



Adrenoceptor Agonists & Sympathomimetic Drugs

SOURCES:

- BERTRAM G. KATZUNG BASIC & CLINICAL PHARMACOLOGY 15TH EDITION
- GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 13TH EDITION.



Motto And Vision



To impart evidence based research oriented medical education

To provide best possible patient care

To inculcate the values of mutual respect and ethical practice of medicine

















- Differentiate between Catecholamine & Non-Catecholamine
- Classify sympathomimetic according to mechanism of action
- Discuss the pharmacological effects of Sympathomimetic
- Discuss clinical pharmacology of sympathomimetic



Sympathomimetics



- Adrenergic Agonists/Sympathomimetics
 - Catecholamines
 - Non Catecholamines
- Receptor Types
 - Alpha receptors
 - Beta receptors
 - Dopamine receptors





Chemistry

Benzene ring with difference in substitutions

- Mechanism Of Action.....
 - Direct acting
 - Indirect acting
 - Mixed acting



Classification Of Sympathomimetic (According to chemistry)



<u>Catecholamine</u>

- Epinephrine
- Nor-epinephrine
- Dopamine
- Isoproterenol

Non-catecholamine

- Phenylephrine
- Methoxamine
- Ephedrine
- Amphetamine



Main difference between Catecholamine and Non-Catecholamine is substitution of –OH group at 3rd and 4th position of benzene ring

Adrenergic Transmission



A REACT WAY

Core



Classification Of Adrenergic Agonists/ Sympathomimetic









Pharmacological Targeting Of Monoamine Transporters



Source: Bertram G. Katzung, Todd W. Vanderah:





Sympathomimetics. According TO MOA

- Direct acting sympathomimetic:
- Affinity(agonist) for one or more adrenergic receptors
- May have considerable selectivity or specificity
 - e.g Phenylephrine for α_1 , Terbutaline for β_2
- Act on several receptors
 - Epinephrine(α_1 , α_2 , β_1 , β_2 , β_3)
 - Norepinephrine($\alpha_1, \alpha_2, \beta_1$)







Indirect acting sympathomimetic

- By releasing or displacing NE from sympathetic nerve varicosities
- By blocking the transport of NE into sympathetic neuron(Cocaine)
- By blocking the metabolizing enzyme
 - Monoamine oxidase(MAO)(Pargyline)
 - Catechol-o-methyl transferase(COMT)(Entacapone)

Mixed acting sympathomimetic

Ephedrine



Sympathomimetic



- Benzene ring
- Ethylamine side chain
- Substitutions can be made on
 - Benzene ring
 - Terminal amino acid
 - α or β carbons of the ethylamino chain
 - Substitutions by –OH groups at 3 & 4 positions

CATECHOLAMINES







Core



Receptor Types





Beta receptors

Dopamine receptors





MOLECULAR PHARMACOLOGY OF α1 RECEPTOR(MOA)









MOLECULAR PHARMACOLOGY OF α_2 , β RECEPTORS(MOA)





Endogenous Catecholamine

- Epinephrine
- Norepinephrine
- Dopamine









Epinephrine: Pharmacological Actions

- Pharmacokinetics
- Effects....Alpha 1 receptor activation
- Effects....Alpha 2 receptor activation
- Effects....Beta receptor activation
- EffectsDopamine receptors





Epinephrine: Pharmacological Actions

1. Effects on Cardiovascular system:

- Net effect on CVS depends on
 - α and β receptors stimulation
 - Compensatory baroreceptor reflex mechanism
 - Cardiac effects
 - Vascular effects
 - On blood pressure
 - On ECG





EPINEPHRINE: PHARMACOLOGICAL ACTIONS



- 2. On GIT
- 3. On Genitourinary
- 4. Bronchial Smooth Muscles
- 5. On Eye
- 6. Metabolic Effects
- 7.Effect On Sweat Glands
- 8. Anti Allergic Effect
- 9. On CNS

