively.
• For example, the heart contains predominantly $\beta_1$ receptors.
Characteristic responses mediated by adrenoceptors:

• It is useful to organize the physiologic responses to adrenergic stimulation according to receptor type, because many drugs preferentially stimulate or block one type of receptor.

• As a generalization,

  1. stimulation of $\alpha_1$ receptors characteristically produces vasoconstriction (particularly in skin and abdominal viscera) and an increase in total peripheral resistance and blood pressure.

  2. Stimulation of $\beta_1$ receptors characteristically causes cardiac stimulation (increase in heart rate and contractility), whereas

  3. Stimulation of $\beta_2$ receptors produces vasodilation (in skeletal muscle vascular beds) and smooth muscle relaxation.
Characteristic responses mediated by adrenoceptors:

**\( \alpha_1 \)**
- Vasoconstriction
- Increased peripheral resistance
- Increased blood pressure
- Mydriasis
- Increased closure of internal sphincter of the bladder

**\( \alpha_2 \)**
- Inhibition of norepinephrine release
- Inhibition of acetylcholine release
- Inhibition of insulin release

**\( \beta_1 \)**
- Tachycardia
- Increased lipolysis
- Increased myocardial contractility
- Increased release of renin

**\( \beta_2 \)**
- Vasodilation
- Decreased peripheral resistance
- Bronchodilation
- Increased muscle and liver glycogenolysis
- Increased release of glucagon
- Relaxed uterine smooth muscle
Distribution of receptors:

- Adrenergically innervated organs and tissues usually have a predominant type of receptor.
- For example, tissues such as the vasculature of skeletal muscle have both α1 and β2 receptors, but the β2 receptors predominate.

- Other tissues may have one type of receptor almost exclusively.
- For example, the heart contains predominantly β1 receptors.
Characteristic responses mediated by adrenoceptors:

**ADRENOCEPTORS**

- $\alpha_1$
  - Vasoconstriction
  - Increased peripheral resistance
  - Increased blood pressure
  - Mydriasis
  - Increased closure of internal sphincter of the bladder

- $\alpha_2$
  - Inhibition of norepinephrine release
  - Inhibition of acetylcholine release
  - Inhibition of insulin release

- $\beta_1$
  - Tachycardia
  - Increased lipolysis
  - Increased myocardial contractility
  - Increased release of renin

- $\beta_2$
  - Vasodilation
  - Decreased peripheral resistance
  - Bronchodilation
  - Increased muscle and liver glycogenolysis
  - Increased release of glucagon
  - Relaxed uterine smooth muscle
CHARACTERISTICS OF ADRENERGIC AGONISTS

- Most of the adrenergic drugs are derivatives of β-phenylethylamine.
A. Catecholamines

- Sympathomimetic amines that contain the 3,4-dihydroxy benzene 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. Noncatecholamines

• Compounds lacking the catechol hydroxyl groups have longer halflives, because they are not inactivated by COMT.

• These include phenylephrine, ephedrine, and amphetamine.

• 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 noncatecholamines (due to lack of polar hydroxyl groups) permits greater access to the CNS.
D. Mechanism of action of adrenergic agonists

1. Direct-acting agonists:

- These drugs act directly on $\alpha$ or $\beta$ receptors, producing effects similar to those that occur following stimulation of sympathetic nerves or release of epinephrine from the adrenal medulla.

- Examples of direct-acting agonists include epinephrine, norepinephrine, isoproterenol, and phenylephrine.
2. Indirect-acting agonists:

- These agents may block the **reuptake** of norepinephrine (*cocaine*) or cause the **release** of norepinephrine from the cytoplasmic pools or vesicles of the adrenergic neuron (*amphetamines*). The norepinephrine then traverses the synapse and binds to α or β receptors.
3. Mixed-action agonists:

• *Ephedrine* and its stereoisomer, *pseudoephedrine*, both stimulate adrenoceptors directly and release norepinephrine from the adrenergic neuron.
INDIRECT ACTION
Drug enhances release of norepinephrine from vesicles.

DIRECT ACTION
Drug directly activates receptor.

MIXED ACTION
Drug acts both directly and indirectly.

SYNAPSE
POSTSYNAPTIC TARGET CELL MEMBRANE
DIRECT-ACTING ADRENERGIC 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.
• **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.

• *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.
A. Epinephrine

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.
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 histaminines from mast cells.
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**.
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.

