Adrenergic Antagonists
Direct Adrenergic Antagonists

• Beta blockers
• Alpha blockers
• Alpha plus beta blockers
Beta Receptors on body Organs

- **CVS**: Beta 1 receptors are found in the heart. When stimulated $\rightarrow$ Increase in Heart rate
- **Pulm**: Beta 2 receptors $\rightarrow$ Bronchodilation
- **Eyes**: Beta receptors are found in the ciliary epithelium in the eye. When stimulated $\rightarrow$ Produces Aqueous Humor.
- When **blocked**, **decreases** Aqueous Humor production
Effects of BETA-BLOCKADE on ischemic heart

- heart rate
- afterload
- heart size
- wall stress
- contractility
- O2 wastage
- increased diastolic perfusion
- less exercise vasoconstriction
- more spasm

O2 demand vs O2 supply

subendocardial ischemia

collaterals

DEMAND SUPPLY

O2 deficit
Uses of Beta Blockers

- Hypertension - mild to moderate HTN
- Angina pectoris - decreases cardiac work load
- Cardiac arrhythmias
- Myocardial infarction - prevents the reinfarction, prevents the development of ventricular fibrillation
Uses of Beta Blockers

- Glaucoma. Timolol is used
- Migraine. Used for prophylaxis
- Thyrotoxicosis
- Essential tremors
- Congestive cardiac failure (carvedilol and labetolol)
Beta Non-selective

- Non Selective Beta blockers
  - Propranolol
  - Nadolol
  - Timolol
  - Pindolol
- Blocks beta 1 and beta 2 receptors → **Bronchospasms and Decrease in HR**
  - Contraindicated in Asthmatics
- Decreases aqueous humor production → used in Open Angle glaucoma (Timolol)
Beta blockers ($\beta_1$ selective)

- Also known as Cardioselective Beta Blockers, decreases HR
- Metoprolol
- Atenolol
- Betaxolol
- Esmolol (short half life)
- Acebutalol
- ABEAM
Side effects of Beta blockers

• Beta 2 ➔ Exacerbation of Asthma
• Masks the sign of a hypoglycemic episode
• Bradycardia
Alpha and Beta Antagonists

• Carvedilol

• Labetalol (doesn’t cross Placenta, also used in pregnancy)

• Blocks alpha receptors ➔ Decrease BP

• Blocks beta receptors ➔ Decreases HR

• Used in Severe HTN, Angina
Alpha 1 receptors are located postsynaptically.

When activated, alpha 2 receptors inhibit neurotransmitter release from presynaptic neurons.
Alpha receptors

Alpha 1 receptors
- Alpha 1 agonists
  - Treatment of nasal congestion and ophthalmic hyperemia
- Alpha 1 blockers
  - Hypertension treatment
  - Treatment of benign prostatic hyperplasia

Alpha 2 receptors
- Alpha 2 agonists
  - Hypertension treatment
- Alpha 2 blockers
  - Yohimbine
Alpha Blockers (non-selective)

- Phenoxybenzamine (Non-competitive)
- Phentolamine (competitive)
Phenoxybenzamine

• **Non-competitive** alpha adrenergic antagonist.
• Net effect: $\alpha_1$ blockage $> \alpha_2$ blockage
• Uses:
  – malignant HTN,
  – Pheochromocytoma,
  – HTN 2° to Clonidine Withdrawal
Phentolamine

• Non-selective **Competitive** Alpha Blocker
  – Used in HTN
  – Cocaine induced HTN
  – Decreases the workload of the heart, and decreases the risk of MI
Competitive Antagonist Vs. Non-competitive Antagonist
Alpha selective Blockers

• $\alpha_1$ selective: (ends with –sin or –cin)
  • Prazosin,
  • Terazosin
  • Doxazosin,
  • Tamsulosin

• $\alpha_2$ selective: (inhibits Negative feedback)
  • Yohimbine
**α-blockers**

- **α-receptors**
  - Vasodilation
  - Arterioles
    - Peripheral resistance
      - Afterload
    - Veins (capacity vessels)
      - Preload
  - Insulin sensitivity

- In the plasma:
  - Chol ↓
  - LDL ↓
  - TG ↓

- Contractility not increased because of modified catecholamin release (α2-receptors)
Alpha 1 blockers

• Effects: Blocks vaso- and aterioconstriction → vasodilation and arteriodilatation → Decrease in Blood pressure.

