(Released 4m Post-ganglionic sym. neurons)

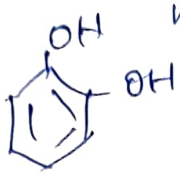
ADRENERGIC DRUGS

Sympathomimetics or Adrenergic Agonists

→ Contains ethylamine as side chain

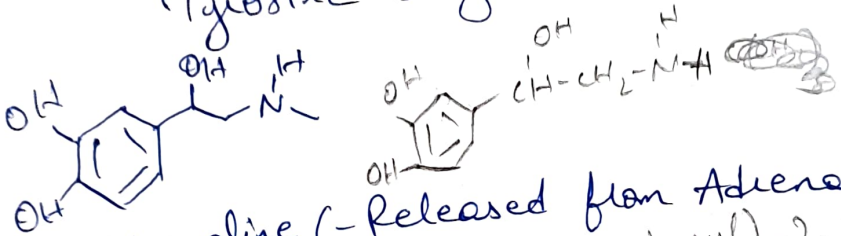
- Catecholamine - monoamine NT c catechol

Catechol – Benzene c 2 (OH) side groups next to each oth.



Catecholamines r drvd 4m a.a tyrosine

Tyrosine is synthesized 4m phenylalanine



Adrenaline (- Released from Adrenal medulla)

(R)-1-(3,4-dihydroxyphenyl)-2-methylaminoethanol

Sympathetic Stimulation in hypothalamus → Sympathetic drug is activated in Adrenal medulla

- Epinephrine
- Nor-Epinephrine

- Catecholamines
  - Endogenous (Already in the body)
    - Adrenaline
    - Nor-Adrenaline
    - Dopamine. (AND)
  - Exogenous (Taking 4m outside)
    - Dobutamine (β_1-selective)
    - Isoprenaline (IO) (β_1, β_2-selective)
- Non-catecholamine
  - Tyramine
  - Ephedrine
  - Amphetamine
  - Salbutamol (EATS)

Synthesis, Storage & Release of Catecholamine

Food intake → Phenylalaine → In liver → Converted to Tyrosine → Tyrosine moves to Adr. neurons → Tyrosine

Tyrosine → (Tyrosine hydroxylase (Rate limiting enzyme) ★) → L-Dopa (Levodopa)

(Inhibited by Metyrosine)

L-Dopa → (Dopa-de-carboxylase (DDC)) → Dopamine

(Inhibited by Carbidopa & Benserazide)

Dopamine → (should be entered to vesicles) moves to vesicles (In the vesicle, Dopamine β-hydroxylase converts Dopamine to Nor-Adrenaline)

(Reserpine (Anti-hypertensive action) inhibits the storage in vesicles) & tetrabenzene

(Disulfiram inhibits Dopamine β-hydroxylase)

Nor-Adrenaline (α & β - Receptors) (stored in vesicles)

Impulse → Depolarization → Ca^{+2} ruptures vesicles. NA is released

- Excess amt of NA not in the synapse gets metabolized by MOA - Mono Amino Oxidase (A, B)

COMT - Catechol - O Methyl Transferase.

- Some of the NA gets re-uptake in vesicle synapse.
- Release of NA → Inhibited by Guanethidin, Bretylium.
- Reuptake of NA → Inhibited by Cocaine, Tricyclic Anti-Depressant.

NA → Adrenaline by N-methyltransferase.

Steps → Syn of Catecholamines
Storage "
Release "
Re-uptake "
Metabolism "
Action on Adr. R

Adrenaline / Nor-Adrenaline —COMT & MAO→ Vanillyl mandelic Acid
Meta-nephrine
Nor metanephrine

- Adr. R — memb bound G-protein coupled Recep
NA acts on < α R / β R

~~Synthesis of AMP~~

- Indirect sympathomimetic
depletion of NA
- Tyramine, Ephedrine
(By Exchange diffusion)

MOA enz - Inhibited by Nialamide
Tranylcypromine.

