Pharmacology of the Sympathetic Nervous System II

Edward JN Ishac, Ph.D.

Department of Pharmacology and Toxicology
Medical College of Virginia
Campus of Virginia Commonwealth University
Richmond, Virginia, USA

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
  - preexisting “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 hyperthropy

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 Prostate Hypertrophy (BPH)

Enlarged prostrate leads to difficulty in urination
Alpha-receptor blocker (ie Phazosin) cause prostrate relaxation
Relaxed prostrate improves urination

Postural (Orthostatic) Hypotension

- Venous return falls
- Blood pressure falls
- Sympathetic activity increases
  ▪ Constriction of great veins
  ▪ Constriction of arteries (↑ TPR)
  ▪ Increase in heart rate

reflex mediated
no reflex
reflex
Phenoxybenzamine
- irreversible alpha1-blocker
- also block Ach, histamine, serotonin (side effects)
- also block uptake I & II (side effects)
- ↓ blood pressure: postural hypotension
- useful in long-term & acute pheochromocytoma

Phentolamine & Tolazoline
- non selective α1 = α2 antagonist activity
- cardiovascular: vasodilation, reflex ↑ HR
- enhance NA release (alpha2-blockade)
- ↓ plasma lipids, dizziness, drowsiness
- toxicity: postural hypotension, headache, nausea

Alpha-adrenergic receptor antagonists

• Prazosin and Terazosin (competitive antagonist)
  - selective α1- > α2-receptors (1000 fold)
  - cardiovascular effects: reduced peripheral resistance, lowered vascular return, no tachycardia
  - Therapy: treat primary hypertension, benign prostrate hypertrophy

Toxicity: postural hypotension, headache, nausea

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

Alpha-adrenergic receptor antagonists

Phentolamine & Tolazoline
- non selective
  - cardiovascular: vasodilation, reflex ↑ HR
  - enhance NA release (alpha2-blockade)
  - ↓ plasma lipids, dizziness, drowsiness

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)

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 unclear, but possibilities:
  - CNS action to reduce sympathetic tone
  - block of presynaptic β-ARs to ↓ NE release
  - decrease in renin release

Beta-Adrenoceptor Blocking Agents (-olol)

(β1-selective exp. Labetalol & Carvedilol)

<table>
<thead>
<tr>
<th>Drug</th>
<th>β1 Selective</th>
<th>Partial Agonist Activity</th>
<th>Local Anaesthetic Action</th>
<th>Lip Solubility</th>
<th>Elimination</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>2-4 hours</td>
<td>50</td>
<td></td>
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<tr>
<td>Metoprolol</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>4-8 hours</td>
<td>90</td>
<td></td>
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<tr>
<td>Carvedilol</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
<td>Low</td>
<td>50</td>
<td></td>
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<tr>
<td>Labetalol</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Low</td>
<td>4-8 hours</td>
<td>50</td>
</tr>
<tr>
<td>Propranolol</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>12 hours</td>
<td>400</td>
<td></td>
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<tr>
<td>Timolol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>12 hours</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

*Partial agonist effect at β receptors. Timolol and β2 selective. Propranolol is β1-selective.*
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)
  - migraine prophylaxis (mechanism unknown)
  - 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

- **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

MERIT-HF: Use of Metoprolol 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%**
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

Inhibition of transmitter release

- Guanethidine (reuptake inhibitor, inhibits release)
- Bretylium (local anesthetic action)
- Uses: hypertension (last resort)
- Side effects: diarrhea, nasal congestion, impotence