Drugs Affecting the Autonomic Nervous System-4 Adrenergic Agonist

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The adrenergic drugs

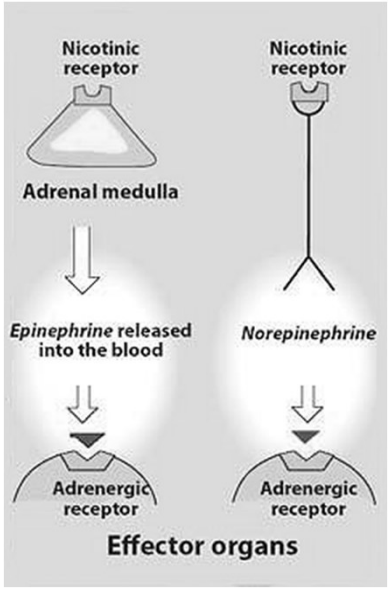
Drugs that affect receptors that are stimulated by norepinephrine or epinephrine.

- Sympathomimetic (adrenergic agonist)
  Adrenergic drugs that either direct -acting agonists on the adrenergic receptor (adrenoceptor) **or** Indirect-acting agonists.
- Sympatholytics
  Block the action of the neurotransmitters at the receptors, whereas other drugs affect adrenergic function by interrupting the release of norepinephrine from adrenergic neurons.

Adrenergic neurons

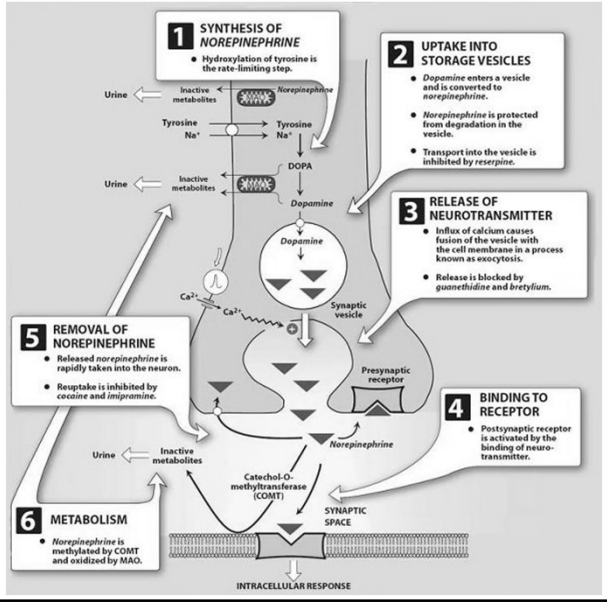
- Release norepinephrine as the primary neurotransmitter.
- These neurons are found in the central nervous system (CNS) and also in the sympathetic nervous system, links between ganglia and the effector organs.

Sites of actions of adrenergic agonists



Synthesis & release of norepinephrine
Neurotransmission in adrenergic neurons involves five 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.)



Adrenergic receptors (adrenoceptors)

α and β were initially identified on the basis of their responses to the adrenergic agonists epinephrine, norepinephrine, and isoproterenol.

α adrenoceptors: High affinity to epinephrine
Low affinity to isoproterenol

B adrenoceptors: High affinity to isoproterenol
Low affinity to nor epinephrine

Alpha-Adrenergic Receptors

$Alpha_1$-Adrenergic Receptors

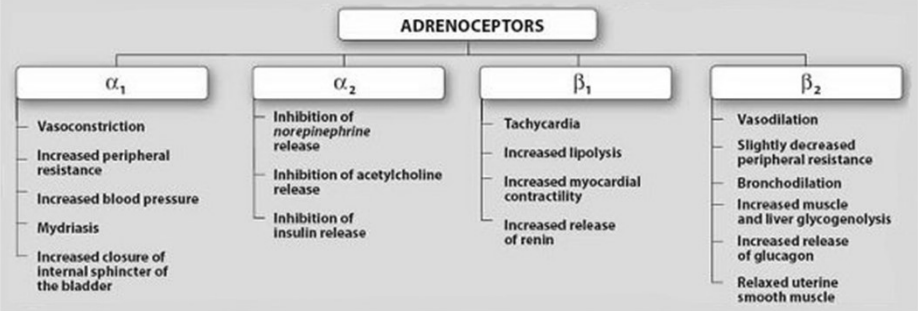
Located on postsynaptic effector cells

$Alpha_2$-Adrenergic Receptors

Located on presynaptic nerve terminals

Control the release of neurotransmitters

Major effects mediated by adrenoceptors



Dopaminergic Receptors

- An additional adrenergic receptor stimulated by dopamin causes dilation of the following blood vessels, resulting in increased blood flow (Renal, Mesenteric, Coronary, Cerebral)

Catecholamines

Sympathomimetic amines that contain the 3,4-dihydroxybenzene group (such as epinephrine, norepinephrine, isoproterenol, and dopamine)
These compounds have the following properties:

- High potency.
- Rapid inactivation:
- Poor penetration into the CNS

Noncatecholamines (phenylephrine, ephedrine, and amphetamine)

- Compounds lacking the catechol hydroxyl groups
- Have longer half-lives (not inactivated by COMT)
- These are poor substrates for MAO (prolonged duration of action).
- Increased lipid solubility permits greater access to the CNS.

