Adrenergic agonists

ASIST. LECTURER

HASAN A. ALMOWLA

MSc. Pharmacology and Toxicology

College of pharmacy

Dept. of Pharmacology

2023 -2024

Adrenergic agonists

- The adrenergic drugs affect receptors that are **stimulated** by **norepinephrine (noradrenaline) or epinephrine (adrenaline)**. These receptors are known as adrenergic receptors or adrenoceptors. Adrenergic drugs that activate adrenergic receptors are termed **sympathomimetics**, and drugs that block the activation of adrenergic receptors are termed **sympatholytics**. Some sympathomimetics directly activate adrenergic receptors **(direct-acting agonists),** while others act indirectly by enhancing release or blocking reuptake of norepinephrine **(indirect-acting agonists).**

DIRECT-ACTING AGENTS

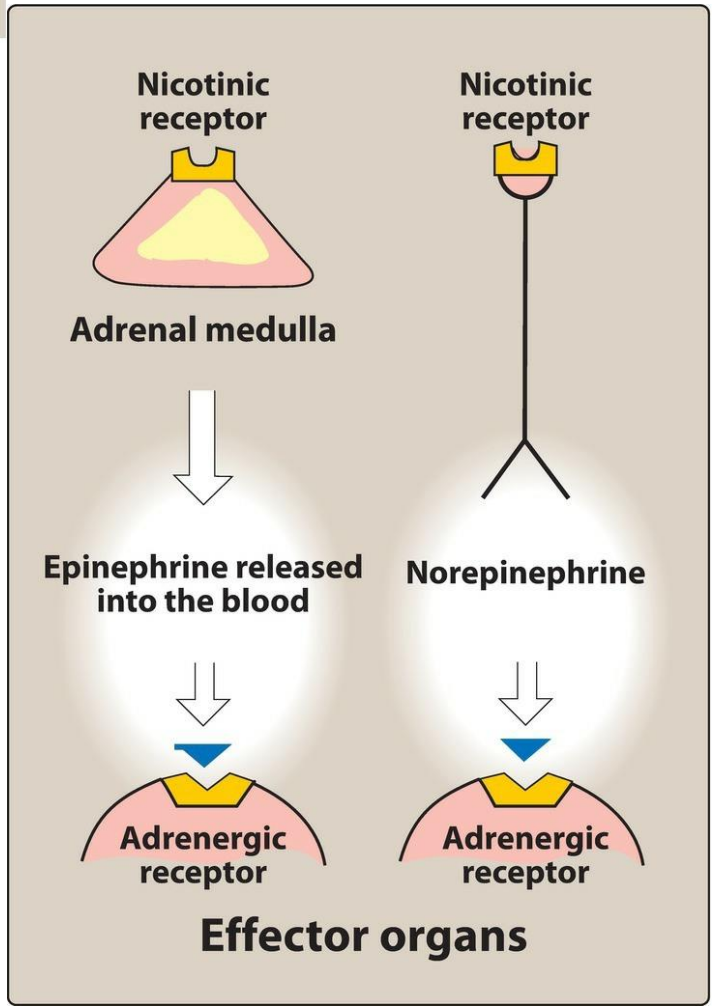
Albuterol ACCUNEB, PROAIR, VENTOLIN
Arformoterol BROVANA
Clonidine CATAPRES, DURACLON
*Dobutamine** GENERIC ONLY
*Dopamine** GENERIC ONLY
*Epinephrine** ADRENALIN, EPIPEN
Fenoldopam CORLOPAM
Formoterol FORADIL, PERFOROMIST
Guanfacine INTUNIV, TENEX
Indacaterol ARCAPTA
*Isoproterenol** ISUPREL
Metaproterenol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

INDIRECT-ACTING AGENTS

Amphetamine ADDERALL
Cocaine GENERIC ONLY

DIRECT AND INDIRECT ACTING (mixed action) AGENTS

Ephedrine AKOVAZ
Pseudoephedrine SUDAFED



- Catecholamines are compounds containing a catechol moiety (a benzene ring with two adjacent hydroxyl groups) and an amine side chain. Pharmacologically, the most important ones are:
- **Noradrenaline** (**norepinephrine**), a transmitter released by sympathetic nerve terminals
- **Adrenaline** (**epinephrine**), a hormone secreted by the adrenal medulla.
- **Dopamine**, the metabolic precursor of noradrenaline and adrenaline, also a transmitter/neuromodulator in the central nervous system.
- **Isoprenaline** (**isoproterenol**), a synthetic derivative of noradrenaline, not present in the body.

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 .

