# Pharmacology of Autonomic Nervous System (3)

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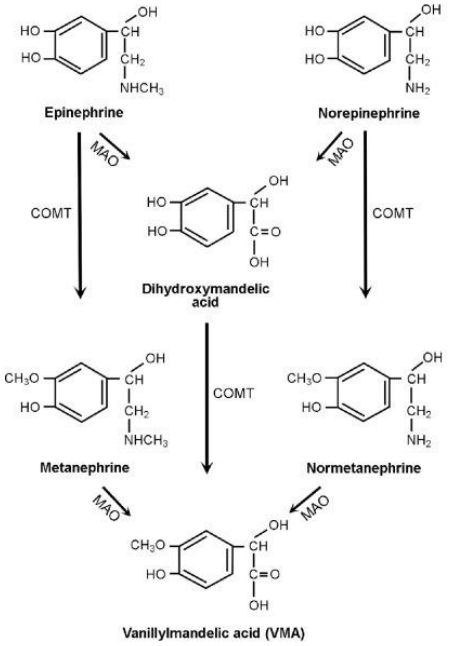
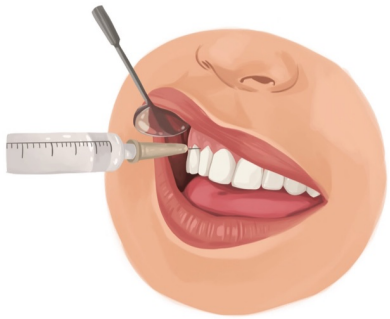
# Administration of Catecholamines

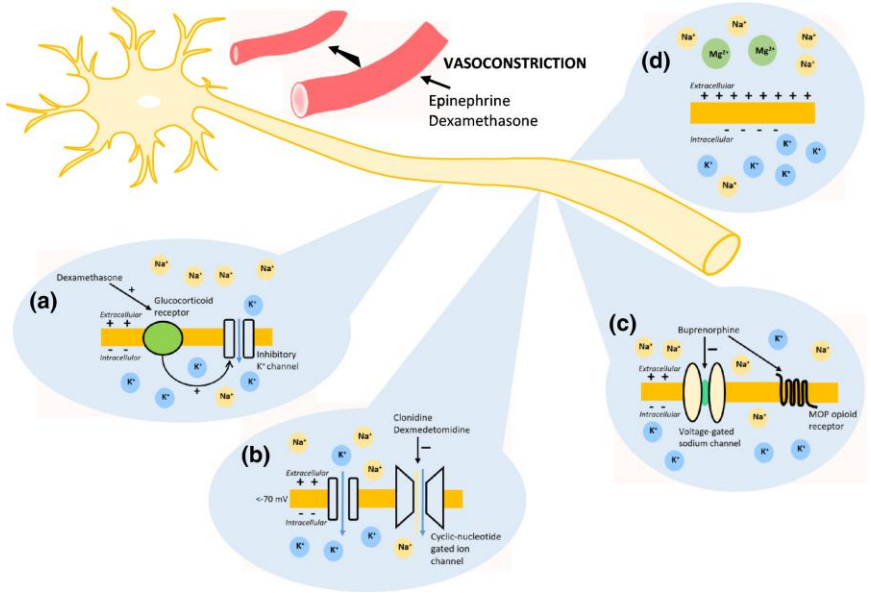
CAs are orally inactive because they are rapidly degraded by COMT in the intestinal wall and liver.

ADR is administered systematically by s.c. or i.m. injection in a dose of 0.2–0.5 mg, (lasts 0.5–2 hours).

In dental practice, it should not be used as a local vasoconstrictor added to local anesthetics for dental anesthesia.





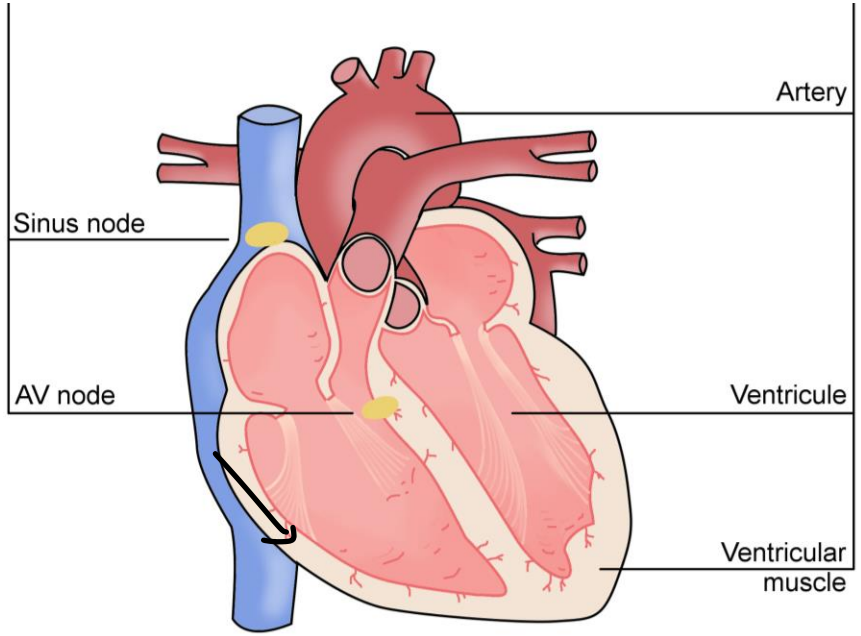
# Contraindications:

