ADRENERGIC ANTAGONISTS

• Course: Integrated Therapeutics 1
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• Materials on: Exam #3
• Required reading: Katzung, Chapter 10
SYMPATHOLYTIC DRUGS: SITES OF ACTION

Pre-Synaptic Neuron

Tyrosine Hydroxylase

Synthesis Inhibitors:
INHIBIT TYROSINE HYDROXYLASE
METYROSINE INDIRECT ACTING

Prevents storage, depletes NE
RESERPINE INDIRECT ACTING

Synapse

Tyrosine

Reuptake

MAO

α2-autoreceptors

Post-Synaptic Neuron

Adrenergic Receptor Antagonists
DIRECT ACTING

α-receptors

β-receptors

Autoreceptor Agonists:
ACTIVATE INHIBITORY ALPHA-2 AUTORECEPTORS
CLONIDINE INDIRECT ACTING
CATEGORIES OF SYMPATHOLYTIC DRUGS

• Direct sympatholytics (adrenoceptor antagonists)
  – $\alpha$ adrenoceptor antagonists
    • $\alpha_1$ and $\alpha_2$ non-selective antagonists
    • $\alpha_1$ receptor selective
    • $\alpha_2$ receptor selective
  – Mixed antagonists
    • $\alpha$ and $\beta$ antagonists
  – $\beta$ adrenoceptor antagonists
    • $\beta_1$ and $\beta_2$ non-selective antagonists
    • $\beta_1$ receptor selective
    • $\beta_2$ receptor selective
• Indirect sympatholytics
ALPHA-ADRENOCEPTOR ANTAGONISTS

• Direct sympatholytics (adrenoceptor antagonists)
  – α adrenoceptor antagonists
    • α₁ and α₂ receptor antagonists
      – Phentolamine
      – Phenoxybenzamine
    • α₁ receptor selective (all end in suffix –osin)
      – Prazosin
      – Terazosin
      – Tamsulosin
      – Doxazosin
      – Alfuzosin
    • α₂ receptor selective
      – Yohimbine
  – Mixed antagonists
    – β adrenoceptor antagonists
• Indirect sympatholytics
**REVERSIBLE vs. IRREVERSIBLE ALPHA ANTAGONISTS**

Reversible antagonist
- Non-covalent binding to receptor
- Shorter acting
- Effect antagonized by high concentrations of agonist

Phenoxybenzamine
- Irreversible antagonist
- Covalent binding to receptor
- Longer acting
- Effect is not antagonized by the agonist
PHARMACODYNAMICS OF ALPHA ANTAGONISTS

• Cardiovascular system: decreased peripheral resistance and blood pressure, reflex tachycardia, postural hypotension
PHARMACODYNAMICS OF ALPHA ANTAGONISTS

• Genitourinary system
  – Relaxation of smooth muscle in prostate
  – Decreased resistance to the flow of urine
• Eye
  – Miosis
• Respiratory system
  – Nasal and upper respiratory tract stuffiness
SPECIFIC ALPHA ANTAGONIST DRUGS

• Phentolamine $\alpha_1 = \alpha_2$
  – Decreased peripheral resistance
    • Block $\alpha_1$ receptors in vascular smooth muscle
  – Cardiac stimulation due to
    • Baroreflex
    • Blocking presynaptic $\alpha_2 \rightarrow$ increase in norepinephrine release onto unblocked $\beta_1$ receptors on heart
  – Agonist at muscarinic, H$_1$ and H$_2$ receptors
  – Very low selectivity – effects on multiple receptor types
  – Poor oral absorption
SPECIFIC ALPHA ANTAGONIST DRUGS

Phentolamine $\alpha_1 = \alpha_2$
– Adverse effects – cardiac stimulation
  • Tachycardia
  • Arrhythmias
  • Myocardial ischemia
  • GI stimulation $\rightarrow$ diarrhea and increased gastric acid secretion
– Used for treatment of
  • Pheochromocytoma
  • Erectile dysfunction
SPECIFIC ALPHA ANTAGONIST DRUGS

• Phenoxybenzamine $\alpha_1 > \alpha_2$, irreversible antagonist of receptor
  – Also inhibits the reuptake of released norepinephrine
  – Blocks acetylcholine, H$_1$ and serotonin receptors
  – Blocks catecholamine induced vasoconstriction
  – Decreases blood pressure, especially if sympathetic tone is high
  – Cardiac output may increase – reflex effects and/or some presynaptic $\alpha_2$ blockade
SPECIFIC ALPHA ANTAGONIST DRUGS

