Adrenergic Antagonists

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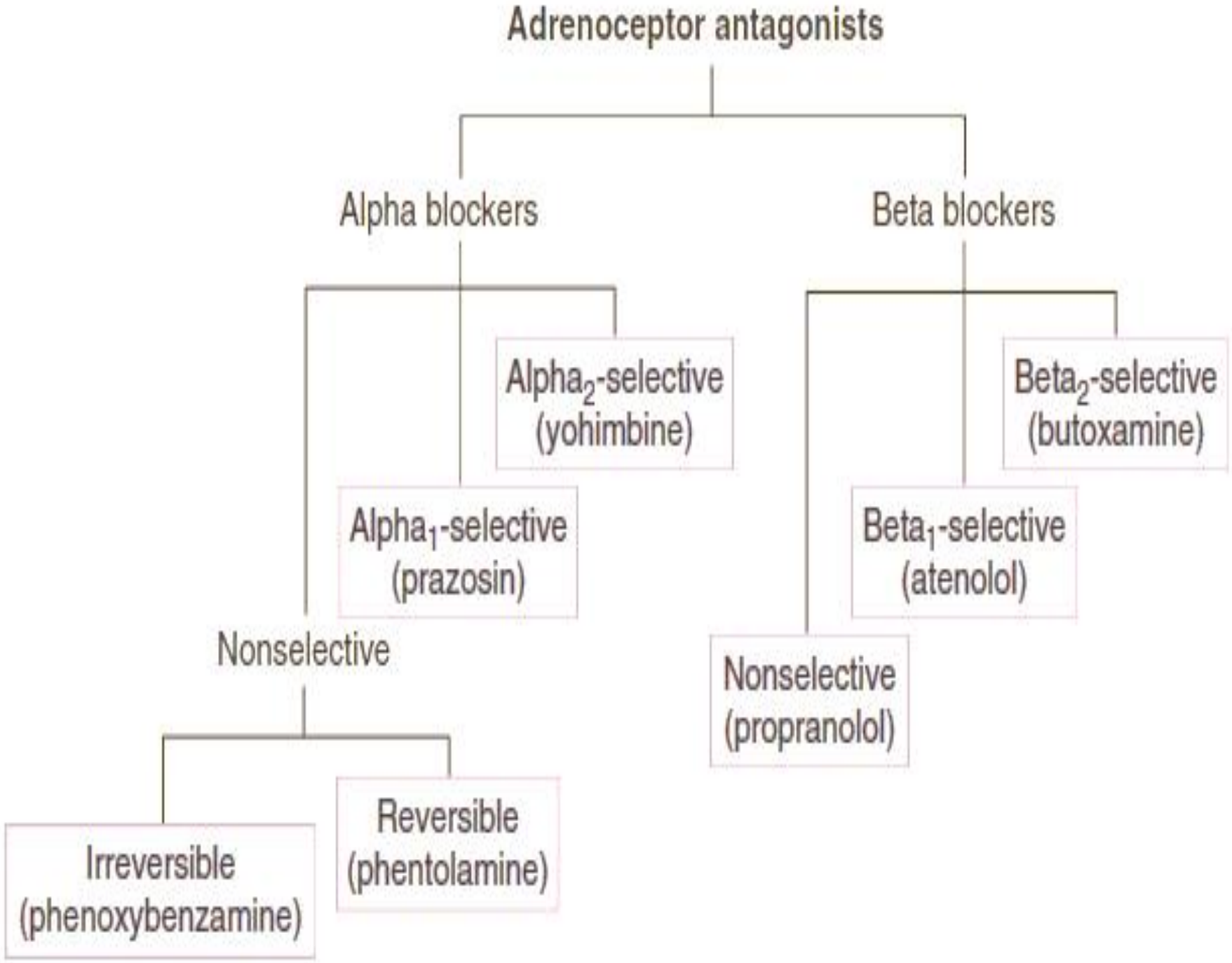
- The adrenergic antagonists (also called adrenergic blockers or sympatholytics)
- These drugs act by either reversibly or irreversibly attaching to the adrenoceptors, thus preventing activation by endogenous catecholamines.
- Like the agonists, the adrenergic antagonists are classified according to their relative affinities for **α** or **β** receptors in the sympathetic nervous system.

