

DRUGS THAT ACT IN THE ANS

Adrenergic Agonists

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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**.

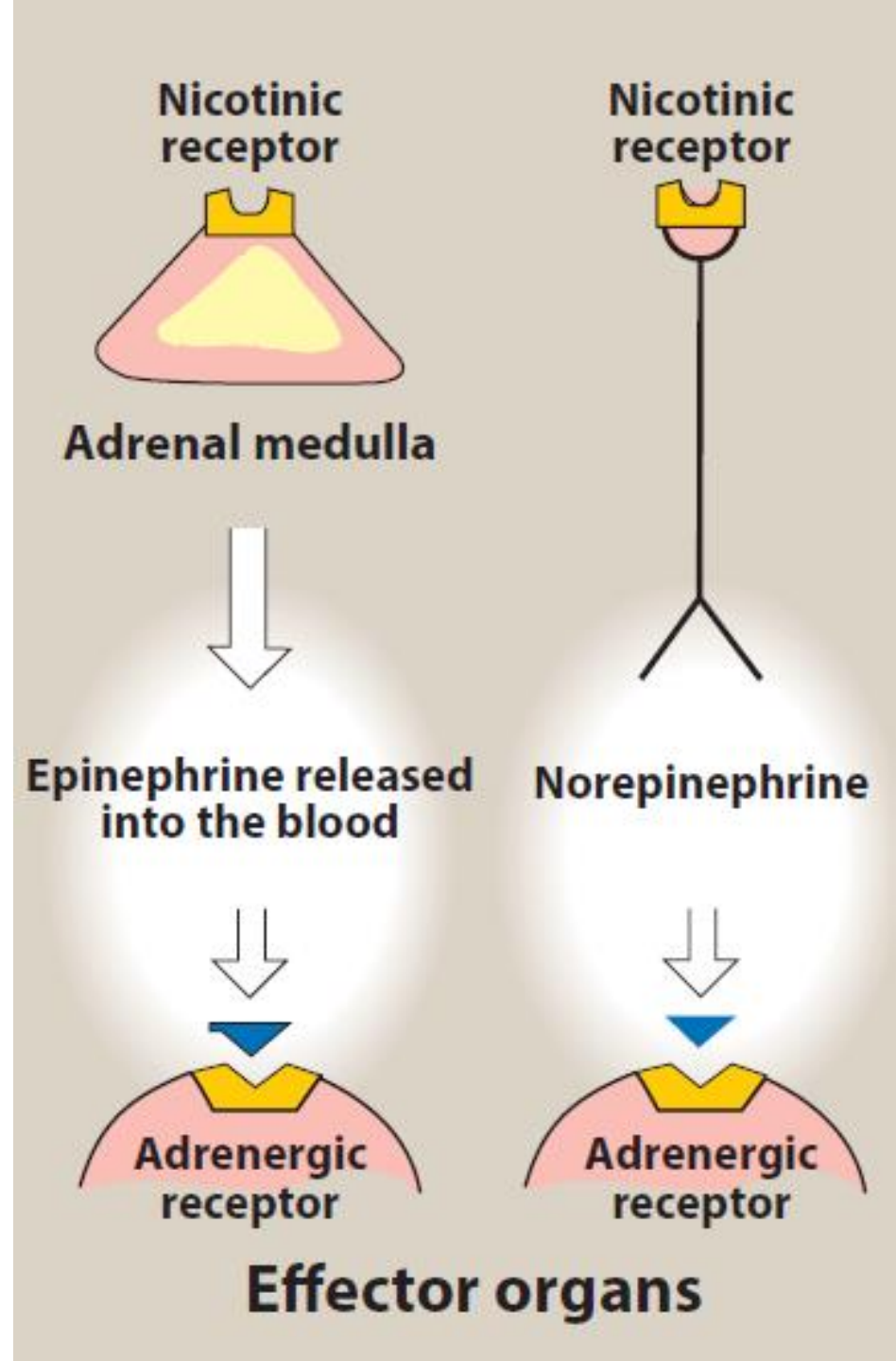
Adrenergic drugs that activate adrenergic receptors are termed **sympathomimetics**, and drugs that block the activation of adrenergic receptors are termed **sympatholytics**.

