2nd pharmacology lecture (Adrenergic Agonist)

Objectives:

1. Be familiar to the sympathetic nervous system and its receptors (their locations and functions).
2. Memorize the drugs names, their uses, adverse effects and the receptors they work on.

NOTE: It's better to take a look to the physiology introduction in order to get a better understanding for this lecture

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THIS WORK QUOTED FORM 431 TEAM WORKS.

Physiological Introduction to the Sympathetic Nervous System

Adrenergic Receptors

Adrenergic responses are those activated by "adrenaline"-like compounds. Within the body, Epinephrine
(the generic name for adrenaline), and Norepinephrine are the primary adrenergic transmitters. Isoproterenol
is an example of an extrinsic drug, which stimulates some adrenergic responses. When the target responses
of adrenergic stimulation are examined in various body systems, they fit into several categories of response,
as summarized in the following table:

Example Tissue (response)	Effect of Epinephrine	Effect of Norepinephrine	Effect of Isoproterenol	Receptor Type
Skin Blood Vessel (constriction)	++	++	0	Alpha-1
Heart (tachycardia)	++++	++++	++++++	Beta-1
Lung Bronchiols (dilation)	++++	0	++++++	Beta-2

These diverse responses to adrenergic stimulation results from the activity of two different classes of adrenergic
receptor, named **Alpha** and **Beta** by Ahlquist in 1948 on the basis of their pharmacology. Each of these classes
is further subdivided into subclasses.

Alpha Receptors

- Epinephrine (E) and norepinephrine stimulate about equally well, and both are much more effective than isoproterenol (I). **E >= NE >> I**.
- Selectively stimulated by Phenylephrine.
- Selectively blocked by Phentolamine and Phenoxybenzamine.
- Two subclasses of alpha receptor have since been identified:

Alpha1

- Predominant form of alpha-receptor in the body.
- Found primarily in the smooth muscles of arterioles, eye, gut, skin, veins, etc., as well as in some other cell types (like salivary glands).
- Usually causes contraction of smooth muscle cells.

Alpha2

- Found at pre-synaptic terminals of adrenergic nerves.
- Functions as an autoreceptor. If stimulated, it decreases the subsequent release of transmitter.

Beta Receptors

- Isoproterenol stimulates best, epinephrine is also effective, and norepinephrine is often weaker. I > E >= NE.
- Blocked by propranalol.
- Several subclasses of beta receptor have been identified on the basis of their detailed pharmacology:

Beta1

- Found in heart muscle, and in the kidney.
- Causes increased heart rate and contractility.
- Promotes release of renin from the kidney.
- EPI and NE are about equally effective in their ability to stimulate beta1 receptors.

Beta2

Found in smooth muscle that relaxes upon stimulation, and in metabolic tissues.

Causes:

- Decrease in gastrointestinal motility.
- Bronchodilation.
- Vasodilation in skeletal and cardiac muscle.
- Glycogenolysis in the liver.

EPI is much more effective than NE. EPI can also stimulate beta2 receptors at lower concentrations than required to stimulate alpha receptors.

Beta-3

- Found in adipose tissue (fat cells).
- Stimulates lipolysis, increasing fatty acids in the blood.
- EPI and NE are about equally effective in their ability to stimulate beta3 receptors. [1]