• Blocks alpha receptors in the eye (pupillary dilator muscle) → Miosis

• Reduces Bladder tone and allows for more motility (especially in patients with Urinary retention, BPH)
Alpha 1 blockers Uses/Side effects

- Increase Urinary Motility, used in Urinary retention or BPH (Prazosin/Tamsulosin is most commonly used in BPH)

- Side effects: **Nasal Congestion**, Hypotension
\( \alpha_2 \) selective blockers

- Yohimbine
- Prevents Negative feedback \( \rightarrow \) Increased Release of Epinephrine and Norepinephrine
- Claimed to be an Aphrodisiac
- **Potential uses:** Impotence, Co-administrated with drug induced sexual dysfunction
<table>
<thead>
<tr>
<th><strong>Phenoxybenzamine</strong></th>
<th>Non-competitive Alpha receptor antagonist - used in <strong>pheochromocytoma</strong>, malignant hypertension, Clonidine Withdrawal,</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prazosin, tamsulosin, doxazosin</strong></td>
<td>$\alpha_1$ selective: uses-mild to moderate HTN, <strong>BPH</strong>,</td>
</tr>
<tr>
<td><strong>Yohimbine</strong></td>
<td>$\alpha_2$ antagonist: Used in impotence</td>
</tr>
</tbody>
</table>
Adrenergic Agonists

– Alpha adrenergic
  • Increases vascular tone
  • May decrease cardiac output
  • May decrease regional blood flow (renal, spleen, cutaneous)

– Beta adrenergic
  • Maintains blood flow
  • May increase cellular metabolism
  • May decrease immune system
Receptors

PRESSURE

PE  NE  Dopa  Epi  Dobut  Dopex  Iso

α  β
<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-1 Adrenergic</td>
<td>Vascular wall</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>Heart</td>
<td>Increase duration of contraction without increased chronotropy</td>
</tr>
<tr>
<td>Beta Adrenergic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-1</td>
<td>Heart</td>
<td>↑Inotropy and chronotropy</td>
</tr>
<tr>
<td>Beta-2</td>
<td>Blood vessels</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Renal</td>
<td>Vasodilation</td>
</tr>
<tr>
<td></td>
<td>Splanchnic (mesenteric)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coronary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerebral</td>
<td></td>
</tr>
</tbody>
</table>
# Vasoactive Medication Receptor Activity and Clinical Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Alpha-1</th>
<th>Beta-1</th>
<th>Beta-2</th>
<th>Dopaminergic</th>
<th>Predominant Clinical Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Neosynephrine) Phenylephrine</td>
<td>***</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>SVR ↑ ↑, CO ↔/↑</td>
</tr>
<tr>
<td>(Levophed) Norepinephrine</td>
<td>***</td>
<td>**</td>
<td>0</td>
<td>0</td>
<td>SVR ↑ ↑, CO ↔/↑</td>
</tr>
<tr>
<td>(Adrenalin) Epinephrine</td>
<td>***</td>
<td>***</td>
<td>**</td>
<td>0</td>
<td>CO ↑ ↑, SVR ↓ (low dose) SVR/↑ (higher dose)</td>
</tr>
<tr>
<td>(Intropin) Dopamine (mcg/kg/min)</td>
<td>0.5 to 2</td>
<td>0</td>
<td>*</td>
<td>0</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>0.5 to 2</td>
<td>0</td>
<td>*</td>
<td>0</td>
<td>**</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>0/*</td>
<td>***</td>
<td>**</td>
<td>0</td>
<td>CO ↑, SVR ↓/↑ (higher dose)</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>0</td>
<td>***</td>
<td>***</td>
<td>0</td>
<td>CO ↑, SVR ↓</td>
</tr>
</tbody>
</table>

