β_3-Adrenergic Receptor Agonists

The β_3-receptor has been shown to mediate various pharmacological effects such as lipolysis, thermogenesis, and relaxation of the urinary bladder. 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. Selective β_3-agonists have been developed, but they have not been approved for therapeutic use.

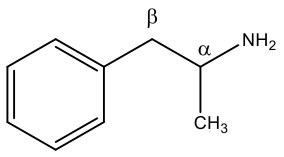
Indirect-Acting Sympathomimetic

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

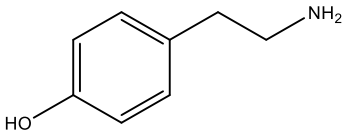
SAR

1. The indirect-acting drugs that are used therapeutically are **not catechol derivatives** and, in most cases, do not even contain an OH moiety.
2. The presence of a β-hydroxyl group decreases, and an **α-methyl group increases**, the effectiveness of indirect-acting agents.
3. The presence of nitrogen substituents decreases indirect activity, with substituents larger than methyl groups rendering the compound virtually inactive. Phenylethylamines that contain a tertiary amino group are also ineffective as NE-releasing agents.

Amphetamine and p-tyramine are often cited as prototypical indirect-acting sympathomimetics.



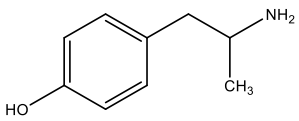
amphetamine
Log P=2.81



p- tyramine

1. Hydroxyamphetamine (Paredrine)

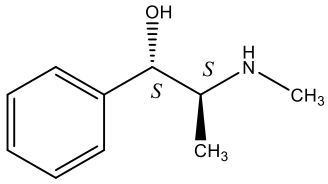
Is an effective, indirect-acting sympathomimetic drug. It differs from amphetamine in the presence of p-OH group and so it has little or no CNS-stimulating action. It is used to dilate the pupil for diagnostic eye examinations and for surgical procedures on the eye. It is sometimes used with cholinergic blocking drugs like atropine to produce a mydriatic effect, which is more pronounced than that produced by either drug alone.



p- Hydroxyamphetamine
LogP= 1.07
pKa= 10.71

2. L-(+)-Pseudoephedrine

Is the (S,S) diastereoisomer of ephedrine. Whereas ephedrine has a mixed mechanism of action, L-(+)-pseudoephedrine acts mostly by an indirect mechanism and has virtually no direct activity. In pseudoephedrine, β- OH group possesses the (S) configuration, the wrong stereochemistry at this center for a direct-acting effect at adrenoceptors. It has fewer CNS effects than does ephedrine. This agent is found in many OTC nasal decongestant and cold medications.

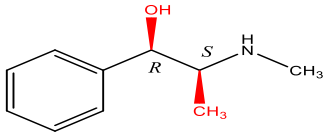


L-(+)-Pseudoephedrine

Sympathomimetics with a Mixed Mechanism of Action

Those phenylethylamine have **no hydroxyls on the aromatic ring** but do have a β-hydroxyl group.

1. D-(-)-Ephedrine.



D-(-)-ephedrine
Log P= 1.05
correct 1R, 2S configuration

The pharmacological activity of (1R,2S)-D-(-)-ephedrine resembles that of E. The drug acts on both -αand β-receptors.

Ephedrine is less polar (Log P = 1.05, pKa = 9.6) and, thus, crosses the BBB far better than do other CAs. Therefore, ephedrine has been used as a CNS stimulant and exhibits side effects related to its action in the brain.

The drug is not metabolized by either MAO or COMT and therefore has more oral activity and longer DOA than E.

This is largely because of the fact that this isomer has the correct (1R,2S) configuration for optimal direct action at adrenergic receptors.

Uses

Ephedrine and its salts are used orally, intravenously, intramuscularly, and topically for various conditions, such as allergic disorders, colds, hypotensive conditions, and narcolepsy. It is used locally to constrict the nasal mucosa and cause decongestion and to dilate the pupil or the bronchi. Systemically, it is effective for asthma, hay fever, and urticaria.

ADRENERGIC RECEPTOR ANTAGONISTS (BLOCKERS)

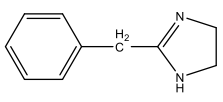
First: α-Blockers

Because α-agonists cause vasoconstriction and raise blood pressure, α-blockers should be therapeutically used as antihypertensive agents. the α-blockers consist of several compounds of diverse chemical structure that bear little obvious resemblance to the α-agonists.

