Adrenergic receptor antagonists

- Drugs that have high affinity but no (or low negative or positive) intrinsic activity
- Competitive vs irreversible antagonists i.e. phentolamine vs phenoxybenzamine

Factors that determine the effect of antagonists in vivo
- absence or presence of intrinsic activity
- pre-existing “tone” at receptor
- net effect at pre- vs postsynaptic receptors
- selectivity for receptor subtype
- compensatory reflex adjustments

Alpha-adrenergic receptor antagonists

- Clinical applications:
  - Hypertensive crisis
  - Phaeochromocytoma
  - ADHD excess Rx
  - Tyramine crisis (MAO inhibitors)
  - Chronic hypertension
  - Benign prostrate hypertrophy

Pheochromocytoma

Tumor: ↑ synthesis, ↑ release of NE & EPI into the circulation.
Result: ↑ BP, ↑ HR → hypertensive crisis
Treatment:
- Surgical removal for solid tumor
- α-/β-blocker i.e. Labetalol
- α-blocker i.e. phenoxybenzamine or phentolamine
- Inhibitor of tyrosine hydroxylase i.e. α-methyl-p-tyrosine
- β-blocker only after α-blockade

Rule of Ten
10% Pheochromocytomas are:
- Malignant
- Bilateral
- Extra-adrenal
- In children
- Familial
- Recur (within 5 to 10 years)
- Present after stroke

Benign Prostrate Hypertrophy (BPH)

Enlarged prostrate leads to difficulty in urination
Alpha1-receptor blocker (i.e. Prazosin) cause prostrate relaxation
Relaxed prostrate improves urination

Postural (Orthostatic) Hypotension

Venous return falls, blood pressure falls (>20mmHg SBP, >10mmHg DBP)
- Sympathetic activity increases
- Constriction of great veins
- Constriction of arteries (↑ TPR)
- Increase in heart rate (>20bpm)

Reflex mediated
- no reflex
- reflex

BP (mmHg) 55 100 195
100
95
95
**Alpha-adrenergic receptor antagonists**

Phenoxybenzamine
- irreversible alpha1-blocker (5-10 fold)
- also block Ach, histamine, serotonin (side effects)
- also inhibit Uptake I & II (side effects)
- ↓ blood pressure, postural hypotension, tachycardia
- useful in long-term & acute pheochromocytoma

Phentolamine & Tolazoline
- non selective α1 = α2 antagonist activity
- cardiovascular: vasodilation, reflex ↑ HR
- enhance NA release (alpha2-blockade)
- toxicity: hypotension, tachycardia, arrhythmias, myocardial infarction

**Toxicity - Alpha-blockers**

Cardiovascular effects:
- reduced peripheral resistance
- lowered vascular return
- postural hypotension (main)
- tachycardia (reflex, usually) → arrhythmias

Others:
- headache, dizziness, nausea, drowsiness
- Impotence (Phenoxybenzamine)
- ↓ plasma lipids

**Beta-adrenergic receptor antagonists**

- Clinically a more useful class of drugs than α-adrenoceptor antagonists.
- β-Adrenoceptor antagonists vary in respect to:
  - Relative affinity for beta1- and beta2-adrenoceptors
    - propranolol (β1, β2) vs atenolol (β1)
  - Intrinsic β-activity (ISA): also act as agonists at β-adrenoceptors
    - propranolol (no) vs pindolol (yes)
  - local anaesthetic activity (LA-action):
    - their ability to stabilize membranes
      - propranolol (yes) vs atenolol (no)
  - lipid solubility: propranolol (high) vs atenolol (low)

**Beta-Adrenoceptor Blocking Agents (-olol)**

(β1-selective exp. Labetalol & Carvedilol)

**Clinical uses: Beta-Blockers - Hypertension**

- Hypertension: frontline class
  - gradual ↓ TPR in spite of long-term ↓ cardiac output
  - non-selective and β1-selective drugs are effective
  - Mechanism of action: Multiple sites
    - CNS action to reduce sympathetic tone
    - block of cardiac β-ARs
    - block of presynaptic β-ARs to ↓ NE release
  - decrease in renin release
### Clinical uses: Beta-Blockers

- **Angina (non-selective or β1-selective)**
  - Cardiac: $\downarrow$ O$_2$ demand more than O$_2$ supply
  - Exercise tolerance ↑ in angina patients
- **Arrhythmia (β1-selective, LA-action)**
  - ↓ catecholamine-induced increases in conductivity and automaticity in heart, and ↓ serum K+ (action in skeletal muscle)
- **Glucoma (non-selective)**
  - ↓ aqueous humor formation (Timolol)
- **Congestive Heart Failure (non-selective or β1-selective)**
  - CI: unstable CHF, bronchospasm, depression, bradycardia
- **Other**
  - block of tremor of peripheral origin (β2-AR in skeletal muscle)
  - migraine prophylaxis (mechanism unknown)
  - hyperthyroidism: ↓ cardiac manifestation (only propranolol)
  - panic attacks, stage fright