Some **sympathomimetics** directly activate adrenergic receptors (**direct-acting agonists**), while others act indirectly by enhancing release or blocking reuptake of norepinephrine (**indirect-acting agonists**).

THE ADRENERGIC NEURON

Adrenergic neurons release norepinephrine as the primary neurotransmitter.

Adrenergic drugs act on adrenergic receptors, located either **presynaptically** on the neuron or **postsynaptically** on the effector organ.



A. Neurotransmission at adrenergic neurons

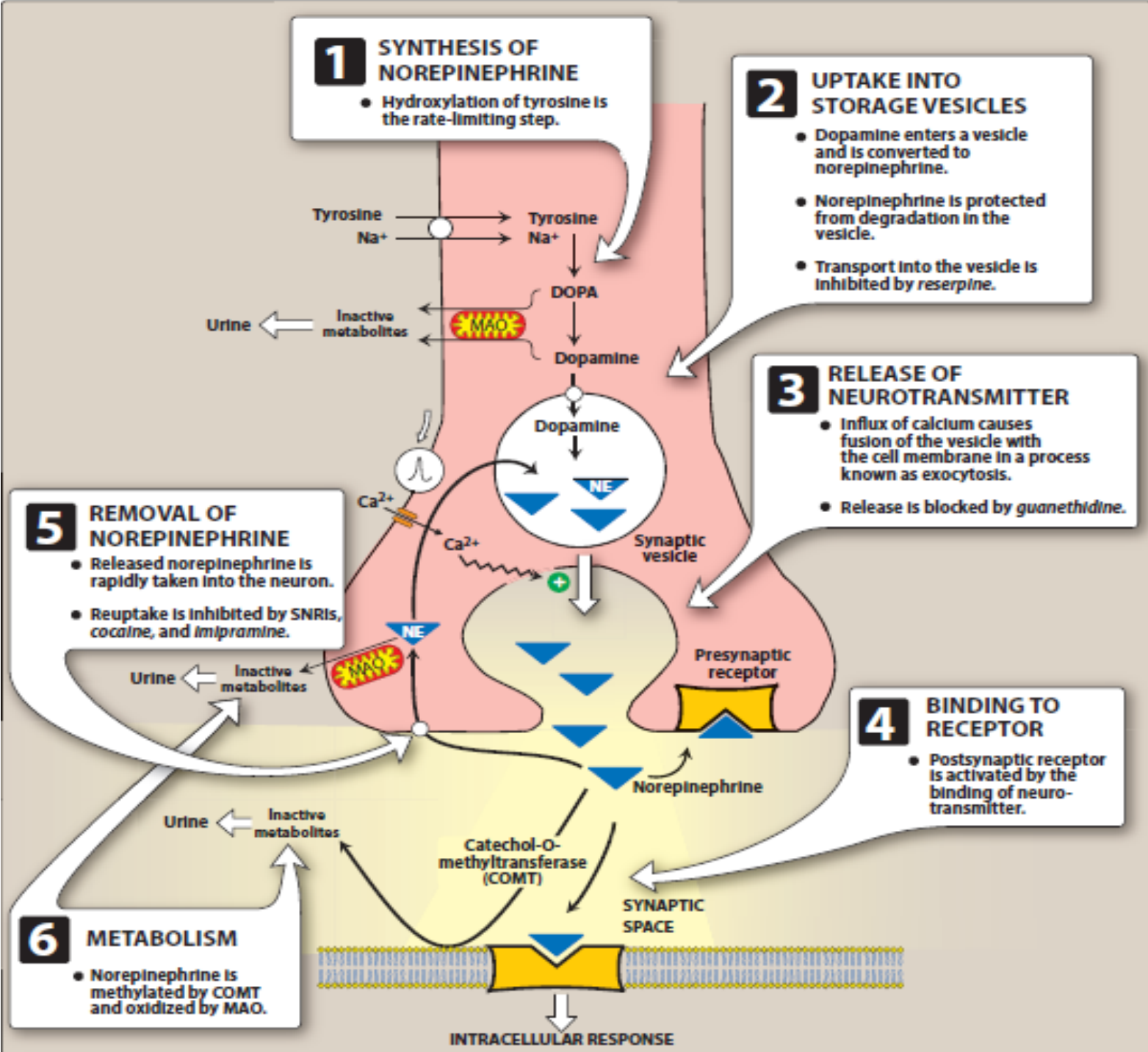


Neurotransmission in adrenergic neurons closely resembles that described for the cholinergic neurons, except that norepinephrine is the neurotransmitter instead of acetylcholine.

