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**
  - **preexisting "tone" at receptor**
  - **net effect at pre- vs postsynaptic receptors**
  - **selectivity for receptor subtype**
  - **compensatory reflex adjustments**

Alpha-adrenergic receptor antagonists

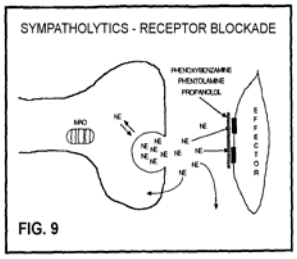


FIG. 9

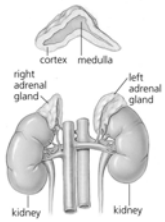
- **Clinical applications:**
  - **Hypertensive crisis**
    pheochromocytoma
    ADHD excess Rx
    tyramine crisis
    (MAO inhibitors)
  - **Chronic hypertension**
  - **Benign postrate hyperthropy**

Pheochromocytoma

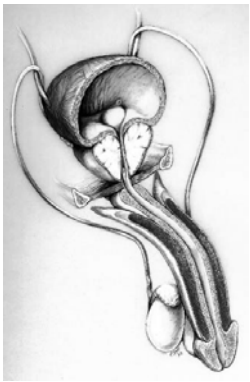
Tumor: ↑synthesis, ↑release of NE & EPI into the circulation.
Result: ↑BP, ↑HR → hypertensive crisis
Treatment:
- surgical removal for solid tumor
- α- / β-blocker ie. Labetatol
- α-blocker ie, phenoxybenzamine or phentolamine
- inhibitor of tyrosine hydroxylase ie. α-methyl-p-tyrosine
- β-blocker only 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



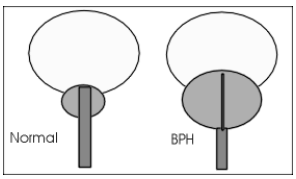
Benign Prostrate Hypertrophy (BPH)



Enlarged prostrate leads to difficulty in urination

Alpha-receptor blocker (ie Prazosin) cause prostrate relaxation

Relaxed prostrate improves urination

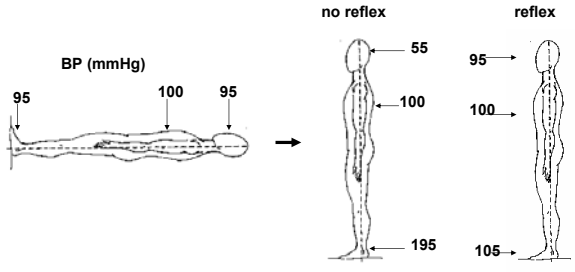


Postural (Orthostatic) Hypotension

- **Venous return falls**
- **Blood pressure falls**

- **Sympathetic activity increases**
  - **Constriction of great veins**
  - **Constriction of arteries (↑ TPR)**
  - **Increase in heart rate**

reflex mediated



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 α1 = α2 antagonist activity
- cardiovascular: vasodilation, reflex ↑ HR
- enhance NA release (alpha2-blockade)
- toxicity: hypotension, tachycardia, arrhythmias, myocardial infarction

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 ↓plasma lipids, dizziness, drowsiness

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

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

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 ß-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 β1-selective exp. Labetalol & Carvedilol)

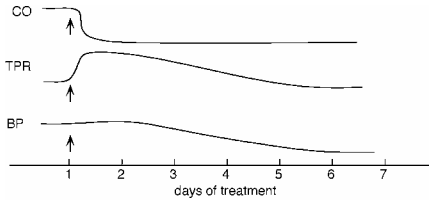
Properties of several beta-receptor blocking drugs

	Selectivity	Partial Agonist Activity	Local Anesthetic Action	Lipid Solubility	Elimination Half-Life	Approximate Bioavailability
Acebutolol	β_1	Yes	Yes	Low	3–4 hours	50
Atenolol	β_1	No	No	Low	6–9 hours	40
Betaxolol	β_1	No	Slight	Low	14–22 hours	90
Bisoprolol	β_1	No	No	Low	9–12 hours	80
Carteolol	None	Yes	No	Low	6 hours	85
Celiprolol	β_1	Yes[1]	No	...	4–5 hours	70
Esmolol	β_1	No	No	Low	10 minutes	...
Labetalol[2]	None	Yes[1]	Yes	Moderate	5 hours	30
Metoprolol	β_1	No	Yes	Moderate	3–4 hours	50
Nadolol	None	No	No	Low	14–24 hours	33
Penbutolol	None	Yes	No	High	5 hours	>90
Pindolol	None	Yes	Yes	Moderate	3–4 hours	90
Propranolol	None	No	Yes	High	3½–6 hours	30
Sotalol	None	No	No	Low	12 hours	90
Timolol	None	No	No	Moderate	4–5 hours	50

[1]Partial agonist effects at β_2 receptors. [2]Labetalol also causes α_1-selective blockade. [3]Bioavailability is dose-dependent.