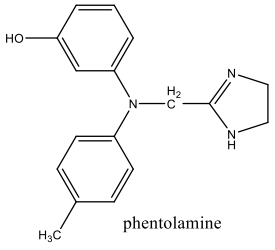
I. NONSELECTIVE α-BLOCKERS

1. Tolazoline (Priscoline) and phentolamine (Regitine)

Are imidazoline competitive α-blockers, The structure of tolazoline are similar to the imidazoline α_1-agonists, but does not have the lipophilic substituents required for agonist activity. The type of group attached to the imidazoline ring thus **dictates whether an imidazoline is an agonist or a blocker.**



tolazoline



phentolamine

Neither drug is useful in treating essential hypertension for following reasons:

a. Tolazoline and phentolamine have both α_1- and α_2-blocking activity and produce tachycardia. Both agents also have a direct vasodilatory action on vascular smooth muscle that may be more prominent than their α-blocking effects.
b. The blocking action of tolazoline is relatively weak, but **its histamine-like** and **acetylcholine-like agonistic** actions probably contribute to its vasodilatory activity.

Its histamine-like effects include stimulation of gastric acid secretion, rendering it inappropriate for administration to patients who have gastric or peptic ulcers.

Uses

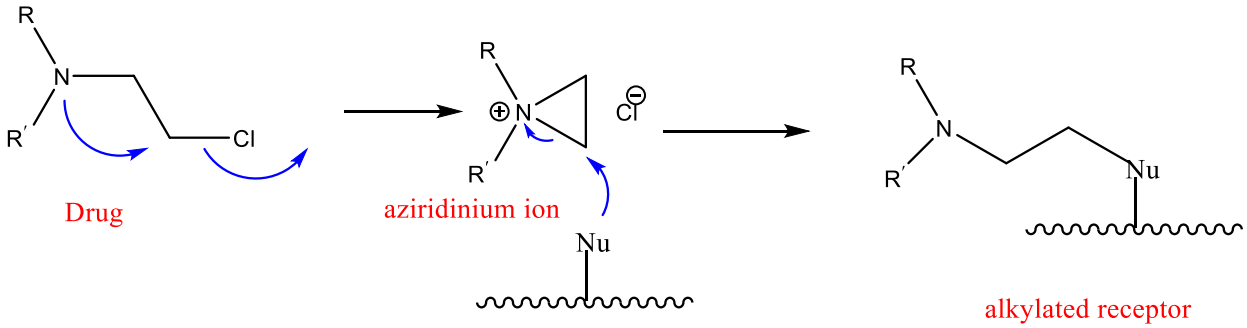
Tolazoline is available in an injectable form and is indicated for use in persistent pulmonary hypertension of the newborn when supportive measures are not successful. Phentolamine is used to prevent or control hypertensive episodes that occur in patients with pheochromocytoma. It also has been used in combination with papaverine to treat impotence.

II. IRREVERSIBLE α-BLOCKERS

Agents in this class, when given in adequate doses, produce a slowly developing, prolonged adrenergic blockade that is **not overcome by E**. They are irreversible α-blockers, because β-haloalkylamines in the molecules alkylate α-receptors (recall that β-haloalkylamines are present in nitrogen mustard anticancer agents and are highly reactive alkylating agents).

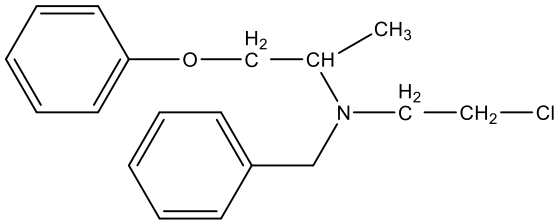
Mechanism of irreversible blocker

The initial step involves the formation of an intermediate aziridinium ion (ethylene iminium ion). The positively charged aziridinium ion electrophile then reacts with a nucleophilic group on the α-receptor (if this occurs in the vicinity of the α-receptor), resulting in the formation of a covalent bond between the drug and the receptor. Unfortunately, these nonselective drugs alkylate not only α-receptors but also other biomolecules, leading to their toxicity. It is thus used only to relieve the sympathetic effects of pheochromocytoma[1].



[1] Pheochromocytoma is a type of neuroendocrine tumor that grows from cells called chromaffin cells. These cells produce hormones needed for the body and are found in the adrenal glands.

1. Phenoxybenzamine



phenoxybenzamine

Is a haloalkylamine that blocks α_1- and α_2- receptors irreversibly. Although phenoxybenzamine is capable of blocking acetylcholine, histamine, and serotonin receptors, its primary pharmacological effects, especially that of vasodilation, may be attributed to its α-adrenergic blocking capability.

The onset of action of phenoxybenzamine is slow, but the effects of a single dose of drug may last 3 to 4 days.