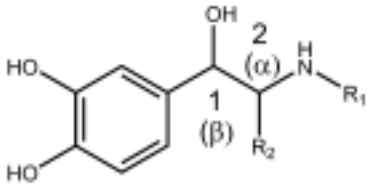
Direct-Acting Sympathomimetics

STRUCTURE–ACTIVITY RELATIONSHIPS

The parent structure of many adrenergic drugs is β-phenylethylamine.



The modifications of β-phenylethylamine influence not only the mechanism of action, the receptor selectivity, but also their absorption, oral activity, metabolism, and thus duration of action (DOA).

For the direct-acting sympathomimetic amines, maximal activity is seen in β-phenylethylamine derivatives containing (a) a catechol and (b) a (1R)-OH group on the ethylamine portion of the molecule.

Such structural features are seen in the prototypical direct-acting compounds NE, E, and ISO.

Optical Isomerism

For CAs, the more potent enantiomer has the (1R) configuration.

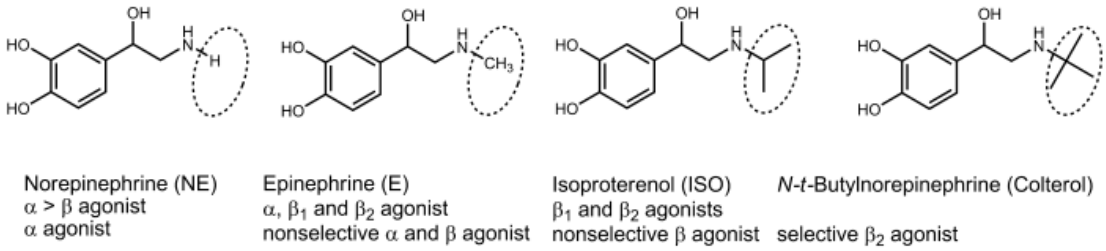
Separation of Aromatic Ring and Amino Group

The greatest adrenergic activity occurs when two carbon atoms separate the aromatic ring from the amino group.

R_1, Substitution on the Amino Nitrogen Determines α- or β-Receptor Selectivity

Primary and secondary amines have good adrenergic activity, whereas tertiary amines and quaternary ammonium salts do not.

The nature of the amino substituent also affects the receptor selectivity of the compound. As the size of the nitrogen substituent increases, α-receptor agonist activity generally decreases and β-receptor agonist activity increases.



Thus, NE has more α-activity than β-activity and E is a potent agonist at α-, β_1-, and β_2-receptors.

N-tert-butyl group enhances β_2-selectivity.

R_2, Substitution on the α-Carbon (Carbon-2).

Substitution by small alkyl group (e.g., CH_3- or C_2H_5-) slows metabolism by MAO. This is very important for non-catechol compounds where the addition of small alkyl group increases the resistance to metabolism and lipophilicity, so such compounds often exhibit enhanced oral effectiveness and greater CNS activity than other compounds that do not contain an α-alkyl group.

OH substitution on the β-carbon (carbon-1)

1- Greatly enhances agonist activity at both α- and β-receptors.
2- Largely decreases CNS activity because it lowers lipid solubility.

Substitution on the Aromatic Ring

Maximal α- and β-activity also depends on the presence of 3′ and 4′ OH groups.

Compounds without one or both phenolic OH substituents are not metabolized by COMT, and they are orally active and have longer duration of action.

Although the catechol moiety is important maximal agonist activity at adrenoceptors, it can be replaced with other substituted phenyl moieties to provide selective adrenergic agonists.