Neurotransmission involves the following steps:

- Synthesis,
- Storage,
- Release, and
- Receptor binding of norepinephrine, followed by
- Removal of the neurotransmitter from the synaptic gap

Synthesis and release of norepinephrine from the adrenergic neuron. MAO = monoamine oxidase, SNRI = serotonin norepinephrine reuptake inhibitor



A. Neurotransmission at adrenergic neurons



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 L-amino acid decarboxylase to form dopamine in the presynaptic neuron.

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.

A. Neurotransmission at adrenergic neurons

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.

A. Neurotransmission at adrenergic neurons

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 α_2 subtype**) that modulate the release of the neurotransmitter.

A. Neurotransmission at adrenergic neurons

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; or
- 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**.

Reuptake of norepinephrine into the presynaptic neuron is the primary mechanism for termination of its effects.

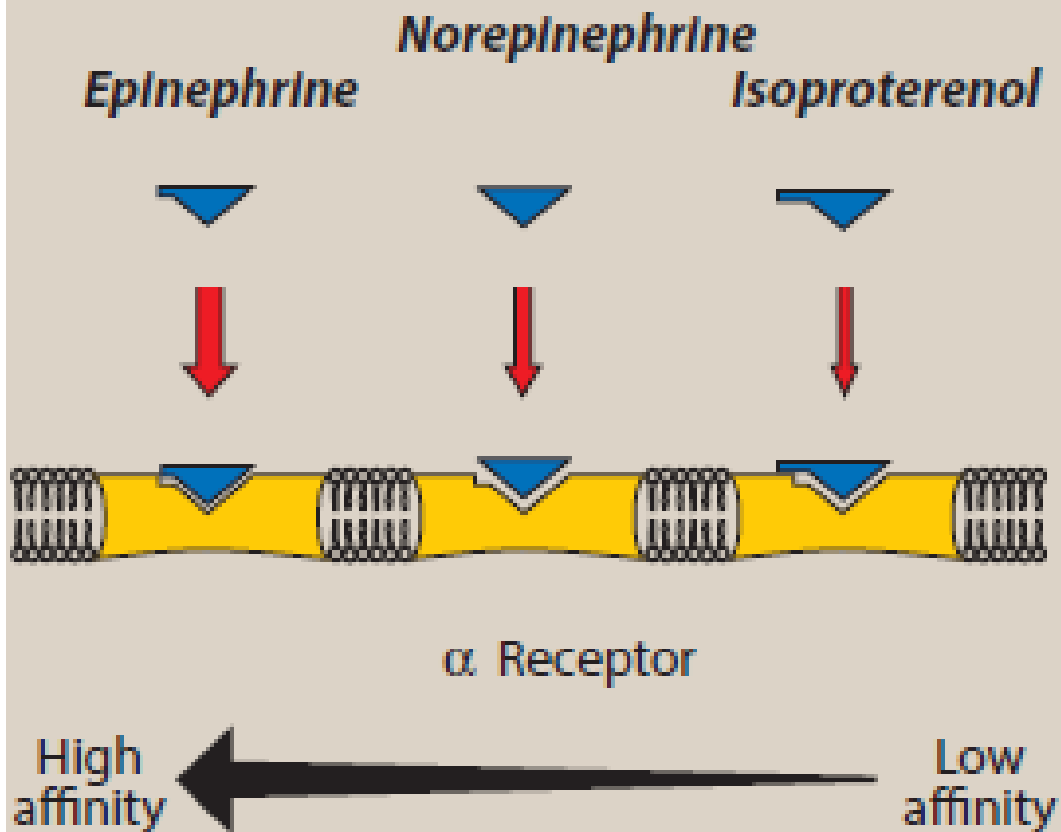
A. Neurotransmission at adrenergic neurons

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.

