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,THR → hypertensive crisis
Treatment:
  - surgical 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 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

BP (mmHg)

no reflex

reflex

95
100
95

195
105
**Alpha-adrenergic receptor antagonists**

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 $\alpha_1 = \alpha_2$ 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
- tachycardia (reflex, usually) → arrhythmias

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

**Alpha-adrenergic receptor antagonists**

- Prazosin and Terazosin (competitive antagonist)
- selective $\alpha_1 > \alpha_2$-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, ↓ plasma lipids, dizziness, drowsiness

Yohimbine (herbal, OTC): $\alpha_2$-blocker, for impotence not clinically available

**Beta-adrenergic receptor antagonists**

- Clinically a more useful class of drugs than $\alpha$-adrenoceptor antagonists.
- $\beta$-Adrenoceptor antagonists vary in respect to:
  - Relative affinity for beta1- and beta2-adrenoceptors
    - propranolol ($\beta_1, \beta_2$) vs atenolol ($\beta_1$)
  - Intrinsc $\beta$-activity (ISA): also act as agonists at $\beta$-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)**

(Drugs A-M are $\beta_1$-selective exp. Labetalol & Carvedilol)

Clinical uses: Beta-Blockers - Hypertension

- Hypertension: frontline class
  - gradual ↓ TPR in spite of longterm ↓ cardiac output
  - non-selective and $\beta_1$-selective drugs are effective

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

\[ \begin{array}{|c|c|c|c|c|c|}
\hline
\text{Drug} & \text{Beta1 Selectivity} & \text{Beta2 Selectivity} & \text{Alpha Blocker} & \text{Elimination} & \text{Arrhythmia} \\
\hline
\text{Amlodipine} & \text{Yes} & \text{No} & \text{Low} & \text{24 hours} & \text{↑} \\
\text{Amlodipine} & \text{Yes} & \text{No} & \text{Low} & \text{6-9 hours} & \text{No} \\
\text{Betalol} & \text{No} & \text{High} & \text{Low} & \text{3-4 hours} & \text{No} \\
\text{Betaxolol} & \text{No} & \text{Low} & \text{Low} & \text{≤1 hour} & \text{No} \\
\text{Carvedilol} & \text{Yes} & \text{No} & \text{Low} & \text{≤6 hours} & \text{No} \\
\text{Cephalpiglumine} & \text{Yes} & \text{No} & \text{Low} & \text{≤6 hours} & \text{No} \\
\text{Carotol} & \text{Yes} & \text{No} & \text{Low} & \text{6-9 hours} & \text{No} \\
\text{Camptol} & \text{Yes} & \text{No} & \text{Low} & \text{≤6 hours} & \text{No} \\
\text{Labetalol} & \text{Yes} & \text{Yes} & \text{Moderate} & \text{≤6 hours} & \text{No} \\
\text{Metoprolol} & \text{Yes} & \text{Yes} & \text{Moderate} & \text{≤6 hours} & \text{No} \\
\text{Timolol} & \text{Yes} & \text{Yes} & \text{Moderate} & \text{≤6 hours} & \text{No} \\
\text{Propranolol} & \text{Yes} & \text{Yes} & \text{Moderate} & \text{≤6 hours} & \text{No} \\
\text{Pindolol} & \text{Yes} & \text{Yes} & \text{Moderate} & \text{≤6 hours} & \text{No} \\
\text{Bisoprolol} & \text{Yes} & \text{Yes} & \text{Moderate} & \text{≤6 hours} & \text{No} \\
\text{Sotalol} & \text{No} & \text{No} & \text{Low} & \text{12-16 hours} & \text{No} \\
\text{Timolol} & \text{No} & \text{No} & \text{Moderate} & \text{≤6 hours} & \text{No} \\
\hline
\end{array} \]

*Some effects affect $\alpha$-receptors. Labetalol also blocks $\alpha_2$-adrenoceptor.

*Time again effect at $\beta$-receptors. Labetalol also blocks $\alpha_2$-adrenoceptor. Bisoprolol is $\beta_1$-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

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)