Sympathomimetic Agents – ANS Pharmacology

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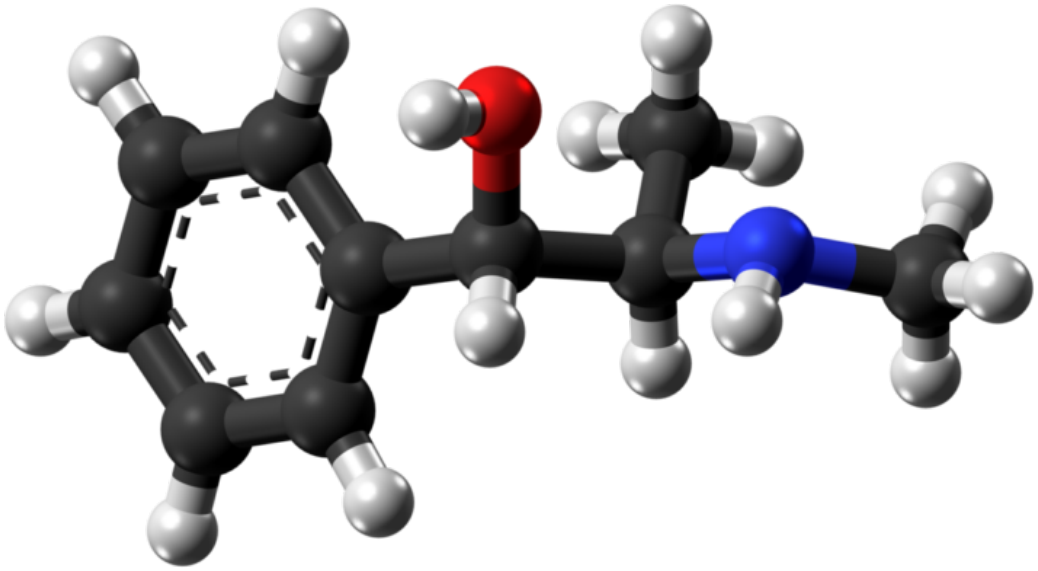
The sympathetic autonomic nervous system (ANS) works by the release of neurotransmitters that act on the adrenoreceptors, with their various types and subtypes. The effects produced can be mimicked by drugs that stimulate these receptors, known as sympathomimetics. Some sympathomimetics have a higher affinity for a certain receptor type or subtype while others are rather non-selective.



Definition of Sympathomimetics

Sympathomimetics are drugs that mimic the action of the stimulators of the sympathetic autonomic nervous system, specifically the adrenoreceptors: α, β or dopamine receptors. They are also known as adrenergic agonists.

Classification of Sympathomimetics

Sympathomimetics can be divided based on the type of receptors, for which they have a higher affinity, i.e. their spectrum of action.

For example, epinephrine is both an α and β agonist, whereas phenylephrine is predominantly an α1 agonist. Dopamine, obviously, is a strong dopamine receptor agonist, but it can also activate α and β receptors at certain doses. Thus, a sympathomimetic drug can be a selective agonist; however, no sympathomimetic is

100% selective or specific.

Sympathomimetics can also be classified based on their mechanism of action into **direct-, indirect-, and mixed-acting drugs**.

Direct-acting drugs are those that directly act on and activate the receptors to produce the desired pharmacological effects, e.g., dobutamine, which acts selectively on the β1 receptors.

Indirect-acting drugs are those that act indirectly to increase the concentration of the endogenous neurotransmitter by causing its release (e.g., amphetamine derivatives) or inhibiting its reuptake (e.g., tricyclic antidepressants).

Mixed-acting drugs employ both mechanisms, e.g., ephedrine, which, in addition to acting on the α and β receptors, causes noradrenaline release.

Always remember that epinephrine, norepinephrine, and dopamine are endogenous catecholamines. Please note that adrenaline is another name for epinephrine, and similarly, noradrenaline is the other name for norepinephrine.

Difference between epinephrine and norepinephrine

Epinephrine is a hormone released from the adrenal medulla, whereas norepinephrine is a neurotransmitter released at the postganglionic neurons. There is a difference in the structure of epinephrine and norepinephrine also; norepinephrine lacks the methyl substitution at the amine group.