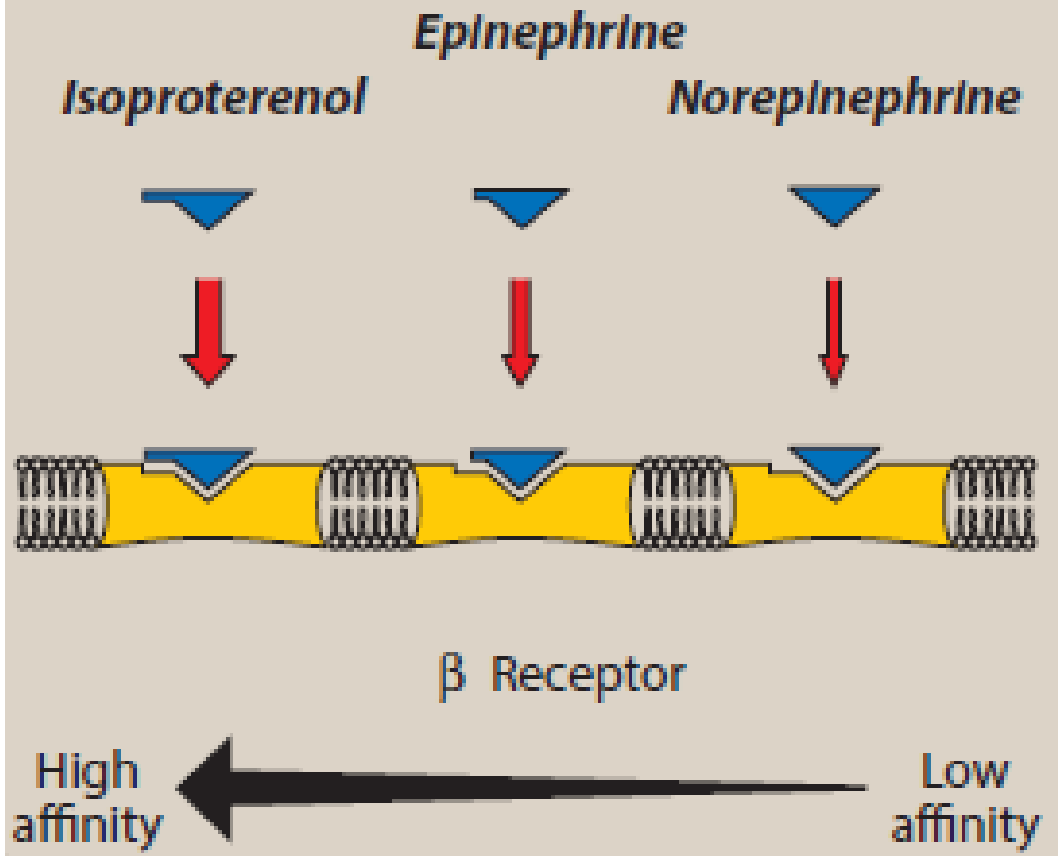
Alternatively, norepinephrine can be oxidized by monoamine oxidase (MAO) present in neuronal mitochondria.