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

- *Epinephrine* has a rapid onset but a brief duration of action (due to rapid degradation).
- The preferred route is **intramuscular** (anterior thigh) due to rapid absorption.
- In emergency situations, *epinephrine* is given intravenously (IV) for the most rapid onset of action.
- It may also be given subcutaneously, by endotracheal tube, and by inhalation.
- It is rapidly metabolized by MAO and COMT, and the metabolites metaepinephrine and vanillylmandelic acid are excreted in urine.
Aerosol into CNS
Metabolites appear in urine
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.

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

• **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.
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.
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

- *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.

- When *atropine*, which blocks the transmission of vagal effects, is given before *norepinephrine*, stimulation of the heart by *norepinephrine* is evident as **tachycardia**.
Norepinephrine induces reflex bradycardia.

Infusion of norepinephrine

Pulse rate (per min)

100
50

Blood pressure (mm Hg)

180
120
60

Peripheral resistance

High
Low

Time (min)

0
15

Norepinephrine causes increased systolic and diastolic pressure.

Norepinephrine constricts all blood vessels, causing increased peripheral resistance.
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*.
C. Isoproterenol

• *Isoproterenol* is a direct-acting synthetic catecholamine that stimulates both $\beta_1$- and $\beta_2$-adrenergic receptors.

• Its **nonselectivity** is one of its drawbacks and the reason why it is rarely used therapeutically.

• Its action on $\alpha$ receptors is **insignificant**.

• *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 ($\beta_2$ 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 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*, 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.
1. Actions:

a. **Cardiovascular**: *Dopamine* exerts a stimulatory effect on the $\beta_1$ receptors of the heart, having both **positive inotropic** and **chronotropic** effects.

• At very high doses, *dopamine* activates $\alpha_1$ 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 $\beta_1$ receptors on the heart to **increase cardiac output** and $\alpha_1$ receptors on blood vessels to **increase total peripheral resistance**.

- In addition, it **enhances perfusion to the kidney and splanchnic areas**.
• 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.

• It is also used to treat hypotension and severe heart failure, primarily in patients with low or normal peripheral vascular resistance and in patients who have oliguria.
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.

• *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.
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F. Dobutamine

- *Dobutamine* is a synthetic, direct-acting catecholamine that is a $\beta_1$ 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.
• **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 $\alpha_1$- and $\alpha_2$-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 $\alpha$ 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 $\alpha_1$ receptors.

- *Phenylephrine* is a vasconstrictor 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* has replaced *pseudoephedrine* in many oral decongestants, since *pseudoephedrine* has been misused to make *methamphetamine*.

• *Phenylephrine* is also used in ophthalmic solutions for **mydriasis**.
I. Clonidine

• *Clonidine* is an $\alpha_2$ 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 $\alpha_2$ 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 $\beta_2$ agonists used primarily as bronchodilators and administered by a metered-dose inhaler.

- Albuterol is the short-acting $\beta_2$ agonist of choice for the management of acute asthma symptoms.

- Inhaled terbutaline is no longer available in the United States, but is still used in other countries.

- 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.
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.

• 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.

• LABAs have been shown to increase the risk of asthma-related deaths.
L. Mirabegron

- *Mirabegron* is a $\beta_3$ agonist that relaxes the detrusor smooth muscle and increases bladder capacity.

- It is used for patients with *overactive bladder*.
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 $\alpha_1$ agonist action on the vasculature, as well as $\beta_1$-stimulatory effects on the heart.
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.
• 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 $\alpha_1$ agonist actions and $\beta$ 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.
Pharmacokinetics

• *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.
Actions

- *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.

• 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*. Therefore, products containing *pseudoephedrine* have certain **restrictions** and must be kept behind the sales counter in the United States.
Arrhythmias
Insomnia
Headache
Nausea
Hyperactivity
Tremors
## Summary of β-adrenergic receptors