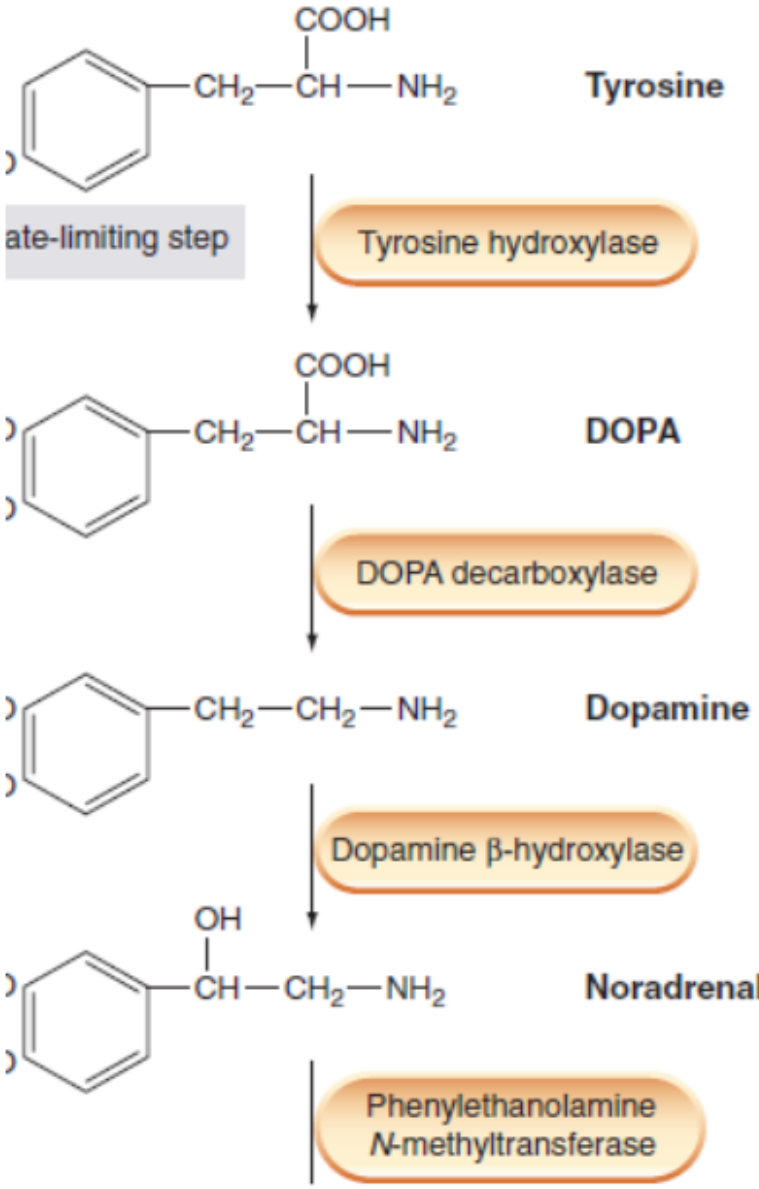


Figure 1: *Structures of the major catecholamines*

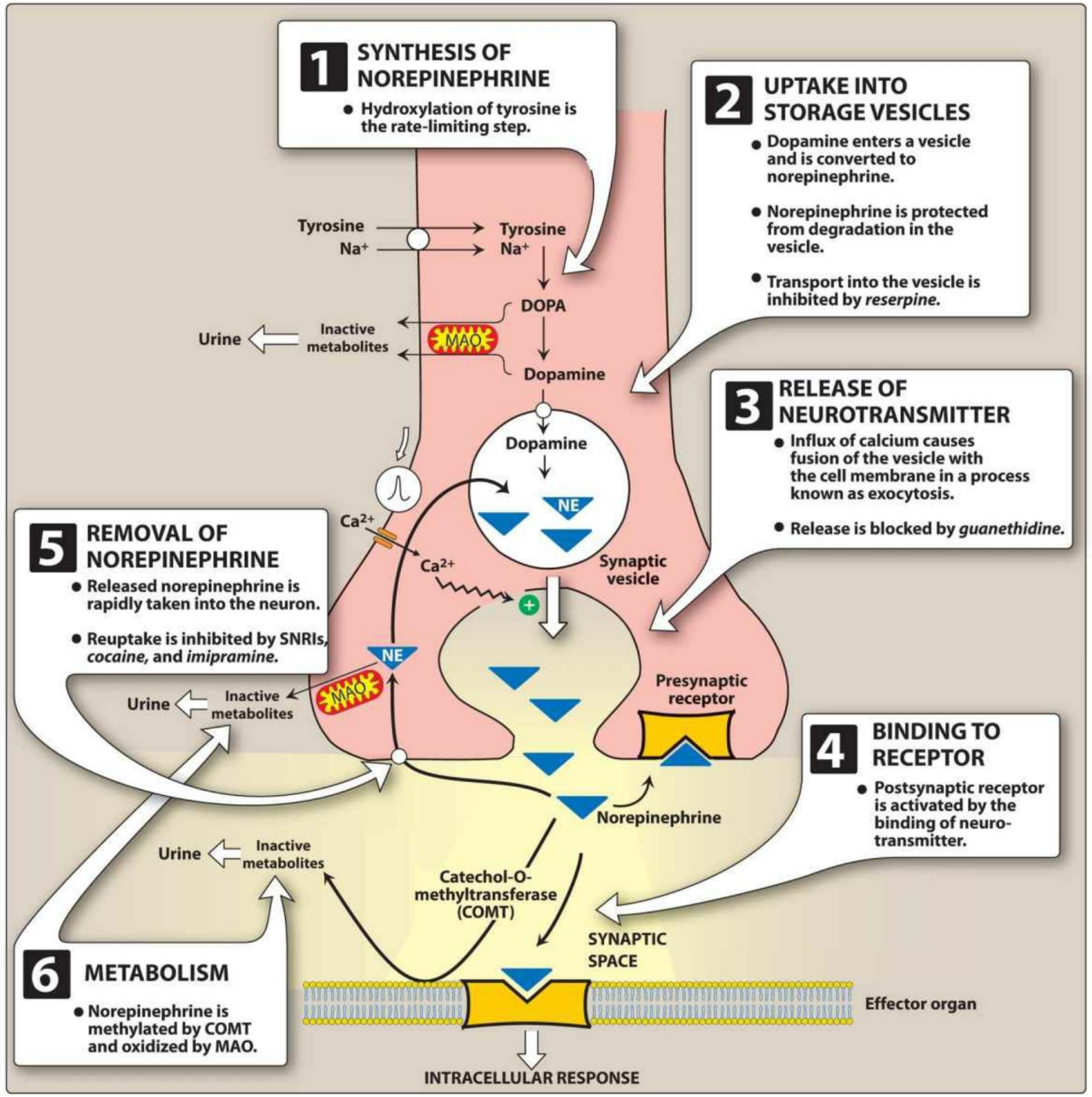


Figure 6.3 Synthesis and release of norepinephrine from the adrenergic neuron. DOPA = dihydroxyphenylalanine; MAO = monoamine oxidase; NE = norepinephrine; SNRI = serotonin–norepinephrine reuptake inhibitor.

- **A. Neurotransmission at adrenergic neurons**
- Neurotransmission in adrenergic neurons closely resembles that described for the cholinergic neurons, except that norepinephrine is the neurotransmitter instead of acetylcholine.
- Neurotransmission involves the following steps: ***synthesis, storage, release, and receptor binding of norepinephrine, followed by removal of the neurotransmitter from the synaptic gap*** (Figure 2).

1. Synthesis of norepinephrine: Tyrosine is transported by a carrier into the adrenergic neuron, where it is hydroxylated to dihydroxyphenylalanine (**DOPA**) by tyrosine hydroxylase. This is the rate-limiting step in the formation of norepinephrine. DOPA is then decarboxylated by the enzyme aromatic I-amino acid decarboxylase to form **dopamine** in the presynaptic neuron (figure 1).

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

- **3. Release of norepinephrine:** An action potential arriving at the nerve junction triggers an influx of calcium ions from the extracellular fluid into the cytoplasm of the neuron. The increase in calcium causes synaptic vesicles to fuse with the cell membrane and to undergo exocytosis to expel their contents into the synapse. Drugs such as ***guanethidine*** block this release.