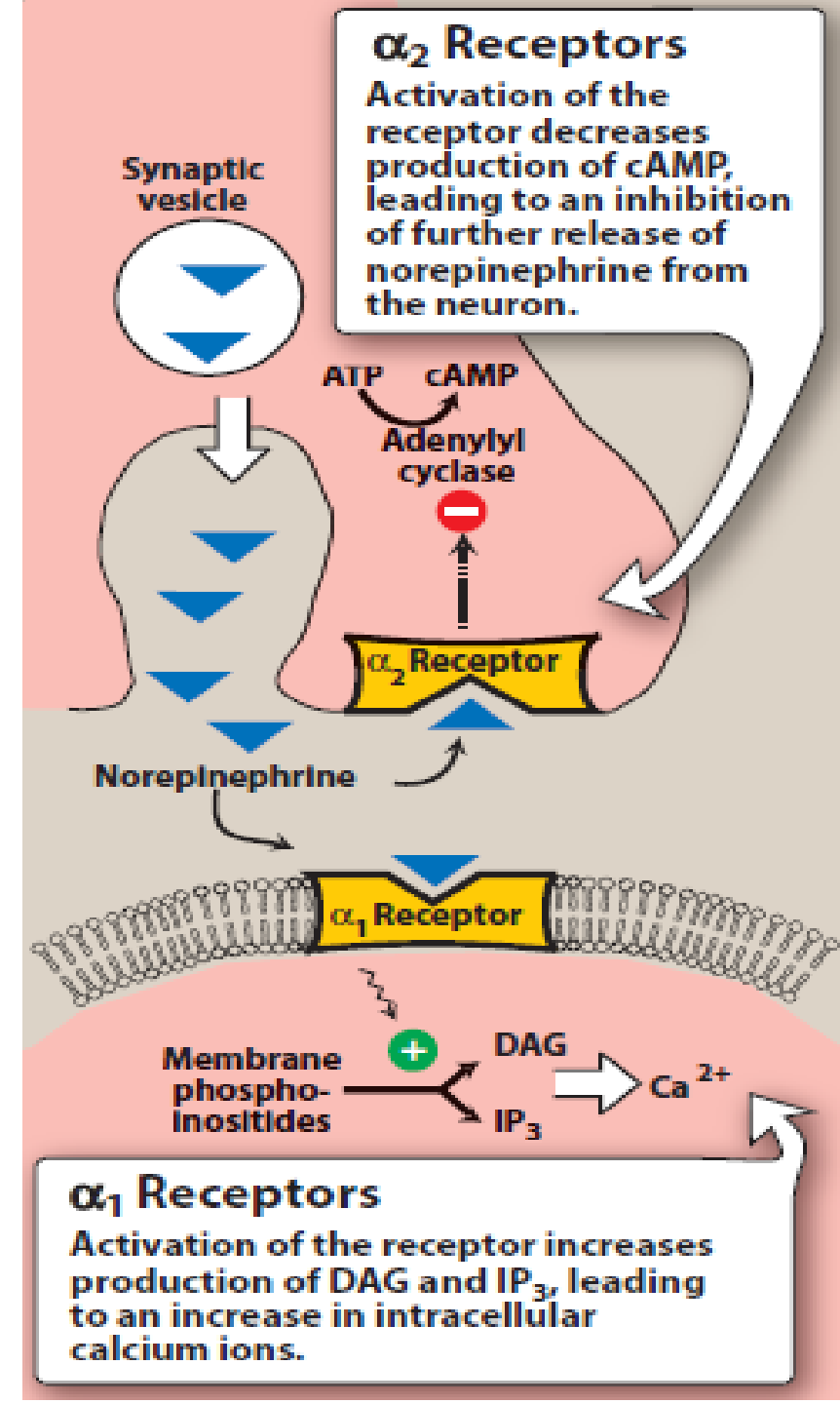
B. Adrenergic receptors (adrenoceptors)

A α -Adrenoceptors



B β -Adrenoceptors





B. 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.

B. Adrenergic receptors (adrenoceptors)

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.

For α receptors, the rank order of potency and affinity is epinephrine \geq norepinephrine \gg isoproterenol.

The α -adrenoceptors are subdivided into two subgroups, α_1 and α_2 , based on their affinities for α agonists and blocking drugs.

For example, the α_1 receptors have a higher affinity for phenylephrine than α_2 receptors. Conversely, the drug clonidine selectively binds to α_2 receptors and has less effect on α_1 receptors.

B. Adrenergic receptors (adrenoceptors)

a. α 1 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 α 1 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 Ca^{2+} from the endoplasmic reticulum into the cytosol, and DAG turns on other proteins within the cell.

B. Adrenergic receptors (adrenoceptors)

b. α 2 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 α 2 receptors on the presynaptic membrane.

Stimulation of α 2 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.

B. Adrenergic receptors (adrenoceptors)

b. α_2 Receptors:

[Note: In this instance, by inhibiting further output of norepinephrine from the adrenergic neuron, these receptors are acting as **inhibitory autoreceptors.**]

α_2 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.

[Note: In these instances, these receptors are behaving as inhibitory heteroreceptors.]

This is another mechanism to modulate autonomic activity in a given area.

In contrast to α_1 receptors, the effects of binding at α_2 receptors are mediated by inhibition of adenylyl cyclase and by a fall in the levels of intracellular cAMP.

B. Adrenergic receptors (adrenoceptors)

c. Further subdivisions:

The $\alpha 1$ and $\alpha 2$ receptors are further divided into $\alpha 1A$, $\alpha 1B$, $\alpha 1C$, and $\alpha 1D$ and into $\alpha 2A$, $\alpha 2B$, and $\alpha 2C$.

