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
  - pheochromocytoma
  - 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
- Alpha-receptor blocker (i.e. Phazosin) cause prostrate relaxation
- Relaxed prostrate improves urination

Postural (Orthostatic) Hypotension

- Venous return falls
- Blood pressure falls
- Sympathetic activity increases
- Constriction of great veins
- Increase in heart rate
- Reflex mediated

BP (mmHg)

95 100 95

95 95 95

55 100 100

105 195 195
**Alpha-adrenergic receptor antagonists**

**Phenoxybenzamine**
- irreversible alpha1-blocker (5-10 fold)
- also block Ach, histamine, serotonin (side effects)
- also block 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

**Alpha-adrenergic receptor antagonists**
- Prazosin, Terazosin, Doxazosin (-azosin; competitive)
- selective α1- > α2-receptors (1000 fold)
- cardiovascular effects: reduced peripheral resistance, lowered vascular return, no reflex tachycardia
- Therapy: treat primary hypertension, benign prostrate hypertrophy

Toxicity: postural hypotension, headache, nausea ↓ plasma lipids, dizziness, drowsiness
Yohimine (herbal, OTC): α2-blocker, for impotence not clinically available

**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 ß-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)

**Clinical uses: Beta-Blockers - Hypertension**
- Hypertension: frontline class
  - gradual ↓ TPR in spite of longterm ↓ cardiac output
  - non-selective and β1-selective drugs are effective
- Mechanism unclear, but possibilities:
  - CNS action to reduce sympathetic tone
  - block of cardiac β-ARs
  - block of presynaptic β-ARs to ↓ NE release
  - decrease in renin release

**Beta-Adrenoceptor Blocking Agents (-olol)**
(Drugs A-M are β1-selective exp. Labetalol & Carvedilol)

Properties of several beta-receptor blocking drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>β1 Selectivity</th>
<th>β2 Selectivity</th>
<th>Local Anesthetic Action</th>
<th>Lipid Solubility</th>
<th>Elimination Rate</th>
<th>Adrenergic Blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pindolol</td>
<td>High</td>
<td>Low</td>
<td>Yes</td>
<td>Low</td>
<td>3 days</td>
<td>No</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Low</td>
<td>High</td>
<td>No</td>
<td>No</td>
<td>8 hours</td>
<td>Yes</td>
</tr>
<tr>
<td>Timolol</td>
<td>Low</td>
<td>Low</td>
<td>No</td>
<td>No</td>
<td>12 hours</td>
<td>No</td>
</tr>
<tr>
<td>Propranolol</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>5 days</td>
<td>Yes</td>
</tr>
<tr>
<td>Ceftolol</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>High</td>
<td>3 days</td>
<td>No</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>2 weeks</td>
<td>Yes</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>2 weeks</td>
<td>Yes</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>8 hours</td>
<td>No</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>12 hours</td>
<td>No</td>
</tr>
</tbody>
</table>

* Some agonist effect at β receptors: Labetalol and Nebivolol. Beta-adrenergic blockade: Timolol is the least potent.
Clinical uses: Beta-Blockers

- Angina (non-selective or β1-selective)
  - Cardiac: ↓O₂ demand more than O₂ 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)
- Glaucoma (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)
  - hyperthyroidism: ↓cardiac manifestation (only propranolol)
  - panic attacks, stage fright

Mixed Alpha- and β-Receptor Blockers

- Labetalol
  - hypertensive crisis, chronic hypertension, CHF
  - competitive antagonist at both α- & β-receptors
  - β1 = β2 activity > α-activity
  - some intrinsic β-adrenoceptor activity
- Carvedilol
  - newest agent
  - no intrinsic β-adrenoceptor activity
  - chronic hypertension, congestive heart failure

β-Blockers: Untoward Effects, Cautions

- Supersensitivity: Rebound effect with β-blockers, less with β-blockers with partial agonist activity (ie. pindolol). Gradual withdrawal
- Asthma: Blockade of pulmonary β2-receptors leads to increase in airway resistance. β1-selective agents preferred
- 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
- Elderly: Effectiveness is decreased, more CNS effects (ie. depression)

β-Blockers: Heart Failure

- Old view (before 2002)
  Contraindicated: β-blockers can precipitate latent heart failure by removing compensatory increase in sympathetic effects on heart. Pindolol has less of this effect due to intrinsic activity.
- New view
  May be used for CHF with caution. Not suitable in unstable heart failure, or evidence of bronchospasm, fluid overload, significant bradycardia (decreased cardiac reserve) or depression.

Use of Beta-blockers in CHF

- Metoprolol (n=1990) vs Placebo (n=2001)
- β₁-selective, no ISA, LA-action
- USA & 13 European countries
- All received conventional medication
- Monitored 1 – 1.5 years
- Mortality ↓34%
- Hospitalization ↓29%
- Felt better ↑25%

MERIT-HF : Use of Metoprolol in CHF

Effects of Controlled-Release Metoprolol on Total Mortality, Hospitalizations, and Well-being in Patients With Heart Failure The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF)
JAMA, Mar 8, 2000 - Vol 283 (10) p1295-1302

Beta blocker news good for heart failure patients
FDA OK awaited; treatment guidelines being updated
**Dopamine antagonists**

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

**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

**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