- **4. Binding to receptors:** Norepinephrine released from the synaptic vesicles diffuses into the synaptic space and binds to postsynaptic receptors on the effector organ or to presynaptic receptors on the nerve ending. Binding of norepinephrine to receptors triggers a cascade of events within the cell, resulting in the formation of intracellular second messengers that act as links (transducers) in the communication between the neurotransmitter and the action generated within the effector cell. Adrenergic receptors use both the cyclic adenosine monophosphate (**cAMP**) second messenger system and the phosphatidylinositol cycle to transduce the signal into an effect. Norepinephrine also binds to ***presynaptic receptors (mainly α2 subtype***) that modulate the release of the neurotransmitter.

5. Removal of norepinephrine: 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.

3) Undergo **reuptake** back into the neuron. The reuptake by the neuronal membrane involves a sodium-chloride (Na+/Cl-)-dependent norepinephrine transporter (NET) that can be inhibited by **tricyclic antidepressants (TCAs),** such as ***imipramine***, by ***serotonin–norepinephrine reuptake inhibitors such as duloxetine, or by cocaine*** (Figure 2). Reuptake of norepinephrine into the presynaptic neuron is the primary mechanism for termination of its effects.

6. Potential fates of recaptured norepinephrine: Once norepinephrine reenters the adrenergic neuron, it may be taken up into synaptic vesicles via the amine transporter system and be sequestered for release by another action potential, or it may persist in a protected pool in the cytoplasm. Alternatively, norepinephrine can be oxidized by monoamine oxidase (MAO) present in neuronal mitochondria.

Adrenergic receptors (adrenoceptors)

In the sympathetic nervous system, several classes of adrenoceptors can be distinguished pharmacologically. Two main families of receptors, designated **α and β**, are classified 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.

TABLE 6–3 Direct effects of autonomic nerve activity on some organ systems.

