“Adrenergic Receptor Antagonists”

α-Adrenergic Receptor Antagonists

Unlike the β-adrenergic receptor antagonists, which bear clear structural similarities to the adrenergic agonists NE, epinephrine, and isoproterenol, the α-adrenergic receptor antagonists consist of a number of compounds of diverse chemical structure that bear little obvious resemblance to the α-adrenergic receptor agonists.

- **Imidazolines**

  The imidazoline α-antagonists are competitive (reversible) blocking agents that are structurally similar to the imidazoline α-agonists, such as naphazoline, tetrahydrozoline, and xylometazoline. The type of group attached to the imidazoline ring dictates whether an imidazoline is an agonist or an antagonist. The two representatives of the imidazoline α-antagonists that are used therapeutically are Tolazoline and Phentolamine. Phentolamine is the more effective α-antagonist, but neither drug is useful as an antihypertensive agent. Theoretically, the vasodilatory effects of an α-antagonist should be beneficial in the management of hypertension. However, tolazoline and phentolamine have both α₁- and α₂-antagonistic activity and produce tachycardia. Presumably, the antagonistic actions of these agents at presynaptic α₂-receptors contribute to their cardiac stimulant effects by enhancing the release of NE. Both agents have a direct vasodilatory action on vascular smooth muscle that may be more prominent than their α-receptor antagonistic effects.
The antagonistic 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. It has been used to treat Raynaud’s syndrome and other conditions involving peripheral vasospasm. Tolazoline is available in an injectable form and is indicated for use in persistent pulmonary hypertension of the new born when supportive measures are not successful.

Phentolamine is used to prevent or control hypertensive episodes that occur in patients with pheochromocytoma. It can be used as an aid in the diagnosis of pheochromocytoma, but measurement of catecholamine levels is a safer and more reliable method of diagnosis.
β-Haloalkylamines

Agents in this class in essence, they are irreversible blockers of the α-adrenergic receptor. Dibenamine is the prototypical agent in this class; it is phenoxybenzamine that is used therapeutically today.
Oral phenoxybenzamine is used for the preoperative management of patients with pheochromocytoma and in the chronic management of patients whose tumors are not amenable to surgery.
➤ Quinazolines

Agents in this class are highly selective competitive antagonists of the $\alpha_1$-adrenergic receptor. Examples include prazosin, terazosin, and doxazosin. Structurally, these three agents consist of three components: the quinazoline ring, the piperazine ring, and the acyl moiety. The 4-amino group on the quinazoline ring is very important for $\alpha_1$-receptor affinity. Although prazosin, terazosin and doxazosin possess a piperazine moiety attached to the quinazoline ring, this group can be replaced with other heterocyclic moieties (e.g., piperidine moiety) without loss of affinity. The nature of the acyl group has a significant effect on the pharmacokinetic properties.
These drugs are used in the treatment of hypertension. They dilate both arterioles and veins. Agents in this class offer distinct advantages over the other α-blockers because they produce peripheral vasodilation without an increase in heart rate or cardiac output. This advantage, at least in part, is attributed to the fact that prazocin blocks postjunctional α₁-receptors selectively without blocking presynaptic α₂-receptors. These agents also find used in the treatment of benign prostatic hyperplasia, where they help improve urine flow rates.

Although the side effects of these drugs are usually minimal, the most frequent one, known as the first-dose phenomenon, is sometimes severe. This is a dose-dependent effect characterized by marked excessive postural hypotension and syncope. This phenomenon can be minimized by initially giving a low dose at bedtime.

The more recently developed Tamsulosin (Flomax)®: is more selective for the subtype of α₁-adrenoceptor found in the prostate gland over those found in vascular tissue. Thus, tamsulosin has no utility in treating hypertension, but far fewer cardiovascular side effects than terazocin and doxazocin in treating BPH.

Yohimbanes

This class is comprised of a number of isomeric indole alkaloids that exhibit different degrees of selectivity toward the α₁ and α₂ adrenergic receptors depending on their stereochemistry. For example, Yohimbine is a selective antagonist of the α₂-receptor, while Corynanthine is a selective antagonist of the α₁-receptor. The only difference between these two compounds is the relative stereochemistry of the carbon containing the carbomethoxy substituent. In yohimbine, this group lies in
the plane of the alkaloid ring system, while in corynanthine it lies in an axial position and thus is out of the plane of the rings.

Yohimbine increases heart rate and blood pressure as a result of its blockade of $\alpha_2$-receptors in the CNS. It is being used experimentally to treat male impotence.
"β-Adrenergic Receptor Antagonists"

**Structure Activity Relations**

The first β-blocker was dichloroisoproterenol (DCI). The structure of DCI is identical to that of isoproterenol, with the exception that two chloro groups have replaced the catechol hydroxyl groups.

Unfortunately, DCI is not a pure antagonist but a partial agonist. The substantial direct sympathomimetic action of DCI precluded its development as a clinically useful drug.

![Dichloroisoproterenol](Image)

**Pronethalol** was the next important β-antagonist to be described, although it had much less intrinsic sympathomimetic activity than DCI. It was withdrawn from clinical testing. Then, the β-blocking actions of Propranolol, (a close structural relative of pronethalol) is the standard against which all other β-antagonists are compared.

