Alpha adrenergic blockers
Introduction

Drugs which **antagonize** the receptor action of Adrenaline and other related drugs at the receptor level

They occupy adrenergic receptors (α and β) but do not produce signal transduction – affinity is there but without IA - - competitive antagonists

Antiadrenergics Vs Adrenergic Neurone Blockers!

For pharmacologic research, adrenoceptor antagonist drugs have been very useful in the experimental exploration of autonomic nervous system function

Effects vary according to the drug's selectivity for and receptors - α and its subtype specific or β and its subtype specific
Antiadrenergic Drugs - Background

Clinically – to modify the responses of endogenous catecholamines (Adrenaline and Noradrenaline) - physiologic and pathophysiologic

Nonselective α-antagonists: have been used in the treatment of pheochromocytoma (tumors that secrete catecholamines), and α-1 selective antagonists are used in primary hypertension and benign prostatic hyperplasia (BHP)

β-receptor antagonist: hypertension, ischemic heart disease, arrhythmias, endocrinologic and neurologic disorders, and many other conditions

Blockade of peripheral dopamine receptors is of no recognized clinical importance at present

In contrast, blockade of central nervous system dopamine receptors is very important – antiemetic, antipsychotic and TCAs
α – receptor adrenergic Blockers

In the presence of prazosin

Vasodilation in arterial and venous vascular beds
Drugs – Classification

- Nonequilibrium type:
  - β-haloalkylamines: Phenoxybenzamine

- Equilibrium:
  I. Nonselective:
  1. Ergots: Ergotamine and Ergotoxine
  2. Hydrogenated ergot alkaloids: DHE, Dihydroergotoxine
  3. Imidazolines: Tolazoline, Phentolamine
  4. Miscellaneous: Chlorpromazine, Histamine and Serotonin

II Selective α-1: Prazosin, Terazosin, Doxazosin and Tamsulosin

III Selective α-2: Yohimbine
Ergot Images (Claviceps purpurea)
Ergots

- **Natural**: considered derivatives of Lysergic acid (LSD) – cognition enhancer
- Amine alkaloid: Ergometrine (ergonovine)
- Amino acid alkaloids: Ergotamine and ergotoxine – vasoconstrictor, *partial agonist and antagonist at* $\alpha$ receptors and 5-HT receptors (1 and 2)
- **Semisynthetic derivatives**: Dihydroergotamine (DHE) and Dihydroergotoxine – more $\alpha$-receptor blocking property
General Effects of alpha Blockade - CVS

- Arteriolar and venous tone are determined to a large extent by receptors on vascular smooth muscle
- **Reduction in Blood Pressure:** Blockade of $\alpha-1$ (also $\alpha-2$) receptor causes – pooling of blood in capacitance vessels – reduced venous return and Cardiac output – fall in mean BP

- **Postural Reflex is interfered** – dizziness and Syncope on standing
  - **Reason:** Normally 700 ml of blood is pooled to legs when a person stands up, and therefore syncope should occur. But do not occur in case of normal person because of Baroreceptor reflex which stimulates VMC and sympathetic system is activated. Contraction of veins occur via $\alpha-1$ receptor. Blockade of such receptor may therefore may lead to Postural hypotension
Effects of alpha Blockade - Others

- Reflex tachycardia due to fall in BP and increased NA release due to presynaptic alpha-2 blockade
- Nasal stuffiness and Miosis
- Increased Intestinal Motility - diarrhoea
- Reduced GFR: Sodium retention and increase in blood volume – also reflex renin release
- Tone of the Bladder trigone, sphincter and prostate is maintained by α1A sympathetic
- Blockade produces increased urine flow
- Inhibition of Ejaculation – due to inhibition of contraction of vas deferens and others
Individual Agents - Phenoxybenzamine

- Non specific, long acting irreversible alpha antagonist
- **MOA:** Spontaneously cyclizes in the body to give ethyleniminium intermediate – forms a strong covalent bond with α receptors – blockade of alpha receptor (lasts for 3–4 days)
  - Also blockade of 5-HT, histaminergic and cholinergic receptors
- **Clinically:**
  - Postural hypotension: Venodilatation>arteriolar
  - In recumbent position, however:
    - Blood flow to many organ increased due to reduction in peripheral resistance and increased venous return
    - Shifts blood from pulmonary to systemic circulation
    - Shifts blood from extravascular to vascular compartment
  - CNS stimulation – nausea, vomiting on IV injection but oral doses cause depression, tiredness and lethargy
Phenoxybenzamine

