Autonomic Nervous System (ANS)

2- Norepinephrine (NE) (Levarterenol)

Nor adrenaline

- It is the chemical mediator liberated by postganglionic sympathetic N. ending & act directly on the effector cells.

- In therapeutic doses: **α** and similar **β**1 effect (on heart) but no **β**2

Action of Nor adrenaline (NA)

***C.V.S**:*

NA increase PR due to intensive vasoconstriction of most vascular bed

(including kidney via **α1**), which lead to increase both **Syst & Diast. BP**

(with increase mean BP). This lead to compensatory vagal reflex by stimulation to the baroreceptor reflex, which cause decrease contraction of heart & decrease HR (called **reflex bradycardia**).

Notes:

1- Due to powerful vasoconstrictor effect of NA:

a- Lead to reflex bradycardia.

b- NA not used as vasoconstrictor in LA solution.

2- The main function of NA appear to be maintenance of normal sympathetic tone and adjustment of circulatory dynamic.

3- Isoproterenol (Isoprenaline):

- Direct acting synthetic C.A.

- It is extremely potent β R agonist (β 1, β 2).

PK: Given sublingually, pranterally & as aerosol.

Uses: Usually to stimulate heart in emergency cases.

SE: as Adrenaline.

Action of Isoproterenol (Isoprenaline)

1- C.V.S: (Like Adrenaline): Lead to increase systolic BP & Slight decrease D BP- ?

2- Pulmonary: B2 :Rapid & profound bronchodilatation.

3- Other effects: β: increase Bl. sugar & increase lipolysis (not significant clinically).

4- Dopamine

--It is immediate metabolic precursor of N.A occurs naturally in C.N.S in basal ganglia (function as N.T) and in adrenal medulla.

- Dopamine activates:

1- **β1 Receptors** (and at higher dose activate also **a** R.),

2- **D1 & D2 R** occur in peripheral mesenteric & renal vascular bed lead to vasodilatation.

Actions of Dopamine

1- C.V.S: Dopamine lead to increase force & rate of contraction of heart (β1 effect).

2- Renal and visceral: Dilatation of renal & splanchnic arterioles (D1,D2 agonist effect), which lead to increase blood flow to kidney & other viscera.

Uses: Dopamine drug of choice (over Adre.) in shock as Adre. cause decrease renal blood supply & may cause renal shutdown.

Overdose: Nausea, hypertension, arrhythmia.

5- Fenoldopam

-**D1 Receptor agonist:** selectively cause peripheral arteriolar vasodilatation in vascular bed.

Uses: in severe hypertension (IV or continuous infusion).

SE: Decrease K, tachycardia, headache, flushing.

Adrenergic Agonists (Sympathomimitic)

I- Direct acting adrenergic agonists:

6- Phenylephrine

-- Direct acting synthetic, bind to α R

- (α 1 > α 2) lead to increase Systo. and Diast BP.

-- No effect on the heart, but it causes reflux bradycardia (if given parentrally).

- Not catecholamine, not metabolized by COMT

Uses of Phenylephrine

1- Eye drops: mydriasis

2- Decongestant on nasal M.M.

3- Used to increase BP and to terminate Supraventricular tachycardia (SVT) (because of the effect on vagus, so lead to reflex bradycardia).

S.E of Phenylephrine:

Large doses (overdose) lead to hypertension, headache, cardiac arrhythmia.

7- Methoxamine

- Direct acting **α1 agonist** as phenylephrine.

Uses:

1. Supraventricular tachycardia (SVT) (because of the effect on vagus that lead to reflex bradycardia).
2. Overcome hypotension during halothane anesthesia (as it does not tend to trigger arrhythmia).

S.E: Hypertension, headache, vomiting.

8- Salbutamol (Albuterol)(Ventolin)

- Selective **β**2 agonist, lead to bronchodilatation & few CV effect < Isoprenaline .
- It may produce tachycardia (common S.E).

Uses:

1- Bronchial Asthma (orally, inhalation, or IV in severe attacks).

2- Treatment of uterine contraction.

9-Terbutaline:

β2 agonist (selective): As Salbutamol (but less tachycardia).

10- Clonidine

Action:

- Centrally acting antihypertensive like **Methyldopa**.
- It is **α** 2 agonist (inhibit release of NA), so reduces the central adrenergic outflow and used in treatment of essential hypertension complicated by renal disease.