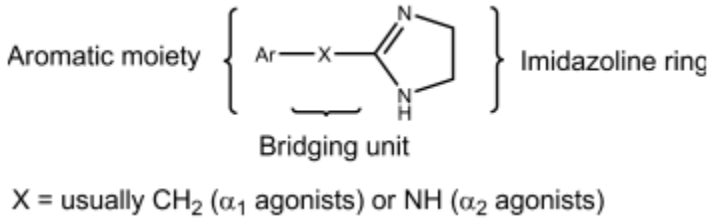
CAs without OH Groups

The loss of OH groups on the ring and the β-OH group on the side chain lead to compounds that:

1- Act almost by causing the release of NE from sympathetic nerve terminals (loss of direct sympathomimetic activity).
2- - Have more central activity (more lipophilic compounds).

Imidazolines and α-Adrenergic Agonists

A second chemical class of α-agonists is the imidazolines. These imidazolines can be nonselective, or they can be selective for either α_1- or α_2-receptors. Structurally, most imidazolines have their heterocyclic imidazoline nucleus linked to a substituted aromatic moiety via some type of bridging unit. The optimum bridging unit (X) is usually a single methylene group or amino group.



X = usually CH_2 (α_1 agonists) or NH (α_2 agonists)

ENDOGENOUS CATECHOLAMINES

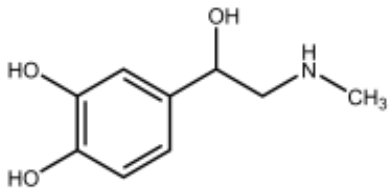
The three naturally occurring catecholamines **DA**, **NE**, and **E** are used as therapeutic agents.

α-ADRENERGIC RECEPTOR AGONISTS

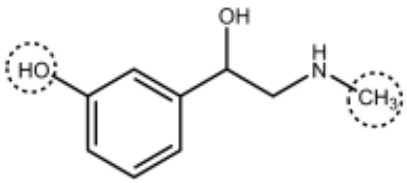
All selective α_1-agonists have therapeutic activity as vasoconstrictors. Structurally, they include (a) phenylethanolamines such as phenylephrine, metaraminol, and methoxamine and (b) 2-arylimidazolines such as xylometazoline, oxymetazoline, tetrahydrozoline, and naphazoline.

Phenylephrine

It differs from E only in lacking a p-OH group. It is orally active, and its duration of action (DOA) is about twice that of E because it lacks the catechol moiety and thus is not metabolized by COMT.



Epinephrine (E)

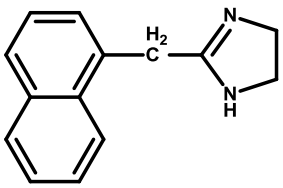


Phenylephrine

It is used for hypotension and as a nasal decongestant in both oral and topical preparations.

Naphazoline, tetrahydrozoline, xylometazoline, and oxymetazoline

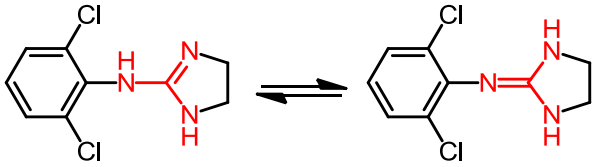
They are 2-aralkylimidazolines α_1-agonists. These agents are used for their vasoconstrictive effects as nasal and ophthalmic decongestants. They have limited access to the CNS, because they essentially exist in an ionized form at physiological pH caused by the very basic nature of the imidazoline ring.



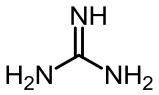
Naphazoline

Clonidine

It differs from 2-arylimidazoline α_1-agonists mainly by the presence of o-chlorine groups and a NH bridge. Clonidine has antihypertensive activity due to its ability to interact with α_2-receptor in the brain which cause a decrease in sympathetic out flow CNS.



