

INDIRECT-ACTING ADRENERGIC AGONISTS

- I. Amphetamine
- II. Tyramine
- III. Cocaine

Amphetamine

Methylphenidate, Dextroamphetamine

CNS stimulation

- Enhance Dopamine and NE release

Peripheral Stimulation

- Enhance NE release, increase BP

Therapeutic uses

- ADHD, “ student abuse”
- Narcolepsy
- Appetite control

Anorexia, Insomnia, nervousness, fever,
CVS (palpitation, hypertension), C/I in glaucoma, HTN, CVD,
and MAOI users

Tyramine

- Clinically inuseful CNS stimulant, *tyramine can enter the nerve terminal and* displace stored norepinephrine
- Fermented foods, such as aged cheese
- It is oxidized by MAO in the gastrointestinal tract
- Serious HTN if co-administered with MAOI

Cocaine

- Blocks the Na⁺/K⁺-activated ATPase (required for cellular uptake of norepinephrine)
- Causes NE accumulation in the synapse thus inducing sympathetic activity

MIXED-ACTION ADRENERGIC AGONISTS

I. Ephedrine and pseudoephedrine

- plant alkaloids that are now made synthetically

- MOA :

1. Release stored norepinephrine from nerve endings

2. Directly stimulate both α and β receptors

- ❖ Not catecholamines i.e not COMT or MAO substrate (long duration)
- ❖ Readily absorbed and reach CNS
- ❖ Ephedrine : vasoconstriction & Bronchodilatation

- ❖ Both cause insomnia , hyperactivity, tremors

Ephedrine

- More CNS actions
- Previously used in asthma
- Cause mild CNS stimulation
- Improves athlete performance
- Banned by FDA due CVS issues
- Excreted unchanged in Urine

Pseudoephedrine

- Less CNS actions
- Undergoes extensive first pass effect
- Used as local nasal decongestant
- Illegally converted to methamphetamine (restriction on Pseudoephedrin products)

TISSUE	RECEPTOR TYPE	ACTION	OPPOSING ACTIONS
Heart			
• Sinus and AV	β_1	↑ Automaticity	Cholinergic receptors
• Conduction pathway	β_1	↑ Conduction velocity, automaticity	Cholinergic receptors
• Myofibrils	β_1	↑ Contractility, automaticity	
Vascular smooth muscle	β_2	Vasodilation	α -Adrenergic receptors
Bronchial smooth muscle	β_2	Bronchodilation	Cholinergic receptors

Kidneys	β_1	↑ Renin release	α_1 -Adrenergic receptors
Liver	β_2, α_1	↑ Glycogenolysis and gluconeogenesis	—
Adipose tissue	β_3	↑ Lipolysis	α_2 -Adrenergic receptors
Skeletal muscle	β_2	↑ Increased contractility ↑ Potassium uptake; glycogenolysis ↑ Dilates arteries to skeletal muscle Tremor	—
Eye-ciliary muscle	β_2	Relaxation	Cholinergic receptors

GI tract	β_2	↓ Motility	Cholinergic receptors
Gall bladder	β_2	Relaxation	Cholinergic receptors
Urinary bladder detrusor muscle	β_2	Relaxation	Cholinergic receptors
Uterus	β_2	Relaxation	Oxytocin

Summing up Adrenergic Agonists

CATECHOLAMINES :

<i>Epinephrine</i>	α_1, α_2 β_1, β_2	Acute asthma Anaphylactic shock In local anesthetics to increase duration of action
<i>Norepinephrine</i>	α_1, α_2 β_1	Treatment of shock
<i>Isoproterenol</i>	β_1, β_2	As a cardiac stimulant
<i>Dopamine</i>	Dopaminergic α_1, β_1	Treatment of shock Treatment of congestive heart failure Raise blood pressure
<i>Dobutamine</i>	β_1	Treatment of acute heart failure

NONCATECHOLAMINES

<i>Oxymetazoline</i>	α_1	As a nasal decongestant
<i>Phenylephrine</i>	α_1	As a nasal decongestant Raise blood pressure Treatment of paroxysmal supraventricular tachycardia
<i>Methoxamine</i>	α_1	Treatment of supraventricular tachycardia
<i>Clonidine</i>	α_2	Treatment of hypertension
<i>Albuterol</i> <i>Terbutaline</i>	β_2	Treatment of bronchospasm (short acting)
<i>Salmeterol</i> <i>Formoterol</i>	β_2	Treatment of bronchospasm (long acting)
<i>Amphetamine</i>	$\alpha, \beta, \text{CNS}$	As a CNS stimulant in treatment of children with attention deficit syndrome, narcolepsy, and for appetite control
<i>Ephedrine</i> <i>Pseudoephedrine</i>	$\alpha, \beta, \text{CNS}$	As a nasal decongestant Raise blood pressure