PK:

- Absorbed orally and excreted by kidney.
- Cause Na & water retention (so given with diuretics).

S.E of Clonidine

1. Sedation.
2. Drying of nasal mucosa.
3. Rebound hypertension when stopped suddenly (so not used now).

II- Indirect acting adrenergic agonists

1- Amphetamine:

Its importance because of use and misuse as CNS stimulant.

Action:

- Acts indirectly in that, following uptake into the sympathetic nerve ending, it displaces NA from storage sites in the synaptic vesicles
- so lead to increase release of NA (**α**1 R effect)

Uses of Amphetamine

1. Treatment of depression (psychomotor stimulant & increase mood).
2. Treatment of Hyperactivity in children.
3. Treatment of Narcolepsy (uncontrollable attacks of sleepiness).
4. Appetite control.

2- Tyramine

- Found in high conc. in fermentated food such as cheese, broad beans, yoghurts, yeast extract and wine.
- **Metabolized by MAO in liver.**

Action:

- This is indirectly acting amines, which causes release of NA from storage sites.

DI: MAO inhibitors, lead to increase level of tyramine in the systemic circulation (because tyramine metabolized by MAO in liver), this lead to hypertensive crises (which may lead even to death).

MAOI:

- Isocarboxazid
- Phenelzine
- Selegiline
- Tranylcypromine

III- Mixed action adrenergic agonists:

1- Ephedrine:

- Plant alkaloid, now made synthetically (drug).

Action:

- It has mixed action, not only stimulate the release of the stored NA but directly stimulate α & β receptor which lead to wide variety of adrenergic actions similar to that of Adre. but less potent.
- Not Catecholamine so not substrate for COMT and MAO so has long duration of action.

Uses of Ephedrine

1. Asthma (prevent attack, mild chronic asthma).
2. Myasthenia gravis: Ephedrine increase contractility particularly when used with anticholinesterase .
3. As nasal decongestant (nasal drops).
4. Increase athletic performance, decrease fatigue and prevent sleep.

PK:

- Excellent absorbed orally and penetrate CNS.

- Excreted unchanged in urine.

2- Metaraminol

- Mixed acting adrenergic drug similar to Ephedrine.
- Given parentrally as a single injection.

Uses:

1. Treatment of shock (when infusion of adrenaline or dopamine is not possible).
2. Treatment of acute hypotension.
3. Increase cardiac activity.

Toxicity of Sympathomimetic Drugs

SE of Sympathomimetic Drugs are extension of their effects on CVS & CNS mainly, include:

A- CVS Toxicity:

1. Increase BP (presser agents).
2. Cerebral hemorrhage.
3. Pulmonary Edema.
4. Cardiac work: may precipitation of severe Angina & MI.
5. **B**-agonist: It causes sinus tachycardia, and may be ventricular arrhythmia.

Note:

- caution is indicated in elderly patients or those with hypertension or coronary artery disease
- Extravasations into SC tissue of NA (when IV), which may lead to ischemia.
- Treated by α- antagonist.

B- CNS Toxicity

- Rarely observed with Catecholamines or a drug as Phenylephrine.
- **Amphetamine:** Restlessness, tremor, Insomnia & anxiety.
- At high dose, may cause paranoid state.

§ **Cocaine:** Precipitates convulsion, cerebral hemorrhage, arrhythmia or MI.

Adrenergic Blockers

Mechanism of action:

- Adrenergic antagonists act by binding to the adrenoceptor

- (reversibly or irreversibly)
- Preventing its activation by endogenous Catecholamines & blocking the usual receptor mediated intracellular effects.

Classification

I- α-Blockers: Doxazosin, Phenoxybenzamine, Phentolamine, Prazosin, Terazosin.

II- β-blockers: Propranolol, Timolol, Nadolol, Atenolol, Metoprolol, Esmolol, Pindolol, Acebutolol, Labetalol.

III- Drugs affecting N.T. uptake and release: Guanethidine, Reserpine, Cocaine.

IV- Centrally acting agents: Methyldopa, Clonidine.

α Adrenoceptor Antagonists (α Blockers)

Uses of α1 & α2 blocking agents:

1- Experimental exploration of ANS fX.

2- Limited uses in the clinical therapeutic

(only Pheochromocytoma & Primary HT).

