Adrenoeceptor Antagonists

(Adrenergic Antagonists)

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α - Adrenoreceptor Blockade

Pharmacodynamics:

A. **Cardiovascular system:**

   Block of α_1-receptors in arterioles leads to vasodilation, lowering of peripheral vascular resistance and blood pressure.

α - Adrenoreceptor Blockade

- Block of α_1-receptors in venules leads to venodilation, postural hypotension and reflex tachycardia.
- Tachycardia is more marked with nonselective α-blockers (α_1, α_2) because of increased release of norepinephrine (why?).

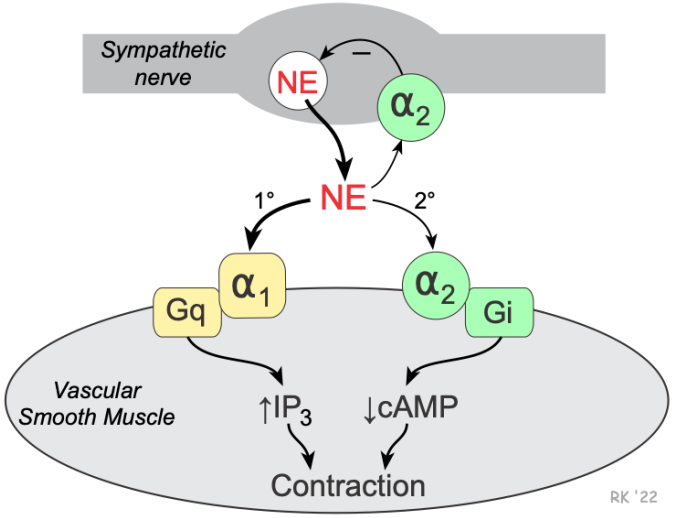
α - Adrenoreceptor Blockade

B. Other effects:

- **Miosis (α_1 receptors in dilator pupillae).**
- **Nasal stuffiness (α_1 receptors in blood vessels)**
- **Decreased resistance to the outflow of urine (α_{1A} and α_{1B} receptors in the base of urinary bladder and the prostate).**

α - Adrenoreceptor Blockade non-selective

- Non-selective α-antagonists have limited beneficial effects on blood pressure reduction, due to associated α2 block which increases norepinephrine effects (remember, block of the negative feedback α2 receptor will increase NE release).
- This may cause increased β1 stimulation with tachycardia



Alpha Adrenergic Antagonists

PHENOXYBENZAMINE

- **Covalent, irreversible blockade**
  - ***may require days to recover***
- **Nonselective (slight preference for alpha-1)**
- **Primary use: pheochromocytoma**
- **Urinary obstruction (BPH)**
- **Side effects**
  - ***orthostatic hypotension***
  - ***nasal congestion***

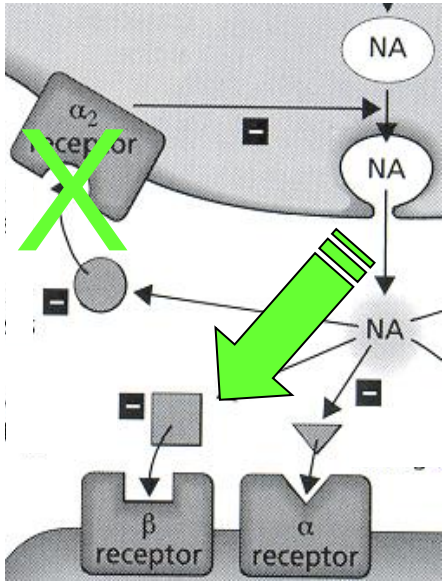
Pheochromocytoma

- A neuroendocrine tumor of the medulla of the adrenal glands that secretes excessive amounts of catecholamines norepinephrine and epinephrine
- Signs and Symptoms:
  - Elevated heart rate
  - Elevated blood pressure
  - Headaches
  - Weight loss
  - Elevated blood glucose

