SYMPATHETIC (ADRENERGIC) NERVOUS SYSTEM

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SYMPATHETIC (ADRENERGIC) NERVOUS SYSTEM

CLASSIFICATION

(I) **SYMPATHOMIMETICS** (Adrenergic Agonists)

(II) **SYMPATHOLYTICS** **(Adrenergic Antagonists)**

SYNTHESIS OF CATECHOLAMINES

Phenylalanine

Hydroxylation ↓ *Phenylalanine Hydroxylase*

Tyrosine

Hydroxylation ↓ *Tyrosine Hydroxylase*

DOPA (Di Hydroxy Phenylalanine)

Decarboxylation ↓ *Dopa Decarboxylase*

Dopamine

Hydroxylation ↓ *Dopamine β- Hydroxylase*

Noradrenaline

Methylation ↓ *N – Methyl Transferase*

Adrenaline

FATE OF CATECHOLAMINES

Catecholamines Effects are Terminated Either By :-

- **By saturation**
- **25 % Destruction by COMT and MAO enzymes**

  - 25% of NA metabolised outside the cell by COMT (Catechol - O – Methyl Transferase Enzyme)

  - Small portion of NA metabolised Intracellularly by MAO - A (Mono Amine Oxidase - A Enzyme in Liver & Kidney)

- **75 % By Uptake 1 (NA) & Uptake 2 (ADR) mechanisms**

SYMPATHETIC (ADRENERGIC) NERVOUS SYSTEM

ADRENOCEPTORS

- **ALPHA-ADRENOCEPTORS :-**

  Agonists :- α1 and its subtypes α1A, α1B, α1D
  α2 and its subtypes α2A, α2B, α2C .

  Antagonists :- α1 and α2

- **BETA-ADRENOCEPTORS :-**

  Agonists :- β1, β2, β3.

  Antagonists :- β1 and β2

* **DOPAMINE RECEPTORS :-**

  Agonists :- Dopamine (DA 1), Dopamine (DA 2)

  Antagonists :- DA 1, DA 2.

SYMPATHOMIMETICS (ADRENERGIC AGONISTS)

DIRECT – ACTING

Epinephrine (Adrenaline), Norepinephrine (Noradrenaline), Isoproterenol (Isoprenaline), Dopamine, Dobutamine, Phenylephrine, Terbutaline, Salmeterol, Albuterol, Clonidine, Methoxamine, Tamsulosin.

INDIRECT – ACTING

Amphetamine and Tyramine

DIRECT AND INDIRECT (MIXED) ACTING

Ephedrine

ADRENERGIC AGONISTS

CATECHOLAMINES

- Contain Catechol Nucleus
- Rapid onset of action
- Brief duration of action
- Not administered orally
- Do not penetrate Blood Brain Barrier (BBB).

Eg. Adrenaline, Noradrenaline

Dopamine, Isoprenaline, Dobutamine

NON-CATECHOLAMINES

* No Catechol Nucleus
* Moderate onset of action
* Longer duration of action
* Administered orally
* Crosses BBB.

Eg. Ephedrine, Amphetamine.
Metaraminol,

Phenylephrine
Mephentermine,

Methoxamine.

SYMPATHOMIMETICS AGENTS(Adrenoceptor Agonists)

Sympathomimetics

Alpha – Adrenoceptor Agonists

- *Alpha-1 Agonists*
  Eg. – Phenylephrine
  - Methoxamine
  Metaraminol, Mephenteramine, Oxymetazoline
- *Alpha-2 Agonists*
  Eg .- Clonidine
  - Alpha Methyl Dopa
- *Alpha + Beta Agonist*
  Eg. - Adrenaline (Epinephrine)

Beta – Adrenoceptor Agonists

* *Beta-1 Agonists*
  Eg.- Dobutamine
* *Beta-2 Agonists*
  Eg. -Terbutaline
  - Salbutamol