Clonidine

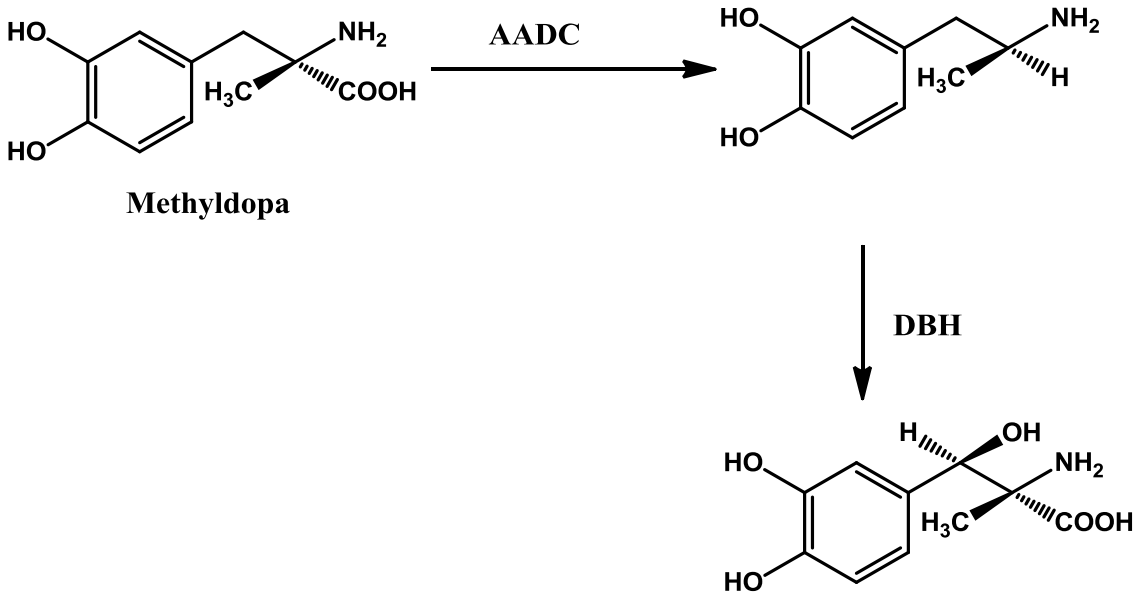


guanidine

The ability of clonidine to exert an antihypertensive effect depends on the ability of these compounds to enter the CNS and interact with the α_2-receptor in the brain. For clonidine, the basicity of the guanidine group (typically pK_a = 13.6) is decreased to 8.0 because of the inductive and resonance effects of the dichlorophenyl ring. Thus, at physiological pH, clonidine will exist to a significant extent in the nonionized form required for passage into the CNS.

Methyldopa (L-α-methyldopa)

It differs structurally from L-DOPA only in the presence of a α-methyl group. Methyldopa is transported actively into CNS, where it is decarboxylated by AADC in the brain to (1R, 2S)-α-methyldopamine. This intermediate, in turn, is stereospecifically β-hydroxylated by DBH to give the (1R, 2S)- α -methylnorepinephrine. This active metabolite is a selective α_2-agonist. It is currently postulated that α -methylnorepinephrine acts on α_2-receptors in the CNS in the same manner as clonidine, to decrease sympathetic outflow and lower blood pressure.

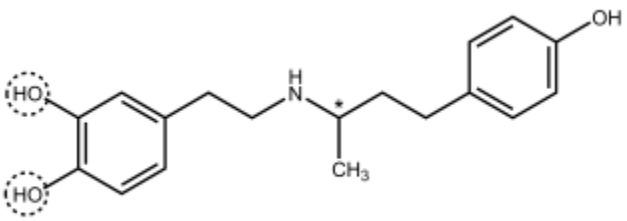


DUAL α- AND β-AGONISTS/ANTAGONISTS

Dobutamine

It possesses a center of asymmetry, and used clinically as racemic mixture. The (-) isomer of dobutamine is a potent α_1-agonist. In contrast, (+)-dobutamine is a potent α_1-antagonist, which can block the effects of (-)-dobutamine. Importantly, the effects of these two isomers are mediated via β_1-receptors. Both isomers appear to be full agonists. It is a positive inotropic agent administered intravenously for congestive heart failure.

Dobutamine contains a catechol group and is orally inactive and thus is given by intravenous infusion.