ADRENERGIC ANTAGONISTS

- Blockers or sympatholytic agents
- Bind reversibly or irreversibly with receptors
- Many play important roles in medicine
- Essential in HTN management

α -ADRENERGIC BLOCKING AGENTS

I. Phenoxybenzamine

II. Phentolamine

III. Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin

IV. Yohimbine

Phenoxybenzamine

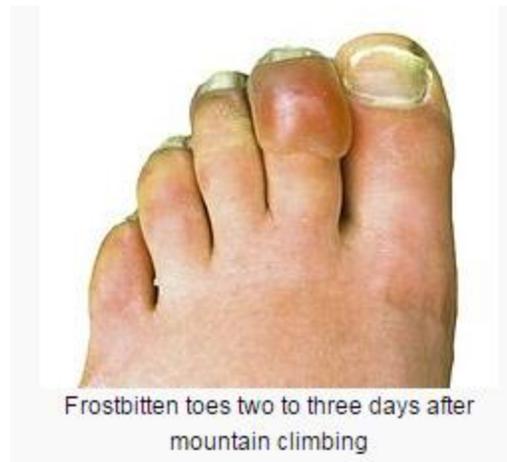
- Nonselective antagonist linking covalently to both α_1 - and α_2 -receptors
- A Noncompetitive , Irreversible Antagonist.
- How its action can be terminated?
- 24 hours duration
- After injection, few hrs to block the receptors.
- Not used in CVS system due to reflex tachycardia (α_1) and higher myocardial contractility due to increase NE release upon α_2 blockage

Phenoxybenzamine

- Pheochromocytoma treatment prior to surgery to preclude HTN crisis.
- Other possible indications :
 - ✓ Raynaud disease
 - ✓ Frostbite

Adverse Effects :

- postural hypotension,
- nasal congestion,
- nausea, and vomiting.
- It may inhibit ejaculation
- It also may induce reflex tachycardia



Phentolamine

- Competitive block of α_1 and α_2 receptors.
- Drug's action lasts for approximately 4 hours after a single administration
- As phenoxybenzamine, phentolamine causes postural hypotension
- Blocking α_2 leads to reflex tachycardia

phentolamine

- C/I with coronary artery disease
- Used in HTN crisis induced by tyramine

Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin

- **Selective competitive blockers of the α_1 receptor.**
- Useful in HTN treatment
- Postural hypotension
- All are inactivated by metabolism via renal system,
- however Doxazosin appears in feces

Cardiovascular effects

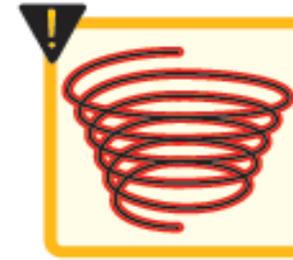
- Reduces PR and lowers BP by relaxing arterial & venous smooth muscles
- Minimal effect on CO, Renal BF .
- Better than phenoxybenzamine and Phentolamine for HTN management.
- **Mainly First dose orthostatic hypotension and syncope**
- Improve lipid & glucose metabolism

Benign Prostate Hyperplasia

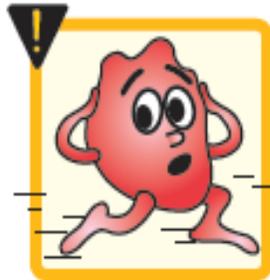
- Blockade of the α receptors decreases tone in the smooth muscle of the bladder neck and prostate and improves urine flow.
- ***Tamsulosin*** is an inhibitor (with some selectivity) of the α_{1A} receptors found on the smooth muscle of the prostate. This selectivity accounts for *tamsulosin's* *relatively* minimal effect on blood pressure, though dizziness (orthostasis) may rarely occur



Orthostatic hypotension



Vertigo



Tachycardia



Sexual dysfunction

- Newer agents are more selective with less s/e
- Doxazocin retains Na^+ and so its given with a diuretic
- For Ejaculation to occur, the smooth muscles in the ejaculatory duct must contract properly and this may be inhibited with this class (non selectives)
- Alpha antagonist use in HTN is now limited due to the emergence of better classes.

Yohimbine

- Selective competitive α_2 blocker
- Found in the bark of Yohimbine tree
- *Yohimbine works at the level of the CNS to increase sympathetic outflow to the periphery.*
- CNS and cardiovascular stimulant
- May be used as a sexual stimulant