Note: Ephedrine and amphetamine may act indirectly by causing the release of stored catecholamines

Sympathomimetic agonists

Direct-acting

- Alpha agonists
  - Alpha2-selective (clonidine)
  - Alpha1-selective (phenylephrine)
  - Nonselective(norepinephrine)
- Beta agonists
  - Beta2-selective (albuterol)
  - Beta1-selective (dobutamine)
  - Nonselective (isoproterenol)

Indirect-acting

- Releasers (amphetamine)
- Reuptake inhibitors (cocaine)

Mechanism of action of the adrenergic agonists

Direct-acting agonists

(epinephrine, norepinephrine, isoproterenol, and phenylephrine)

- Widely used clinically constitute a very important group of drugs used for cardiovascular, respiratory, and other conditions.
- Act directly on α or β receptors
- The activated receptor initiates synthesis of second messengers and subsequent intracellular signals.

Indirect-acting agonists:

- **Reuptake inhibitors:** Block the uptake of norepinephrine ,uptake blockers(cocaine)
- **Releasers** :Cause the release of norepinephrine from the vesicles of the adrenergic neuron (amphetamines)

Mixed-action agonists:

Ephedrine, pseudoephedrine both to stimulate adrenoceptors directly and to release norepinephrine from the adrenergic neuron

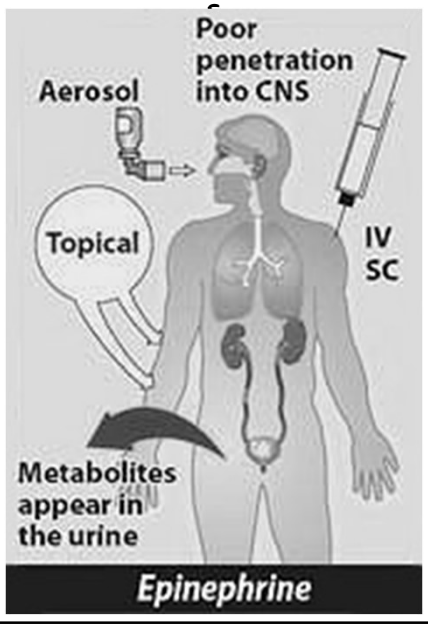
Types of adrenoceptors, some of the peripheral tissues in which they are found, and their major effects.

Type	Tissue	Actions
α_1	Most vascular smooth muscle	Contracts (↑ vascular resistance)
	Pupillary dilator muscle	Contracts (mydriasis)
	Pilomotor smooth muscle	Contracts (erects hair)
	Liver (in some species, eg, rat)	Stimulates glycogenolysis
α_2	Adrenergic and cholinergic nerve terminals	Inhibits transmitter release
	Platelets	Stimulates aggregation
	Some vascular smooth muscle	Contracts
	Fat cells	Inhibits lipolysis
	Pancreatic β (B) cells	Inhibits insulin release
β_1	Heart	Stimulates rate and force
	Juxtaglomerular cells of kidney	Stimulates renin release
β_2	Airways, uterine, and vascular smooth muscle	Relaxes
	Liver (human)	Stimulates glycogenolysis
	Pancreatic β (B) cells	Stimulates insulin release
	Somatic motor neuron terminals (voluntary muscle)	Causes tremor
	Heart	Stimulates rate and force
β_3	Fat cells	Stimulates lipolysis
Dopamine$_1$ (D_1)	Renal and other splanchnic blood vessels	Dilates (↓ resistance)
Dopamine$_2$ (D_2)	Nerve terminals	Inhibits adenylyl cyclase

Epinephrine

- It is one of four catecholamines
- (epinephrine, norepinephrine, dopamine (naturalneurotransmitters) and dobutamine (synthetic compound) commonly used in therapy.
- Epinephrine is synthesized from tyrosine in the adrenal medulla and released, along with small quantities of norepinephrine, into the bloodstream.
- Epinephrine interacts with both α and β receptors.
- At low doses, β effects (vasodilation) on the vascular system
- High doses, α effects (vasoconstriction) are strongest.