α-adrenergic Blocking agents

- Drugs that block α adrenoceptors profoundly affect **blood pressure**.
- Because normal sympathetic control of the vasculature occurs in large part through agonist actions on α-adrenergic receptors, blockade of these receptors reduces the sympathetic tone of the blood vessels, resulting in decreased peripheral vascular resistance.

Classification



Alpha- Antagonists

Phenoxybenzamine

- *Phenoxybenzamine* is nonselective, linking covalently to both **α1 and α2** receptors. The block is irreversible and noncompetitive, and the only way the body can overcome the block?
- Is to synthesize new adrenoceptors, which requires a day or longer. Therefore, the actions of *phenoxybenzamine* last about 24 hours. After the drug is injected.

Actions:

- **Cardiovascular effects:** By blocking α receptors, *phenoxybenzamine* prevents vasoconstriction of peripheral blood vessels by endogenous catecholamines. The decreased peripheral resistance provokes a reflex tachycardia.
- Furthermore, the ability to block presynaptic inhibitory α2 receptors in the heart can contribute to an **increased cardiac output.**
- Thus, the drug has been unsuccessful in maintaining lowered blood pressure in hypertension, and it is no longer used for this purpose.?????

Therapeutic uses

- *Phenoxybenzamine* is used in the treatment of pheochromocytoma, a catecholamine-secreting tumor of cells derived from the adrenal medulla. It may be used prior to surgical removal of the tumor to prevent a hypertensive crisis, and it is also useful in the chronic management of inoperable tumors.

Adverse effects

Phenoxybenzamine can cause

1) Postural hypotension,
2) Nasal stuffiness
3) Nausea
4) Vomiting
5) It may also induce reflex tachycardia, which is mediated by the baroreceptor reflex.

❖ *Phenoxybenzamine* should be used with caution in patients with cerebrovascular or cardiovascular disease.

Phentolamine

- *Phentolamine* produces a competitive block of α1 and α2 receptors that lasts for
- approximately 4 hours after a single injection.
- produces postural hypotension & induced reflex cardiac stimulation and tachycardia are mediated by the baroreceptor reflex.
- The drug can also trigger arrhythmias and anginal pain.
- *phentolamine* is contraindicated in patients with coronary artery disease.
- *Phentolamine* is used for the short-term management of pheochromocytoma.
- *Phentolamine* is useful to treat hypertensive crisis due to abrupt withdrawal of *clonidine* and from ingesting tyramine-containing foods in patients taking monoamine oxidase inhibitors.

Prazosin, terazosin, tamsulosin, & alfuzosin

- *A*re selective competitive blockers of the α1 receptor.
- In contrast to phenoxybenzamine and phentolamine, they are useful in the treatment of hypertension.
- Tamsulosin and alfuzosin are examples of other selective α 1 antagonists indicated for the treatment of benign prostatic hyperplasia (BPH).
- Metabolism leads to inactive products that are excreted in urine except for those of doxazosin, which appear in feces.
- Doxazosin is the longest acting of these drugs.

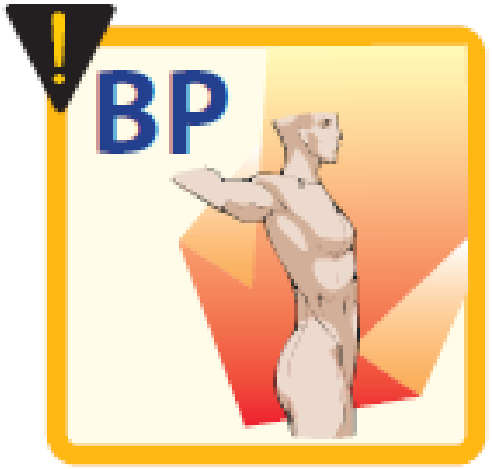
Mechanism of action

- All of these agents decrease peripheral vascular resistance and lower blood pressure by causing relaxation of both arterial and venous smooth muscle.
- These drugs, unlike *phenoxybenzamine* and *phentolamine*, cause minimal changes in cardiac output, renal blood flow, and glomerular filtration rate.
- ***Tamsulosin (Ominec)®*** has the least effect on blood pressure because it is less selective for α1B receptors found in the blood vessels and more selective for α1A receptors in the prostate and bladder.
- Blockade of the α1A receptors decreases tone in the smooth muscle of the bladder neck and prostate and improves urine flow.