ADRENERGIC RECEPTORS

Receptor Type		Result of Stimulation
Alpha – 1 (Postsynaptic)		
Blood Vessels	…..	Contraction, ↑ P.R., ↑ B.P.
Radial Muscles of Iris	…..	Mydriasis (Dilatation) of Pupils
Pilomotor Muscles	…..	Hair Erection
Heart	…..	Increase Force of Contraction (+ ve Ionotropic Effect)
Bladder	-----	↑ Closure of Internal Sphincter of bladder
Alpha -- 2 (Presynaptic)		
Adrenergic N. Terminals	-----	Inhibits transmission release
Liver	-----	Inhibits Insulin release
Alpha -- 2 (Postsynaptic)		
Postsynaptic CNS	-----	Multiple action
Platelets	------	Aggregation

ADRENERGIC RECEPTORS

Receptor Type		Result of Stimulation
Beta – 1		
Heart	…..	↑ Force of Contraction (+ ve Ionotropic effect) ↑ Heart Rates (+ ve Chronotropic effect)
Kidney	…..	Release Renin, Aldosterone
Beta – 2 (Postsynaptic)		
Respiratory tract	------	Bronchodilatation (Relaxation)
Uterus	------	Relaxation
Blood vessels	------	Vasodilatation (Relaxation), ↓ P.R.
Liver / Muscles	------	↑ Glycogenolysis , ↑ Glucagon release
Skeletal Muscles	------	Promotes K – Uptake
Beta -- 3		
Adipose (Fatty) Tissue	-----	Lipolysis

ADRENERGIC RECEPTORS

Receptor Type		Result of Stimulation
Dopamine (D-1)		
Smooth Muscles (Renal Blood Vessels)	-----	Dilate Renal Blood Vessels
Dopamine (D-2)		
Brain	------	Modulates Transmitter Release
Nerve Endings	-------	Modulates Transmitter Release

SPECIFIC AGONIST & ANTAGONIST OF ADRENERGIC RECEPTORS

Receptor Type & Subtypes	Agonist	Antagonist
1) Alpha – 1	- Phenylephrine	- Prazosin
2) Alpha – 2	- Clonidine - Alpha Methyl NE	- Yohimbine
3) Beta – (1 +2)	- Isoprenaline	- Propranolol
4) Beta – 1	- Dobutamine	- Atenolol - Metoprolol
5) Beta – 2	- Terbutaline - Salbutamol	- Butoxamine
6) Dopamine – 1	- Dopamine	---
7) Dopamine – 2	- Bromocriptine	- Metoclopramide

Mechanism of Action

- *Alpha-Adrenoceptor Stimulation :-*

Nor-Adrenaline

↓ Blocked by Alpha-
↓ blockers

Excitatory

E.g.* Vasoconstriction of Blood Vessels

* Dilatation of Pupils by contracting Radial Muscles.

Exception :-

* *Relaxation of G.I.T.*

Mechanism of Action

Postsynaptic Alpha-1 Adrenoceptor Activation (Excitatory)

↓

Stimulate G s – Protein

↓

Activates Phospholipase – C (PLC)

↓

Hydrolyses Membrane Bound Phospho-inositodes

↓

Generates Two Second Messengers (IP3 & DAG)

↓

↑ i Ca++

↓

Stimulatory effect (Vasoconstriction)

Mechanism of Action

Presynaptic Alpha – 2 Adrenoceptor Activation (Inhibitory)

↓

Stimulate G i – Protein

↓

Inhibits Adenyl Cyclase Enzyme

↓

Inhibits Intracellular cAMP levels

↓

↓ i Ca++

↓

Produces Inhibitory Effect

↓

Inhibits Nor-adrenaline Release (Vasodilatation)

Mechanism of Action

- *Beta-Adrenoceptor Stimulation* :-

Isoprenaline

↓ Blocked by Beta -
↓ blockers

Inhibitory

E.g.* Relaxation of Blood Vessels, Bronchial Smooth M.(B – 2)

Exception :-

* *Excitation of Heart - ↑ H.R.; ↑ Contraction (B – 1)*

Mechanism of Action

Activation of Beta - Adrenoceptors
(Excitatory / Inhibitory)