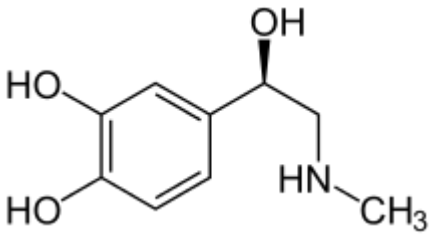


Image: Structure of adrenaline (epinephrine) by NEUROtiker. License: Public Domain

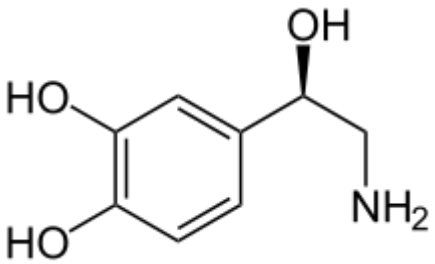


Image: Structure of noradrenaline (norepinephrine). Note the missing methyl substitution at the amine group by NEUROtiker. License: Public Domain

Epinephrine has a profound effect on the heart rate and cardiac output as compared to norepinephrine. Also, norepinephrine doesn't drastically affect the metabolic effects, such as increased blood sugar and lactic acid levels, as seen with the epinephrine.

Pharmacokinetics of Sympathomimetics

Catecholamines (epinephrine, norepinephrine, and dopamine—endogenous adrenoceptor agonists and other related drugs):

- Short duration of action, because of 1 or both of the following:
    - Rapidly metabolized by catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO)
    - Readily taken up into the nerve endings (exception: isoproterenol)
- Inactive orally (midodrine is an orally active α1 agonist)
- Low central nervous system (CNS) penetration but can penetrate CNS at higher doses (‘adrenaline rush’).

Epinephrine and **norepinephrine** are not active orally; they are given by the intravenous (IV) route in an emergency.

Phenylisopropylamine derivatives (amphetamines and ephedrine):

- Resistant to MAO and COMT
- Orally active
- Better CNS penetration
- Longer lasting effects than those of catecholamines.

Mechanism of Action of Sympathomimetics

As previously mentioned, sympathomimetics act by stimulating the α, β and/or dopamine receptors, and/or causing the release or inhibiting the reuptake of neurotransmitters.

Brief review of the neurotransmission of adrenergic neurons

Norepinephrine is synthesized from tyrosine and stored in vesicles at the end of the neuron. The calcium influx from an action potential causes the vesicles to fuse with the synapse membrane and release noradrenaline in the synaptic space. It then binds to the adrenoreceptor on the effector cells and produces effects by various mechanisms. The excess norepinephrine not bound to the postsynaptic receptor binds to the alpha2 (α2) presynaptic receptors to decrease its own release. Then, it either diffuses out, is metabolized by COMT, or is taken back up by the presynaptic neuron.

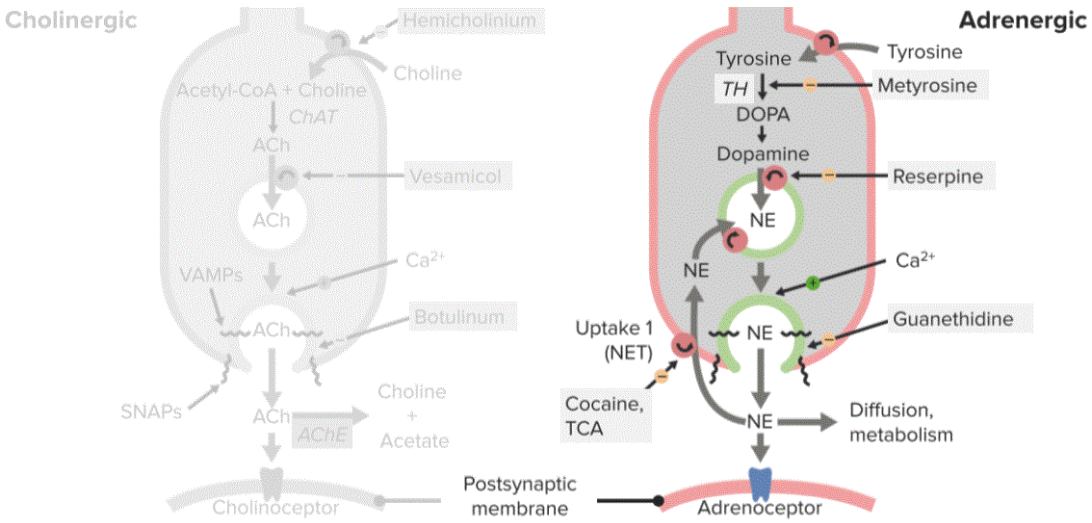


Image: Sympathomimetics. Overview of activity. By Lecturio

Direct-acting sympathomimetics

α–receptor stimulation: alpha1 (α1) agonists act by G-protein activation of the enzyme phospholipase C, resulting eventually in the release of calcium, thereby increasing the intracellular calcium concentration. α2 agonists act by inhibiting adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). This leads to decreased intracellular cAMP levels.