MOA-A - Inhibited by Moclobemide (Potentiation of NA & Tyramine)
MOA-B - Inhibited by Selegiline.
(Potention of DA in brain)

COMT Inhibition - Tolcapone
Entapone.

Adrenergic Receptors

(No glycogenesis takes place only glucose prodn

α & β

α_1 (Post-junctional)
- Prosthetic Urethra

α_2 (Pre and post junctional)
(Auto Receptor)

β_1
- Heart
- JG cells (release renin)

β_2
- Bronchus
- GIT
- Uterus
- Liver
- Skeletal muscle spindle
- Blood vessels

β_3
- Adipose tissue
- Coronary vessels
- Urinary bladder

α_1 (a) — Prosthetic
Urethra
Eye

α_{1b} — Blood vessels

α_2 — (Indirectly Inhibitory in nature) for NA.

(Pre-synaptic)
Acts like Brake to Sympathetic System

(Post-Synaptic)
B.V
Brain.

	α_1	α_2
location	post junctional of effector organs.	Pre-synaptic - on nerve ending Post-synaptic - pancreatic B-cells, B.V, Platelets
Functions	Urinary Bladder (Contraction) B.V: Vasoconstriction Gland: secr^n Anal sphincter: Contraction Liver: - Glycogenolysis	Pre-synaptic: Inhibition of transmitter release. ↓ central sympathetic flow Post-synaptic ↓ insulin release vaso constriction Platelet aggregation.
Selective agonist	Phenylephrine Methoxamine	Clonidine
Selective Antagonist	Prazosin	Yohimbin, Rauwolscine
Coupling protein	G_q	G_i / G_o
Effector Pathway	IP_3 / DAG increase Phospholipase A_2 ↑ & PG release	cAMP ↓ K^+ ch ↑ Ca^{++} ch ↓/↑ IP_3/DAG ↑

A —— C

α —— contraction

β —— Dilation (except β_1)

	β_1	β_2	β_3 (lipolysis)
location	Heart JG cells in Kidney (Renin release)	Bronchi B.V Uterus Liver GIT UT Eye	Adipose Tissue Detrusor muscle of bladder.
Selective agonist	Dobutamine	Salbutamol, Terbutaline	Mirabegron
Selective antagonist	Atenolol Metoprolol	α-methyl propranolol	
Relative potency	Adr > NA	Adr > NA	NA > Adr.

Pharmacological Action

α_1 : Eye - Mydriasis
Urinary Bladder - Trigone Contraction
BV - Vasoconstriction
Gland - Secretion.
Anal Sphincter - Contraction
Liver - Glycogenolysis

α_2 : Present in presynaptic R (mostly)

β_1 : Heart - Tachycardia — +ve Inotropic
+ve chronotropic
+ve Dromotropic

JG cells — Release Renin (stimulates BP)

β_2:

Bronchi - Bronchodilation
GIT - Dilation - Constipation
Bladder - Relax
Uterus - Relaxation (Tocolytic action)
Use to postpone delivery
Skeletal muscle (Tremors)
& Coronary artery muscle - Vasodilation
Liver - Glucose production.

β_3: Adipose Tissue - Lipolysis

Sympathomimetic / Adrenergic Drugs (Based on Receptor)

- Directly Acting
  - Selective
    - α_1 (Phenylephrine, Methoxamine)
    - α_2 - (Clonidine)
    - β_1 - Dobutamine
    - β_2 - Salbutamol, Terbutaline
  - Non-selective
    - α_1, α_2 (Oxymetazoline)
    - β_1, β_2 (Isoproterenol, Isoprenoline)
    - $\alpha_1, \alpha_2, \beta_1, \beta_2$ (Epinephrine)
- Mixed Action
  - Ephedrine ($\alpha_1, \alpha_2, \beta_1, \beta_2$) (Not metabolized by MAO, COMT)
- Indirect Acting
  - Uptake Inhibitor (Cocaine, Tricyclic Anti-Depressa
  - MAO Inhibitor
    - Nialamide, Trianyl cypromi
    - Moclobemide (MAO-A In
    - Selegiline (MAO-B I
  - COMT Inhibitor: Tolcapone, Entapone