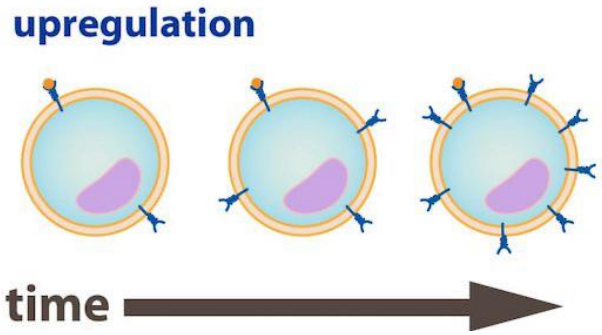
ADR is contraindicated in hypertensive, hyperthyroid, and angina patients.

ADR mixed local anesthetic should NOT be used in dental anesthesia.

It should not be given to patients receiving β blockers (a marked rise in BP can occur).

Certain anesthetics (chloroform, halothane) sensitize the heart to the arrhythmic action of ADR.

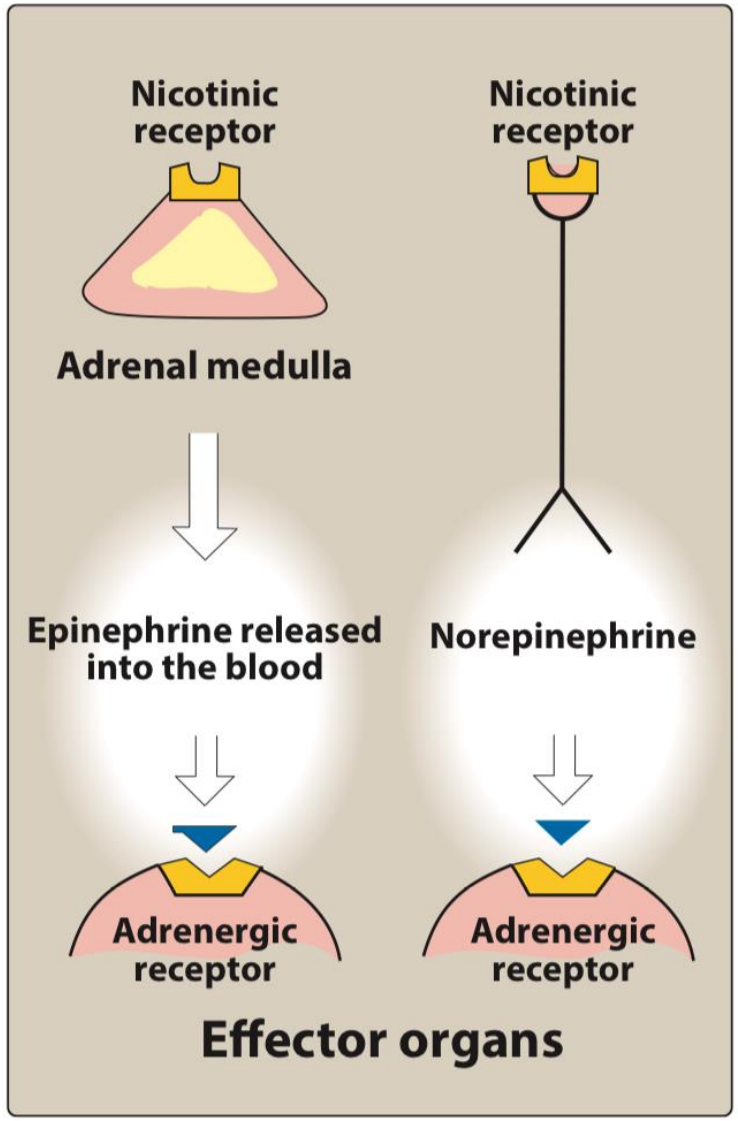


# Adrenergic antagonists

Adrenergic antagonists (Adrenoblockers) are drugs that antagonize the action of ADR and related drugs.