This extended classification is necessary for understanding the selectivity of some drugs. For example, tamsulosin is a selective $\alpha 1A$ antagonist that is used to treat benign prostatic hyperplasia.

The drug has fewer cardiovascular side effects because it targets $\alpha 1A$ subtype receptors found primarily in the urinary tract and prostate gland and does not affect the $\alpha 1B$ subtype found in the blood vessels.

B. Adrenergic receptors (adrenoceptors)

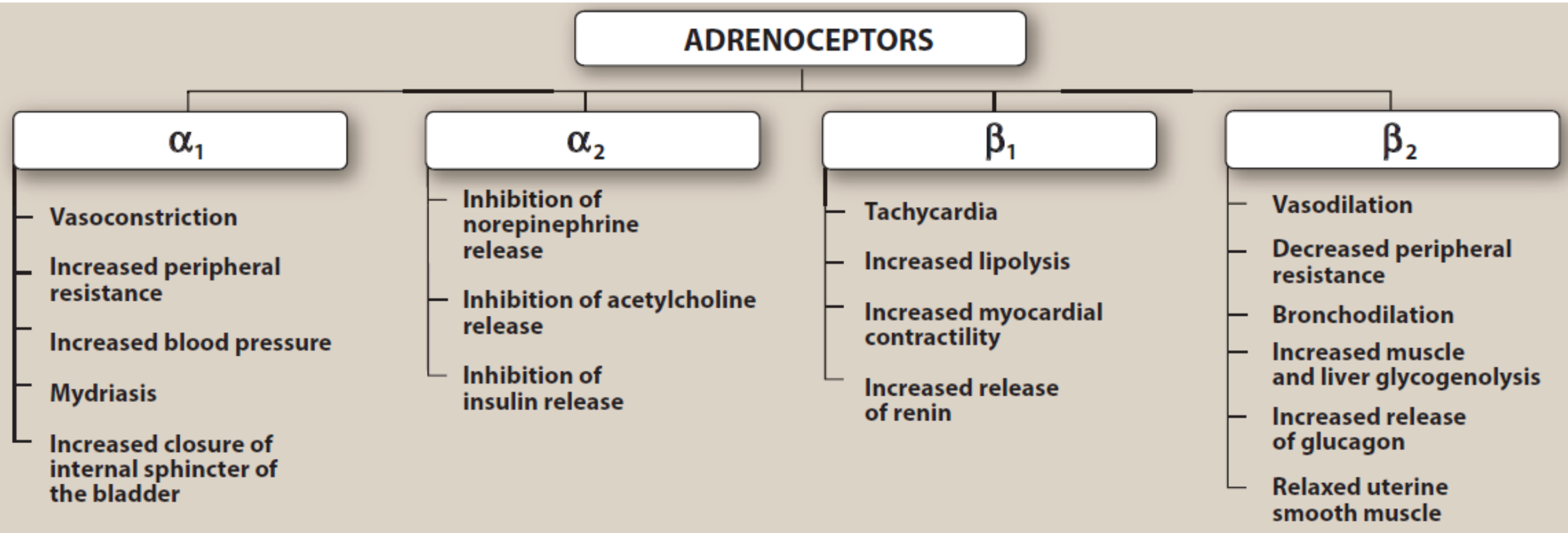
2. β -Adrenoceptors: Responses of β receptors differ from those of α receptors and are characterized by a strong response to isoproterenol, with less sensitivity to epinephrine and norepinephrine.

For β receptors, the rank order of potency is isoproterenol > epinephrine > norepinephrine.

The β -adrenoceptors can be subdivided into three major subgroups, β_1 , β_2 , and β_3 , based on their affinities for adrenergic agonists and antagonists.

β_1 receptors have approximately equal affinities for epinephrine and norepinephrine, whereas β_2 receptors have a higher affinity for epinephrine than for norepinephrine.

B. Adrenergic receptors / Characteristic responses mediated by adrenoceptors



Major effects mediated by α- and β-adrenoceptors.

B. Adrenergic receptors (adrenoceptors)/ 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 α_1 and β_2 receptors, but the β_2 receptors predominate.

Other tissues may have one type of receptor almost exclusively. For example, the heart contains predominantly β_1 receptors.

