Adrenoceptor Antagonists

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Adrenoceptor Antagonists

1. α-Adrenoceptor Antagonists.
2. β-Adrenoceptor Antagonists.

α-Adrenoceptor Antagonists

Prazosin: $\alpha_1 >>>> \alpha_2$

Terazosine: $\alpha_1 >>>> \alpha_2$

Tamsulosin: α_{1A} and α_{1B}

Phentolamine: $\alpha_1 = \alpha_2$

α-Adrenoceptor Antagonists

Pharmacodynamics:

A. **Cardiovascular system:**

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

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- **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?).**

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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).**

β-Adrenoceptor 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.**

β-Adrenoceptor 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.**

β-Adrenoceptor Antagonists

- **Propranolol undergoes extensive hepatic first-pass metabolism → low bioavailability → oral dose is much larger than IV dose.**
- **Metoprolol and carvedilol are metabolized.**
- **Atenolol is mainly excreted unchanged in urine. Its half-life is prolonged in renal failure.**
- **Bisoprolol is partly exceted unchanged and partly metabolized.**

β-Adrenoceptor Antagonists

Pharmacodynamics:

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

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

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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.

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

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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).

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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.**

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- **Carvedilol is extensively metabolized in the liver.**
- **It attenuates oxygen free radical-initiated lipid peroxidation.**
- **It inhibits vascular smooth muscle mitogenesis. (the last 2 are important for its use in the treatment of chronic heart failure).**

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- **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.**

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- **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.**