- **Pharmacokinetics:**
  - Erratic oral absorption and painful on IM or SC injections
  - Most of the administered drug excretes in urine in 24 Hrs
  - Small amount may remain in tissue bound covalently - leading to accumulation in adipose tissue

- **ADRs:** Postural hypotension, nasal stuffiness, miosis and inhibition of ejaculation

- **Uses:**
  - Phechromocytoma, Secondary shock and Peripheral vascular disease (Raynaud's disease)

- **Preparation and dosage:**
  - 20-60 mg orally
  - 1 mg/kg IV infusion for 1 Hr.
Phentolamine

- Non specific, short acting **reversible alpha antagonist**
- Potent competitive antagonist at both 1 and 2 receptors
- Quick acting (in minutes)
- **Reduction in Peripheral Resistance** - blocking both $\alpha$-1 and $\alpha$-2 receptors - causes NA release and venodilatation more than arteriolar
- **Cardiac stimulation:**
  - Enhanced NA release due to alpha-2 blockade
  - Inhibits serotonin release – muscarinic agonist (?)
- **Uses:** Pheochromocytoma, clonidine withdrawal, cheese reaction and in extravasations of NA and Adr injection
- **Dose:** 5 mg IV injection as and when needed
Prazosin

- Highly selective alpha-1 blocker (1:1000)
- Non-specific blockade of all subtypes - $\alpha_{1A}$, $\alpha_{1B}$ and $\alpha_{1D}$
- Blockade of sympathetic vasoconstriction - fall in BP
- NA is not released as $\alpha$-2 is not blocked (only mild tachycardia)
- Dilates arterioles more than veins – Postural hypotension is less – only 1st dose effect (dizziness and fainting)
- Also inhibits PDE – rise in smooth muscle cAMP - vasodilatation
- **Kinetics:** effective orally (70%), metabolized in liver and half life is 6-8 Hrs
- **Uses:**
  - Hypertension
  - Raynaud`s disease
  - BHP
- **Dose:** start with 0.5 mg bed time and then 1-4 mg tds.
Other alpha Blockers

Terazosin:
- Similar to Prazosin but better bioavailability (90%)
- Duration of action is longer – 24 Hrs
- Use: Preferred in BHP – single dose and apoptosis, also in hypertension
- Similar is Doxazosin

Tamsulosin:
- Uroselective (vasicoselective) - $\alpha_{1A}$ and $\alpha_{1D}$ but not $\alpha_{1B}$
- No change in BP and HR at therapeutic doses and Postural hypotension
- Preferred drug in BHP
- Only once dosing regime (MR caps)
- ADRs: Retrograde ejaculation and dizziness
## Comparison of alpha blockers

<table>
<thead>
<tr>
<th>Antagonists</th>
<th>Receptor affinity</th>
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<tbody>
<tr>
<td>Prazosin, terazosin, doxazosin</td>
<td>$\alpha_1 \gg \alpha_2$</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>$\alpha_1 &gt; \alpha_2$</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>$\alpha_1 = \alpha_2$</td>
</tr>
<tr>
<td>Rauwolscine, yohimbine, tolazoline</td>
<td>$\alpha_2 \gg \alpha_1$</td>
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Uses of α-blockers

**Pheochromocytoma:**
- Tumor of medullary cells of Adrenals
- VMA and normetanephrine estimation is diagnostic
- **Phentolamine test:** Injection of 5 mg IV over 1 minute (recumbent)
  - 35 mm (Systolic) and 25 mm (Diastolic) of Hg
- **Treatment:**
  - Surgery
  - Phenoxybenzamine in preoperatively and intra-operative because:
    - To Normalize blood volume: Excess CA shifts blood from vascular to extra vascular
    - To prevent outpouring of CA during surgery
    - To prevent unwanted hypotension due to dilatation of blood vessels following removal of tumor

(Previously - **Clonidine suppression test** – Measurement of plasma CA levels)
Uses of α-blockers – contd.

Hypertension:
- Not useful except Prazosin due to Compensated cardiac stimulation
- Postural hypotension, Impotence, nasal blockage etc.
- Phentolamine and Phenoxybenzamine – in clonidine withdrawal and cheese reaction

BHP:
- **Static component:** Size of prostate (5-alpha reductase)
- **Dynamic component:** Tone of Prostate and bladder neck (alpha-1 mediated)
- Converts testosterone to active dihydrotestosterone
- Effects of α blocking – relaxation of neck and prostate structures – reduction in obstruction
- 5-α reductase inhibitors like Finesteride decreases size of the prostate – better voiding
- α blockers – 2 weeks and 5-alpha reductase inhibitors – 6 months
- Remember – BHP is a progressive disease
Other uses of α-blockers

- Secondary Shock – Phenoxybenzamine
- Peripheral vascular disease – beneficial in Raynaud`s disease
- Congestive Heart Failure – short term
- Papaverine/Phentolamine induced penile erection (PIPE) for impotence
Beta blockers are prescription medications used to treat many different conditions, such as high blood pressure (hypertension) or irregular heart rhythms (arrhythmias).