3- Treatment of symptoms of prostatic hyperplasia (BPH).

Pharmacological actions of α-Blockers

I- CVS:

1- α-antagonists cause decrease PR& BP, which lead to Reflex tachycardia.

2- Postural hypotension due to antagonism of a1 in venous sm.m.

II- Other effects:

1- Minor effects: Miosis & nasal stuffiness.

2- Decrease resistance to the flow of urine (due to a blocked of the sm.m contraction of base of UB & prostate).

Specific α-Antagonists

1- Phenoxybenzamine:

- Irreversible blockade & non competitive so has long duration of action about 24 h.

- Non selective block **a1& a2.**

Contraindications: In patients with decrease coronary perfusion.

Uses of Phenoxybenzamine

1- Pheochromocytoma (prior or during surgery or inoperable cases).

2- Reynaud's diseases.

SE:

1- Postural hypotension.
2- Nasal stuffiness.
3- Nausea & vomiting.
4- Inhibit ejaculation.

2- Phentolamine:

- Imidazol derivative
- Potent competitive, reversible
- Non selective α1& α2 blocker.

Action:

Similar to Phenoxybenzamine but short duration of action (4h) (because it has reversible action).

PK:
- It has limited absorption after oral dose.

Uses

1. Hypertensive crises due to Pheochromocytoma.

2. Hypertensive crises associated with cheese reaction (which occur sometime between MAOI & food stuff containing the presser amine tyramine).

3. Treatment of male erectile function.

SE of Phentolamine: (due to cardiac stimulation)

a. Severe tachycardia.
b. Trigger of arrhythmia.
c. Postural hypotension.
d. Myocardial Ischemia.

3-Prazosin 4-Terazosin 5- Doxazosin

Action:

- Selective competitive antagonist of **α 1** receptors in arterioles & venous lead to decrease PR which lead to decrease venous return to heart (more effective in case of little cardiac work).
- They have similar actions, although Terazosin is longer acting (22h).

Uses: Prazosin, Terazosin, Doxazosin

1- Treatment of hypertension.

- Doxazosin approved for uses in hypertension.

2- BPH :

- Terazosin approved for male treatment of BPH.

SE: Prazosin, Terazosin, Doxazosin

1- 1st dose effect orthostatic hypotension.

(less with Doxazosin).

2- Reflex tachycardia (agent with α2 R Blocker).

3- Prazosin & Terazosin: dizziness, lack of energy, nasal decongested of headache, drowsiness.

4- Prazosin is frequently used with diuretic due to tendency to retain Na & fluid.

5- Male sexual function is not severely affected.

α 2 selective antagonist (Yohimbine)

- It has no established clinical role
- Theoretically it could be useful in autonomic insufficiency by promoting neurotransmitter release through blockade presynaptic **α**2 R.
- Yohimbine can abruptly (quickly) reverse the antihypertensive effects of an **α**2-adrenoceptor agonist such as clonidine which is potentially serious adverse drug interaction.

Newer α antagonists

a- Alfuzosin.

b- Tamsulosin. approved for the use in the treatment of BPH.

β- Adrenoceptor Antagonist drugs (β Blockers)

Classification:

I- Nonselective β -blockers: (act at both **β1** & **β2** R)

Propranolol, Timolol, Nadolol, Pindolol, Oxprenolol, Sotalol.

II- Selective β1 (cardioselective) β -blockers:

Atenolol, Metoprolol, Esmolol.

III- β -Antagonists with partial agonist activity:

Pindolol, Acebutolol.

IV- α & β blockers: Labetalol.

V- Nonselective β -antagonist with some α 1 blocker (Carvedilol, Medroxalol, Bucindolol)

VI- Selective β 2 blocker (Butoxamine)

Pharmacokinetics:

- Absorbed well after oral administration.
- Rapidly distributed with large volumes of distribution.

Propranolol and **Penbutolol** are lipophilic & so can cross B.B.B, **(Nadolol & Atenolol)** are water soluble.

- Most β-blockers have t ½ (3-10h), with exception of **Esmolol** (t ½ = 10 minute).

- Propranolol and **Metoprolol** are extensively metabolized in the liver, other less metabolized, while **Nadolol** is excreted unchanged in urine, and has longest t ½ of β-blockers.

