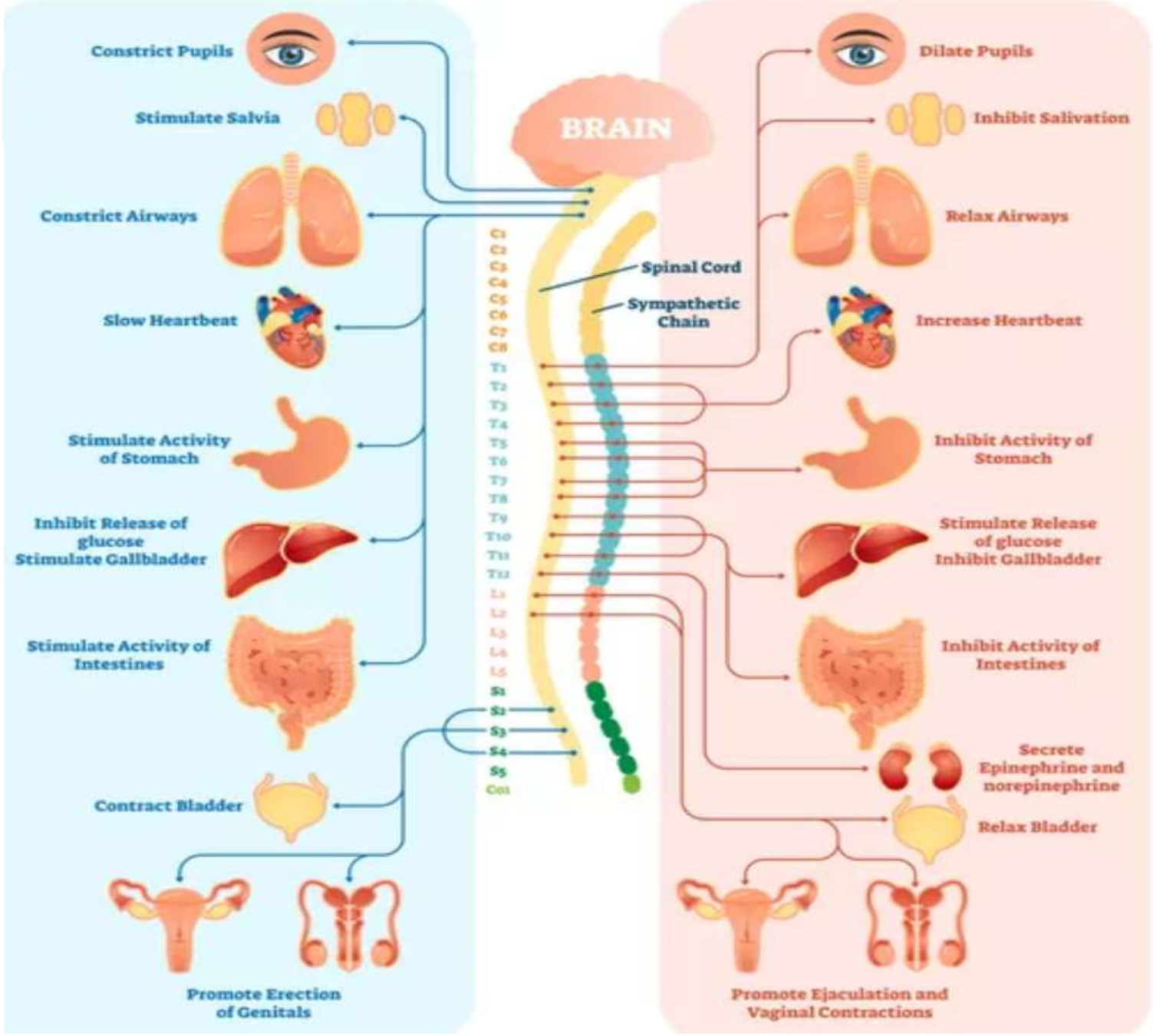
Adrenergic drugs

Samar Hunaiti Pharm, PhD



Parasympathetic "Rest and digest"

Sympathetic "Fight or Flight"