Phenoxybenzamine $\alpha_1 > \alpha_2$, irreversible antagonist of receptor

– Major use – pheochromocytoma – preparation for surgery

– Adverse effects
  • Postural hypotension
  • Tachycardia
  • Nasal stuffiness
  • Inhibition of ejaculation
  • Enters CNS – fatigue, sedation, nausea
SPECIFIC ALPHA ANTAGONIST DRUGS

- Prazosin $\alpha_1 >>> \alpha_2$ highly selective antagonist
- Relative absence of tachycardia and cardiac stimulation, as compared with phentolamine or phenoxybenzamine
SPECIFIC ALPHA ANTAGONIST DRUGS

• Prazosin
  – Relaxes smooth muscle in arteries, veins, and prostate
  – May increase HDL levels and decrease LDL
  – Used primarily in the treatment of hypertension

• Terazosin

• Doxazosin
  – Used in hypertension and urinary symptoms of prostate hyperplasia

• Tamsulosin
  – Greater selectivity for $\alpha_{1a}$ than $\alpha_{1b}$
  – $\alpha_{1a}$ most important $\alpha$ receptor mediating prostate smooth muscle contraction
  – Less potent inhibition of $\alpha_1$ mediation of vascular smooth muscle contraction
  – Used in benign prostate hyperplasia
Pheochromocytoma – tumor of the adrenal medulla producing catecholamines

- Catecholamine excess causes
  - Tachycardia
  - Arrhythmias
  - Hypertension

- Diagnosis – increased amounts of CA and their metabolites in plasma and urine

- Treatment
  - Phentolamine – during surgery to remove the tumor – get release of stored catecholamines
  - Phenoxybenzamine – used before surgery, useful in inoperable or metastatic pheochromocytoma
CLINICAL PHARMACOLOGY OF ALPHA ANTAGONISTS

• Hypertensive emergencies
  – Limited use
  – Phentolamine may be indicated when have high concentration of circulating $\alpha$ agonists are present
    • Pheochromocytoma
    • Overdose of agonists
    • Clonidine withdrawal
  – Nitrates or nitroprusside preferred

• Chronic hypertension
  – Prazosin family – $\alpha_1$ selective
    • Work well in moderate hypertension
    • Generally well tolerated
    • Nonselective $\alpha$-blockers not used
CLINICAL PHARMACOLOGY OF ALPHA ANTAGONISTS

• Erectile dysfunction
  – Consistent inability to maintain erection sufficient for the intercourse
  – Combination of phentolamine and nonspecific vasodilator papaverine
    • Injected into penis
    • Some systemic absorption → orthostatic hypotension
    • Priapism may need direct $\alpha$-agonist – phenylephrine
CLINICAL PHARMACOLOGY OF ALPHA ANTAGONISTS

• Benign prostate hyperplasia (BPH)
  – Chronic urinary obstruction
  – Many surgical treatments available
  – Tamsulosin
    • Effective with little effect on blood pressure
    • Good for individuals who have experienced postural hypotension with other $\alpha_1$-blockers
    • Has been shown to exceed effectiveness of $5\alpha$-reductase inhibitors – finasteride
  – Prazosin, doxazosin, terazosin are also effective
CLINICAL PHARMACOLOGY OF ALPHA ANTAGONISTS

• Adverse effects
  – Most significant effects are on the CVS
  – Seen less with $\alpha_1$ selective antagonists
  – Postural hypotension – antagonism of $\alpha_1$ in venous smooth muscle
  – Reflex tachycardia
    • Block $\alpha_2$ presynaptic receptors in the heart will increase the release of norepinephrine
    • Baroreflex response to lowering blood pressure
  – Retention of fluid and salt
  – Impaired ejaculation
CATEGORIES OF SYMPATHOLYTIC DRUGS

• Direct sympatholytics
  – $\alpha$ adrenoceptor antagonists
  – Mixed antagonists
    • Labetalol
    • Carvedilol
  – $\beta$ adrenoceptor antagonists
    • $\beta_1$ and $\beta_2$ antagonists
      – Propranolol
      – Pindolol
    • $\beta_1$ selective
      – Metoprolol
      – Acebutolol
      – Atenolol
    • $\beta_2$ selective
      – Butoxamine
• Indirect sympatholytics
TYPES OF THE ACTION AT THE RECEPTORS