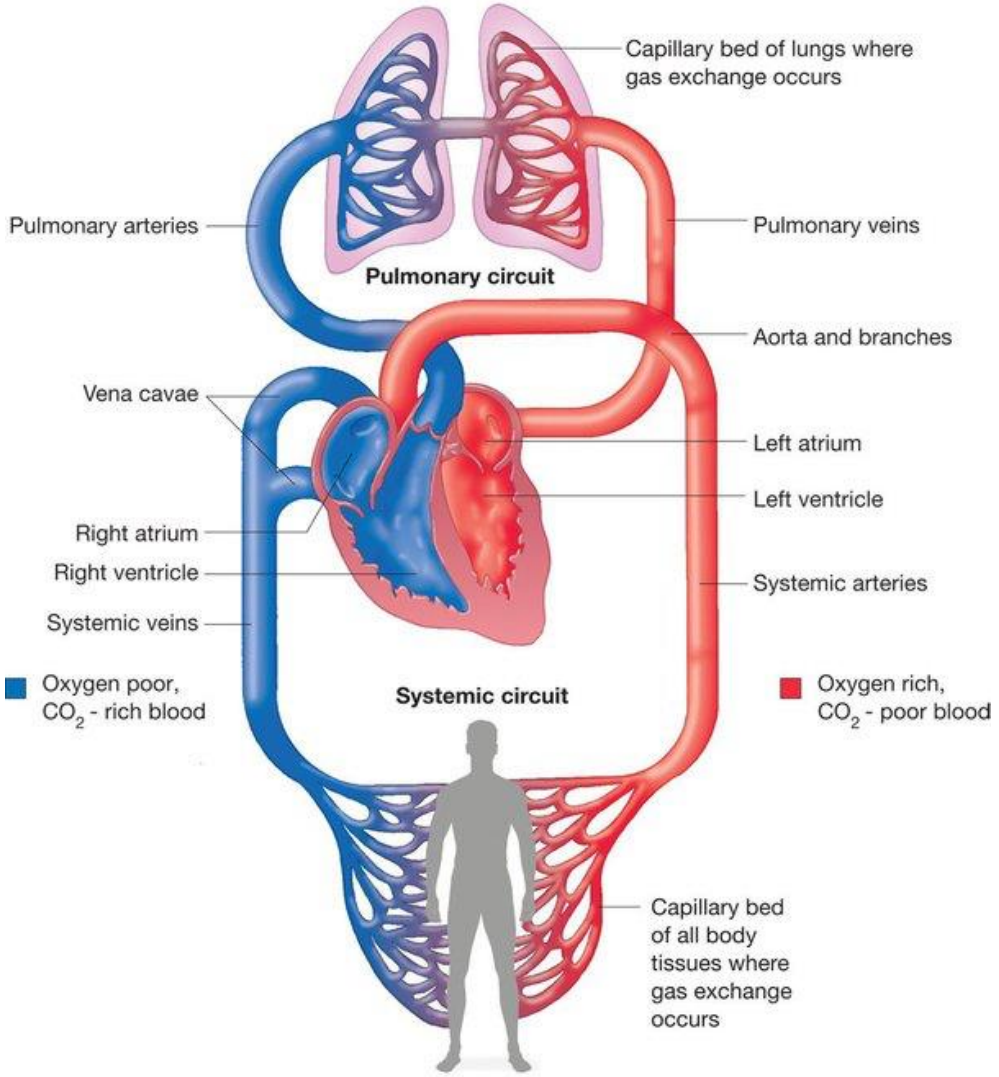
They are competitive antagonists at α or β or both receptors



# General effects of α blockers:

Blockade of vasoconstrictor α1 also α2 receptors decreases peripheral resistance and causes pooling of blood (Hypovolemia), and thus decreases venous return and cardiac output leading to decreased BP.

They inhibit adrenergic responses mediated by α receptors without affecting β receptors.



# Classification of α blockers

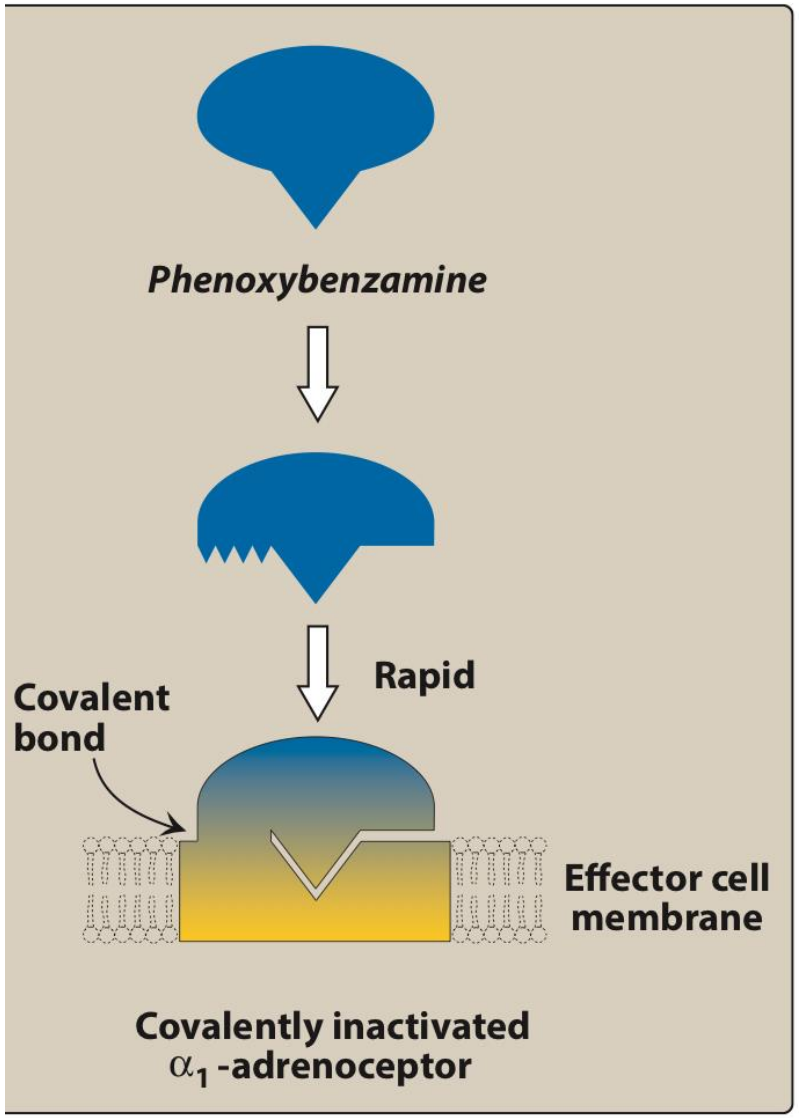
Nonequilibrium α blockade could not be reversed by large concentrations of ADR.