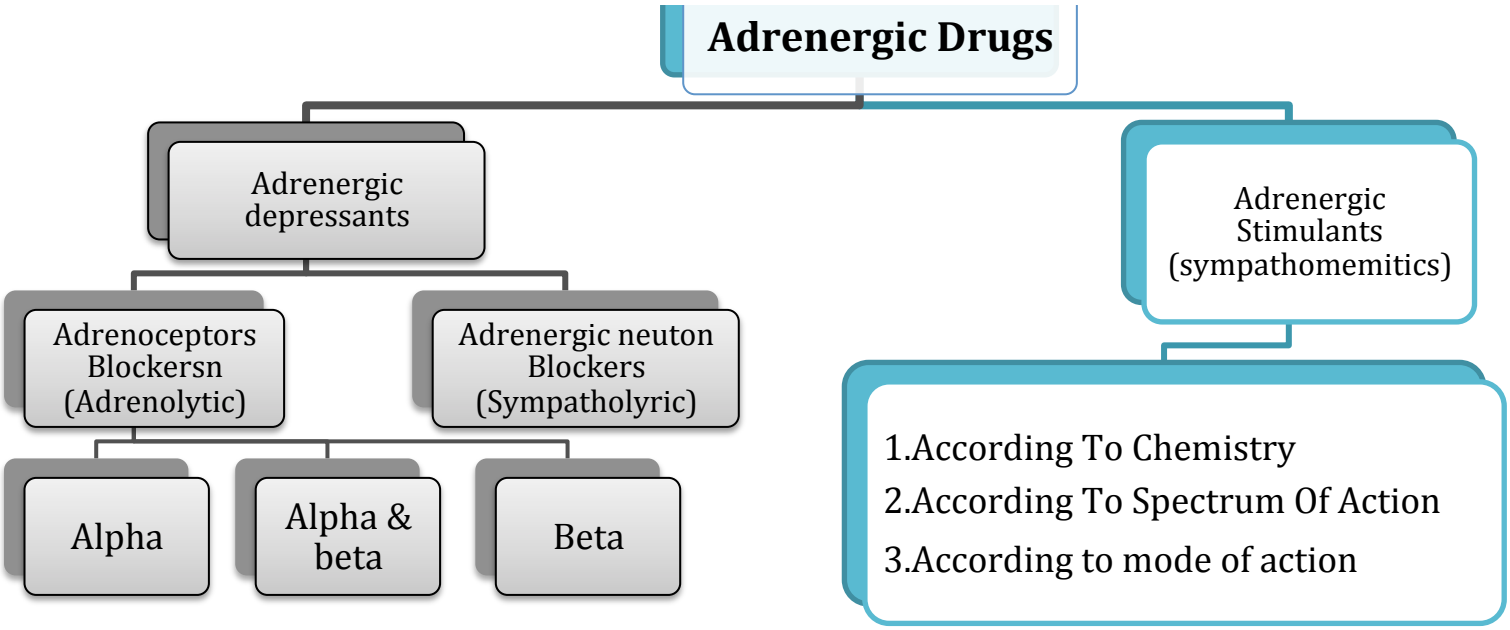
- **Definitions :**

Iotrope / is an agent that alters the force or energy of muscular contraction.
Chronotropic / is an agent that changes the heart rate
Dromotropic / is an agent of one which affects the condition speed in the atrioventricular node
Lusitropy / is myocardial relaxation

The cardiac cycle consists of a period of relaxation called **diastloe** during which the heart fills with blood.
Followed by a period of contraction called **systole**.

Tocolytic / relaxation of uterus

Organ	Affect	Receptor
Heart	inotropic, chronotropic, dromotropic & lusiotropic (↑excitability) ((Tachycardia in general))	B1
Blood pressure	Increase systolic	B1
	Decrease diastolic with low dose → B2 Increase diastolic with high dose → a1	
Vascular smooth muscle cell (SMC) : Skin and peripheral	Constrict	a1
Vascular smooth muscle cell (SMC) : coronary and skeletal	Dilate	B2
Lung	Bronchodilatation	B2
GIT	Decrease motility	B2
	contract sphincter	a1
Bladder	Decrease detrusor m Contract trigone and sphincter	B2 a1
Pregnant uterus	Tocolytic	B2
Eye	Mydriasis ((No effect on accommodation or intraoculat pressure))	a1
Metabolism	Decrease the insulin Increase the glucagon Increase liver glycogenolysis + sk.m. glycolysis Increase adipose lipolysis	A2 B2 B2 B3 and B2
CNS	Little, headache, tremors and restlessness.	____



❖ According To Chemistry:

Catecholamines:

Natural: Norepinephrine, Epinephrine, and Dopamine.

Synthetic: Isoprenaline

Rapidly acting, Degraded by MAO & COMT1, Sparse CNS effects, parenteral administration

Noncatecholamines

Ephedrine, phenylephrine, amphetamine.

Delayed action, Resist degradation by MAO1, Prominent CNS effects, orally administered

❖ According To Spectrum Of Action:

Non-Selective

Norepinephrine, epinephrine, dopamine, isoprenaline, ephedrine.