• Full Agonists
  • Fully activate receptors
  • Produce a maximal pharmacological effect when all receptors are occupied
  • Maximal intrinsic activity

• Partial Agonists
  • Partially activate the receptor upon binding
  • Produce a sub-maximal pharmacological effect when all receptors are occupied
  • Intrinsic efficacy varies depending on drug, but is always submaximal
TYPES OF THE ACTION AT THE RECEPTORS

• Inverse Agonists
  • Decrease receptor signaling
  • Decrease response at receptors with a significant level of constitutive receptor activity
  • Intrinsic activity is present and related to the inhibition of receptor function
• Antagonists
  • Do not activate the receptor upon binding
  • No pharmacological effect in the absence of agonist
  • No intrinsic efficacy
TYPES OF THE ACTION AT THE RECEPTORS

- $E_{\text{MAX}}$ is lower in partial agonists than in full agonists
- Inhibition of a baseline receptor activity by inverse agonists
TYPES OF INTERACTION OF BETA-BLOCKERS WITH RECEPTORS

• Pure antagonists
  – Atenolol
  – Carvedilol
  – Nadolol
  – Propranolol

• Partial agonists (blockers with ISA)
  – Acebutolol
  – Labetalol
  – Penbutolol
  – Pindolol

• Inverse agonists
  – Betaxolol
  – Metoprolol
**PARTIAL AGONISTS: BETA-BLOCKERS WITH ISA**

- Beta blockers with ISA (Intrinsic Sympathomimetic Activity) are partial agonists at beta adrenergic receptors.
- Block sympathetic effects BUT have submaximal effects of their own = a blunted sympathetic response.
- Less risk for bradycardia, changes in VLDL/HDL, and other effects of beta receptor blockade.

![Bar chart showing percent reduction in heart rate](chart.png)
**PHARMACOKINETICS OF BETA-BLOCKERS**

- Most of them are lipophilic drugs – well absorbed and rapidly distributed, with large volumes of distribution
- **Propranolol** is able to cross BBB
- Metabolism – **propranolol** and **metoprolol** are extensively metabolized in the liver
  - Extensive first-pass metabolism – low bioavailability with oral administration
  - Metabolized by CYP2D6 – poor metabolizers will show up to 10X increased blood levels
  - Half-life of these drugs may increase as a result of liver disease or hepatic enzyme inhibition
- **Nadolol** is not metabolized and is excreted unchanged in the urine – longest half-life of all beta-blockers (24 h)
  - Half-life of the drug may increase in renal failure
PHARMACODYNAMICS OF BETA-BLOCKERS

- Cardiovascular system
  - Chronic use – lowers blood pressure in hypertensive individuals
  - Will not produce hypotension in normotensive individuals
  - Heart
    - Negative inotropic effect
    - Negative chronotropic effect
    - Block AV node
      - Slowed atrioventricular conduction
      - Increased PR interval
  - Blood vessels
    - Initially – rise in peripheral vascular resistance
    - Chronic use → decrease in PVR
PHARMACODYNAMICS OF BETA-BLOCKERS

Effect of Propranolol on cardiovascular system
PHARMACODYNAMICS OF BETA-BLOCKERS

• Respiratory tract
  – Increase airway resistance especially seen in asthmatics
  – Some patients with COPD may tolerate them

• Eye – reduce intraocular pressure by decreasing the production of aqueous humor

• Metabolic and endocrine effects
  – Inhibit sympathetic stimulation of lipolysis
  – Glycogenolysis partially inhibited by $\beta_2$ blockade
    • Not known how much $\beta$-antagonists impair recovery from hypoglycemia
      – Care when used with patients with IDDM
      – Much safer in non-IDDM – who do not have hypoglycemic reactions
PHARMACODYNAMICS OF BETA-BLOCKERS

• Metabolic and endocrine effects
  – Inhibit renin release
  – Chronic use – increase VLDL and decreases HDL – LDL usually not changed but ratio LDL/HDL changes
  • Mechanism of changes unknown
  • Might be significant in patients with coronary artery disease
  • May see less of an effect with drugs with partial agonist and $\beta_1$ selective activity
PHARMACODYNAMICS OF BETA-BLOCKERS

• Local anesthetic ("membrane-stabilizing") action
  – not related to $\beta$ blockade
    – Propranolol
    – Pindolol
    – Acebutolol
    – Labetalol
    – Metoprolol