This implies that mass-action equilibration between agonist and antagonist is prevented (nonequilibrium α blockade).

This blockade is produced only by specific compounds having the ability to form stable covalent bonds at α site

Nonequilibrium type:

β Haloalkylamines, Phenoxybenzamine



# Classification of α blockers

- Equilibrium type (nonselective and competitive):
- Ergot alkaloids: Ergotamine and Ergotoxine.
- Hydrogenated ergot alkaloids: Dihydroergotamine (DHE) and Dihydroergotoxine.
- Imidazolines: Tolazoline and Phentolamine.
- α1 selective: Prazosin, Terazosin, Doxazosin, Tamsulosin and Alfuzosin.
- α2 selective: Yohimbine.

# Natural and hydrogenated ergot alkaloids

Ergotamine and ergotoxine from ergot fungus. They are partial agonists and antagonists at α, serotonergic and dopaminergic receptors.

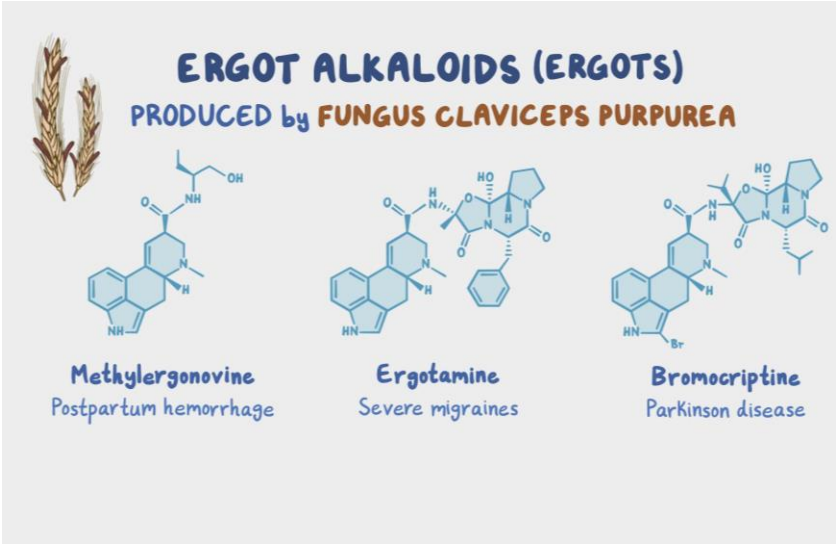
They produce long-lasting vasoconstriction more than α blockade.

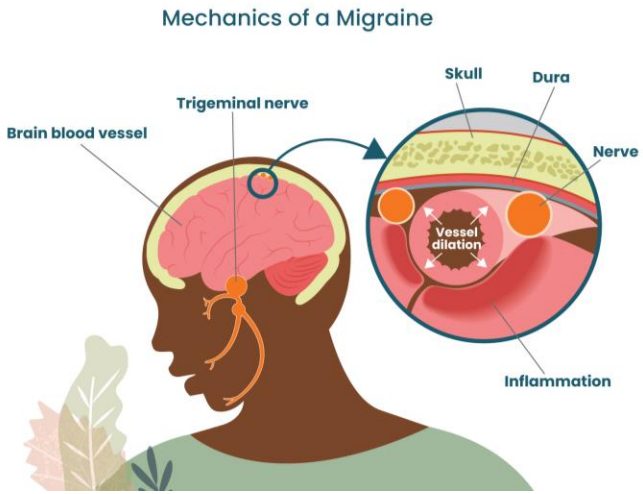
Their principal use is in migraine.

Hydrogenation reduces vasoconstrictors and increases α blocking activity.

Hydrogenated ergot alkaloids are used for symptoms of mental decline in elderly. Dihydroergotamine has been used as a cognition enhancer.