<table>
<thead>
<tr>
<th>TISSUE</th>
<th>RECEPTOR TYPE</th>
<th>ACTION</th>
<th>OPPOSING ACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus and AV</td>
<td>β₁</td>
<td>↑ Automaticity</td>
<td>Cholinergic receptors</td>
</tr>
<tr>
<td>Conduction pathway</td>
<td>β₁</td>
<td>↑ Conduction velocity, automaticity</td>
<td>Cholinergic receptors</td>
</tr>
<tr>
<td>Myofibrils</td>
<td>β₁</td>
<td>↑ Contractility, automaticity</td>
<td></td>
</tr>
<tr>
<td>Vascular smooth muscle</td>
<td>β₂</td>
<td>Vasodilation</td>
<td>α-Adrenergic receptors</td>
</tr>
<tr>
<td>Bronchial smooth muscle</td>
<td>β₂</td>
<td>Bronchodilation</td>
<td>Cholinergic receptors</td>
</tr>
<tr>
<td>Kidneys</td>
<td>β₁</td>
<td>↑ Renin release</td>
<td>α₁-Adrenergic receptors</td>
</tr>
<tr>
<td>Liver</td>
<td>β₂, α₁</td>
<td>↑ Glycogenolysis and gluconeogenesis</td>
<td>—</td>
</tr>
<tr>
<td>Tissue/Muscle</td>
<td>Subtype</td>
<td>Effect</td>
<td>Receptors</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------</td>
<td>---------------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>$\beta_3$</td>
<td>$\uparrow$ Lipolysis</td>
<td>$\alpha_2$-Adrenergic receptors</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>$\beta_2$</td>
<td>$\uparrow$ Increased contractility; Potassium uptake; glycogenolysis; Dilates arteries to skeletal muscle; Tremor</td>
<td>—</td>
</tr>
<tr>
<td>Eye-ciliary muscle</td>
<td>$\beta_2$</td>
<td>$\rightarrow$ Relaxation</td>
<td>Cholinergic receptors</td>
</tr>
<tr>
<td>GI tract</td>
<td>$\beta_2$</td>
<td>$\downarrow$ Motility</td>
<td>Cholinergic receptors</td>
</tr>
<tr>
<td>Gall bladder</td>
<td>$\beta_2$</td>
<td>$\rightarrow$ Relaxation</td>
<td>Cholinergic receptors</td>
</tr>
<tr>
<td>Urinary bladder detrusor muscle</td>
<td>$\beta_2$</td>
<td>$\rightarrow$ Relaxation</td>
<td>Cholinergic receptors</td>
</tr>
<tr>
<td>Uterus</td>
<td>$\beta_2$</td>
<td>$\rightarrow$ Relaxation</td>
<td>Oxytocin</td>
</tr>
</tbody>
</table>
## Summary of the Therapeutic Uses of Adrenergic Agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Receptor Specificity</th>
<th>Therapeutic Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>$\alpha_1, \alpha_2$</td>
<td>Acute asthma, Anaphylactic shock, In local anesthetics to increase duration of action</td>
</tr>
<tr>
<td></td>
<td>$\beta_1, \beta_2$</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>$\alpha_1, \alpha_2$</td>
<td>Treatment of shock</td>
</tr>
<tr>
<td></td>
<td>$\beta_1$</td>
<td></td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>$\beta_1, \beta_2$</td>
<td>As a cardiac stimulant</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Dopaminergic</td>
<td>Treatment of shock, Treatment of congestive heart failure, Raise blood pressure</td>
</tr>
<tr>
<td></td>
<td>$\alpha_1, \beta_1$</td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>$\beta_1$</td>
<td>Treatment of acute heart failure</td>
</tr>
</tbody>
</table>

### Catecholamines
- Rapid onset of action
- Brief duration of action
- Not administered orally
- Do not penetrate the blood-brain barrier
<table>
<thead>
<tr>
<th>Drug</th>
<th>Receptors</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxymetazoline</td>
<td>$\alpha_1$</td>
<td>As a nasal decongestant</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>$\alpha_1$</td>
<td>As a nasal decongestant, raise blood pressure, treatment of paroxysmal supraventricular tachycardia</td>
</tr>
<tr>
<td>Clonidine</td>
<td>$\alpha_2$</td>
<td>Treatment of hypertension</td>
</tr>
<tr>
<td>Albuterol/Tebutaline</td>
<td>$\beta_2$</td>
<td>Treatment of bronchospasm (short acting)</td>
</tr>
<tr>
<td>Salmeterol/Formoterol</td>
<td>$\beta_2$</td>
<td>Treatment of bronchospasm (long acting)</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>$\alpha, \beta, CNS$</td>
<td>As a CNS stimulant in treatment of children with attention deficit syndrome, narcolepsy, and for appetite control</td>
</tr>
<tr>
<td>Ephedrine/Pseudoephedrine</td>
<td>$\alpha, \beta, CNS$</td>
<td>As a nasal decongestant, raise blood pressure</td>
</tr>
</tbody>
</table>

**NONCATECHOLAMINES**

Compared to catecholamines:
- Longer duration of action
- All can be administered orally or via inhalation