Selective

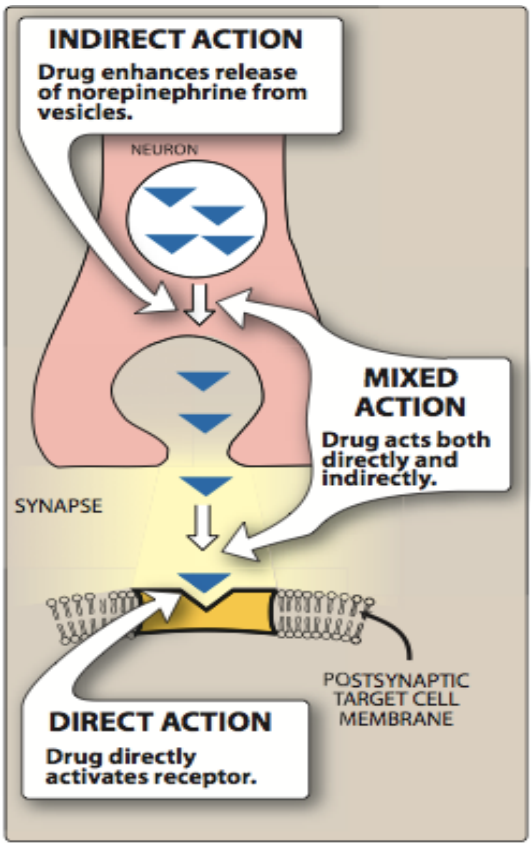
a_1 :Phenylephrine; b_1 :Dobutamine
a_2 :Clonidine ; b_2 :Salbutamol

❖ According to mode of action

Direct: Stimulate adrenergic receptors directly.
Such as: Adrenaline, noradrenaline, dopamine, isoprenaline,

Indirect: Release of NE from presynaptic stores at adrenergic nerve terminals.
Such as: Amphetamine, Cocaine & antidepressants.

Dual (Mix): Direct and indirect stimulation of adrenergic receptors.
Such as: Ephedrine, pseudoephedrine



➢ Direct Acting Sympathomimetics(non-Selective):

Adrenaline (Epinephrine)	
Selectivity	Interacts with both α and β receptors.
Action	At low doses, **β effects** (vasodilation) on the vascular system predominate, whereas at high doses, **α effects** (vaso- constriction) are strongest. **A. Cardiac:** strengthens the contractility of the myocardium (positive inotropic: **β1 action**) and increases its rate of contraction (positive chronotropic: **β 1 action**). **B. BP:** increase in *systolic blood pressure, decrease in *diastolic pressure. **C. Lung:** powerful bronchodilation (**β_2 action**). **D. Hyperglycemia:** increased glycogenolysis in the liver (**β2 effect**), increased release of glucagon (**β2 effect**), and a decreased release of insulin (**α2 effect**). **F. Pregnant uterus ➔** *tocolytic (**β_2**)

Indication	**1-locally:** • Haemostatic: (in epistaxsis) & as decongestant α1 • Local anesthetics: to ↓ its absorption & toxicity + ↓ bleeding from incision **2-Systemically:** 1-Allergeic reaction, 2-Status asthmatics, 3-Cardiac arrest
Side effects	• Tachycardia, palpitation, arrhythmias, angina pains • Headache, weakness, tremors anxiety and restlessness. • Hypertension → cerebral hemorrhage and pulmonary edema. • Coldness of extremities → tissue necrosis and gangrene if extravasation • Nasal stuffiness; rebound congestion if used as decongestion
Contraindi-cation	• *CHD1, hypertension, peripheral arterial disease. • Hyperthyroidism. • Closed - angle glaucoma →may ↑ *IOP1

*CHD: Congestive heart failure, *IOP: Intraocular pressure

***systolic:** The phase of blood circulation in which heart's pumping chambers (ventricle) are actively pumping blood. The ventricles are squeezing (contracting) forcefully. And pressure against the walls of the arteries is at it's highest.

***diastolic:** The phase of blood circulation in which heart's pumping chambers (ventricles) are being Filled with blood. During this phase, the ventricle are at most relaxed, and the pressure against the walls of the arteries is at it's lowest.

***tocolytic:** Anti-contraction medication, which used to suppress premature labor(Childbirth).

NOREPINEPHRINE = NORADRENALINE	
Selectivity	Non-selective, Acts on **α** > **β1 (given IV only)**
Action	Reflex Bradycardia.
Indication	Systemically; hypotensive states Topically; as a local haemostatic
ISOPRENALINE	
Selectivity	Non-selective, Acts on **β** > **α**
Action	Used by inhalation in acute asthma Cardiac arrest
Indication	Hyperthyroidism & Congestive heart failure
DOPAMINE	
Selectivity	Non-selective, Acts on D1 > **β 1** > **α 1**
Action	**Heart** Inotropic, no chronotropic effect **BP:** According to dose; First ↓ BP D1, then ↑ BP due to **β 1,** followed by **a1** effect
Indication	Treatment of shock (without causing renal impartment) & Acute heart Failure (Dobutamine is better)
DOBUTAMINE	
Selectivity	Non-selective, Acts on **β1** > **β2** > **α1**(very selective to cardiac shock **β1**) **Given IV**
Action	Heart: Inotropic & little chronotropic effect BP: No or little decrease in therapeutic dose (**β1** & **β2** counterbalance + no **α1**)
Indication	Short term management of cardiac decompensating it doesn't increase oxygen demand