### Clinical use – Beta-blockers

<table>
<thead>
<tr>
<th>Class/Drug</th>
<th>HT</th>
<th>Angina</th>
<th>Arrh</th>
<th>MI</th>
<th>HF</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-selective β1</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
| Metoprolol | | | | | | ISA; long acting; also for glaucoma
| Carvedilol | | | | | | α-blocking activity
| Nadolol | | | | | | long acting
| Propranolol | | | | | | ISA
| Timolol | | | | | | MSA; prototypical beta-blocker
| Betaxolol | | | | | | primarily used for glaucoma
| Atenolol | | | | | | ISA
| Acebutolol | | | | | | ISA; MSAXX
| Pindolol | | | | | | ISA; MSA
| Penbutolol | | | | | | ISA; long acting
| Labetalol | | | | | | ISA; α-blocking activity
| Carteolol | | | | | | ISA; long acting

### MERIT-HF: Use of Metoprolol in CHF

- Metoprolol vs Placebo, USA & 13 other countries
- β1-selective, no ISA, LA-action
- LVEF <0.40 and NYHA class II-IV heart failure
- Stabilized by optimum standard therapy (diuretics/ACEI)
- 2.4 years, terminated early after 1 year

- Mortality ↓ 34%
- Risk ↓ 39%
- Hospitalization ↓ 29%
- Felt better ↑ 25%
- Prevent 1 death per 27 patients treated per year

### Beta-Blockers in CHF: 2002 Guideline

- Labetalol
  - hypertensive crisis, chronic hypertension, CHF
  - competitive antagonist at both α- & β-receptors
  - $\beta_1 = \beta_2$ activity > α-activity
  - some intrinsic β-adrenoceptor activity
- Carvedilol
  - newest agent
  - no intrinsic β-adrenoceptor activity
  - chronic hypertension, congestive heart failure

### Mixed Alpha- and β-Receptor Blockers

- Labetalol
  - competitive antagonist at both α- & β-receptors
  - $\beta_1 = \beta_2$ activity > α-activity
  - some intrinsic β-adrenoceptor activity
**β-Blockers: Untoward Effects, Cautions**

- Supersensitivity: Abrupt withdrawal → Rebound HT, less with β-blockers with partial agonist (ie. pindolol).
- Cardiac: ↓ reserve, fatigue, dizziness
- Asthma: Blockade of pulmonary β2-receptors leads to increase in airway resistance. β1-selective better
- Diabetes: Compensatory hyperglycemic effect of EPI in insulin-induced hypoglycemia is removed by block of β2-ARs in liver. β1-selective agents preferred
- Raynaud D: Decreased peripheral circulation
- CNS: nightmares, mental depression, insomnia
- Elderly: ↓ Effectiveness, ↑ adverse effects (ie. depression)

**Schizophrenia**

- Altered perception or expression of reality
- Affects 1% of the population
- Affects men and women equally
- Strong genetic component
- Dopamine (DA) excess theory:
  - Amphetamine exacerbates symptoms and high doses → paranoia, delusions, auditory hallucination. Effects blocked by DA antagonist chlorpromazine.

Antipsychotic Pharmacotherapy:
Typical: chlorpromazine, haloperidol
Atypical: risperidone, olanzapine, sertindole

**Dopamine antagonists**

Haloperidol, chlorpromazine:
- used for treatment of: schizophrenia & nausea
- SE: tachycardia, hypo/hypertension
- need to discontinue gradually.

**Quality of transmitter in nerve terminals altered**

- Direct inhibition of synthesis
  - Alpha-methyl-p-tyrosine (inhibits tyrosine hydroxylase (rate limiting step in NE synthesis)
  - treat pheochromocytoma (acute & chronic)
- False transmitters (not norepinephrine)
  - Alpha-methyl-DOPA → alpha-methyl-NE (alpha2-action)
  - Alpha-methyl-m-tyrosine → metaraminol
    - Metaraminol also has activity at α-receptor (<NE)
  - Tyramine + MAO inhibition → octopamine

**Synthesis of “False Transmitters”**

Utilize the same enzymes as those involved in norepinephrine synthesis

Result in changes in the quantity and quality of transmitter in the storage vesicles

**Reserpine**

- Inhibits NE uptake into storage vesicle
  - from cytosol, "leaky" vesicle (also depletes 5-HT stores)
  - Use: Antihypertensive (last resort)
  - Major side effects: lethargy, diarrhea, depression (very long lasting)
Inhibition of transmitter release

- Guanethidine (inhibits release, reuptake inhibitor)
- Bretylium (also K+ channel blocker, some LA action)
- Uses: hypertension (last resort)
- Side effects: diarrhea, nasal congestion, impotence