*** Very Strong Effect, ** Moderate effect, * Weak effect, 0 No effect.
<table>
<thead>
<tr>
<th>Clinical Application</th>
<th>1st Line Agent</th>
<th>2nd Line Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic Shock</td>
<td>Norepinephrine (Levophed)</td>
<td>Vasopressin</td>
</tr>
<tr>
<td></td>
<td>Phenylephrine (Neosynephrine)</td>
<td>Epinephrine (Adrenalin)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>Dobutamine</td>
<td>Milrinone</td>
</tr>
<tr>
<td></td>
<td>Dopamine</td>
<td></td>
</tr>
<tr>
<td>Cardiogenic Shock</td>
<td>Norepinephrine (Levophed)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dobutamine</td>
<td></td>
</tr>
<tr>
<td>Anaphylactic Shock</td>
<td>Epinephrine (Adrenalin)</td>
<td>Vasopressin</td>
</tr>
<tr>
<td>Neurogenic Shock</td>
<td>Phenylephrine (Neosynephrine)</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>Anesthesia-induced Phenylephrine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Following CABG Phenylephrine (Neosynephrine)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Following CABG Epinephrine (Adrenalin)</td>
<td></td>
</tr>
</tbody>
</table>
Cardiovascular effects of sympathomimetics

- **Pulse Rate (min)**: Norepinephrine increases, Epinephrine increases, Isoproterenol increases.
- **Blood Pressure (mm Hg)**: Norepinephrine increases, Epinephrine increases, Isoproterenol increases.
- **Peripheral Resistance**: Norepinephrine increases, Epinephrine increases, Isoproterenol increases.
Direct acting adrenergic receptor agonists: 

$\beta$ receptor agonists

- Resorcinol derivatives
- Selective $\beta_2$ receptor agonists
- Bronchodilation
- Cardiac effects observed only at high doses
- Not metabolized by MAO or COMT
- Longer duration of action than isoproterenol
- Administration: Oral, parenteral, local (inhaled)
- Uses: Asthma, COPD; Terbutaline used as tocolytic (prevent premature labor)

Terbutaline

Metaproterenol
Direct acting adrenergic receptor agonists:

β receptor agonists

Albuterol (Ventolin, Proventil)  Salmeterol (Serevent)

- *Meta* hydroxymethyl derivatives
- Selective β2 receptor agonists
- Bronchodilation
- Cardiac effects observed only at high doses
- Not metabolized by MAO or COMT
- Longer duration of action than isoproterenol
- Administration: Oral, local (inhaled); Salmeterol only inhaled
- Uses: Asthma, COPD
At low epinephrine concentrations, the beta 2-AR will be occupied because these receptors have a higher affinity for epinephrine.

At high epinephrine concentrations the alpha 1-AR would be occupied. Because there are more of these receptors the predominant effect at the high epinephrine concentration is vascular smooth muscle contraction.
Questions

• What drugs can be given in HTN in pregnancy?

• Which is given orally (For home dosing)?

• Which is given IV (for immediate tx)?
Questions

The nonselective β-adrenergic blocking agent that is also a competitive antagonist at α1-adrenoceptors is

- a. Timolol
- b. Nadolol
- c. Pindolol
- d. Acebutolol
- e. Labetalol
A predictably dangerous side effect of nadolol that constitutes a contraindication to its clinical use in susceptible patients is the induction of

- a. Hypertension
- b. Cardiac arrhythmia
- c. Asthmatic attacks
- d. Respiratory depression
- e. Hypersensitivity
All of the following drugs are used topically in the treatment of chronic wide-angle glaucoma. Which of these agents reduces intraocular pressure by decreasing the formation of the aqueous humor?

- a. Timolol
- b. Echothiophate
- c. Pilocarpine
- d. Isofluorphpate
- e. Physostigmine
Questions

Both phentolamine and prazosin
a. Are competitive antagonists at α1-adrenergic receptors
b. Have potent direct vasodilator actions on vascular smooth muscle
c. Enhance gastric acid secretion through a histamine-like effect
d. Cause hypotension and bradycardia
e. Are used chronically for the treatment of primary hypotension
A 58-year-old male with angina is treated with atenolol. Select the mechanism of action of atenolol.

- a. α-adrenergic agonist
- b. α-adrenergic antagonist
- c. β-adrenergic agonist
- d. β-adrenergic antagonist
- e. Mixed α and β agonist
- f. Mixed α and β antagonist
A 75-year-old female with CHF is treated with carvedilol. Select the mechanism of action of carvedilol.