➢ Direct Acting Sympathomimetics (Selective):

PHENYLPHERINE

Selectivity	Selective on **α1**
Action	**Heart:** reflex bradycardia BP: increase due to vasoconstriction **α1**
Indication	**Systemically:** Pressor agent to terminate atrial tachycardia (reflex bradycardia) Nasal decongestant. Oral **Topically:** Local haemostatic, with local anesthesia, Decongestant, Mydriatic.

MIDODRINE

Selectivity	Selective on **α1**
Indication	Hypotension, peaks in 20 min t1/2 30 min

Nasal & Ocular Decongestants

Pseudoephedrine: used in flu remedies.	**Phenylethylamines** • Phenylephrine • Methoxamine	**Imidazoline** • Naphazoline • Oxymetazoline HCI (Afrin) **Xylometazoline HCI (Otrivine)** **Otrivine can cause Rebound nasal stuffiness**

Colonidine

Selectivity	Acts selectively on presynaptic **α2** , Imidazoline Receptors
Action	Decrease BP by acting on **α2** which inhibit nor-epinephrine relieve
Indication	Antihypertensive agent

Brimonidine

Selectivity	Acts selectively on presynaptic **α2**
Indication	Glucoma

Salbutamol

Selectivity	Acts *selectively* on **β2**
Action	**Bronchodilater** ➔**asthma** & chronic obstructive airway disease (COPD)
Indication	Salmeterol & Formoterol

Other selective β agonist

Ritodrine: Tocolytic	**Terbutaline:** Bronchodilator & Tocolytic

Indirect Acting Sympathomimetics:

Amphetamine	
Selectivity	Acts on a& β
Action	Tachyphylaxis Absorbed orally, not destroyed by MAO, excreted mostly unchanged (↑ by *acidification of urine)*
Effect	Similar to epinephrine but has CNS stimulant effects • Increase mental alertness • Increase euphoria causes its abuse • Decrease weight by reducing appetite
Indication	No more used therapeutically induces → **psychic & physical dependence** and psychosis + the CVS side effects

Dual Acting Sympathomimetics:

Ephedrine	
Selectivity	Acts on a& β
Action	Tachyphylaxis due to receptor down regulation and depletes stores Absorbed orally, not destroyed by MAO or COMT→ prolonged action.
Effect	▪ Facilitation of neuromuscular transmission. ▪ Retention of urine. ▪ CNS stimulant effects (less than amphetamine).
Indication	No more therapeutically used→but is abused by athletes and prohibited during games.
Pseudo Ephedrine	
Indication	▪ Nasal & ocular decongestant ▪ In flue remedies Used Orally

Important notes:

Direct:

Epinephrine:Act in all Receptors, it's the drug of choice for anaphylactic shock. The unique characteristic is releasing **ALLERGY**.

NOREPINEPHRINE: Act in all Receptors EXCEPT **β2**, Not good for anaphylactic shock neither Asthma.

ISOPRENALINE: Act on **β** ONLY, it's the drug of choice for cardiac arrest.

DOPAMINE: Act on all receptors + D receptor EXCEPT **β2.**
It increase contractility of heart, it protect the kidney.

DOBUTAMINE: act on **β1** ONLY
Dose not cause tachycardia because of increased inotropic lead to ↑ **systolic, so it** will reduces adrenaline secretion = **JUST↑ contractility without TECHYCARDIA**

Indirect:

Amphetamine: it increase the release of Dopamine + Norepinephrine and inhibit the re uptake.
Dopamine used for loosing weight + hyperactive in children, but it has CNS effect.
It cause psychiatric & physical dependent.

Dual:

Ephedrine: like the epinephrine acting but in addition it release norepinephrine.
Abuse in athletes.

Pseudo Ephedrine: same Ephedrine but low CNS effects.
It causes insomnia.