



Alpha Adrenergic Agonists and Beta-2 Agonists

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Alpha Adrenergic Agonists

- Selective Alpha-1 Agonists.

Phenylephrine

Methoxamine

Metaraminol

Mephentermine

- Selective Alpha-2 Agonists.

Clonidine

α -methyldopa

Guanfacine, Guanabenz

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Alpha Agonists – Nasal Decongestants

- Ephedrine
- Phenylephrine
- Xylometazoline
- Oxymetazoline
- Naphazoline
- Tetrahydrazoline

Beta-2 Adrenergic Agonists

- Salbutamol – W.H.O, E.D. No.22.2 as Antioxytocic or Tocolytic and 25.1 as Antiasthmatic.
- Terbutaline . Reproterol
- Salmeterol . Oxiprenaline
- Fenoterol . Isoxsuprine
- Rimiterol . Ritodrine
- Bitolterol
- Isoetharine

Molecular Basis of Adrenergic Receptor Functions

Gq protein mediated effects produced by occupation of α_1 receptor by agonist leads to **activation** of phospholipase C (PLC) and increased formation of Inositol triphosphate (IP₃) and Diacylglycerol (DAG)

This increases release of Ca²⁺ from intracellular stores and produces responses:-

Contraction of vascular smooth muscle.

Contraction of non-vascular smooth muscle except **intestine**.

Increased rate & force of contraction of myocardium.

Glycogenolysis in liver.

Molecular Basis of Adrenergic Receptor Functions

Gi protein mediated effects produced by occupation of α_2 receptor by agonist leads to **inhibition** of adenylyl cyclase decreasing formation of cAMP. This decreases formation and activity of cellular proteins producing **inhibitory** responses:-

Inhibition of NA release from presynaptic adrenergic nerve ending and gluconeogenesis.

Inhibition of insulin release from pancreatic β cells.

Inhibition of aggregation of platelets.

Molecular Basis of Adrenergic Receptor Functions

β_2 receptor occupation by agonist produces Gs mediated effects leading to **stimulation** of adenylyl cyclase and increased formation of cAMP.

This increases activity of cellular protein kinases and activation of voltage sensitive Ca^{2+} channels in cell membrane and produces Ca^{2+} influx

Vascular & non-vascular smooth muscle **relaxation**.

Liver glycogenolysis and gluconeogenesis.

Skeletal muscle – Glycogenolysis & uptake of K^+ .

Stimulation of NA release from presynaptic adrenergic nerve ending.

Phenylephrine

Selective, synthetic and direct α_1 –agonist.

Administered parenterally & topically (eye, nose)

Long duration of action.

Resistant to MAO and COMT.

Peripheral vasoconstriction leads to rise in BP.

Reflex bradycardia.

Produces mydriasis and nasal decongestion.

Phenylephrine

Used in hypovolaemic shock as pressor agent.

Sinusitis & Rhinitis as nasal decongestant.

Mydriatic in the form of eye drops and lowers intraocular pressure.

Does not cross BBB, so no CNS effects.

Actions qualitatively similar to noradrenaline.

Photosensitivity, conjunctival hyperemia and hypersensitivity.

Clinical Aspects of Adrenoceptor Functions of Agonists

- **α_1 adenoceptor effects**

- Eye -- Mydriasis.

- Arterioles -- Constriction.

- Uterus -- Contraction.

- Skin -- Sweat.

- Platelet -- Aggregation.

- Male ejaculation.

- Hyperkalaemia.

- Bladder Sphincter Contraction.

- **α_2 adrenoceptors on nerve endings mediate negative feedback which inhibits noradrenaline release.**

β_2 Adrenoceptor Effects

- Bronchi -- Relaxation.
- Arterioles -- Dilatation.
- Uterus -- Relaxation.
- Skeletal Muscle -- Tremor.
- Hypokalaemia.
- Hepatic Glycogenolysis.