Pharmacokinetic



Clinical Uses OF Adrenergic Agonist

Anaphylaxis

Epinephrine is the drug of choice for the immediate treatment of anaphylactic shock because it is an effective physiologic antagonist of many of the mediators of anaphylaxis.

Note: Antihistamines and corticosteroids may also be used, but epinephrine is more efficacious & rapid acting.

Central Nervous System

- Amphetamine are widely used and abused for their CNS effects.
- The CNS stimulant effects of amphetamine and its derivatives have led to their use for treating hyperactivity in children, narcolepsy, and appetite control.
- Its use in pregnancy should be avoided because of adverse effects on the fetus..
- Methylphenidate and other amphetamine analogs have been heavily used in attention deficit disorder. The drugs are abused or misused for the purpose of deferring sleep and for their mood elevating, euphoria-producing action.
- They have a high addiction liability

Eye

- The α agonists, especially phenylephrine and tetrahydrozoline, are often used to reduce the conjunctival itching and congestion caused by irritation or allergy.
- Phenylephrine is an effective mydriatic. These drugs do not cause cycloplegia.
- Newer α2 agonists are in current use for glaucoma and include apraclonidine and brimonidine (reduce aqueous synthesis)

Bronchi

- The β agonists, especially the β2-selective agonists, are drugs of choice in the treatment of acute asthmatic bronchoconstriction.
- The short-acting β2-selective agonists (eg, albuterol, metaproterenol, terbutaline) are not recommended for prophylaxis, but they are safe and effective in the treatment of bronchospasm.
- Much longer-acting β2-selective agonists, salmeterol, formoterol are used in combination with corticosteroids for prophylaxis; they are not indicated for the treatment of acute symptoms.

Cardiovascular Applications

1. Conditions in which an increase in blood flow is desired-In acute heart failure and some types of shock, an increase in cardiac output and blood flow to the tissues is needed.
   - Beta1 agonists may be useful in this situation because
   - They increase cardiac contractility and reduce (to some degree) afterload by decreasing the ventricular ejection through a small β2 effect.
   - Norepinephrine, is an effective agent in septic and cardiogenic shock.
   - Dobutamine and dopamine are also used

2. Conitions in which a decrease in blood flow or increase in blood pressure is desired Alpha1 agonists are useful (cause vasoconstriction) These include local hemostatic (epinephrine) and decongestant effects (phenylephrine) as well as spinal shock (norepinephrine, phenylephrine), in which temporary maintenance of blood pressure may help maintain perfusion of the brain, heart, and kidneys.

Alpha agonists are often mixed with local anesthetics to reduce the loss of anesthetic from the area of injection into the circulation.
Chronic orthostatic hypotension due to inadequate sympathetic tone can be treated with oral ephedrine or a newer orally active α1 agonist, midodrine

3. Conditions in which acute cardiac stimulation is desired
   - Epinephrine has been used in cardiac arrest by intravenous and direct intracardiac injection.
   - Isoproterenol has been used for atrioventricular (AV) block

Genitourinary Tract

- Suppress premature labor Beta2 agonists (ritodrine, terbutaline) are used to, but the cardiac stimulant effect may be hazardous to both mother and fetus.
- Nonsteroidal anti-inflammatory drugs, calcium channel blockers, and magnesium are also used for this indication.
- Long-acting oral sympathomimetics such as ephedrine some time used in Urinary continence in the elderly and in children with enuresis
- This action is mediated by α receptors in the trigone of the bladder and, in men, the smooth muscle of the prostate.

Toxicity catecholamines

- Have little CNS toxicity when given systemically (Because of their limited penetration into the brain)
- In the periphery, their adverse effects are extensions of their pharmacologic alpha or beta actions: excessive vasoconstriction, cardiac arrhythmias, myocardial infarction, hemorrhagic stroke, and pulmonary edema or hemorrhage.

The phenylisopropylamines eg (amphetamine, ephedrine).

- Mild to severe CNS toxicity, depending on dosage. In small doses, they induce nervousness, anorexia, and insomnia; in higher doses, they may cause anxiety, &Convulsions.
- Peripherally acting agents have toxicities that are predictable on the basis of the receptors they activate.
- α1 agonists cause hypertension
- β1 agonists cause sinus tachycardia and serious arrhythmias.
- β2 agonists cause skeletal muscle tremor.
- It is important to note that none of these drugs is perfectly selective; at high doses, β1-selective agents have β2 actions and vice versa.

Cocaine is of special importance as a drug of abuse: its major toxicities include cardiac arrhythmias or infarction and convulsions.

Some adverse effects observed with adrenergic agonists