EFFECTS ON SKELETAL MUSCLES

EPI does not directly excite *skeletal muscle,* it facilitates neuromuscular transmission, particularly that following prolonged rapid stimulation of motor nerves



ANTERIOR CHAMBER OF EYE







EPINEPHRINE



ADVERSE EFFECTS

- Restlessness, Throbbing headache, Tremor & palpitations
- Cerebral haemorrhage(Due to sharp rise in BP)
- Ventricular arrhythmias
- Precipitation of Angina in pts. with coronary artery disease

<u>CONTRAINDICATIONS:</u>

- In pts taking non selective β receptor antagonists
- In hypertensive, hyperthyroid & angina patients
- Pheocromocytoma







THERAPEUTIC USES

- Anaphylaxis
- To prolong the effects of local anaesthetic agent
- To restore cardiac rhythm in patients with cardiac arrest
- Topical Hemostatic agent on bleeding surfaces like mouth or bleeding peptic ulcers during endoscopy



NOREPINEPHRINE



- Nor epinephrine(Levarterenol, nor adrenaline)
- Differs from Epinephrine by lacking methyl substitution in the amino group
- A major neurotransmitter on mammalian post ganglionic Sympathetic fibres
- 10-20% secreted from adrenal medulla
- Act on both α & β receptors with affinity

 $\alpha_1 = \alpha_2, \beta_1 >> \beta_2$

- PHARMACOKINETICS: Absorption, Fate & Excretion
- Effects:
- On CVS







- Immediate metabolic precursor of Epinephrine & Norepinephrine
- <u>Central neurotransmitter</u>: Important in movement regulation, reward stimulus with addiction, target for antipsychotic drugs
- <u>In periphery</u>: Synthesized by epithelial cells of proximal tubule(Local diuretic a& natriuretic effects)
- Substrate for both MAO & COMT
- Receptors(D_1 , D_2 , D_3 , D_4 , D_5 , β , α)
- Affinity (D1=D2>>β>>α)



DOPAMINE PHARMACOLGICAL ACTIONS



- At lower concentration, only dopamine receptors are stimulated
- At moderate levels beta receptors are stimulated
- At higher concentrations, alpha receptors are stimulated





ISOPROTERENOL

- Non-selective Catecholamine
- Readily absorbed when given parenterally
- Metabolized in liver by COMT
- Duration of action longer than epinephrine & NE
- Affinity for receptors: $\beta_1 = \beta_2 >>> \alpha$
- Effects on CVS







EFFECTS OF I/V INFUSION OF NOREPINEPHRIN EPINEPHRINE OR ISOPROTERENOL







ISOPROTERENOL



- ADVERSE EFFECTS:
- Palpitations, tachycardia, headache
- Cardiac ischemia, Arrythmia
- THERAPEUTIC USES:
- Stimulate heart rate in heart block
- Bradycardia associated with insertion of artificial cardiac pacemaker or with ventricular arrhythmias(Torsades de pointes)



DOBUTAMINE



- Semi synthetic Catecholamine
- PHARMACOKINETIC:
 - Can not be given orally
 - Duration of action shorter
 - $T_{1/2} = 2$ minutes
- Receptor affinity= $\beta_1 > \beta_2 > > > \alpha$
- More inotropic than chronotropic effect
- Adverse effect: Increase BP, ventricular ectopic activity

THERAPEUTIC USES:

- Short term treatment of cardiac de compensation(cardiac surgery, CCF, MI)
- Stress angiography



ADRENERGIC AGONISTS



• α SELECTIVE ADRENERGIC AGONISTS

<u>α AGONISTS</u>

- Xylometazoline, Oxymetazoline(Both used as nasal decongestants)
- <u>α1 AGONISTS</u>
 - Phenylephrine, Midodrine, Methoxamine
- <u>α2 AGONISTS</u>
 - Clonidine, Methyldopa, Guanfacine, Guanabenz
 - Newer agonists (Moxonidine, Dexmeditomedine, Tizanidine)
- <u>β₂ SELECTIVE ADRENERGIC AGONISTS</u>
- SHORT ACTING
 - Metaproterenol, Albuterol (Salbutamol),
- LONG ACTING:
 - Formoterol, Carmoterol, Indacterol, Ritodrine