B. Adrenergic 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, stimulation of **α 1** receptors characteristically produces **vasoconstriction** (particularly in skin and abdominal viscera) and an increase in total peripheral resistance and blood pressure.

Stimulation of **β 1** receptors characteristically causes cardiac stimulation (increase in heart rate and contractility), whereas stimulation of **β 2** receptors produces **vasodilation** (in skeletal muscle vascular beds) and smooth muscle relaxation.

B. Adrenergic receptors / 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) down-regulation, 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 AGONISTS

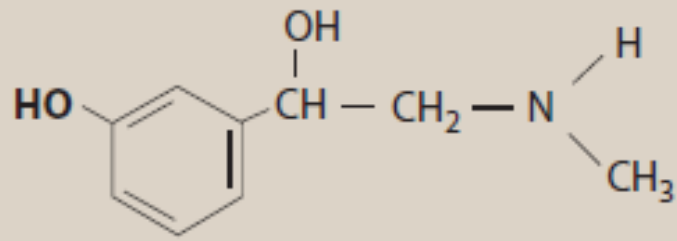


Most of the adrenergic drugs are derivatives of **β -phenylethylamine**.

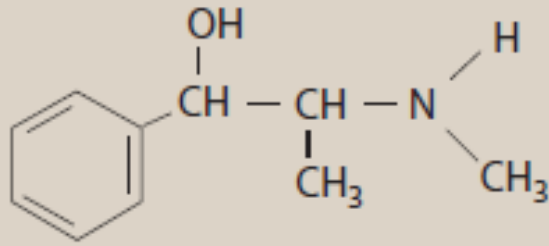
Substitutions on the benzene ring or on the ethylamine side chains produce a variety of compounds with varying abilities to differentiate between α and β receptors and to penetrate the CNS.

Two important structural features of these drugs are

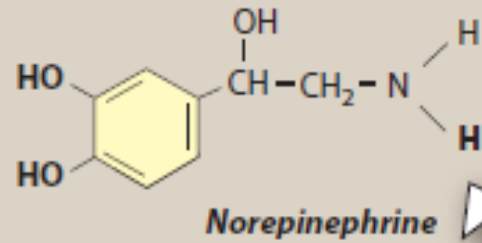
- 1) the number and location of **OH substitutions** on the benzene ring and**
- 2) the nature of the substituent on the **amino nitrogen**.**



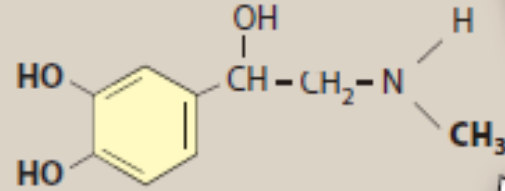
Phenylephrine



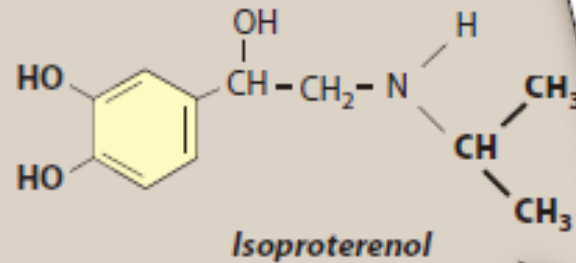
Ephedrine



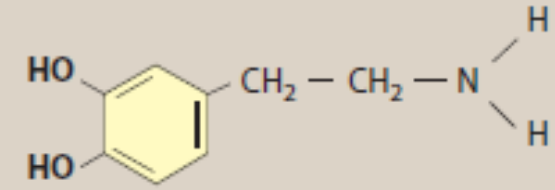
Norepinephrine



Epinephrine



Isoproterenol



Dopamine

Affinity for β receptors increases as group on the amine nitrogen gets larger.

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

CHARACTERISTICS OF ADRENERGIC AGONISTS/ 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.

CHARACTERISTICS OF ADRENERGIC AGONISTS/ B. Noncatecholamines

Compounds **lacking the catechol hydroxyl groups** have longer half-lives, 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**.

CHARACTERISTICS OF ADRENERGIC AGONISTS/ Substitutions on the amine nitrogen

The nature of the substituent on the amine nitrogen is important in determining β selectivity of the adrenergic agonist.