Alpha Adrenergic Antagonists

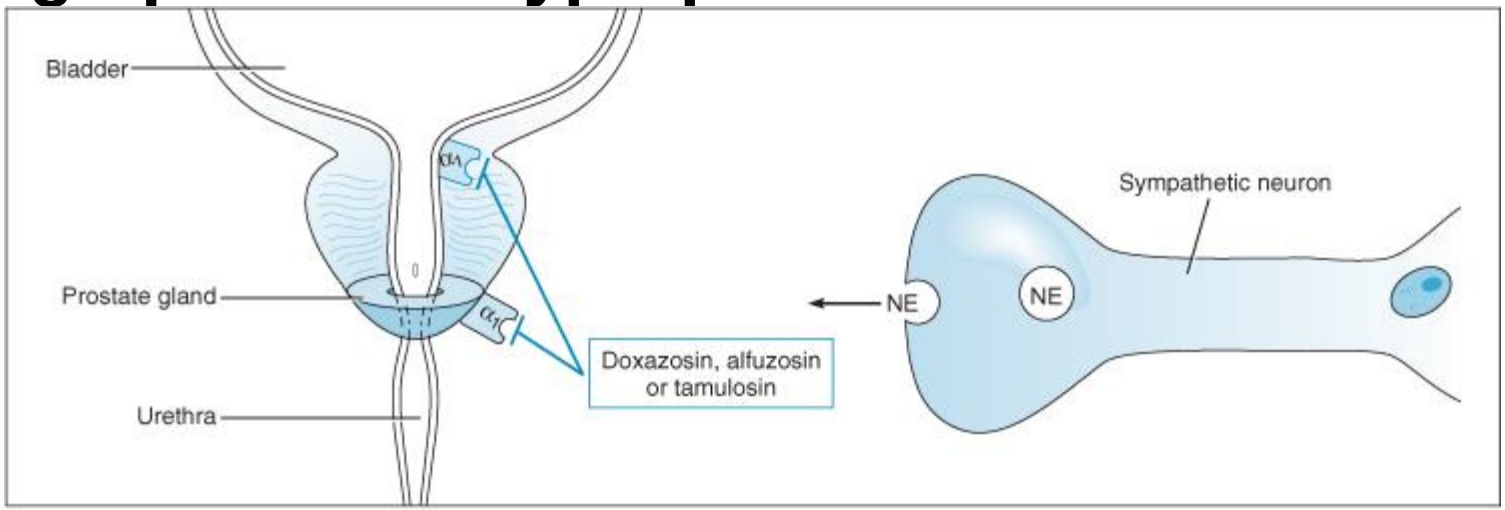
PHENTOLAMINE

- Nonselective (equal affinity for both)
- Competitive blockade
- Primary use: pheochromocytoma
- Not good general antihypertensive
  - *reflex tachycardia (α-2 block)*
- Side effects
  - *orthostatic hypotension*
  - *reflex cardiac stimulation*
  - *nasal congestion*



Selective α1-blockers

- **Selectively block α_1 receptors**
  - **–ie. Prazosin , Alfuzosin, Doxazosin,, Terazosin, Tamsulosin**
  - **– Used in the treatment of chronic hypertension**
- **Also used to treat urinary retention in men with benign prostatic hyperplasia**



Alpha Adrenergic Antagonists

PRAZOSIN

- **Selective alpha-1 antagonist**
- **Primary use: antihypertensive**
- **Little or no alpha-2 blockade**
  - ***limited reflex tachycardia***
- **Dilates arterial and venous beds**
  - Lower blood pressure by causing relaxation of both arterial and venous smooth muscle.
- **Improve urinary flow in BPH**
- ***"First-Dose Phenomenon"***
  - ***give it at bedtime***

Beta Adrenergic Antagonists

- The drugs which block β-receptors are very widely used in therapeutics, mostly for their antihypertensive effect, and efficacy in the treatment of angina and some arrhythmias.

- In the 1960's β-blockers were developed, and the earliest prototype β-blocker was Propanolol, a non-specific β receptors antagonist, which is still widely used.

Beta Adrenergic Antagonists

- These drugs occupy β receptors and competitively inhibit occupation of these receptors by catecholamines.

Classifications:

- β-Adrenoceptor antagonists are not the same, regarding their antagonism of receptors and lipophilicity.
- Lipophilic antagonists cross the blood brain barrier and affect the central nervous system in addition.

Beta Adrenergic Antagonists

1. Non-selective ($\beta_1 = \beta_2$): Propranolol, Timolol, Sotalol.
2. Non-selective ($\beta_1 = \beta_2 \geq \alpha_1 > \alpha_2$): Carvedilol, Labetalol. They have alpha blocking activity also.
3. β_1- selective or cardioselective ($\beta_1 >>> \beta_2$): Atenolol, Bisoprolol, Metoprolol, Esmolol.