NA - does not work on β_2 & β_3 (only $\alpha_1, \alpha_2, \beta_1$)

Based on Therapeutic Uses

→ Pressor Agents (Improves the pressures)

- NA
- Ephedrine
- Dopamine
- Phenylephrine
- Methoxamine } Vaso-pressers
- Mephetaramine
- Midodrine

→ CNS Stimulants

(AMD) Amphetamine
Nor-Amphetamine
Dexamphetamine
Methamphetamine
(MAD) Methylphenidate

→ Cardiac Stimulants (β_1)

- Adrenaline
- Isoprenaline (Prenalterol)
- Dobutamine

→ Nasal decongestants (α) (0.05-0.1%)

Oxymetazoline
Xylometazoline } α_1 → causes stinging sensation
Naphazoline
Phenylephrine (Mydriatic)
Pseudoephedrine

→ causes vasoconstriction in nasal mucosa

C.I! in Hypertension & those receiving MOA Inhibitors

→ Bronchodilators: (β_2)

- Salbutamol (Albuterol)
- Terbutaline
- Salmeterol
- Formoterol
- Bambuterol
- Isoprenaline (β_1 β_2)

→ Uterine Relaxants (β_2)

- Isoxsuprine
- Ritodrine
- Salbutamol
- Terbutaline.

→ Anorectics (Anorexia) ↓ the appetite

- Amphetamine
- Phenfluramine
- Sibutramine (APS)

→ Releasing Agents:- Amphetamine
Tyramine.

Exch. NA & A um neurons without Ca^{+2}

IV Infusion of Adrenaline

	Adr.	NA (have slightly action on heart & 2nd Brand musc.)	Isoprenaline
Heart rate	↑	↓	↑↑
Cardiac output	↑↑	-	↑↑
BP	↑↑	↑↑	↑
Bronchial muscle	↓↓	-	↓↓
Intestinal muscle	↓↓	↓	↓
Blood sugar	↑↑	↑	↑

Adrenaline;

Absorbed frm intestine but rapidly degraded MAO & COMT (+nt in ~~intestinal~~ intestinal wall & liver) - orally inactive.

↑ systolic BP
↓ diastolic BP

ABCDE##G
A - Anaphylactic shock
B - Bronchial Asthma
C - Cardiac resuscitation (↑ the cardiac function)
D - Duration of anaesthesia (Prolong)
E - Epistaxis (control)
G - Glaucoma.

Adr - $\alpha_1, \alpha_2, \beta_1, \beta_2$ & β_3 (wk)
NA - $\alpha_1, \alpha_2, \beta_1$
Isoprenaline - β_1, β_2 & β_3 (wk)
Dobutamine - selective β_1 agonist.

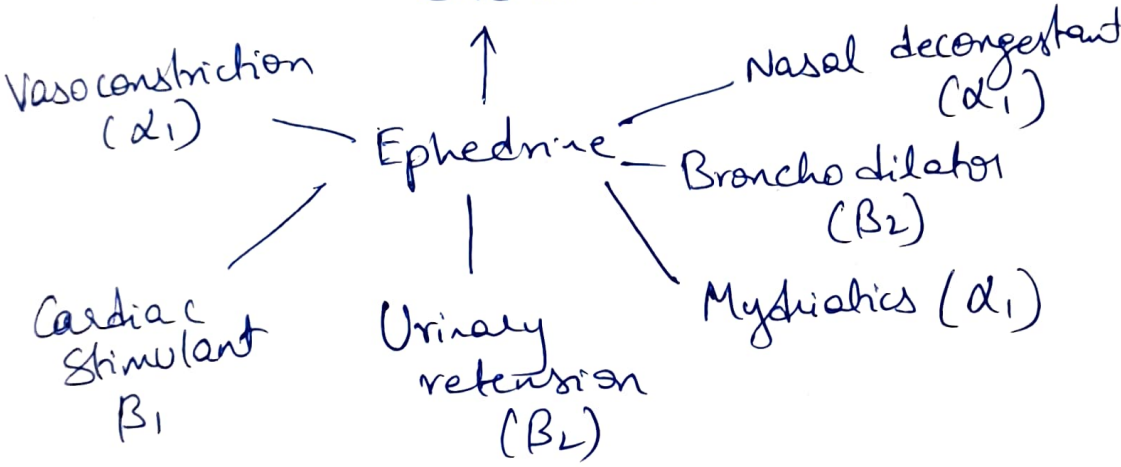
- Adr is C.I in hypertensive, hyperthyroid and Angina patient.