Therapeutic uses

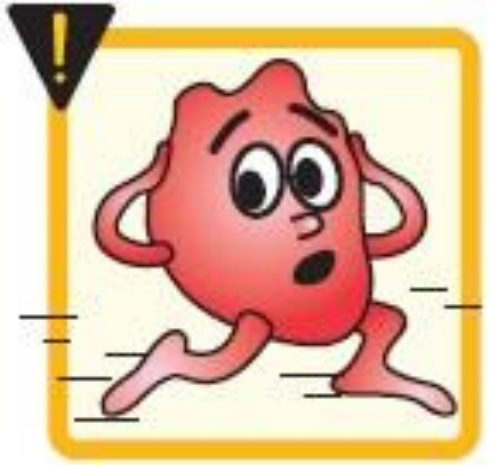
- Individuals with elevated blood pressure treated with one of these drugs do not become tolerant to its action. However, the first dose of these drugs may produce an exaggerated orthostatic hypotensive response.
- These drugs may cause modest improvement in lipid profiles and glucose metabolism in hypertensive patients.
- Because of inferior cardiovascular outcomes as compared to other antihypertensives, α1 antagonists are not used as monotherapy for the treatment of hypertension.
- The α1 receptor antagonists have been used as an alternative to surgery in patients with symptomatic **BPH.**

Adverse effects:



Orthostatic hypotension

Dizziness and headache



Tachycardia

Sexual dysfunction

Yohimbine

- *Yohimbine* is a selective competitive **α2-blocker**.
- It is has been used as a sexual stimulant and in the treatment of **erectile dysfunction**.
- Its use in the treatment of these disorders is not recommended, due to lack of demonstrated **efficacy**.
- *Yohimbine* works at the level of the CNS to increase sympathetic outflow to the periphery.
- It is contraindicated in cardiovascular disease, psychiatric conditions, and renal dysfunction because it may worsen these conditions.

β-ADRENERGIC BLOCKING AGENTS

- All of the clinically available β-blockers are competitive antagonists, Nonselective β-blockers act at both β1 and β2 receptors
- β antagonists primarily block β1 receptors.
- Note: There are no clinically useful β2 antagonists.
- Although all β-blockers lower blood pressure, they do not induce postural hypotension.???
- β-Blockers are effective in treating hypertension, angina, cardiac arrhythmias, M.I., heart failure, hyperthyroidism, and glaucoma.
- prophylaxis of migraine headaches.

Propranolol: A nonselective β antagonist

- *Propranolol* is the prototype β-adrenergic antagonist and blocks both β1 and β2 receptors with equal affinity.
- Sustained release
- preparations for once-a-day dosing are available.