Alpha receptors are further subdivided into α1A, α1B, α1C, and α1D as well as α2A, α2B, and α2C. This differentiation is important as the search for more selective newer drugs continues, and selectivity at the sub-type level helps narrow down the effects of a drug.

Receptor	Drug
Non-selective	Norepinephrine
α1 selective	Phenylephrine
α2 selective	Clonidine

β-receptor stimulation: β agonists – selective to a subtype (β1, β2, and β3) or non-selective – stimulate adenylyl cyclase, causing increased intracellular cAMP levels.

Receptor	Drug
Non-selective	Epinephrine, isoproterenol
β1 selective	Dobutamine
β2 selective	Albuterol, salbutamol, terbutaline

Dopamine-receptor stimulation: Dopamine receptor agonists can act on D1 or D2 receptors. D1 receptors activate adenylyl cyclase and increase intracellular cAMP mainly in neurons and vascular smooth muscle. D2 receptors reduce intracellular cAMP and are found in the brain and as pre-synaptic receptors.

Receptor	Drug
Non-selective	Dopamine
D1 selective	Fenoldopam

Indirect acting sympathomimetics

Indirect-acting drugs are those that act indirectly to increase the concentration of the endogenous neurotransmitter by causing its release (e.g., amphetamine derivatives and ephedrine) or inhibiting its reuptake (e.g., cocaine and tricyclic antidepressants).

Mixed-acting sympathomimetics

Mixed-acting drugs employ both mechanisms, e.g., ephedrine**,** which, in addition to acting on the α and β receptors, also causes the release of noradrenaline.

Ephedrine is used to treat nasal congestion.

Effects on Various Organ Systems and Clinical Uses of Sympathomimetics

Sympathomimetics (α and β agonists) have varying effects on various organ systems. The effects of sympathomimetics on various organ systems are summarized in the following table:

Organ system	Effects	Receptor	Clinical uses/Other comments
Bronchi	Bronchiolar smooth muscle relaxation	**β2**	Relieving acute bronchoconstriction in asthma (e.g., short-acting β2 agonists such as albuterol and terbutaline) and chronic obstructive pulmonary disease (COPD) (long-acting β2 agonists such as salmeterol and formoterol)
Gastrointestinal tract	Smooth muscle relaxation	α or β	
Eye	Contraction of the smooth muscle of the iris dilator muscle (mydriasis) **Mnemonics:** the α receptors look like an eye. Always correlate the **α** with **eyes (α)** to remember its action on the eyes. Increase aqueous humor outflow (a lower IOP) Reducing synthesis of aqueous humor (a lower IOP)	**α1** **α2**	Phenylephrine is an effective mydriatic. Brimonidine (α2 agonist) is used in open-angle glaucoma and ocular hypertension.
Genitourinary (bladder and prostate)	Constriction of the bladder sphincter. Control of urine flow (no urination in stressful situations). Causes ejaculation by inducing contraction of the prostate.	**α1**(Antagonistic action)	Tamsulosin is an α blocker or antagonist used to improve urination in benign prostate hyperplasia (BPH) because it causes relaxation of the bladder muscles (opposite actions to the **α** agonists). **Always remember:** To remember the effects of the α antagonists on various organ systems, first learn the effects of alpha agonist and just reverse the actions of alpha agonists.
CNS	Amphetamines: Mild increase in alertness or decrease in fatigue, followed by mild anorexia, euphoria, and insomnia. Amphetamine is used as a CNS stimulant and used to treat narcolepsy and ADHD.	DA receptor Probably due to dopamine release	Modafinil, an amphetamine derivative, is an atypical weak dopamine reuptake inhibitor and is used for narcolepsy.
Uterus	Relaxation of uterus	**α1**	Terbutaline (selective β2 agonist) and ritodrine are used to suppress premature labor.

Cardiovascular effects of sympathomimetics

α and β agonists have significant effects on vascular systems. These effects are essential to understand and learn the cardiovascular pharmacology of α and β agonists/sympathomimetics.

It is interesting to mention the mechanism of action of clonidine. Other α agonists increase the blood pressure; however, clonidine is used in the treatment of hypertension (it decreases the blood pressure). Clonidine acts on α adrenoceptors in the medulla of the brain. It is a centrally acting α2 agonist. It decreases the blood pressure by decreasing peripheral vascular resistance, thus lowering blood pressure, and reduces the release of catecholamine levels in the blood. It also decreases the heart rate and cardiac output, though decreased blood return eventually results in reflex tachycardia.