NON-CATECHOLAMINE





NON-CATECHOLAMINE



- <u>Chemistry</u>: Absence of catechol nucleus
- <u>ROA</u>: Oral , Parenteral
- Duration of action: Longer
- Can cross BBB
- Excretion: Mainly Renal



AMPHETAMINE

NH₂ CH₃

- Indirect acting synthetic non catecholamine
- Included in "Dope test" for athletes
- Schedule II drug under federal regulation(Drugs which have potential for physical & psychological dependence But have medicinal value as well)
- Pharmacokinetics
- Mechanism of action
- Pharmacological actions
- Adverse effects
- Therapeutic Uses







- First orally active sympathomimetic
- Source: Plant Alkaloid(Ephedra, Ma huang)
- Non catecholamine

PHARMACOKINETICS:

- ROA: Oral, Parenteral, High bioavailability, Can cross BBB
- Excretion: Renal, Weak base(accelerated with acidification of urine)
- t1/2:3-6 hours
- Mechanism of action, Pharmacological action, adverse effects, Therapeutic uses
- Pseudoephedrine



NON -CATCHOLAMINE



- PHENYLEPHRINE: Potent α1 stimulant
- Used as mydriatic agent and nasal decongestant

- <u>ALBUTEROL:</u> (salbutamol, Ventolin) Potent β2 stimulant
- Used as a bronchodilator

- <u>COCAINE:</u> Catecholamine reuptake inhibitor
- Drug of abuse, Local anaesthetic effect



THERAPEUTIC CLASSIFICATION OF SYMPATHOMIMETIC



DRUGS USED IN CARDIOVASCULAR <u>CONDITIONS:</u>

- Dopamine
- Dobutamine
- Epinephrine

BRONCHODILATORS:

- Albuterol
- Salmeterol
- Formoterol

- CNS STIMULANT:
 - Amphetamine
 - Modafinil

OPHTHALMIC USES:

- Phenylephrine(MYDRIATIC)
- Apraclonidine & Brimonidine GLAUCOMA)

• MUSCLE RELAXANT:

• Tizanidine



THERAPEUTIC CLASSIFICATION OF SYMPATHOMIMETIC



• NASAL DECONGESTANTS:

- Oxymetazoline
- Xylometazoline

GENITOURINARY APPLICATION:

Ritodrine, Terbutaline..TOCOLYSIS

• <u>ANAPHYLAXIS:</u>

Epinephrine

• LOCAL VASOCONSTRICTION:

Epinephrine(Epistaxis, Mucosal bleeding surfaces)





- Epinephrine is contraindicated in pts taking non selective β receptor antagonists
- Reason of using Epinephrine with local anaesthetic agents
- Hypovolemia should be corrected prior to Dopamine administration
- Dopamine dose much reduced in Pts. Who are taking MAO inhibitors
- Careful adjustment of Dopamine dose in pts taking tricyclic anti depressants



Spiral

Research, Ethics, AI, Family Medicine



- Role of family Physician in use of Epi injections, Counselling about the adverse effects and appropriate method of use
- Injudicious use of Non catecholamine
- Drugs included in doping







- Groom MJ, Cortese S. Current pharmacological treatments for ADHD. New Discoveries in the Behavioral Neuroscience of Attention-Deficit Hyperactivity Disorder. 2022 Apr 30:19-50.
- Tachmazidis I, Chen T, Adamou M, Antoniou G. A hybrid AI approach for supporting clinical diagnosis of attention deficit hyperactivity disorder (ADHD) in adults. Health Information Science and Systems. 2020 Nov 20;9(1):1.
- Watson CJ, Stone GL, Overbeek DL, Chiba T, Burns MM. Performance-enhancing drugs and the Olympics. Journal of Internal Medicine. 2022 Feb;291(2):181-96.