Pharmacology of the Sympathetic Nervous System II

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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, THR → 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 Prostate Hypertrophy (BPH)

- Enlarged prostrate leads to difficulty in urination
  - Alpha1-receptor blocker (ie 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

95
BP (mmHg)
100
95
100
105
195

reflex

95
BP (mmHg)
100
100
55
**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

**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, MSA):
    - their ability to stabilize membranes
    - propranolol (yes) vs atenolol (no)
  - lipid solubility: propranolol (high) vs atenolol (low)

**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

Yohimbine (herbal, OTC): α2-blocker, for impotence not clinically available

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

(Drugs A-M are β1-selective exp. Labetalol & Carvedilol)

**Beta-adrenoceptor blocking drugs**

<table>
<thead>
<tr>
<th></th>
<th>Selectivity</th>
<th>Non-Selective Activity</th>
<th>Local Anesthetic Activity</th>
<th>ISA</th>
<th>Elimination half-life (h)</th>
<th>Aromatase Inhibitory Activity</th>
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</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>β1</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>2-4 hours</td>
<td>0</td>
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<tr>
<td>Metoprolol</td>
<td>β1</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>8-12 hours</td>
<td>0</td>
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<tr>
<td>Nebivolol</td>
<td>β1</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>1-2 hours</td>
<td>0</td>
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<tr>
<td>Bisoprolol</td>
<td>β1</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>8-12 hours</td>
<td>0</td>
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<tr>
<td>Carvedilol</td>
<td>β1</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>12-24 hours</td>
<td>2</td>
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<tr>
<td>Labetalol</td>
<td>α1, α2</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>1-2 hours</td>
<td>0</td>
</tr>
<tr>
<td>Inderal</td>
<td>α1, α2</td>
<td>No</td>
<td>No</td>
<td>1-2 hours</td>
<td>0</td>
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<tr>
<td>Propranolol</td>
<td>α1, α2</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>1-2 hours</td>
<td>0</td>
</tr>
<tr>
<td>Pindolol</td>
<td>α1, α2</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>1-2 hours</td>
<td>0</td>
</tr>
<tr>
<td>Timolol</td>
<td>α1, α2</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>1-2 hours</td>
<td>0</td>
</tr>
</tbody>
</table>

Clinic 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

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**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
Clinical uses: Beta-Blockers

- **Angina** (non-selective or β1-selective)
  - Cardiac: $O_2$ 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)

- **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
  - $β_1 = β_2$ activity > α-activity
  - some intrinsic β-adrenoceptor activity

- **Carvedilol**
  - newest agent
  - no intrinsic β-adrenoceptor activity
  - chronic hypertension, congestive heart failure

<table>
<thead>
<tr>
<th>Class/Drug</th>
<th>HT</th>
<th>Angina</th>
<th>Arh</th>
<th>M</th>
<th>HF</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Non-selective β&lt;sub&gt;1&lt;/sub&gt;/β&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Carteolol</td>
<td>X</td>
<td>x</td>
<td>ISA, long acting; also for glaucoma</td>
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<tr>
<td>Carvediol</td>
<td>x</td>
<td>x</td>
<td>$α$-blocking activity</td>
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<td>Labetalol</td>
<td>X</td>
<td>X</td>
<td>ISA, $α$-blocking activity</td>
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<td></td>
<td></td>
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<tr>
<td>Nadolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>long acting</td>
<td></td>
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<tr>
<td>Penbutolol</td>
<td>X</td>
<td>X</td>
<td>ISA</td>
<td></td>
<td></td>
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<tr>
<td>Pindolol</td>
<td>X</td>
<td>X</td>
<td>ISA, MSA</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Propranolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>MSA; prototypical beta-blocker</td>
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<tr>
<td>Betaxolol</td>
<td>X</td>
<td>also K-channel blocker</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Timolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>primarily used for glaucoma</td>
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</table>

<table>
<thead>
<tr>
<th>β&lt;sub&gt;1&lt;/sub&gt;-selective</th>
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<tbody>
<tr>
<td>Acebutolol</td>
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<tr>
<td>Atenolol</td>
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<tr>
<td>Betaxolol</td>
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<tr>
<td>Bisoprolol</td>
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<tr>
<td>Esmolol</td>
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<tr>
<td>Metoprolol</td>
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</table>

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)

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.
- Altered perception or expression of reality
- Affects 1% of the population
- Affects men and women equally
- Strong genetic component

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

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)

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

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

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

Sympathetic Nervous System Review