Classes of β-blockers

I- Nonselective β -Blockers

Propranolol: prototype, nonselective β-blocker (β1 & β2).

Nadolol: very long duration of action, excreted unchanged by kidneys.

Timolol: Decrease IOP by reduce the production of aqueous humor in the eye & is used topically in chronic glaucoma (occasionally used for hypertension).

Pharmacological actions of β-blockers

C.V.S:

- -ve inotropic (decrease contraction)
- -ve chronotropic effects (decrease HR) lead to decrease cardiac output (CO).
- Hypotensive effect (decrease BP) due to decrease CO.

- β-blockers not cause postural hypotension (because α1 R remain intact).
- Peripheral vasoconstriction (by prevention of β2 mediated vasodilatation)
- Na & water retention (by decrease BP, so decrease renal perfusion, which lead to increase renin secretion) (β blockers often combine with diuretics) .
- Respiratory system: Bronchoconstriction.
- Eye: Decrease IOP by decrease production of aqueous humor by vasoconstriction of ciliary body blood vessels.

Metabolic Effect:

- Fasting hypoglycemia due to decrease glycogenolysis & decrease glucagon secretion.
- Delay recovery from hypoglycemia in insulin dependent DM (as glucose release from liver controlled by β 2 receptor).
- Attenuate normal physiological response to hypoglycemia in DM.
- Increase VLDL & decrease HDL cholesterol.(unfavorable in CVS risk)

Therapeutic uses β-blockers

- Hypertension.
- Angina pectoris (chronic & stable angina).
- Antiarrhythmic Prophylaxis after Myocardial infarction.
- Cardiac Arrhythmia.
- Anxiety state.
- Prophylaxis of Migraine (chronic).
- Hyperthyroidism.

- Glaucoma

Side effects of β-blockers (Propranolol)

- Fatigue & disturbance of sleep e.g. Night mares (more in lipophilic drugs **Propranolol**).
- Bronchoconstriction.
- Cold extremities due to peripheral vasoconstriction.
- Disturbance in metabolism
- Precipitation of cardiac failure in certain patients (those with impaired myocardial function)
- Arrhythmias: (if suddenly stopped due to up regulation of **β**R).
- B-blockers must be stopped gradually.
- Sexual impairment.

Drug interactions of β-blockers

(Propranolol)

- Drugs that decrease with metabolism of Propranolol such as **Cimetidine, Frusemide, Chlorpromazine** lead to increase its antihypertensive effect.
- Drugs that stimulate its metabolism such as **Barbiturates, Phenytoin and Rifampicin** lead to decrease effect of Propranolol.

Contraindications of β-blockers (Propranolol)

- Compensated heart failure (impaired myocardial function).
- Bronchospasm.
- Raynaud disease.
- DM.

II- Selective β1 antagonists Atenolol, Metoprolol, Esmolol

Clinical Uses:

- ✓ Hypertension and angina.
- ✓ Hypertensive patients with impaired pulmonary function and asthma.

- ✓ In patients need β -blocker with history of peripheral vascular disease.
- ✓ Diabetic hypertensive patients.
- ✓ **Betaxolol** used for topical eye drops in glaucoma.

III- Antagonist with partial agonist activity

Pindolol, Acebutolol, Oxprenolol

- These have intrinsic sympathomimetic activity (ISA), that is not pure blockers but have ability to weak β1 and β2 agonist activity .
- Minimize the disturbance of lipid and CHO metabolism occur with other β blockers

Clinical Uses:

1. Hypertension with moderate bradycardia.
2. Acebutolol and Pindolol used in D.M. with hypertension.

IV- **α & β-blocker (Labetalol)**

Action

reversible **B**&**a** blocker, so produce peripheral vasodilatation so decrease BP

Uses of Labetalol:

- It is useful in elderly or black hypertensive patients (with increase PR).
- **Labetalol** used as alternative to **Hydralazine** in pregnancy induced hypertension (P.I.H).

S.E of Labetalol: Orthostatic (postural) hypotension and dizziness.

V- Nonselective β-antagonist + some α1 bloc (Carvedilol, Medroxalol, Bucindolol)

- **Carvedilol**: reversible +concurrent **α1** blocking actions that produce peripheral vasodilatation, thereby reducing BP.
- This is in contrast with the other β-blockers (which produce peripheral vasoconstriction), and so therefore **Carvedilol** useful in treating hypertensive patients for whom increased peripheral vascular resistance undesirable.
- **Carvedilol** decreases lipid peroxidation and vascular wall thickening, this effects that have benefit in heart failure.