↓

Stimulate G s – Protein

↓

Activates Plasma Membrane Enzyme Adenyl Cyclase

↓

Increase Intracellular c AMP Levels

↓

Stimulates Protein Kinase

↓

Alter Cellular Functions

↓

Stimulatory Effect (β – 1 on Heart)

↓ **(or)**

Inhibitory Effect (β – 2 on Bronchial Smooth Muscles)

CLASSIFICATION OF SYMPATHOMIMETIC AGENTS

(I) BASED ON MECHANISM OF ACTION

(A) Direct Acting :

E.g. Adrenaline, Nor-adrenaline
Isoprenaline, Dopamine

(B) Indirectly Acting : (Releases NA)

E.g. Tyramine, Amphetamine,

(C) Direct + Indirectly Acting :

E.g. Ephedrine

CLASSIFICATION OF SYMPATHOMIMETIC AGENTS

(I) BASED ON RECEPTOR STIMULATION

(A) Alpha - Receptors :

E.g. Nor-adrenaline , Phenylephrine

(B) Beta – Receptors :

E.g. Isoprenaline, Isoxsuprine

(C) Alpha + Beta Receptors :

E.g. Adrenaline

CLINICAL CLASSIFICATION OF SYMPATHOMIMETIC AGENTS

(A) ***PRESSOR AGENTS (Vasoconstrictors)***:

E.g. , Nor-adrenaline , Phenylephrine, Mephentermine, Metaraminol.

(B) ***CARDIAC STIMULANTS (INOTROPIC):***

E.g. Adrenaline, Isoprenaline, Dobutamine

(C) ***BRONCHODILATORS*** :

E.g. Adrenaline, Salbutamol, Terbutaline

(D) ***NASAL DECONGESTANTS*** :

E.g. Xylometazoline, Phenylephrine, Ephedrine, Phenylpropranolamine, Pseudoephedrine.

CLINICAL CLASSIFICATION OF SYMPATHOMIMETIC AGENTS

(E) ***ANORECTIC AGENTS*** :

E.g. , Fenfluramine, Dexfluramine.

(F) *UTERINE RELAXANTS:*

E.g. Isoxsuprine, Salbutamol, Terbutaline, Ritodrine

(G) ***CNS STIMULANTS*** :

E.g. Amphetamine, Dexamphetamine, Ephedrine

THERAPEUTIC USES OF SYMPATHOMIMETIC AGENTS

(1) **Cardiogenic/Septic shock :** Dopamine, Dobutamine.

(2) **Hypotension/After Spinal Anaesthesia :** Mephentermine, Metaraminol.

(3) **Hypertension :** Clonidine

(4) **Cardiac Arryhthmias/Cardiac Arrest :** Intracardiac Adrenaline.

(5) **Heart Failure :** Dobutamine, Clonidine

(6) **Local Vasoconstrictor (vascular) Effects :**

Adrenaline -To limit Haemorrhage, improve visualization

Adrenaline +Lignocaine – Increase Anaesthesia duration

THERAPEUTIC USES OF SYMPATHOMIMETIC AGENTS

(7) **Bronchial Asthma :** Salbutamol, Terbutaline

(8) **Allergic Reactions :** Adrenaline.

(9) **Ophthalmic Uses :** Phenylephrine, Adrenaline

(10) **Narcolepsy :** Amphetamine.

(11) **Weight Reduction (Anti-obesity):** Amphetamine, Fenfluramine

(12)**Attention Deficit Hyperactivity Disorder in Children**

Dextroamphetamine.

ADVERSE EFFECTS OF SYMPATHOMIMETIC AGENTS

(1) **CVS :** ↑ B.P. → Cerebral Haemorrhage
→ Pulmonary Oedema
↑ C.O. → Myocardial Infarction
→ Angina Pectoris
- Tachycardia
- Ventricular Arrhythmias

(2) **CNS :** Fear, Anxiety, Throbbing Headache, Restlessness, Tremor.

(3) **Others :** * Gangrene of Toes/Fingers→ Dopamine
* Extravasation → Local Tissue Necrosis (NA)
* Tolerance, Mental Depression (Amphetamine)

THANK YOU