Propranolol belongs to the group of β-blocking agents known as “aryloxypropanolamines”. This term reflects the fact that an –OCH₂- group has been incorporated into the molecule between the aromatic ring and the ethylamino side chain. Because this structural feature is frequently found in β-antagonists, the assumption is made that the –OCH₂- group is responsible for the antagonistic
properties of the molecules. However, this is not true; in fact, the –OCH₂- group is present in several compounds that are potent β-agonists. This latter fact again leads to the conclusion that it is the nature of the aromatic ring and its substituents that is the primary determinant of β-antagonistic activity. The aryl group also affects the absorption, excretion and metabolism of the β-blockers.

The nature of the aromatic ring is also a determinant in the β₁-selectivity of the antagonists. One common structural feature of many cardioselective antagonists is the presence of a para-substituent of sufficient size on the aromatic ring along with absence of meta-substituent. Practolol is the prototypical example of a β₁-antagonist of this structural type. It was the first cardioselective β₁-antagonist to be used extensively in humans. However, because it produced several toxic effects, it is no longer in general used in most countries.
As in the sympathomimetics, bulky aliphatic groups, such as the tert-butyl and isopropyl groups, are normally found on the amino function of the aryloxypropanolamine β-receptor antagonists. It must be a secondary amine for optimal activity.

The β-blocking agents exhibit a high degree of stereoselectivity in the production of their β-blocking effects. As with the sympathomimetic agents, the configuration of the hydroxyl-bearing carbon of the aryloxypropanolamine side chain plays a critical role in the interaction of β-antagonist drugs with β-receptors. This carbon must possess the (S)-configuration for optimal affinity to the β-receptors. The enantiomer with the (R)-configuration is typically 100 times less potent.

Nonselective β-blockers

Propranolol (Inderal)® is the prototypical β-adrenergic receptor antagonist. It is nonselective in that it blocks the β₁-and β₂-receptors equally well. Propranolol, similar to the other β-receptor antagonists that are discussed, is a competitive antagonist, the receptor-blocking actions of which can be reversed with sufficient concentrations of β-agonists. Currently, propranolol is approved for treating hypertension, cardiac arrhythmias, angina pectoris caused by coronary atherosclerosis, hypertrophic subaortic stenosis, myocardial infarction, pheochromocytoma, and essential tremor, as well as for prophylaxis of migraine headache.

Because it exhibits no selectivity for β₁-receptors, it is contraindicated in the presence of conditions such as asthma and bronchitis.
Several other nonselective $\beta$-blockers are used clinically. These include **nadolol, pindolol, penbutolol, carteolol, timolol, levobunolol and metipranolol**.

### $\beta_1$-selective blockers

Cardioselective $\beta$-antagonists are drugs that have a greater affinity for the $\beta_1$-receptors of the heart than for $\beta_2$-receptors in other tissues. Such cardioselective agents should provide two important therapeutic advantages. The first advantage would be the lack of an antagonistic effect on the $\beta_2$-receptors in the bronchi. Theoretically, this would make $\beta_1$-blockers safe for use in patients who have bronchitis or bronchial asthma. The second advantage would be the absence of blockade of the vascular $\beta_2$-receptors, which mediate vasodilation. This would be expected to reduce or eliminate the increase in peripheral resistance that sometimes occurs after the administration of nonselective $\beta$-antagonists.

At present the following $\beta_1$-selective agents are used therapeutically: **acebutolol, atentolol (Tenormin)$^\text{®}$, betaxolol, bisoprolol, esmolol and metoprolol**.

All of these agents except esmolol are indicated for the treatment of hypertension. Atenolol and metoprolol are also approved for use in treating angina pectoris and in therapy following MI. Betaxolol is the only $\beta_1$-selective blocker indicated for the treatment of glaucoma.

Acebutolol and esmolol are indicated for treating certain cardiac arrhythmias.
**Beta-blockers with Alpha 1-receptor Antagonistic Activity**

Several drugs have been developed that possess both β and α-receptor-blocking activities within the same molecule.

Two examples of such molecules are labetalol (Trandate)® and carvedilol (Dilatrend)®.

Labetalol is a phenylethanolamine derivative that is a competitive inhibitor at both β₁- and β₂- adrenergic receptor. It is a more potent β- antagonist than α-antagonist. Since it has two asymmetric carbon atoms (1 and 1’), it exists as a mixture of four isomers. It is this mixture that is used clinically. The different isomers, however, possess different α- and β- antagonistic activities. The β-blocking activity resides solely in the (1R, 1’R)- isomer, while the α₁-antagonistic activity is seen in the (1S, 1’R)- and (1S, 1’S)- isomers, with the (1S, 1’R)- isomer possessing the greater activity. Labetalol is a clinically useful antihypertensive agent. The rationale for its use in the management of hypertension is that its α-receptor blocking effect produce vasodilation and its β-receptor-blocking effects prevent the reflex tachycardia usually associated with vasodilation.

Carvedilol like labetalol is a β-blocker that possesses α₁-adrenergic receptor-blocking activity. Only the (S)-enantiomer possesses the β-blocking activity, while both enantiomers are antagonists of the α₁-adrenergic receptor. This drug is also unique in that it possesses antioxidant activity and an antiproliferative effect on vascular smooth muscle cells. It thus has a neuroprotective effect and the ability to provide major cardiovascular organ protection.