

Adrenergic Drugs

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Sympathomimetics (Adrenergic Agonists)

- Agents that **mimic actions of sympathetic system & stimulate adrenergic receptors (adrenoceptors)**
- Adrenergic neurons release **norepinephrine** as **primary neurotransmitter**

Classification of Sympathomimetics

➤ Direct-acting:

- **Selective:** salbutamol (B2), dobutamine (B1)
- **Non-selective:** adrenaline, noradrenaline (B & alpha receptors)

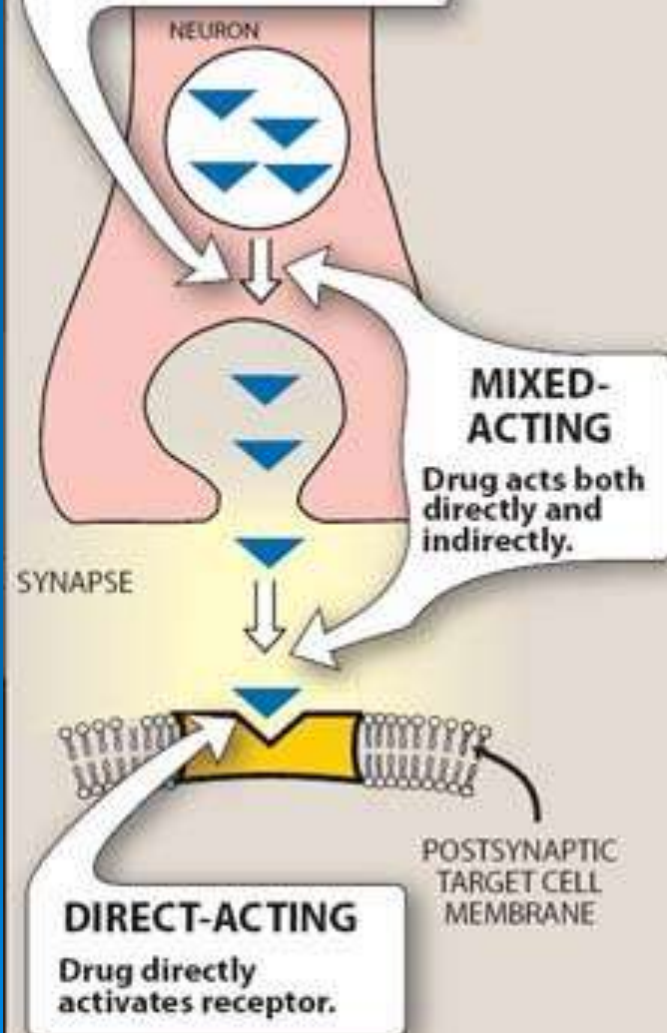
➤ Indirect-acting

- **Releasing agents** (amphetamine)
- **Uptake inhibitors** (cocaine, tricyclic antidepressants TCAs)
- **MAO Inhibitors**

➤ Mixed-acting (ephedrine, pseudoephedrine)

INDIRECT-ACTING

Drug enhances release of *norepinephrine* from vesicles.



MIXED-ACTING

Drug acts both directly and indirectly.

DIRECT-ACTING

Drug directly activates receptor.

POSTSYNAPTIC
TARGET CELL
MEMBRANE

Actions of sympathomimetics

- These are mediated through stimulation of alpha, beta & dopaminergic adrenoceptors

Sympathomimetics

They are also classified into:

- **Catecholamines:** (adrenaline, NA, dopamine, dobutamine, isoprenaline)
- **Non-catecholamines:**
(synthetic alpha-agonists & beta-agonists, e.g. phenylephrine, ephedrine, amphetamine)

PK of Sympathomimetics

➤ Catecholamines

- Parenteral
- Rapid onset of action, brief duration of action (have short $t_{1/2}$)
- Enzymatic metabolism by **MAO & COMT**
- Poor penetration into CNS

PK of Sympathomimetics

➤ Non-catecholamines

- Oral & parenteral
- Slower onset & longer duration of action
- Less enzymatic degradation
- More central effects (CNS effects)

Locations & Functions of adrenoceptors

- α -adrenoceptors: $\alpha 1$ & $\alpha 2$
- β -adrenoceptors: 2 subtypes of β -receptors
- Dopamine receptors: 4 subtypes

α 1-Adrenoceptors

- Vascular smooth M Vasoconstriction
- Radial M. of iris Mydriasis
- Bladder sphincter Contraction
- Intestine sphincter Contraction
- Male sex organs Ejaculation
- Inhibits entry of K into cells Hyperkalemia
- **Increase peripheral vascular resistance (PVR)**