There are numerous different beta blockers available, and there are several important differences among the various beta blockers.
Beta Blockers By Type

- Usually, beta blockers are categorized in a few different ways.

- Some are "cardioselective" (meaning they are more likely to affect the heart and blood vessels rather than other parts of the body), some have "intrinsic sympathomimetic activity" (slightly stimulate beta receptors while also blocking them), and some are alpha blockers as well as beta blockers.

- Some beta blockers fall into more than one category.
Cardioselective beta blockers

- Acebutolol
- Atenolol
- Betaxolol
- Bisoprolol
- Esmolol
- Nebivolol
- Metoprolol
Beta blockers with intrinsic sympathomimetic activity (ISA)

- Acebutolol
- Carteolol
- Penbutolol
- Pindolol
Beta blockers + alpha-blockade

- CARVEDILOL
- LABETALOL
Beta blockers that are non-selective, do not have ISA, and do not block alpha receptors

- Levobunolol
- Metipranolol
- Nadolol
- Propranolol
- Sotalol
- Timolol
Sotalol is unique among beta blockers in that it also blocks potassium channels in the heart.
Drugs which inhibit beta adrenergic receptors are called beta-blocking agents and also beta-blockers.

They inhibit competitively the beta effects of endogenous catecholamines.
To understand the consequences of inhibition of beta receptors, it is necessary to keep in mind the effects of stimulation of beta receptors.
The stimulation of the postsynaptic beta-1 receptors induces:

- cardiac inotropic, chronotropic, dromotropic and bathmotropic positive effects with increase of cardiac output and oxygen requirement.

- increase of renin secretion.
The stimulation of the postsynaptic beta-2 receptors induces:

- vasodilation, bronchodilatation, uterine relaxation, metabolic effects, cardiac inotropic and chronotropic positive effects but less than those which result from beta-1 stimulation.

- The stimulation of presynaptic beta-2 receptors increases noradrenaline release.
The inhibition of beta adrenergic receptors elicits a decrease or a suppression of the effects of endogenous catecholamines.

The effects are more important when endogenous stimulation is there.

Inhibition of beta receptors has beneficial and adverse effects.
Common effects

- The effects of beta-blockers are primarily cardiovascular.

- They slow heart rate by decreasing the slope of slow diastolic depolarization and constitute group II of antiarrhythmic drugs.

- They decrease heart oxygen requirement, which explains their use in the preventive treatment of angina pectoris.
They decrease, after a latency period, pathological arterial hypertension, by complex mechanisms, decrease of cardiac output, inhibition of renin secretion, and perhaps inhibition of the sympathetic tone by a central effect.
• But they are not true hypotensive agents because they do not lower, at therapeutic doses, normal arterial pressure.

• Beta-blockers lower intraocular pressure by decreasing aqueous humor secretion.
Particular effects

- Some beta-blockers have a slight beta-mimetic activity, called intrinsic sympathomimetic activity or ISA, whose consequence is that a low beta stimulation persists.

- They have a high affinity for beta receptors but no or only a low capacity to activate these receptors.
Being bound to beta receptors, they prevent endogenous catecholamines from inducing beta effects and are thus true beta-blockers.
Beta-blockers are classified according their selective inhibition of beta-1 and/or beta-2 receptors.

Some beta-blockers inhibit at the same time beta-1 and beta-2 receptors, others inhibit only beta-1 receptors.

The latter are known as cardio-selective.

It did not appear interesting in therapeutics to selectively inhibit beta-2 receptors.
In addition to their beta-blocking activity, some beta-blockers like propranolol and acebutolol, have a membrane-stabilizing effect which reduces transmembrane ion exchanges.

This activity, sometimes called local anesthetic or antiarrhythmic effect, results from a decrease of the rate of depolarization by sodium entry.
Labetolol and carvedilol have an alpha-1-blocking effect, celiprolol a beta-2-agonist effect.

Propranolol inhibits the transport of iodine in the thyroid follicle.

Carvedilol would have, at least in vitro, antioxidant properties.