	Effect of			
	Sympathetic		Parasympathetic	
Organ	Action[a]	Receptor[b]	Action[a]	Receptor[b]
Eye				
Iris				
Radial muscle	Contracts	α_1	...	...
Circular muscle	...	...	Contracts	M_3
Ciliary muscle	[Relaxes]	β	Contracts	M_3
Heart				
Sinoatrial node	Accelerates	β_1, β_2	Decelerates	M_2
Ectopic pacemakers	Accelerates	β_1, β_2	...	...
Contractility	Increases	β_1, β_2	Decreases (atria)	$[M_2]$
Blood vessels				
Skin, splanchnic vessels	Contracts	α	...	...
Skeletal muscle vessels	Relaxes	β_2	...	...
	Contracts	α	...	...
	[Relaxes]	[M[c]]	...	...
Bronchiolar smooth muscle	Relaxes	β_2	Contracts	M_3
Gastrointestinal tract				
Smooth muscle				
Walls	Relaxes	α_2,[d] β_2	Contracts	M_3
Sphincters	Contracts	α_1	Relaxes	M_3
Secretion	Inhibits	α_2	Increases	M_3
Myenteric plexus	...	...	Activates	M_1
Genitourinary smooth muscle				
Bladder wall	Relaxes	β_2	Contracts	M_3
Sphincter	Contracts	α_1	Relaxes	M_3
Uterus, pregnant	Relaxes	β_2	...	...
	Contracts	α	Contracts	M_3
Penis, seminal vesicles	Ejaculation	α	Erection	M
Skin				
Pilomotor smooth muscle	Contracts	α	...	...
Sweat glands			...	...
Thermoregulatory	Increases	M	...	...
Apocrine (stress)	Increases	α	...	...
Metabolic functions				
Liver	Gluconeogenesis	β_2, α	...	...
Liver	Glycogenolysis	β_2, α	...	...
Fat cells	Lipolysis	β_3	...	...
Kidney	Renin release	β_1	...	...
Autonomic nerve endings				
Sympathetic	...	...	Decreases NE release	M[e]
Parasympathetic	Decreases ACh release	α	...	...

Comparative Sympathomimetic Pharmacology								
Drug	alpha	$beta_1$	$beta_2$	Mechanism ofaction	Peripheral resistance	Renal blood flow	Mean arterial pressure	CNS stimulation
Epinephrine	●	●●	●●	Direct	+/-	●●	●	Yes
Norepinephrine (Levophed)	●● ●	●●	0	Direct	●●●	●● ●	●●●	No
Dopamine (Intropin)	●●	●●	●	Direct	●	●● ●	●	No
Isoproterenol (Isuprel)	0	●● ●	●	Direct	●●	●	+/-	Yes
Dobutamine (Dobutrex)	0	●● ●	0	Direct	NC	●●	●	

● decreased effect ● increased effect;

TISSUE	RECEPTOR TYPE	ACTION	OPPOSING ACTIONS
Heart			
• Sinus and AV	β_1	↑ Automaticity	Cholinergic receptors
• Conduction pathway	β_1	↑ Conduction velocity, automaticity	Cholinergic receptors
• Myofibrils	β_1	↑ Contractility, automaticity	
Vascular smooth muscle	β_2	Vasodilation	α-Adrenergic receptors
Bronchial smooth muscle	β_2	Bronchodilation	Cholinergic receptors
Kidneys	β_1	↑ Renin release	α_1-Adrenergic receptors
Liver	β_2, α_1	↑ Glycogenolysis and gluconeogenesis	—
Adipose tissue	β_1, β_3	↑ Lipolysis	α_2-Adrenergic receptors
Skeletal muscle	β_2	↑ Increased contractility Potassium uptake; glycogenolysis Dilates arteries to skeletal muscle Tremor	—
Eye-ciliary muscle	β_2	Relaxation	Cholinergic receptors
GI tract	β_2	↓ Motility	Cholinergic receptors
Gall bladder	β_2	Relaxation	Cholinergic receptors
Urinary bladder detrusor muscle	β_2, β_3	Relaxation	Cholinergic receptors
Uterus	β_2	Relaxation	Oxytocin

1. α-Adrenoceptors: The α-adrenoceptors **show a weak response to the synthetic agonist *isoproterenol***, but they are **responsive to the naturally occurring catecholamines *epinephrine* and *norepinephrine*** (Figure 3).

For α receptors, the rank order of potency and affinity is

epinephrine ≥ norepinephrine >> isoproterenol.

The α-adrenoceptors are subdivided into two subgroups, **α1 and α2**, based on their affinities for α agonists and blocking drugs.

For example, the α1 receptors have a higher affinity for *phenylephrine*

than **α2 receptors. Conversely, the drug *clonidine*** selectively binds to α2 receptors and has less effect on α1 receptors.