• Antiarrhythmic action (not related to $\beta$ blockade)
  – blocking potassium channels
    – Sotalol
CLINICAL PHARMACOLOGY OF BETA BLOCKERS

• Hypertension
  – Antihypertensive effect is delayed
  – Beta-blockers are usually used in combination with diuretics and/or vasodilators
  – Both pure beta-blockers and mixed (α and β) blockers (Labetalol, α₁ and β-blocker) are used

• Ischemic heart disease – angina pectoris
  – Blocking cardiac beta-receptors decreases cardiac work and reduces oxygen consumption
  – Beta-blockers reduce the frequency of anginal episodes and improve exercise tolerance
CLINICAL PHARMACOLOGY OF BETA BLOCKERS

• Ischemic heart disease – myocardial infarction
  – Long-term use in post-infarction period – prolong the survival
    • Timolol
    • Propranolol
    • Metoprolol
  – Acute phase of myocardial infarction
    • Contraindications – bradycardia, hypotension, acute heart failure, AV block, active airway disease
CLINICAL PHARMACOLOGY OF BETA BLOCKERS

• Cardiac arrhythmias
  – Effective in ventricular and supraventricular arrhythmias: atrial flutter and atrial fibrillation, ventricular ectopic beats
  – Sotalol – has direct antiarrhythmic action (not mediated by beta-blocking activity)

• Heart failure
  – Effective for the treatment of chronic heart failure in selected patients
  – Metoprolol, bisoprolol, carvedilol shown in clinical trials to be effective
  – Contraindicated in acute congestive heart failure
**CLINICAL PHARMACOLOGY OF BETA BLOCKERS**

- **Gluacoma**
  - The mechanism involves the reduction in the production of aqueous humor by the ciliary body
  - Timolol, Betaxolol – blockers w/o local anesthetic activity
- **Hyperthyroidism**
  - One of the important aspects of the disease: excessive catecholamine action on the heart
  - Thyroid storm – severe form of hyperthyroidism
  - Tachycardia, supraventricular and ventricular ectopic arrhythmias
  - Propranolol
ADVERSE EFFECTS OF BETA-BLOCKERS

• CNS effects (switch to hydrophilic drugs)
  – Sedation
  – Sleep disturbances
  – Depression
• Respiratory system (switch to beta-1 selective)
  – Bronchospasm, triggering asthma attack in susceptible individuals (chronic asthma, COPD, chronic bronchitis)
ADVERSE EFFECTS OF BETA-BLOCKERS

• Cardiovascular system
  – Depression of cardiac contractility and excitability
  – Exacerbation of peripheral vascular disease (switch to beta-1 selective)
• Metabolic effects (switch to beta-1 selective)
  – Unfavorable blood lipoprotein profile
  – Increased incidence of hypoglycemic episodes
• Abrupt discontinuation of beta-blocker therapy
1. Normal condition
Norpinephrine

\[ \beta \text{ adrenergic receptors} \]

Response (e.g., increase in heart rate)

2. Antagonism with a beta blocker
Norpinephrine

\[ \beta \text{ adrenergic receptors antagonized by propranolol} \]

Diminished response

3. Compensatory up-regulation of receptor in presence of propranolol
Norpinephrine

\[ \beta \text{ adrenergic receptors antagonized by propranolol} \]

Diminished response

4. Compensatory upregulation of receptor in absence of propranolol
Norpinephrine

\[ \beta \text{ adrenergic receptors no longer antagonized} \]

INCREASED RESPONSE
ADVERSE EFFECTS OF BETA-BLOCKERS

• Abrupt discontinuation of beta-blocker therapy
  – Increased risk in patients with ischemic heart disease
  – Gradually taper beta blocker dosing to prevent sympathetic hyper-responsiveness and potential toxicity

• Use with caution in:
  – Patients with COPD and asthma
  – Patients with diabetes who are susceptible to hypoglycemia
  – Patients with impaired cardiac function
  – Patients with peripheral vascular disease
INDIRECT SYMPATHOLYTICS

• Direct sympatholytics (adrenoceptor antagonists)
  – $\alpha$ adrenoceptor antagonists
  – Mixed antagonists
  – $\beta$ adrenoceptor antagonists

• Indirect sympatholytics
  – Reserpine: depletes vesicles of neurotransmitter to inhibit release
  – Clonidine: agonist at presynaptic autoreceptors, inhibits NE release
  – Metyrosine: alpha-methyl tyrosine, inhibits tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of catecholamines