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, ↑ HR → hypertensive crisis
Treatment: - surgucal removal for solid tumor
  - α-/β-blocker ie. Labetalol
  - α-blocker ie, phenoxybenzamine or phentolamine
  - inhibitor of tyrosine hydroxylase ie. 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 (ie Prazosin) cause prostrate relaxation
Relaxed prostrate improves urination

Postural (Orthostatic) Hypotension

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

reflex mediated

BP (mmHg)

95
100
95

no reflex

95
100
195
105

reflex

100
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

• 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

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

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

Toxicity - Alpha-blockers

Alpha-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)

Beta-Adrenoceptor Blocking Agents (β1)

(Compounds A-M are β1-selective except Labetalol & Carvedilol)

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 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:

Hypertension:
- Gradual decrease in TPR in spite of long-term decrease in cardiac output
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Mechanism of action:
- CNS action to reduce sympathetic tone
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Graph showing changes in CO and TPR over time with treatment.
### Clinical uses: Beta-Blockers

- **Angina (non-selective or β1-selective)**
  - Cardiac: \( J_W \) demand more than \( O_2 \) supply
  - Exercise tolerance ↑ in angina patients
- **Arrhythmia (β1-selective, LA-action)**
  - ↓ catecholamine-induced increases in conductivity and automatically in heart, and ↓ serum K+ (action in skeletal muscle)
- **Glaucus (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:** 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 better
- **Raynaud D:** Decreased peripheral circulation
- **CNS:** nightmares, mental depression, insomnia
- **Elderly:** ↓ Effectiveness, ↑ adverse effects (ie. depression)

### 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

### 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”

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

Sympathetic Nervous System Review