Beta Adrenergic Antagonists

- Non-selective
  - ie Nadolol, pindolol, propranolol, tomilol
  - Block both β_1 receptors in cardiac tissue and β_2 in smooth muscle, liver and other tissues
- Blockade of β_1 reduces sympathetic stimulation of heart…

  Therefore, negative chronotrope
  Inotrope

- Blockade of β_2 may cause bronchoconstriction and limit glycogenlysis → Adverse effects

Beta Adrenergic Antagonists

Pharmacodynamics:

A. **Effects on the cardiovascular system:**

.1Lowering of blood pressure in patients with hypertension. The mechanism is probably multifactorial and may involve:

Beta Adrenergic Antagonists

a) Negative inotropic effect on the heart → reduction of cardiac output.
b) Suppression of renin-angiotensin system.
c) A centrally-mediated effect due to reduction of sympathetic outflow from the CNS.

Beta Adrenergic Antagonists

2. **Negative chronotropic effect → bradycardia.**
3. **Slowing of AV nodal conduction and prolonging its refractory period. This is useful for treating supraventricular arrhythmias.**

Beta Adrenergic Antagonists

B. Effects on respiratory tract: Increased airway resistance (bronchoconstriction) due to block of β_2 receptors.

C. Effects on the eye: Reduce intraocular pressure (useful for glaucoma) due to reduction in aqueous humor production (timolol.(

Beta Adrenergic Antagonists

D. Metabolic and endocrine effects:

1. **Inhibition of lipolysis (β_3)**
2. **Inhibition of glycogenolysis (β_2).**
3. **Impair recovery from hypoglycemia in insulin-dependent diabetic patients.**
4. **Chronic use increase plasma concentrations of VLDL and decreased concentration of HDL→ atherosclerosis → increased risk of coronary artery disease.**

Beta Adrenergic Antagonists

- **Abrupt discontinuation of these drugs leads to rebound effects (exaggeration of the condition they were used to treat) because of upregulation (increased number) of receptors during treatment.**
- **Therefore, when these drugs are to be discontinued, tapering of the dose (gradual reduction) rather than sudden withdrawal is recommended.**

Propranol

- **Therapuetic uses are wide and include:**
- Antihypertensive: the antihypertensive effect is still not clear. However, it inhibit the renal secretion of the renin, which may play a role.
- Prophylaxis of angina pectoris and ventricular and superventricular arrhythmia, long-term prophylaxis of myocardiac infarction (with a high risk of infarction and sudden death).
- It is also used as a prophylactic of migraine.
- In treatment of Hyperthyroidism, effective in blunting the widespread sympathetic stimulation that occur in acute hyperthyroidism.
- Propanolol and other β blocker may be lifesaving in protecting against serious cardiac arrhythmias

Propranol

- Contraindications:

  a. Propanolol must never given to any individual with chronic obstruction pulmonary disease because it causes an immediate contraction of the bronchiolar smooth muscles, which may result in a serious and potential lethal side effect.

  b. Propanolol effect the carbohydrate metabolism, and may increase the action of insulin, so diabetics treated with insulin should use it with caution.

Selective Beta-1 Blockers

- Have greater affinity for β_1 than for β_2 receptors
  - ie: Acebutolol, Atenolol, Esmolol, Metoprolol

CARDIOSELECTIVE b-BLOCKERS

- Produce fewer adverse effects than non-selective, but their selectivity is not absolute

Beta Adrenergic Antagonists

ESMOLOL

- Esmolol is an ultra-short-acting β_1-selective adrenoceptor antagonist.
- It is rapidly inactivated by red blood cells esterases. (t½ ~ 10 min).
- It is useful in controlling supraventricular arrhythmias, arrhythmias associated with thyrotoxicosis.

Beta-1 Adrenergic Antagonists

METOPROLOL

- Selective beta-1 blocker
- Metoprolol has a significantly longer half-life
- (3-7 hours) compared to esmolol
- Primary uses:
  - antihypertensive
  - ischemic heart disease (depress HR)
  - little effect on normal heart or BP at rest
- Less tendency for bronchoconstriction

Labetalol and carvedilol

- These two agents are reversible β blockers and α1 blocker (producing peripheral vasodilatation).
- Non-selective (β1 = β2 ≥ α1 > α2)They have alpha blocking activity also.
- **Carvedilol** is extensively metabolized in the liver.
- It attenuates oxygen free radical-initiated lipid peroxidation.
- It inhibits vascular smooth muscle mitogenesis.

- **Labetalol: Unique Feature – Does *not* significantly decrease uteroplacental blood flow**
  - Important in **preeclampsia** and **pregnancy-induced hypertension**
  - Better maternal/fetal safety profile compared to some other agents
- Labetolol is also used to treat hypertensive emergencies because it can rapidly lower blood pressure.