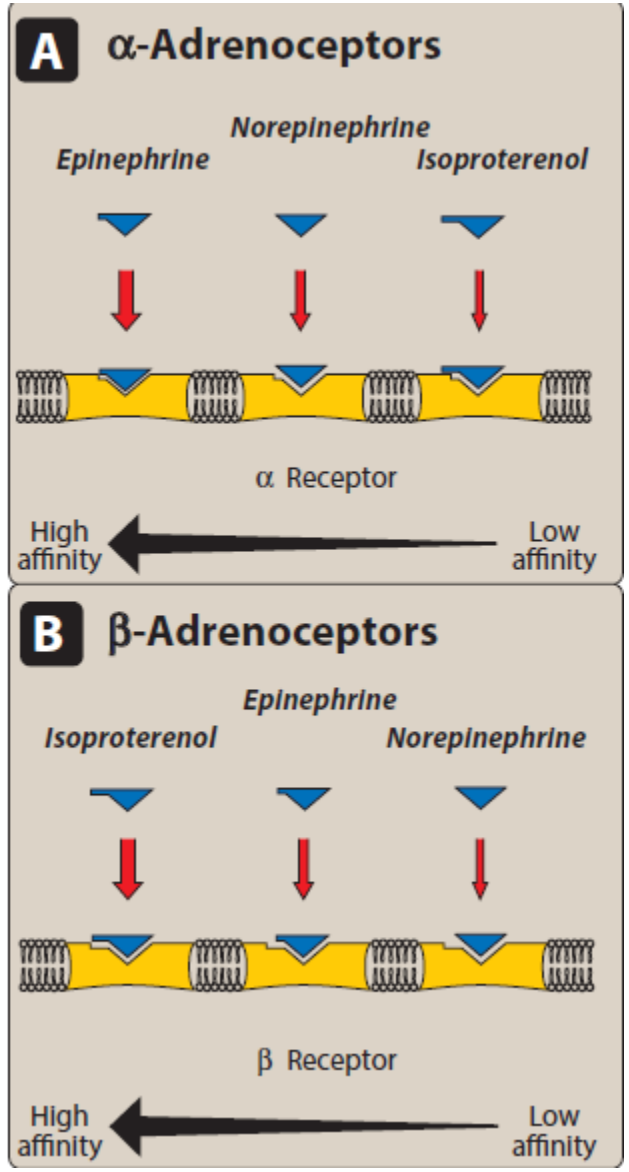
a. **α1 Receptors:** These receptors are present on the postsynaptic membrane of the effector organs and mediate many of the classic effects, originally designated as α-adrenergic, involving **constriction of smooth muscle**.

Activation of α1 receptors initiates a series of reactions through the G protein activation of phospholipase C, ultimately resulting in the generation of second messengers inositol-1,4,5-trisphosphate (**IP3**) and diacylglycerol (**DAG**). IP3 initiates the release of Ca2+ from the endoplasmic reticulum into the cytosol, and DAG turns on other proteins within the cell (Figure 3).

Receptor	Agonist	Antagonist	G Protein	Effects
α_1 type	Phenylephrine	Prazosin	G_q	↑ IP3, DAG common to all
α_{1A}		Tamsulosin		
α_{1B}				
α_{1D}				
α_2 type	Clonidine	Yohimbine	G_i	↓ cAMP common to all
α_{2A}	Oxymetazoline			
α_{2B}		Prazosin		
α_{2C}		Prazosin		
β type	Isoproterenol	Propranolol	G_s	↑ cAMP common to all
β_1	Dobutamine	Betaxolol		
β_2	Albuterol	Butoxamine		
β_3	Mirabegron			

b. α2 Receptors: These receptors are located primarily on sympathetic **presynaptic nerve endings and control the release of norepinephrine**. When a sympathetic adrenergic nerve is stimulated, a portion of the released norepinephrine "circles back" and reacts with α2 receptors on the presynaptic membrane (Figure 2). Stimulation of α2 receptors causes feedback inhibition and inhibits further release of norepinephrine from the stimulated adrenergic neuron. This inhibitory action serves as a local mechanism for modulating norepinephrine output when there is high sympathetic activity. [Note: In this instance, by inhibiting further output of norepinephrine from the adrenergic neuron, these receptors are acting as inhibitory autoreceptors.] α2 receptors are also found on presynaptic parasympathetic neurons. Norepinephrine released from a presynaptic sympathetic neuron can diffuse to and interact with these receptors, inhibiting acetylcholine release.

- **c. Further subdivisions:** 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.



- **2. β-Adrenoceptors:** Responses of β receptors differ from those of α receptors and are characterized by a **strong response to *isoproterenol***, with **less sensitivity to *epinephrine* and *norepinephrine*** (Figure 3).
- For β receptors, the rank order of potency is ***isoproterenol > epinephrine > norepinephrine***. The β-adrenoceptors can be subdivided into three major subgroups, **β1, β2, and β3,** based on their affinities for adrenergic agonists and antagonists.
- **β1** receptors have approximately equal affinities for ***epinephrine* and *norepinephrine***, whereas **β2 receptors** have a higher affinity for ***epinephrine* than for *norepinephrine***. Thus, tissues with a predominance of **β2 receptors (such as the vasculature of skeletal muscle**)
- are particularly responsive to the effects of circulating epinephrine released by the adrenal medulla. **β3 r**eceptors are involved in **lipolysis** and also have effects on the **detrusor muscle of the bladder**. Binding of a neurotransmitter at any of the three types of β receptors results in activation of adenylyl cyclase and increased concentrations of cAMP within the cell.

- **3. Distribution of receptors:** Adrenergically innervated organs and tissues usually have a predominant type of receptor. For example, 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.**
- **4. 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. Figure below summarizes the most prominent effects mediated by the adrenoceptors. As a generalization, 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**),
- whereas stimulation of **β2** receptors produces **vasodilation (in skeletal muscle vascular beds) and smooth muscle relaxation**.
- b3 Receptors are involved in lipolysis (along with b1), and also have effects on the detrusor muscle of the bladder.