EPHEDRINE

- Plant alkaloid, indirect sympathomimetic actions resembling adrenaline peripherally.
- Centrally – Increased alertness, anxiety, insomnia, tremor and nausea in adults. Sleepiness in children.
- Effects appear slowly but lasts longer ($t^{1/2}$ -4h)
- Tachyphylaxis on repeated dosing.
- Used as bronchodilator, mydriatic, in heart block, mucosal vasoconstriction & in myasthenia gravis.
- Pseudoephedrine is similar.
- Phenylpropanolamine(PPA) on prolonged administration to woman as anorectic causes pulmonary valve abnormality.

Mucosal Decongestants

- Nasal and bronchial decongestants are used in allergic rhinitis, colds, coughs and sinusitis as nasal drops.
- Sympathomimetic vasoconstrictors with α -effects are used.
- Mucosal ischaemic damage occurs if used excessively (more often than 3hrly) or for prolonged periods (>3weeks).
- Rebound congestion leads to overuse.
- Use ephedrine, phenylephrine, xylometazoline for only a few days since longer application reduces ciliary action.

Mucosal Decongestants Contd..

- Do not use Naphazoline and Adrenaline.
- Do not use mixtures of vasoconstrictor, antihistaminic, adrenal steroid & antibiotic.
- Oily drops & sprays may cause lipid pneumonia.
- They lead to failure of antihypertensive therapy.
- Fatal hypertensive crisis in patients on MAOIs.

α_2 Adrenoceptor Agonist - Clonidine

- Agonist to postsynaptic α_2 adrenoceptors in brain, stimulation suppresses sympathetic outflow and reduces blood pressure.
- High dose activates peripheral presynaptic autoreceptors on adrenergic nerve ending mediating negative feedback suppression of noradrenaline release.
- Overdose stimulates peripheral postsynaptic α_1 adrenoceptors & cause **hypertension** by vasoconstriction.
- Clonidine reduces blood pressure.

Clonidine Contd...

- Abrupt or gradual withdrawal causes **rebound hypertension**.
- Onset may be rapid (a few hours) or delayed for as long as 2 days and subsides over 2-3 days.
- Treatment is to reinstitute clonidine, i.m or treat for phaeochromocytoma.
- Never use Clonidine with β -adrenoceptor blockers.

Clonidine - ADRs

- Sedation, dry mouth.
- TCAs antagonise antihypertensive action & increase rebound hypertension of abrupt withdrawal.
- Low dose Clonidine (50-100µg/dl) is used in migraine prophylaxis, menopausal flushing and chorea.
- Moxonidine, Rilmenidine – Newer Imidazolines.

β_2 Adrenergic Agonists

- Short acting : Salbutamol, Metaproterenol, Terbutaline, pirbuterol.
- Selective for β_2 receptor subtype.
- Used for acute **inhalational treatment** of bronchospasm.
- Onset of action within 1 to 5 minutes.
- Bronchodilatation lasts for 2 to 6 hours.
- Duration of action longer on oral administration.
- Directly relax airway smooth muscle.
- Relieve dyspnea of asthmatic bronchoconstriction.

Long Acting β_2 Adrenergic Receptor Agonists

- **Salmeterol xinafoate** inhalation provides persistent bronchodilatation lasting over 12 hours.
- 10,000 times more lipophilic than salbutamol.
- Dissociation from receptor environment is slow.
- Used only for prophylaxis of bronchospasm
- **Bitolterol** – rapid onset of action, long duration, highly selective β_2 agonist used for acute treatment of bronchospasm. Biological action is due to active metabolite **colterol**.
- Fixed dose combination of Salmeterol with Fluticasone.
- Only higher doses cause increased heart rate & cardiac arrhythmias.

Uterine Relaxants

- Antioxytocics or tocolytic agents.
- β_2 agonists relax uterus.
- Used by i.v. infusion to inhibit premature labour.
- Isoxsuprine, Terbutaline, Ritodrine, Salbutamol.
- Tachycardia & hypotension occurs.
- Use minimum fluid volume using 5% dextrose as diluent
- Ritodrine 50 $\mu\text{g}/\text{min}$, increase by 50 $\mu\text{g}/\text{min}$ every 10 minutes until contractions stop or maternal heart rate is 140 beats/minute. Continue for 12-48 hours after contractions stop.



Thank You

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