Cardiovascular effects of sympathomimetics are summarized in the following table:

Receptor	Effects	Examples/Clinical Uses
α1	Vascular smooth muscle contraction (increased peripheral resistance, increased blood pressure, and reflex bradycardia). **Mnemonics:** α1= ↑ This correlation will help in remembering that α1 agonists increase **(α1= ↑)** the blood pressure	**Phenylephrine**: spinal shock and can also be used locally, e.g., nasal sprays and to relieve congestion (stimulates the mucous secretion) **Midodrine:** chronic orthostatic hypotension
α2	Stimulation of presynaptic α2 agonists in the central nervous system; inhibits the sympathetic autonomic system	**Clonidine:** refractory hypertension and hypertension complicated by renal disease (as it does not affect renal blood flow/glomerular filtration) **Methyldopa**: Hypertension in pregnancy and eclampsia (use otherwise limited because of side effects)
β1	**Heart** Increased heart rate, conduction velocity, and increased contractility. Increased atrioventricular (AV) node conduction.	Dobutamine, adrenaline, and isoprenaline are used in: Cardiogenic shock Hypotensive crisis Acute heart failure Cardiac arrest **Remember:** Beta-blockers are used in the treatment of hypertension.
β2	Promote the dilation of arterioles and veins, and consequently a decrease in TPR, blood pressure, and afterload.	
D1	Vasodilatation in the kidney and spleen	Dopamine

Other clinical uses of sympathomimetics

Epinephrine is a mixed-acting agonist. It is the drug of choice for **anaphylaxis** and cardiac arrest. This is because it antagonizes the effects of many mediators of anaphylaxis. It counteracts hypotension through β1 receptor stimulation and causes bronchial muscle relaxation, thereby relieving bronchospasms through β2 receptor stimulation.

Toxicity of Sympathomimetics

Toxicities of sympathomimetic drugs are basically an extension of their physiologic effects of α or β receptor stimulation—excessive vasoconstriction, cardiac arrhythmias, myocardial infarction, stroke, pulmonary edema, pulmonary hemorrhage, etc.

Obviously, drugs that have more selective subtype affinity will have toxicities more related to stimulation of that subtype. For example, β1 agonists will cause tachycardia and arrhythmias, and toxicity of α1 agonists will manifest as hypertension.

Side Effects of Sympathomimetics

Common side effects of α agonists

- Headache
- Reflex bradycardia
- Excitability
- Restlessness

Common side effects of β agonists

- Cardiac arrhythmia
- Headache
- Tremors
- CNS effects of catecholamines are limited because of their low CNS penetration; however, higher doses can cause some CNS effect. CNS toxicity of phenylisopropylamine derivatives depends on the dosage. It can be mild to severe, ranging from nervousness and insomnia to anxiety and aggressiveness and even paranoid behavior and convulsions.
- As mentioned in the introduction, the selectivity is only relative, and, at high doses, other receptor types can be activated.
- An important interaction is observed between tyramine and MAOa inhibitors. Both of these drugs should be contraindicated as MAOa inhibitors as they increase the bioavailability, resulting in a severe increase in blood pressure (hypertensive crisis).

References

Harvey, R. A., Clark, M. A., Finkel, R., Rey, J. A., & Whalen, K. (2012). Lippincott's illustrated reviews: Pharmacology. Philadelphia: Wolters Kluwer.

Katzung, B. G. (Ed.). (2012). Basic & clinical pharmacology (Vol. 12). New York, NY, USA: Lange Medical Books/McGraw-Hill.

Katzung, B. G., & Trevor, A. J. (1998). Examination & board review pharmacology. Appleton & Lange.

Kawasuji, T., Koike, K., & Saito, H. (1996). Chronotropic Effects of Optical Isomers of Ephedrine and Methylephedrine in the Isolated Rat Right Atria and in Vitro Assessment of Direct and Indirect Actions on. β. 1-Adrenoceptors. Biological and pharmaceutical bulletin, 19(11), 1423-1428.

Brunton, Laurence L., Bruce Chabner, and Björn C. Knollmann, eds. Goodman & Gilman's the pharmacological basis of therapeutics. Vol. 12. New York: McGraw-Hill Medical, 2011. pp 172-218.

Calipari, E. S., & Ferris, M. J. (2013). Amphetamine mechanisms and actions at the dopamine terminal revisited. *The Journal of Neuroscience*, *33*(21), 8923-8925.

Reid, J. L. (1986). Alpha-adrenergic receptors and blood pressure control. The American journal of cardiology, *57*(9), E6-E12.

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