Actions

Cardiovascular

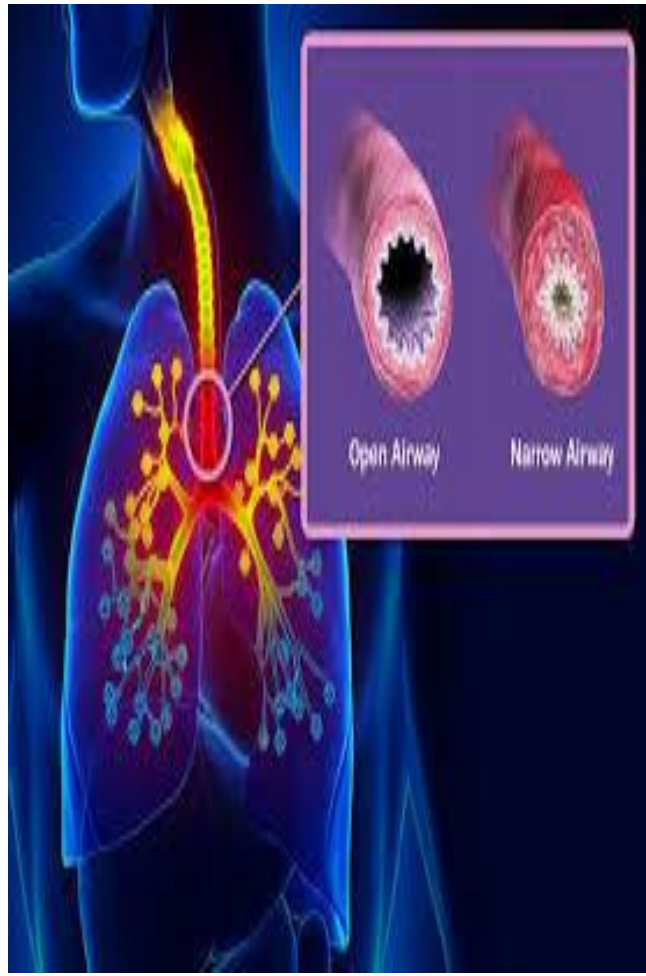
- *Propranolol* diminishes cardiac output, having both negative inotropic and chronotropic effects. **Who???**
- The resulting bradycardia usually limits the dose of the drug.
- During exercise or stress, when the sympathetic nervous system is activated, β-blockers attenuate the expected increase in heart rate.
- Cardiac output, workload, and oxygen consumption are decreased by blockade of β1 receptors, and these effects are useful in the treatment of angina

Peripheral vasoconstriction

- Nonselective blockade of β receptors prevents β2-mediated vasodilation in skeletal muscles.
- The reduction in cardiac output produced by all β-blockers leads to decreased blood pressure, which triggers a reflex peripheral vasoconstriction that is reflected in reduced blood flow to the periphery.
- In patients with hypertension, total peripheral resistance returns to normal or decreases with long term use of *propranolol*.
- There is a gradual reduction of both systolic and diastolic blood pressures in hypertensive patients.

Bronchoconstriction

- Blocking β2 receptors in the lungs of susceptible patients causes contraction of the bronchiolar smooth muscle.
- This can precipitate an exacerbation in patients with chronic obstructive pulmonary disease (COPD) or asthma.
- Therefore, β-blockers, particularly, nonselective ones, are contraindicated in patients with COPD or asthma.



Disturbances in glucose metabolism

- β blockade leads to decreased glycogenolysis and decreased glucagon secretion.
- Therefore, if *propranolol* is given to a diabetic patient receiving *insulin*, careful monitoring of blood glucose is essential, because pronounced hypoglycemia may occur after ***insulin*** **injection**.

Therapeutic uses

i. Hypertension
ii. Angina pectoris
iii. Myocardial infarction(M.I.)
iv. Migraine
v. Hyperthyroidism

Adverse effects:

Fatigue

Sexual dysfunction

Broncho-constriction

Arrhythmias (upon abrupt withdrawal)

Acebutolol, atenolol, betaxolol, bisoprolol,

esmolol, metoprolol, and nebivolol:

SELECTIVE β1 ANTAGONISTS

- Drugs that preferentially block the β1 receptors minimize the unwanted bronchoconstriction (β2 effect) seen with *propranolol* use in asthma patients.
- Cardioselective β-blockers, such as *acebutolol*, *atenolol*, and *metoprolol*, antagonize β1 receptors at doses 50- to 100-fold less than those required to block β2 receptors.
- This cardioselectivity is most pronounced at low doses and is lost at high doses. [Note: Since β1 selectivity of these agents is lost at high doses, they may antagonize β2 receptors.]

Therapeutic uses

- The cardioselective β-blockers are useful in hypertensive patients with **impaired pulmonary function.???**
- These agents are also first-line therapy for chronic stable angina.
- *Bisoprolol* and the extended-release formulation of *metoprolol* are indicated for the management of chronic heart failure.
- Because these drugs have less effect on peripheral vascular β2 receptors, coldness of extremities (Raynaud phenomenon), a common side effect of β-blockers, is less frequent.

Thank YOU