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 presynaptic β-ARs to ↓NE release - decrease in renin release



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)**
  - **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- & ß-receptors**
  - **ß1 = ß2 activity > α-activity**
  - **some intrinsic ß-adrenoceptor activity**
- **Carvedilol**
  - **newest agent**
  - **no intrinsic ß-adrenoceptor activity**
  - **chronic hypertension, congestive heart failure**

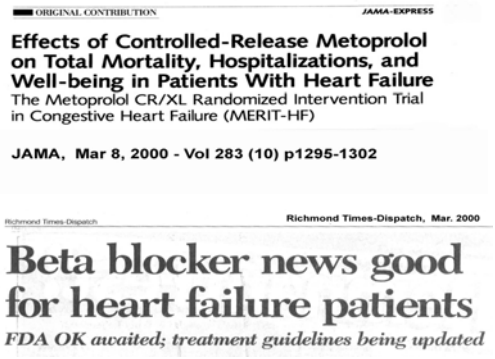
β-Blockers: Untoward Effects, Cautions

- **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


ORIGINAL CONTRIBUTION JAMA-EXPRESS

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

Richmond Times-Dispatch Richmond Times-Dispatch, Mar. 2000

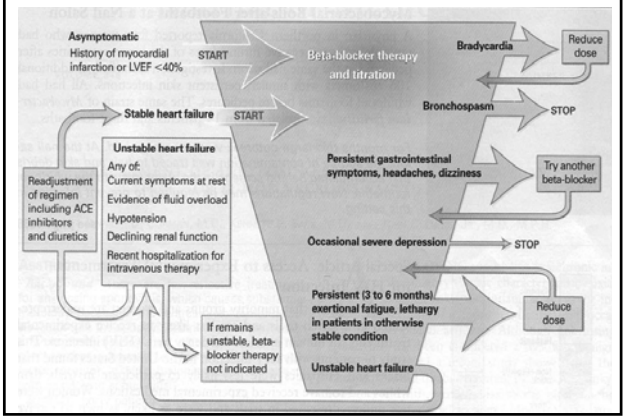
Beta blocker news good for heart failure patients

FDA OK awaited; treatment guidelines being updated

MERIT-HF : Use of Metoprolol in CHF

- **Metoprolol (n=1990) vs Placebo (n=2001)**
- **β_1-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%**

Beta-Blockers in CHF: 2002 Guideline



Quality of transmitter in nerve terminals altered

- **Direct inhibition of synthesis**

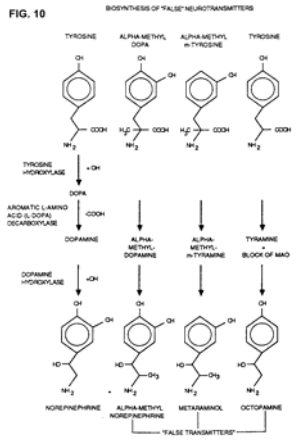
  - Alpha-methyl-p-tyrosine (inhibits tyrosine hydroxylase (rate limiting step in NE synthesis
  - treat pheochromocytoma (acute & chronic)

- **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



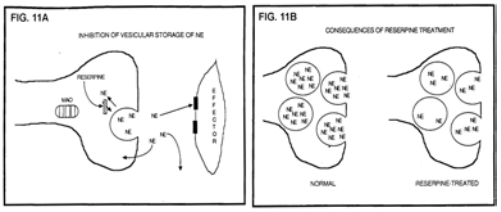
Synthesis of "False Transmitters"

Utilize the same enzymes as those involved in norepinephrine synthesis

Result in changes in the quantity and quality of transmitter in the storage vesicles

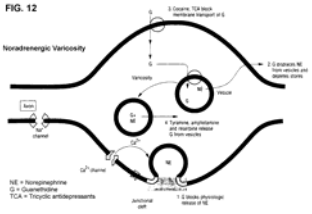
Reserpine

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



Sympathetic Nervous System Review