Nebivolol has a NO-mimetic vasodilatator effect.
Therapeutic uses

Cardiovascular uses

- **Angina pectoris**: in prevention of attacks

- **Tachycardia of various origins** including those of hyperthyroidism, in particular the of grave's disease where one uses especially propranolol

- **Arterial hypertension**

- **Myocardial infarction**,

- **Unstable angina**
- **Congestive heart failure**, an apparent paradoxical indication.

- Actually, there is in patients with congestive heart failure a sympathetic overstimulation with an increase of plasma noradrenaline concentration and a decrease of beta receptors reactivity.

- Inhibition of beta receptors can, by withdrawing the heart from the sympathetic overstimulation, improve its activity.
Starting treatment of congestive heart failure by beta-blockers requires a narrow monitoring.

The three beta-blockers having shown efficacy in this therapeutic use are bisoprolol, metoprolol and carvedilol.

It is possible that beta-blockers having alpha-1 antagonist effect like carvedilol, are more appropriate in this indication.
Other therapeutic uses

- Prevention of primary and secondary digestive bleeding in portal hypertension by rupture of esophageal varices; propranolol is usually used.
Treatment of migraine, tremor, transitory somatic symptoms of anxiety, alcohol addiction in which there appears a beta overstimulation.

In this case propranolol is usually prescribed.

Treatment of glaucoma by ophthalmic solutions, but they can diffuse into the general circulation and give adverse effects.
Generally dosage of beta-blockers must be gradually increased at the beginning of the treatment and gradually decreased at cessation with monitoring and rest.
Beta-blockers are presented in the form of tablets or of capsules, some of them in injectable form are intended for treatment of acute disorders of heart rhythm and acute phase of myocardial infarction.
- Beta-blockers, not cardioselective, without Intrinsic sympathomimetic activity are propranolol, nadolol, sotalol, tertatolol, timolol, labetolol, carvedilol
Beta-blockers not cardioselective, with ASI. Oxyprenolol; carteolol and pindolol
Beta1-blockers, cardioselective, without A.S.I. atenolol; betaxolol, bisoprolol, metoprolol, esmolol and nebivolol
Bêta1-blockers, cardioselective, with A.S.I. Acebutolol, Celiprolol
Beta-blockers combined with a diuretic.

Many beta-blockers are combined under proprietary names with a diuretic such as hydrochlorothiazide, chortalidone, clopamide, amiloride.
For treatment of glaucoma
Beta-blockers in ophthalmic solutions are used in treatment of glaucoma.

Beta-blockers presented in ophthalmic formulations are betaxolol, befunolol, carteolol, metipranolol, timolol and levobunolol.
Adverse effects

- Aggravation of congestive heart failure.

- Congestive heart failure is both an indication and a contraindication to the use of beta-blockers.
In any case, starting a beta-blocking treatment cannot be done without a rigorous analysis of the state of the patient and necessitates a close monitoring.
- Aggravation of bradyarrythmia; bradycardia, atrioventricular blocks are contraindications to their prescription.

- Coldness of the extremities, possible aggravation of arteritis, especially with nonselective beta-blockers but sometimes also with beta-1 selective.
A gravitation of asthmatic disease, especially with nonselective beta-blockers - but also sometimes with beta-1selective blockers.
Metabolic disorders

• Increase in triglycerides

• Increase in cholesterol and the VLDL (very low density lipoproteins); hypoglycemia in diabetics

• Raised risk of developing a type II diabetes after antihypertensive treatment during several years by beta-blockers.
In overdoses, accidental or voluntary, beta-blockers cause hypotension, bradycardia, heart rhythm disorders and shock.
Therapeutic uses of beta blockers
Used for HYPERTENSION

- Drugs (atenolol, propranolol, metoprolol, timolol)

- Effect > reduced cardiac output, reduced renin secretion
Angina pectoris

- Drugs: propranolol, nadolol

- Effects: -ve chron: and -ve ionot: effect
Arrhythmia prophylaxis after MI

- Propranolol, metoprolol, timolol

- Effects......reduced automaticity of all cardiac pacemakers
Supraventricular tachycardias

- Propranolol, esmolol, acebutolol

- Effects.....slowed AV conduction velocity
Hepertropic cardiomyopathy

- Propranolol

- Effects.....slowed rate of cardiac contraction

- Migraine

- Propranolol
Thyroid storm, thyrotoxicosis

- Propranolol
  - Effects: Reduced cardiac rate & arrhythmogenesis

Glaucoma

- Timolol
  - Effects: reduced secretion of aqueous humor