- After SC/IM → Restlessness, headache, tremor, anxiety, palpitation.

- Not with halothane (risk of arrhythmias)
  Not with β-blockers

→ IV Adr → ↑ Tachycardia, Angina, MI.
Cerebral ~~edema~~ haemorrhage.

Ephedrine: (Vasopressor in choice in pregnancy)



Amphetamine (Modafinil) - Releasing agent

- Highly lipid soluble, crosses BBB.
- Tachyphylaxis, ↑ B.P, arrhythmia causes.
- Amphetamine poisoning - make urine acidic by NH_4Cl.
- Dope test for athletes.
- Amphetamine inhibit neuronal uptake of Dopamine RRA.

Amphetamine gets intake through Nor Epinephrine Transporter. (NET)

Amphetamine uptakes → In Vesicles. Amp → (NA) (moves inside) goes out. → Through Nor-Epi. Transporter

Amphetamine → (Inside)
NE ← (outside)

Selective α_1 Receptor agonists

* Phenylephrine (α_1 & negligible β-action) - Para-OH group.
  - Vasoconstriction ↑ B.P
  - Nasal decongestant (Topical)
  - Mydriasis without cycloplegia

* Methoxamine (α_1 without β action)

Selective α_2 - Receptor agonists

Clonidine: Antihypertensive
↑ B.P (vasoconstriction)

α-methyl DOPA → α-methyl norepinephrine for essential hypertension

Tizanidine (fused thiadiazole ring) → In Diabetic Diarrhoea.
Prophylaxis of migraine, glaucoma
Analgesic
ADHD
Tourette syndrome, Withdrawal symptoms.

Dexmetto.
Dexmeditomidine — Sedative

Apraclonidine } Glaucoma
Bromonidine

Tizanidine — Muscle Relaxant.

Selective β_1 agonists

→ Dopamine :- (IV)
D_1 & D_2 - Dopaminergic
Weaker β_1
very weak α agonist.
In septic shock or cardigenic & acute heart failure
↑ BP & Urine outflow.

(-) enantiomer is 10 times less potent at β_1 & β_2 R

→ Dobutamine:
Drvd frm Dopamine but not D_1 & D_2 R agonist
- β_1 R agonist.
- Inotropic agent in M.I

→ Dopexamine:
β_1 & D_1 R
& NA inhibitory action

→ Selective β_2 agonist. (In Asthma)
Salbutamol, Terbutaline, Salmeterol, Formoterol, Metaproterenol.
Uterus (Relaxation)

Isoxsuprine :- (orally long acting β_2 R)
- Uterine relaxant
- dysmenorrhoea.

Ritodrine: (β_2 R)
Uterine Relaxant.
(for postpone delivery)

Anorectic Agents

↓ Appetite.

Appetite Stimulant – orexigenic

Classification

- NA Agents; (PPDM)
  - phentermine
  - Phenyl propolamine
  - Diethyl propion
  - Mazindol
- Serotonergic
  - fenfluramine
  - Dexfenfluramine

NA + Serotonergic agent → Sibutramine

Mazindol, Phentermine } Inhibits uptake of NA → Enhances NorAdr Transmission to Brain → ↓ Inhibit Hypothalamus → ↓ Feeding centre Inhibited → Supress appetite

Sibutramine → Inhibits NA & 5HT reuptake → ↑ Supress appetite