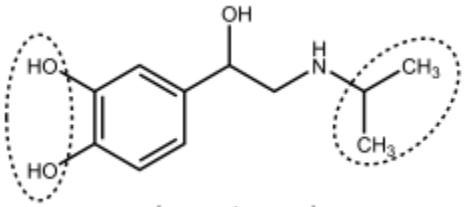


Dobutamine

β-ADRENERGIC RECEPTOR AGONISTS

Isoproterenol

Because of an isopropyl substitution on the nitrogen atom, it has virtually no α-activity. However, it does act on both β_1- and β_2-receptors.



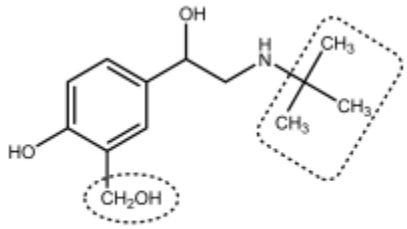
Isoproterenol

The cardiac stimulation caused by its β_1-activity and its lack of oral activity (why?) have led to its diminished use and favoring the more selective β – agonists.

β_2-Adrenergic Receptor Agonists

Albuterol, pirbuterol, salmeterol and Formoterol

They are selective β_2 mainly used as bronchodilator. They are not metabolized by either COMT or MAO. They are thus exhibit a longer duration of action than isoproterenol.



Albuterol

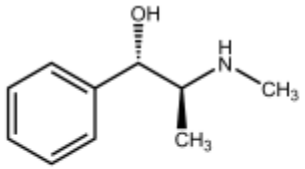
β3-Adrenergic Receptor Agonists.

Activation of the β_3-receptor is thought to be a possible approach for the treatment of obesity, type 2 diabetes mellitus, and frequent urination. Therefore, it is an attractive target for drug discovery. Selective β 3-agonists have been developed, but they have not been approved for therapeutic use.

Indirect-Acting Sympathomimetics

Indirect-acting sympathomimetics act by releasing endogenous NE. They enter the nerve ending by way of the active-uptake process and displace NE from its storage granules.

L-(+)-Pseudoephedrine



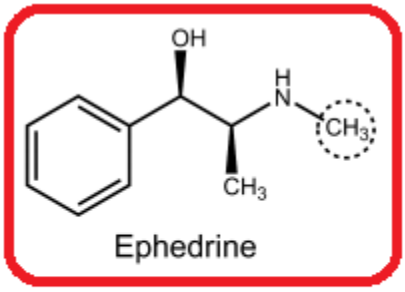
(1*S*,2*S*)-*L*-(+)-Pseudoephedrine
Virtually no direct activity
Mostly indirect activity

It is a naturally occurring alkaloid. This agent is found in many OTC nasal decongestant and cold medications.

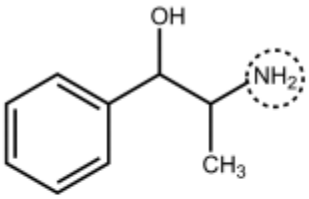
Whereas ephedrine has a mixed mechanism of action, L-(+)-pseudoephedrine acts mostly by an indirect mechanism and has virtually no direct activity. The structural basis for this difference in mechanism is the stereochemistry of the carbon atom possessing the β-OH group.

Sympathomimetics with a Mixed Mechanism of Action

They have no hydroxyls on the aromatic ring but do have a β-hydroxyl group.



Ephedrine



Phenylpropanolamine

D-(-)-Ephedrine

This drug is an alkaloid. It is not metabolized by either MAO or COMT and therefore has more oral activity and longer duration of action than E. Ephedrine has two asymmetric carbon atoms so it has four isomers.

D (-) isomer is the most active of the four isomers as a pressor amine because has the correct (1R,2S) configuration for optimal direct action at adrenergic receptors.

Lacking phenolic OH groups, ephedrine is less polar and, thus, crosses the BBB far better than do other CAs.