The amine alkaloid ergometrine has no α blocking activity



# Nonselective α blockers

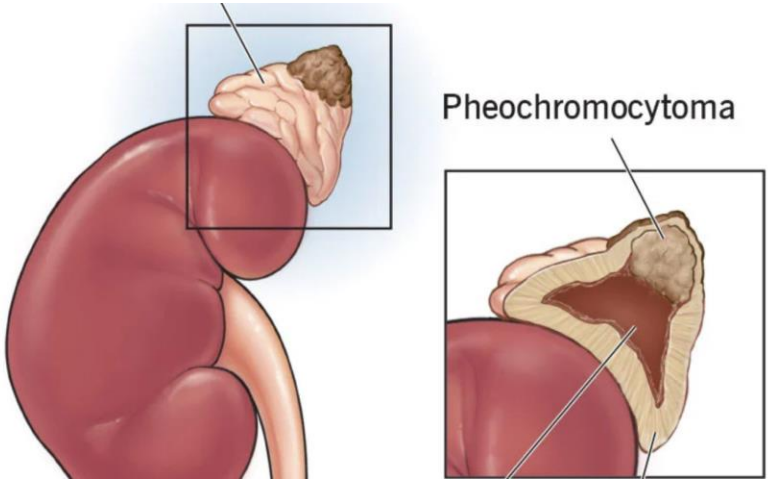
Phentolamine: short acting (in minutes) used for management of pheochromocytoma and control of hypertension due to clonidine withdrawal, cheese reaction.

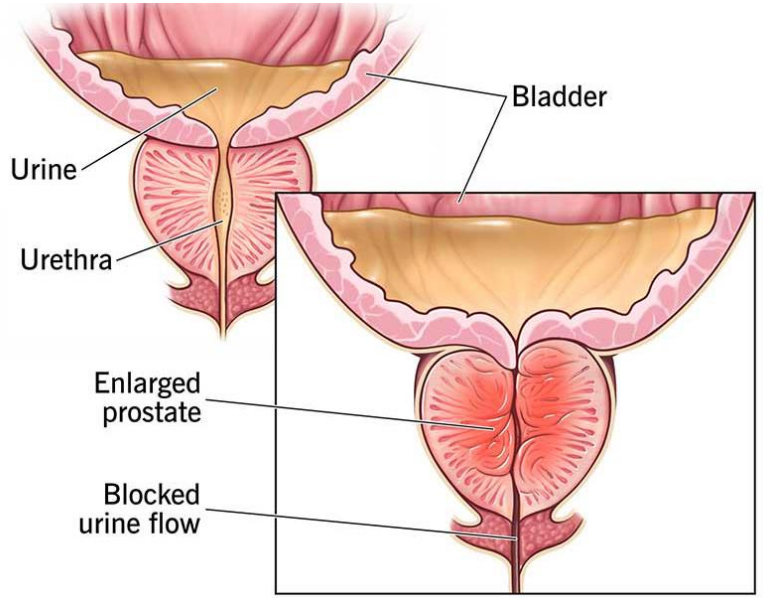
Prazosin: It is the first of the highly selective α1 blockers with α1:α2 selectivity ratio of 1000:1. It is primarily used as an anti-hypertensive.

It is also used in benign prostatic hypertrophy (BHP).

Patients receiving prazosin for hypertension or BPH should not suddenly stand up after being supine on the dental chair.

Terazosin and doxazosin longer half-life than prazosin suitable for once-daily dosing, particularly in BHP.



# Nonselective α blockers

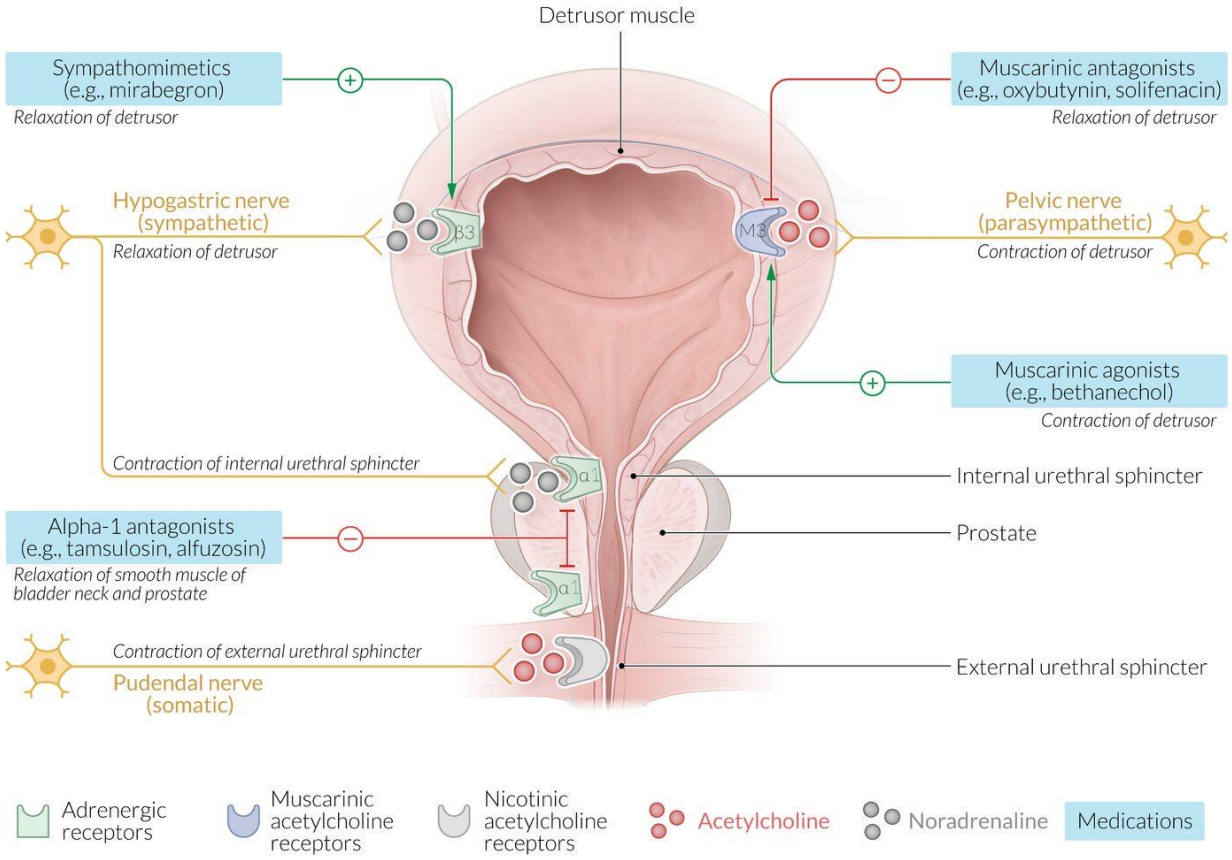
Tamsulosin: Is relatively uroselective due to higher affinity for α1 A subtype.

