Pharmacology of the Sympathetic Nervous System II

Edward JN Ishac, Ph.D.
Professor

Smith Building, Room 742
eishac@vcu.edu
828-2127

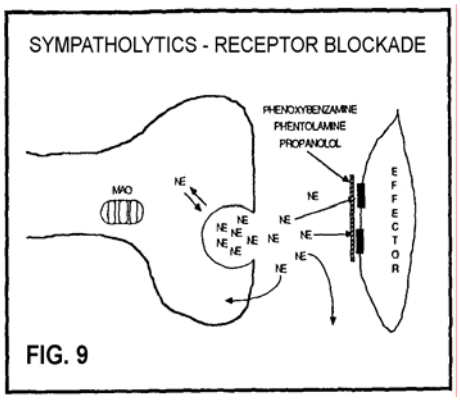
Department of Pharmacology and Toxicology
Medical College of Virginia
Campus of Virginia Commonwealth University
Richmond, Virginia, USA

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
  - 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

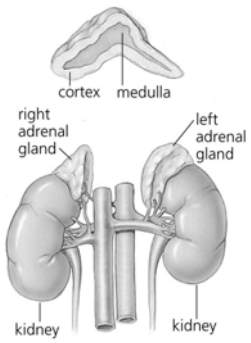
- Benign prostrate hypertrophy

Pheochromocytoma

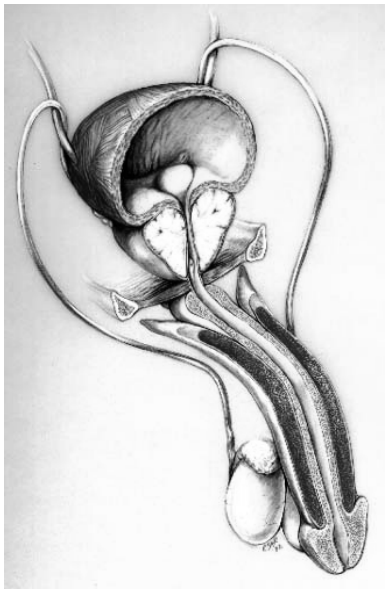
Tumor: ↑synthesis, ↑release of NE & EPI into the circulation.
Result: ↑BP, ↑HR → hypertensive crisis
Treatment:
- surgical removal for solid tumor
- α- / β-blocker ie. Labetatol
- α-blocker ie, phenoxybenzamine or phentolamine
- inhibitor of tyrosine hydroxylase ie. α-methyl-p-tyrosine
- β-blocker only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



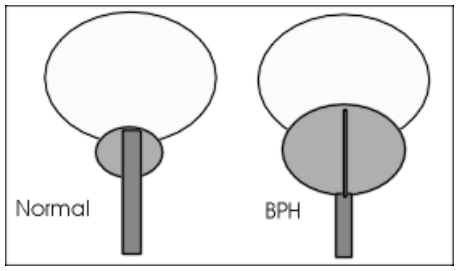
Benign Prostrate Hypertrophy (BPH)



Enlarged prostrate leads to difficulty in urination

Alpha1-receptor blocker (ie Prazosin) cause prostrate relaxation

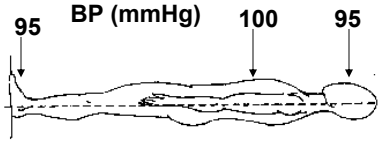
Relaxed prostrate improves urination

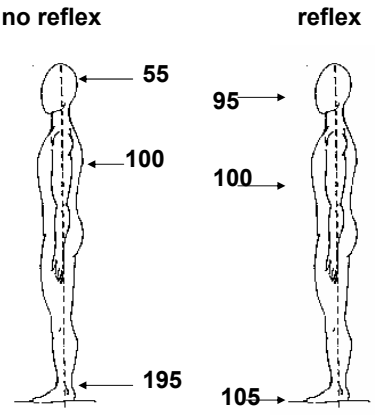


Postural (Orthostatic) Hypotension

- **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





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

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

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**

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, MSA):**
  - 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)

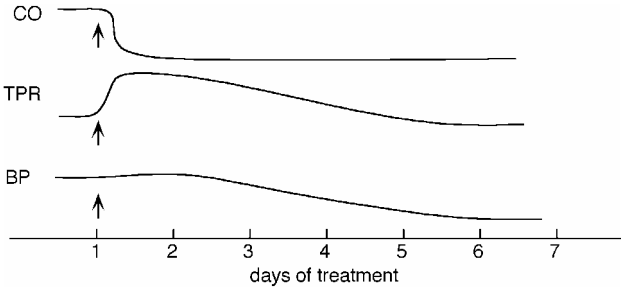
Properties of several beta-receptor blocking drugs

	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[3]
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 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**