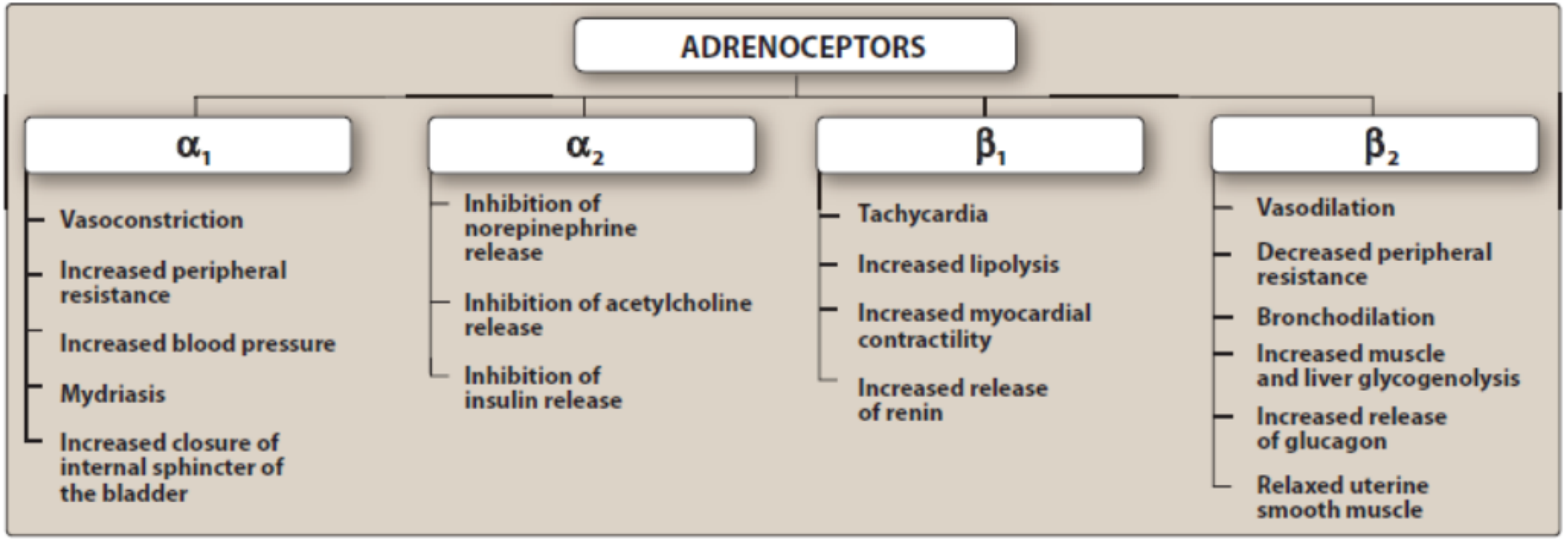


Figure 5: Major effects mediated by α- and β-adrenoceptors

- **5. Desensitization of receptors:** Prolonged exposure to the catecholamines reduces the responsiveness of these receptors, a phenomenon known as desensitization. Three mechanisms have been suggested to explain this phenomenon: 1) sequestration of the receptors so that they are unavailable for interaction with the ligand; 2) downregulation, that is, a disappearance of the receptors either by destruction or by decreased synthesis; and 3) an inability to couple to G protein, because the receptor has been phosphorylated on the cytoplasmic side.

- **Characteristics of Adrenergic 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).

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.

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.