It does not cause significant changes in BP or HR at doses that relieve urinary symptoms of BHP.

Its modified-release capsule needs only once-daily dosing.

Yohimbine: An alkaloid from the West African plant Yohimbehe. It is a relatively selective α2 blocker with a short duration of action.

There are no valid indications for the clinical use of yohimbine.



# Side effects

Palpitation.

Postural hypotension.

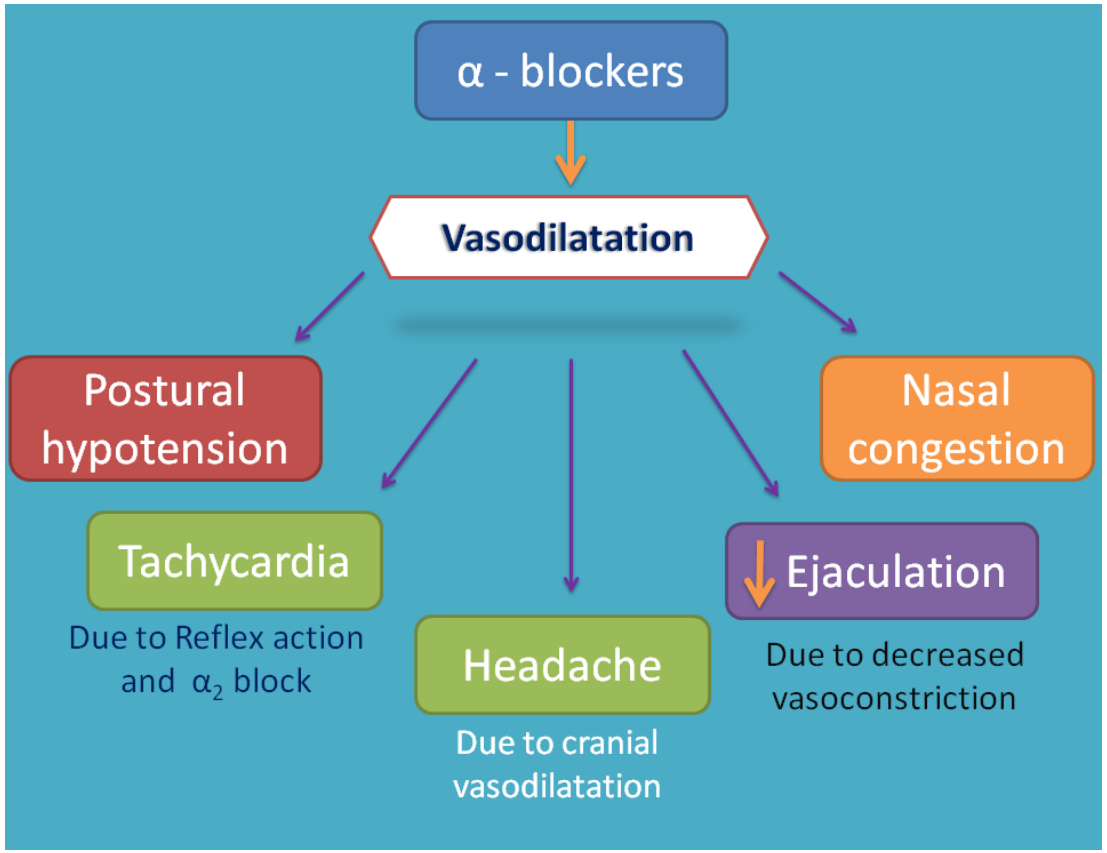
Nasal blockage.

Loose motions.

Fluid retention.

Inhibition of ejaculation and impotence.