α 2-adrenoceptors

- **Presynaptic** **Inhibits NA release**

Alpha-stimulants

- **Pressor agents:**
 - **Phenylephrine**
- **Mucosal decongestants:**
 - **Pseudoephedrine, Oxymetazoline**
- **Alpha 2-agonists:**
 - **Clonidine & alpha-methyldopa**

Alpha-stimulants

1- Pressor agents

- These are **non-catecholamines** that **increase peripheral vascular resistance (PVR)** & arterial blood pressure (**both SBP & DBP**)
- They **reduce renal blood flow (RBF)** & **splanchnic blood flow** due to **α_1 -vasoconstriction**

Phenylephrine

- Is **a direct acting**, synthetic adrenergic drug
- It has predominantly direct **α 1-agonist effect**, a **vasoconstrictor** & It is used as:
 - **Pressor agent**
 - **Nasal decongestant agent (vasoconstriction)**
 - **Mydriatic agent** (ophthalmic solutions)
 - **Vasoconstrictor agent** with local anesthetics (LA)

2. Mucosal decongestants: Pseudoephedrine, Oxymetazoline



- Oxymetazoline (**Otrivin**)
- Useful in **allergic rhinitis, common cold & sinusitis**
- **Oxymetazoline** is used in **Ophthalmic drops** for relief of **redness of eye** associated with swimming, colds or contact lens



2. Mucosal decongestants: Pseudoephedrine, Oxymetazoline

➤ Avoid:

- Prolonged use (rebound congestion)
- In hypertensive patients
- Children below 2 years of age

Alpha 2-agonists (Clonidine & methyldopa)

- **Centrally acting antihypertensive drugs: clonidine & methyldopa (Aldomet)**
- These act centrally to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery
- **Methyldopa** is used in hypertension during pregnancy
- They are **rarely used** because of risk of **rebound hypertension** on withdrawal of therapy

Beta-adrenoceptors (receptors)

Two subgroups β_1, β_2

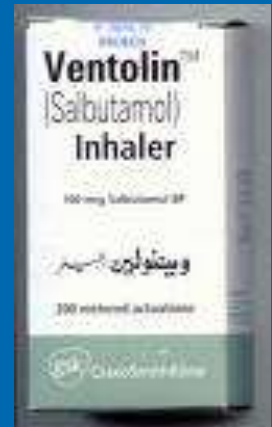
β_1 -adrenoceptors:

- **Heart** Increase HR, contractility & conductivity
- **Kidneys** Increase renin release

β_2 -adrenoceptors

- Bronchi Bronchodilatation
- Bladder wall Relaxation
- Skeletal M. arterioles Vasodilatation
- Glycogenolysis Increase blood glucose
- Gluconeogenesis Increase blood glucose
- Uterus Relaxation
- Enhances entry of K into cells Hypokalemia

β -Stimulants



1. Selective β_2 agonists:
Salbutamol (Albuterol) (Ventolin)
 - non-catecholamine
 - can be given by inhalation, orally & injection
 - Short acting bronchodilator
 - Its $t_{1/2}$ is about **4 hours**
 - Has a rapid onset of action (**acute asthmatic attacks**)

1. Selective β_2 agonists:

It is used in treatment of:

- **Acute bronchial asthma attacks**
- **Premature labour** or threatened abortion
- **Adverse effects:**

**Tremor, tachycardia & hypokalemia,
hyperglycemia**

Salmeterol & Formoterol



- is a **long acting bronchodilator** similar to salbutamol with **longer t_{1/2} (12 hr)**
- **Have a delay onset of action**
- It is useful in **prophylaxis of bronchial asthma**
- **Not useful for acute attacks**
- Not recommended as monotherapy & highly efficacious when combine with **corticosteroid**

2. Selective β_1 -agonist



Dobutamine

- Is a synthetic, direct acting catecholamine
- Inotropic sympathomimetic
- is used in congestive heart failure (CHF) to increase cardiac output
- Inotropic support after cardiac surgery
- Septic and cardiogenic shock

3. Non-selective β -stimulants:

Isoprenaline (Isoproterenol)

- A synthetic, direct acting drug
- It is a catecholamine with non-selective β_1 & β_2 agonistic activities
- It increases SBP & HR (β_1 effect) & decreases DBP (β_2 effect)
- It is rarely used to increase heart rate in heart block & to stimulate heart in cardiac arrest

Mixed Alpha & Beta agonists

Adrenaline (Epinephrine)