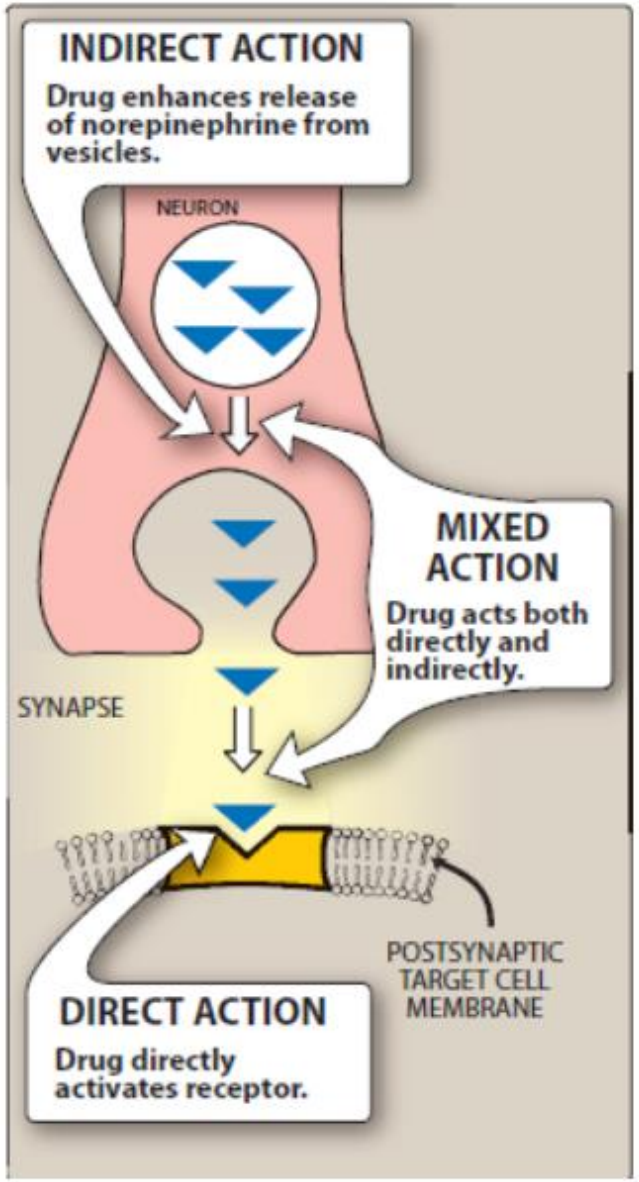


Figure 2: Sites of action of direct-, indirect-, and mixed-acting adrenergic agonists.

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

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.

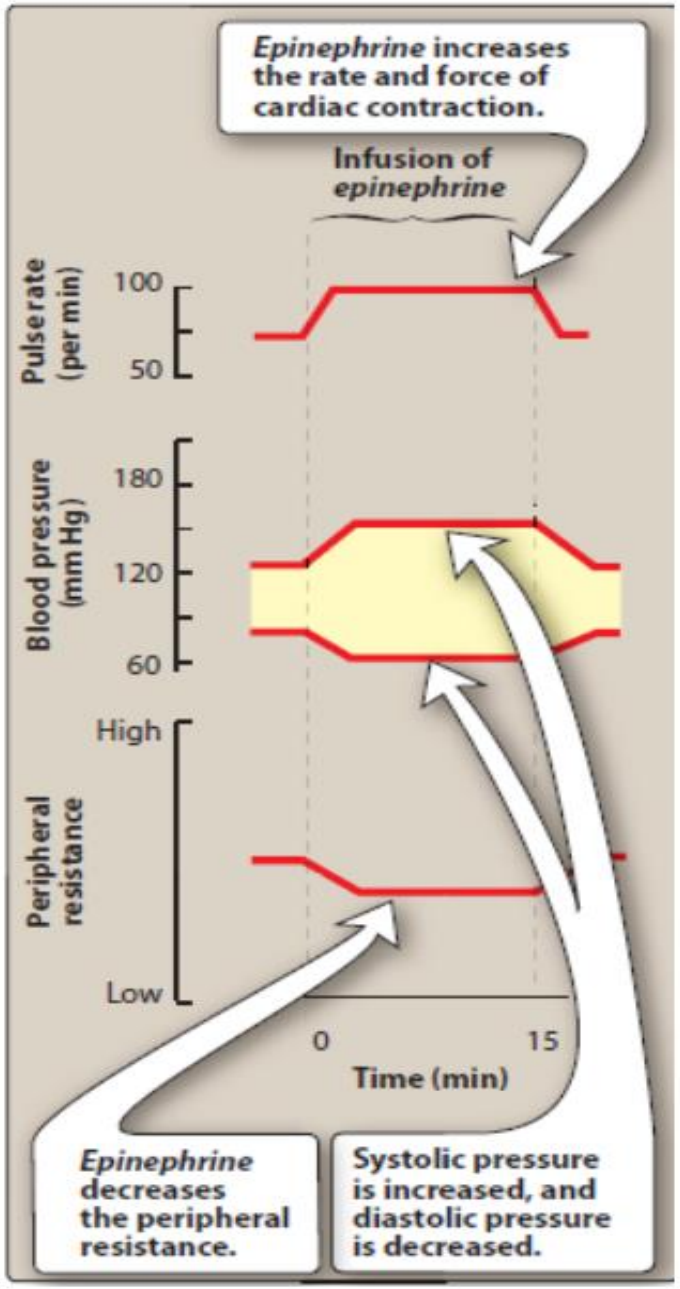


Figure 3: Cardiovascular effects of intravenous infusion of low doses of *epinephrine*.

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. 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. Epinephrine also reduces systemic absorption of the local anesthetic and promotes local hemostasis. **e. Intraocular surgery:** Epinephrine is used in the induction and maintenance of mydriasis during intraocular surgery.

- **Pharmacokinetics:** Epinephrine has a **rapid onset** but a **brief duration of action** (due to rapid degradation).
- The preferred route for anaphylaxis in the outpatient setting is **intramuscular** (anterior thigh) due to rapid absorption.
- In emergencies, epinephrine is given **intravenously** (IV) for the most rapid onset of action. It may also be given **subcutaneously**, by **endotracheal** tube, or by **inhalation**. It is rapidly metabolized by **MAO and COMT**, and the metabolites metanephrine and vanillylmandelic acid are excreted in urine.

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.
- **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.]