α blockers have no effect on adrenergically induced cardiac stimulation, bronchodilatation, or vasodilatation because these are predominantly mediated through β receptors.



| First generation (older, nonselective) | Second generation ($\beta_1$ selective) | Third generation (with additional α blocking and/or vasodilator property) |
|---|---|---|
| Propranolol | Metoprolol | Labetalol |
| Timolol | Atenolol | Carvedilol |
| Sotalol | Acebutolol | Celiprolol |
| Pindolol | Bisoprolol | Nebivolol |
| | Esmolol | |

# β blockers

Propranolol is described as prototype β blocker, has negative chronotropic and inotropic effects leading to a reduction in cardiac output.

Pindolol, Acebutolol has partial agonistic (intrinsic sympathomimetic action).

# β blockers

Nonselective ( β1 and β2):

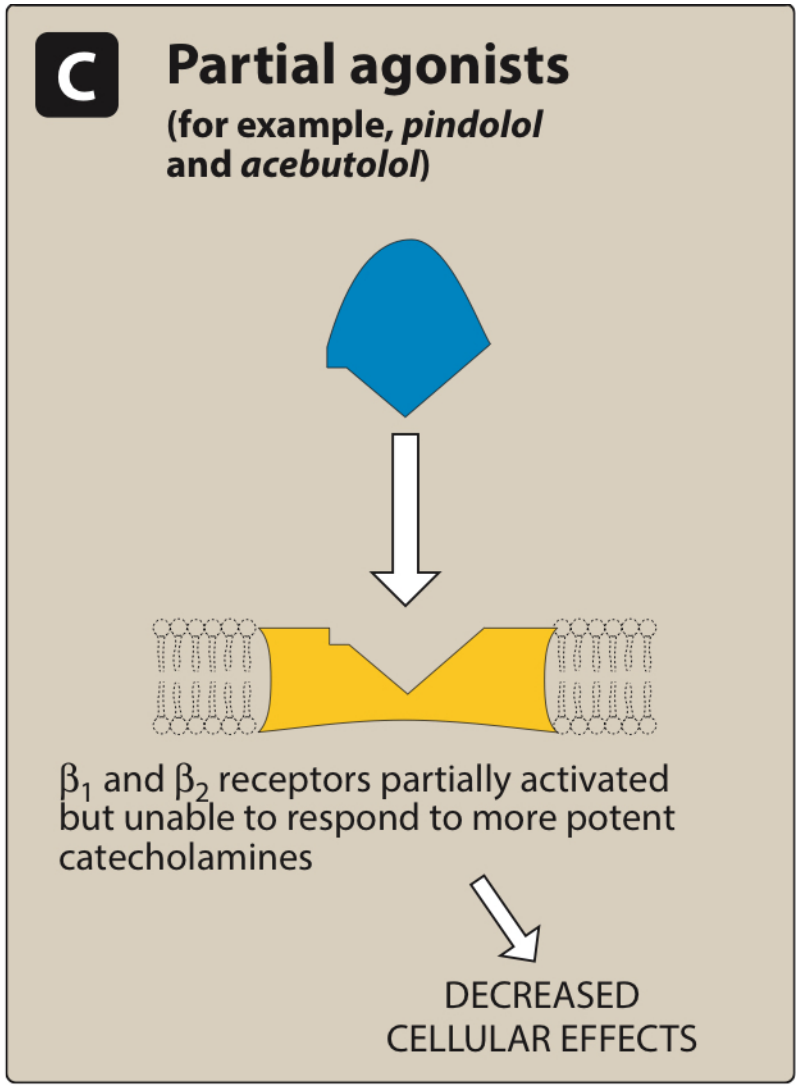
Without intrinsic sympathomimetic activity: Propranolol, Sotalol, Timolol.

With intrinsic sympathomimetic activity: Pindolol.

With additional α blocking property: Labetalol, Carvedilol.

Cardioselective (β1):