- a. \( \alpha \)-adrenergic agonist
- b. \( \alpha \)-adrenergic antagonist
- c. \( \beta \)-adrenergic agonist
- d. \( \beta \)-adrenergic antagonist
- e. Mixed \( \alpha \) and \( \beta \) agonist
- f. Mixed \( \alpha \) and \( \beta \) antagonist
A 35-year-old male with a pheochromocytoma is treated with labetalol. Select the mechanism of action of labetalol.

- a. α-adrenergic agonist
- b. α-adrenergic antagonist
- c. β-adrenergic agonist
- d. β-adrenergic antagonist
- e. Mixed α and β agonist
- f. Mixed α and β antagonist
A 65-year-old male has a blood pressure of 170/105 mmHg. Which of the following would be effective in lowering this patient’s blood pressure?

a. Methylphenidate
b. Terbutaline
c. Dobutamine
d. Pancuronium
e. Prazosin
f. Scopalamine
Which of the following agents might mask the hypoglycemia in treated diabetics?

a. An α-adrenergic agonist
b. An α-adrenergic antagonist
c. A β-adrenergic agonist
d. A β-adrenergic antagonist
e. A cholinergic agonist
f. A cholinergic antagonist
A 66-year-old male with a one-year history of essential hypertension has minimal response to diet and a diuretic. His blood pressure is now 160/105 mmHg. The diuretic is discontinued, and propranolol is given.

- a. α-adrenergic antagonist
- b. β-adrenergic antagonist
- c. Calcium (Ca) channel antagonist
- d. Carbonic anhydrase inhibitor
- e. Histamine (H1) receptor antagonist
- f. H2 receptor antagonist
- g. MAOI
Pretest Questions

• Which drug is used in pheochromocytoma?
  • a. Pilocarpine
  • b. Methylphenidate
  • c. Propranolol
  • d. Ritodrine
  • e. Phenoxybenzamine
Clinical Scenario I

- 72 year-old woman with DM type II, hypertension and Stage II CKD is transferred from a Skilled Nursing Facility for altered mental status. Her vitals upon arrival are as follows: Temp 101F, BP 70/45, Hr 140, RR 20, O2 Sat 95% RA. Pertinent lab findings: WBC 21, Cr 3.5, Lactic Acid 3.4, Positive UA.

- After adequate IVF resuscitation, pt continues to remain hypotensive BP 60-70s/30-40s and tachycardic Hr 130s. What is the most appropriate 1\textsuperscript{st} line vasopressor/inotropic agent?

A. Epinephrine (Adrenalin)
B. Dobutamine
C. Norepinephrine (Levophed)
D. Dopamine
Clinical Scenario II

- 64 year-old man with PMH significant for CAD s/p MI and PCI (2004; drug-eluting stents), ischemic cardiomyopathy (EF 20-25%) with AICD (2007), who presents to ED with 1 week history of progressively worsening shortness of breath, orthopnea and bilateral lower extremity edema, after running out of all medications about 10 days ago.

- In ED, vitals: Temp 99F, BP 75/48, Hr 75, RR 25, O2 Sat 91% on RA. CXR reveals vascular congestion and bilateral pleural effusion. Bedside ultrasound reveals significantly diminished EF.

- What is the most appropriate 1st line vasopressor/inotropic agent?

  A. Epinephrine (Adrenalin)
  B. Dobutamine
  C. Norepinephrine (Levophed)
  D. Dopamine
Clinical Scenario III

- 56 year-old obese man with PMH significant for COPD and OSA, who was initially admitted to the medicine floor for acute COPD exacerbation secondary to community-acquired pneumonia, was found to be in acute respiratory failure.

- Versed and Succinylcholine were given for emergent intubation. Vitals after intubation are as follows: Temp 99.8F, BP 74/48, Hr 74. What is the most appropriate 1\textsuperscript{st} line vasopressor/inotropic agent?

A. Phenylephrine (Neosynephrine)
B. Dobutamine
C. Norepinephrine (Levophed)
D. Dopamine