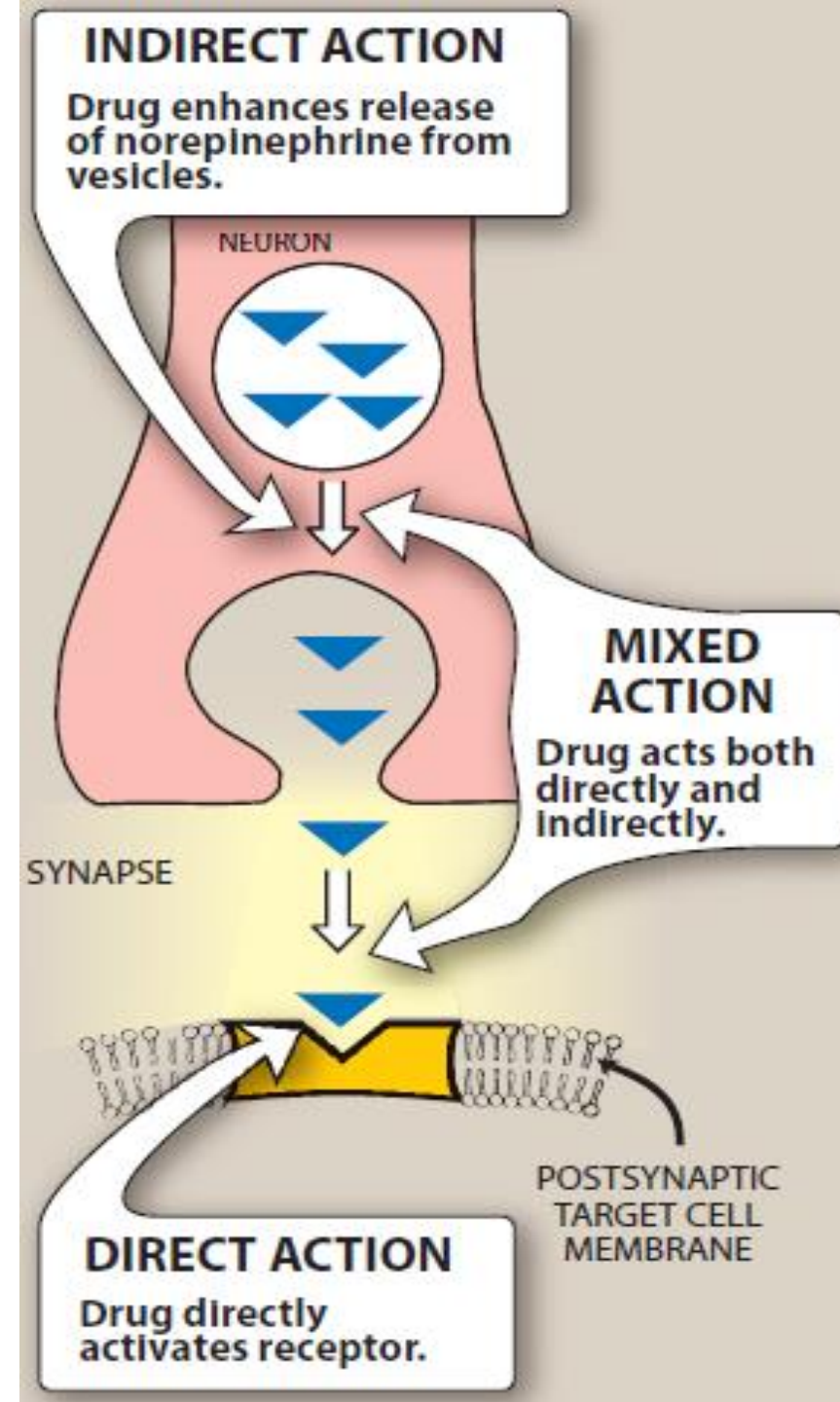
For example, epinephrine, with a $-\text{CH}_3$ substituent on the amine nitrogen, is more potent at β receptors than norepinephrine, which has an unsubstituted amine.

Similarly, isoproterenol, which has an isopropyl substituent $-\text{CH}(\text{CH}_3)_2$ on the amine nitrogen, is a strong β agonist with little α activity (Figure 6.4).

D. 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.

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



D. Mechanism of action of adrenergic agonists

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. 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