Metoprolol, Atenolol, Acebutolol, Celiprolol, Nebivolol

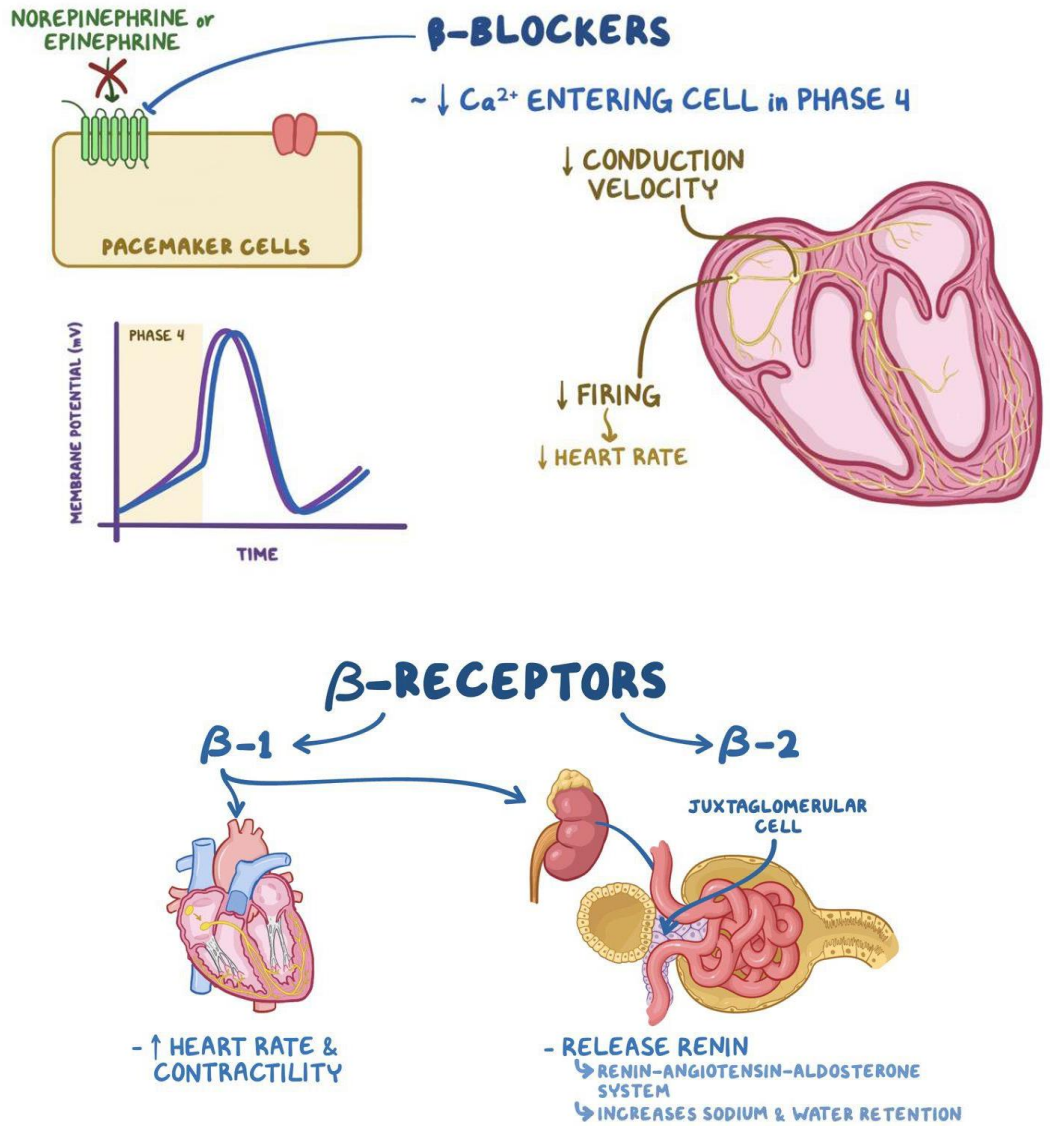


# Therapeutic uses

Hypertension: β blockers are relatively mild anti-hypertensives. All agents are nearly equally effective. They are one of the first-choice drugs because of good patient acceptability and cardioprotective potential.

Angina pectoris: All β blockers benefit angina of effort. Taken regularly they decrease the frequency of attacks and increase exercise tolerance.

Cardiac arrhythmias: β blockers suppress adrenergically mediated tachycardias during anesthesia or digitalis induced (IV).



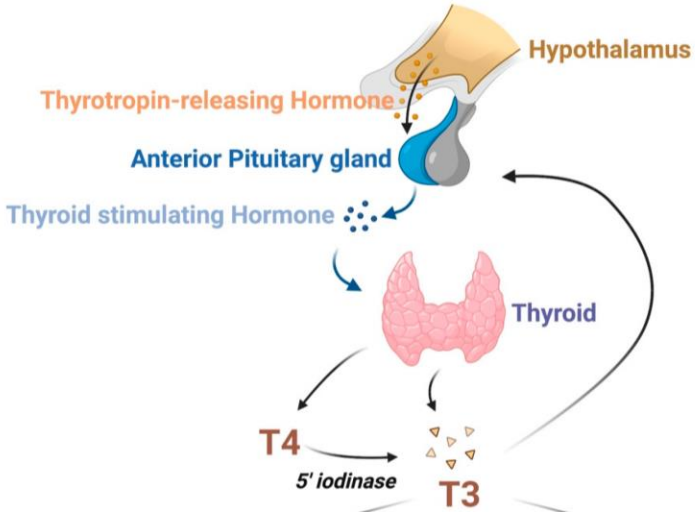
# Therapeutic uses

Migraine: Propranolol is the most effective drug for chronic prophylaxis of migraine.

Anxiety: Propranolol exerts an apparent anti anxiety effect, especially under conditions that provoke nervousness and panic such as: Post-traumatic stress disorder (PTSD) and specific phobias like dentophobia (Dental fear) and unaccustomed public appearance (stage fright).

Thyrotoxicosis: Propranolol rapidly controls symptoms (palpitation, nervousness, tremor, and sweating) without significantly affecting thyroid status.

It is used pre-operatively while awaiting the response to anti-thyroid drugs/radioactive iodine.

# Propranolol-drug interactions

- Clinically significant interactions particularly occur with:
- ADR.
- Salbutamol.
- Clonidine.
- Ergot alkaloids.
- Isoprenaline.
- Nonsteroidal anti-inflammatory drugs (NSAIDs).
- Lidocaine.