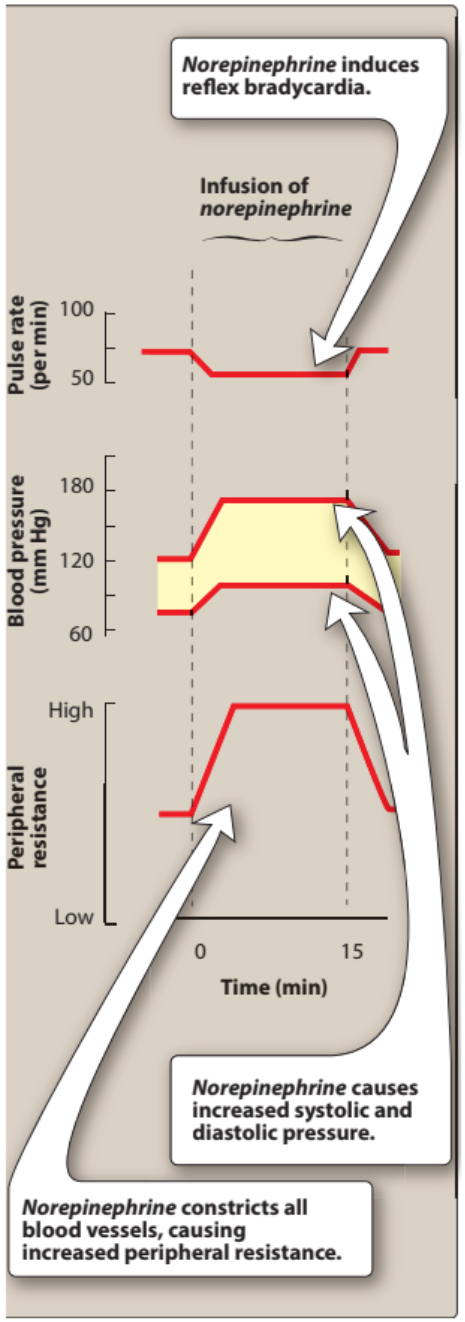


Figure 4: Cardiovascular effects of intravenous infusion of *norepinephrine*.

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.

- **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*, 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.

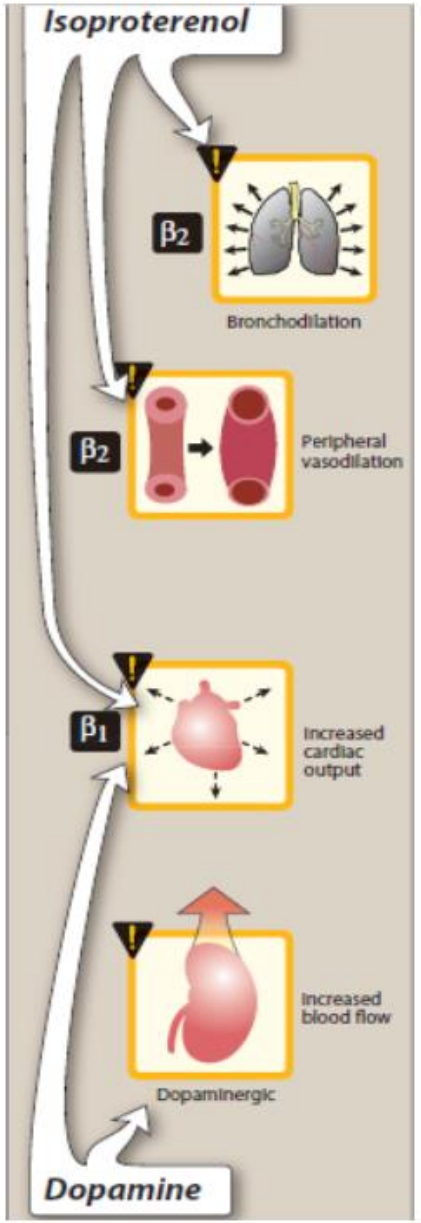


Figure 5: Clinically important actions of *isoproterenol* and *dopamine*.

1. Actions:

a. Cardiovascular: *Dopamine* exerts a stimulatory effect on the β1 receptors of the heart, having both positive inotropic and chronotropic effects. At very high doses, *dopamine* activates α1 receptors on the vasculature, resulting in vasoconstriction.

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

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. 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.

E. Fenoldopam

Fenoldopam is an agonist of peripheral dopamine D1 receptors. It is used as rapidacting 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 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. 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. Use for greater than 3 days is not recommended, as rebound congestion and dependence may occur.

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. Midodrine: a prodrug, is metabolized to the pharmacologically active desglymidodrine. It is a selective a1 agonist, which acts in the periphery to increase arterial and venous tone. Midodrine is indicated for the treatment of orthostatic hypotension. The drug should be given three times daily, with doses at 3- or 4-hour intervals. To avoid supine hypertension, doses within 4 hours of bedtime are not recommended.

J. Clonidine

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.

K. Albuterol, metaproterenol, and terbutaline

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. Inhaled terbutaline is no longer available in the United States, but is still used in other countries. Injectable terbutaline is used off-label as a uterine relaxant to suppress premature labor, and use for this indication should

not exceed 72 hours. 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.

L. Salmeterol, formoterol, and indacaterol

Salmeterol, formoterol, arformoterol (the [R,R]-enantiomer of 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.

M. 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.

To be continued

good luck