III-Drugs affecting N.T. uptake and release

(Adrenergic Neuron blocking Agents)

1. Reserpine
2. Inhibitors of Transmitter release Guanethidine
3. Cocaine

Reserpine: plant alkaloid.

Action:

- blocks the Mg/ATP-dependent transport of biogenic-amines (NA, dopamine) from the cytoplasm into storage vesicles in the adrenergic nerves of all body tissues.
- This lead to ultimate depletion of NA level in the adrenergic neuron which cause reduction in the sympathetic outflow to the B. vessels & so decrease BP.

Toxicity of Reserpine

- At low doses: causes little postural hypotension
- **Brain:** Sedation, lassitude, nightmares, sever mental depression (even in low doses 0.25 mg/d). Extrapyramidal effect resemble Parkinson's disease(dopamine depletion).
- **GIT:** Mild diarrhea, GIT cramps, gastric acid (avoid in PU).

2- Inhibitors of Transmitter release (Guanethidine), (Bethanidine & Deprisoquine) are similar.

Action: (Guanethidine)

- Transported across symp. neurons membrane by the same mechanism of NA & when it replaces NA, this will lead to gradual depletion of NA stores in nerve ending except those in CNS.

Uses:

- Moderate to severe hypertension (+ diuretic).
- Not often used today because:

I. *Its effect on BP is affected by postural changes.*

II. *Better drugs are now available.*

Toxicity (SE)

1. Symptomatic postural hypotension, hypotension following exercise.
2. Excessive dose cause decrease in B. flow to heart and brain even shock.
3. Delayed retrograde ejaculation.
4. Diarrhea (due to increase GIT motility).

Drug interaction:

- Phenylpropanolamine (in cold preparation) lead to Hypertension.
- **TCA:** Decrease antihypertensive effect of guanethidine (as TCA block uptake 1 of NA into the cytoplasm of the sympath nerve ending).

Cocaine

- It is unique among LA in having the ability to block the cellular uptake of NA across the cell membrane of adrenergic neuron so lead to increase NA accumulation in synaptic space sympathetic activity.

SE:

- Cocaine is a CNS stimulant & drug of abuse.
- Cocaine can produce hallucination, delusion, paranoia, motor activity & high doses causes tremor & convulsion followed by respiratory & vasomotor depression.
- Only LA that causes vasoconstriction. This effect is responsible for the necrosis & perforation of nasal septum occur with chronic inhalation of Cocaine powder.

Centrally acting Agents – IV: **Methyldopa (Aldomate):**

Actions:

- Acts centrally in the brain stem vasomotor centre in which methyldopa acts as a substrate for dopa- decarboxylase enzyme,lead to formation of a methyldopa, then formation of a methylnoradrenaline (false transmitter), which results in tonic stimulation of CNS α 2 receptor , which inhibit the sympathetic (act as **clonidine**).

PK of Methyldopa

- Absorbed readily from GIT & enter CNS.
- $t_{1/2}$ = 1.5h.
- Max. conc. Reached in about 3 h.
- It is excreted unchanged in the urine & some as metabolites.

Clinical Uses:

- Moderate to mild hypertension in conjunction with diuretic.
- Treatment of hypertension with pregnancy**.**

SE of Methyldopa (Aldomate)

- Drowsiness, sedation (nightmares, depression.
- Other involuntary movement, nausea, flatulence, constipation, scare or black tongue.

- Coomb's test positive, with occasionally anemia, leucopenia, thrombocytopenia & hepatitis.
- Gynecomastia & lactation occur due to interference with dopaminic suppression of prolactin secretion.
- Drug related SLE has been reported with use of methyldopa.

2- Clonidine

Action:

- Centrally acting antihypertensive like Methyldopa.
- Clonidine is **α2** agonist (inhibit release of NA), so reduces in the central adrenergic outflow
- Used in Essential hypertension complicated by renal disease.

S.E of Clonidine

1. Sedation.
2. Drying of nasal mucosa.
3. Rebound hypertension if withdrawn suddenly.
4. Absorbed orally and excreted by kidney.
5. Causes Na & water retention (so given with diuretics).