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**

Clinical use – Beta-blockers

Class/Drug	HT	Angina	Arrh	MI	HF	Comments
Non-selective β_1/β_2						
Carteolol	X					ISA; long acting; also for glaucoma
Carvedilol	X				X	α-blocking activity
Labetalol	X	X				ISA; α-blocking activity
Nadolol	X	X	X	X		long acting
Penbutolol	X	X				ISA
Pindolol	X	X				ISA; MSA
Propranolol	X	X	X	X		MSA; prototypical beta-blocker
Sotalol			X			also K-channel blocker
Timolol	X	X	X	X		primarily used for glaucoma
β_1-selective						
Acebutolol	X	X				ISA
Atenolol	X	X	X	X		CI: Pregnancy
Betaxolol	X	X	X			MSA
Bisoprolol	X	X	X		X	
Esmolol			X			short acting; operative arrhythmia
Metoprolol	X	X	X	X	X	MSA

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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: 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

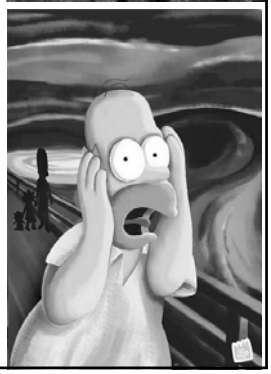
• Dopamine (DA) excess theory:

- Amphetamine exacerbates symptoms and high doses → paranoia, delusions, auditory hallucination. Effects blocked by DA antagonist chlorpromazine.

Antipsychotic Pharmacotherapy:

Typical: chlorpromazine, haloperidol

Atypical: risperidone, olanzapine, sertindole



Quality of transmitter in nerve terminals altered

- **Direct inhibition of synthesis**

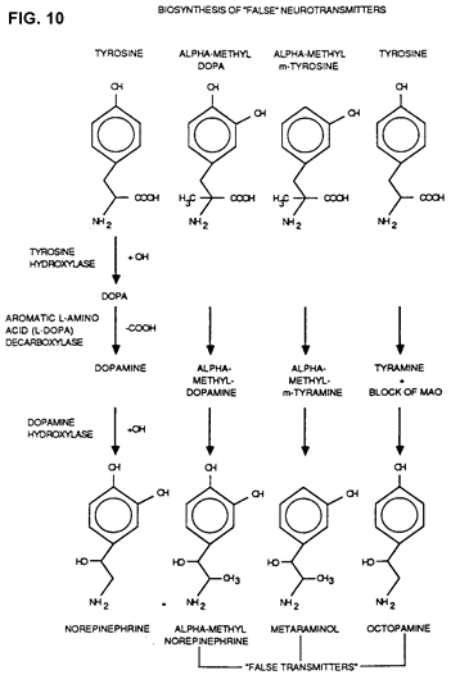
  - Alpha-methyl-p-tyrosine (inhibits tyrosine hydroxylase (rate limiting step in NE synthesis
  - treat pheochromocytoma (acute & chronic)

- **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



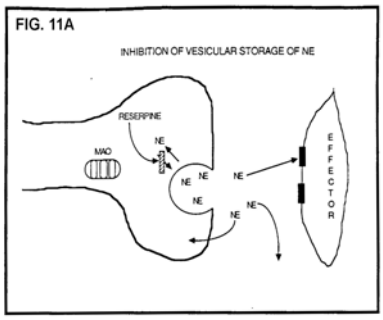
Synthesis of "False Transmitters"

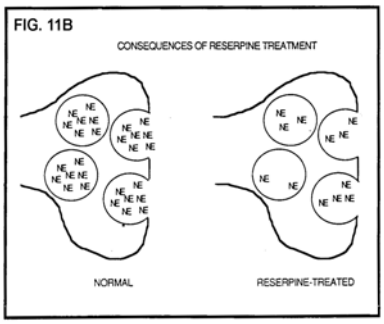
Utilize the same enzymes as those involved in norepinephrine synthesis

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

Reserpine

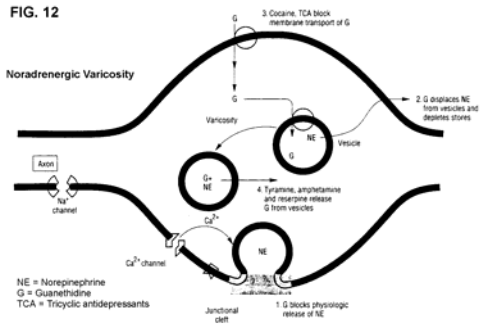
- **Inhibits NE uptake into storage vesicle**
  from cytosol, "leaky" vesicle (also depletes 5-HT stores)
  Use: Antihypertensive (last resort)
  Major side effects: lethargy, diarrhea, depression (very long lasting)





Inhibition of transmitter release

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



Dwight Eisenhower

Sympathetic Nervous System Review