- It is an **endogenous catecholamine** synthesized in **adrenal medulla** & certain areas in brain
- **Commonly used therapy (drug of choice in emergency situations)**

Pharmacodynamic effects

➤ On blood vessels:

Response differs according to site of vessels:

- **Skin, mucous membrane & viscera arterioles** contain α_1 receptors & show vasoconstriction
- **Skeletal muscle vessels** contain mainly β_2 -receptors that show vasodilatation

Pharmacodynamic effects

- **Veins** contain $\alpha 1$ vasoconstrictors
- **Heart** shows **+ve inotropic**
+ve chronotropic effects

Effect on blood pressure:

- Small doses of adrenaline given by Sc or i.m will **increase SBP** (β_1 effect on heart) & **decrease DBP** (β_2 vasodilatation of skeletal BV) (**β effect predominate**)
- Giving adrenaline in large doses or by IV administration will **increase both SBP & DBP** (predominant **α_1 effect**)

- **Iris (mydriasis), bronchi (bronchodilatation)**
- **Sphincters of gut & bladder show contraction**, while walls of gut & bladder show relaxation
- **Metabolic effects: adrenaline increases blood glucose**

Adrenaline (Epinephrine)

Pharmacokinetics:

- ❑ Has rapid onset & brief duration of action
- ❑ **Is given Iv, Sc, by inhalation or topically to the eye**

Therapeutic uses

- **Cardiac arrest** (cardiopulmonary resuscitation-CPR)
- **Severe allergic reactions** (anaphylactic shock & angioedema):
 - Physiological antagonist to histamine & stabilizer of mast cells
- **Vasoconstrictor with LA**
- **Chronic open angle glaucoma (topically):**
vasoconstriction; reduces aqueous humor production & IOP

Adverse effects

- **CNS disturbances:** Headache, tremor, anxiety
- **High doses may increase BP, precipitate cerebral haemorrhage, cardiac arrhythmias**

Noradrenaline (Norepinephrine)

- It has **alpha agonist**, **β_1 -agonist** & **weak β_2 agonist** effects
- It increases both **SBP & DBP** (**potent α_1 effect**)
- It is **mainly used to treat shock** as a **vasoconstrictor**

Dopamine

- It is an **alpha, beta & dopaminergic** agonist
- **Increases renal blood flow** due to **D1 vasodilatory** effect on renal circulation
- **At low dose**, activates B1 receptors on heart, **increases cardiac output, heart rate & BP**
- **At very high doses, activates alpha receptors**, causes **vasoconstriction**
- Is the drug of choice for **shock (cardiogenic & septic)** and is given by **continuous infusion to improve renal blood flow**

Indirect-acting sympathomimetics



Amphetamines

- Are important because can be **misused as a central psychostimulants** that **improve mood & alertness**
- Acts by **releasing endogenous NA** from adrenergic neurons after being taken up into neurons

Amphetamines

- Its effects include increase **alertness & improved mood & decreased fatigability**
- It has also **central anorectic effects (depress appetite)** due to its action in hypothalamic feeding center

Amphetamines

- **Paradoxically**, it produces **sedation in children**
- **Peripheral** effects include **increase in BP & arrhythmias**
- It produces **emotional dependence**

Therapeutic uses of amphetamines

- **Narcolepsy** (excessive abnormal sleep in adults- daytime)
- **Attention deficit hyperkinetic disorder (ADHD) in children** (abnormal pathological hyperactivity):
amphetamines improve attention, reduce hyperkinesia)

Adverse effects

- **CNS:** insomnia, irritability, dizziness, tremor
- **CVS:** Palpitations, cardiac arrhythmias, HTN, angina pain
- **Emotional dependence**
- **Psychosis** (Schizophrenia-like with hallucinations & delusions)
- **Anorexia**

Direct & indirect sympathomimetics

Ephedrine

- **Mixed-action drugs induce release of NA from pre-synaptic terminals and they activate adrenergic receptor on postsynaptic membrane**
- **Non-catecholamine**

Ephedrine

- It is **non-selective agonist**, **stimulate both alpha & beta receptors** & its effects are **similar to that of adrenaline**
- **Ephedrine** raises systolic & diastolic blood pressure by **vasoconstriction** & cardiac stimulation
- It causes bronchodilation
- Is give **orally**

Therapeutic uses

- **Bronchial asthma**
- **Mydriatic agent & nasal mucosal decongestant**
- **Pressor agent in chronic orthostatic hypotension**
- **Heart block to increase heart rate**