Definitions

- **Neurotramsmitters**: Neurotransmitters are the chemical mediators released by the neurons to transmit the signals through the synapse.
- **Sympathomimetic:** a drug that activates sympathetic nervous system
- **Parasympathomimetic**: a drug that activates parasympathetic nervous system
- **Sympatholytic:** a drug that decreases or blocks sympathetic response
- **Parasympatholytic**: a drug that decreases or blocks parasympathetic response
- **Adrenaline** (ADR) = **epinephrin**e
- Noradrenaline (NA)= norepinephrine

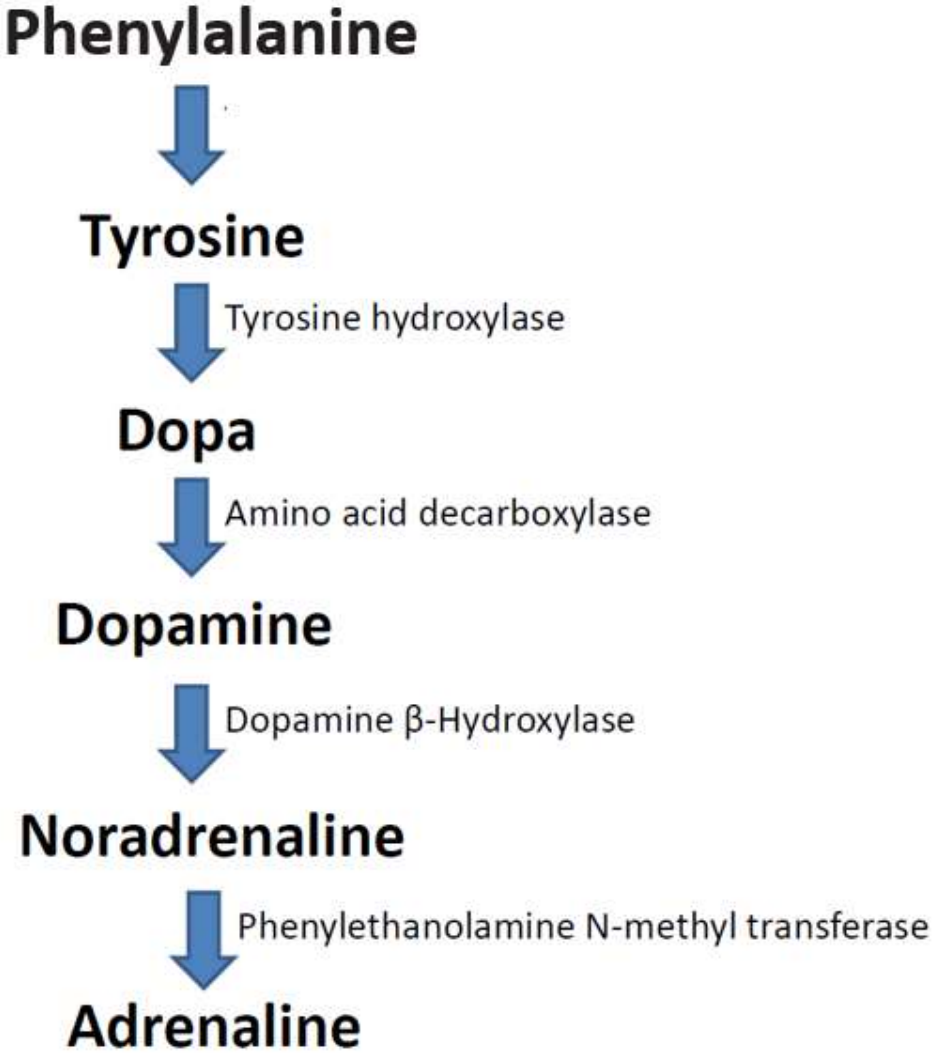
Synthesis and metabolism of catecholamines

- Catecholamines (CAs) are synthesized from the amino acid phenylalanine

- Synthesis of NA occurs in all adrenergic neurons
- Synthesis of ADR occurs only in the adrenal medullary cells

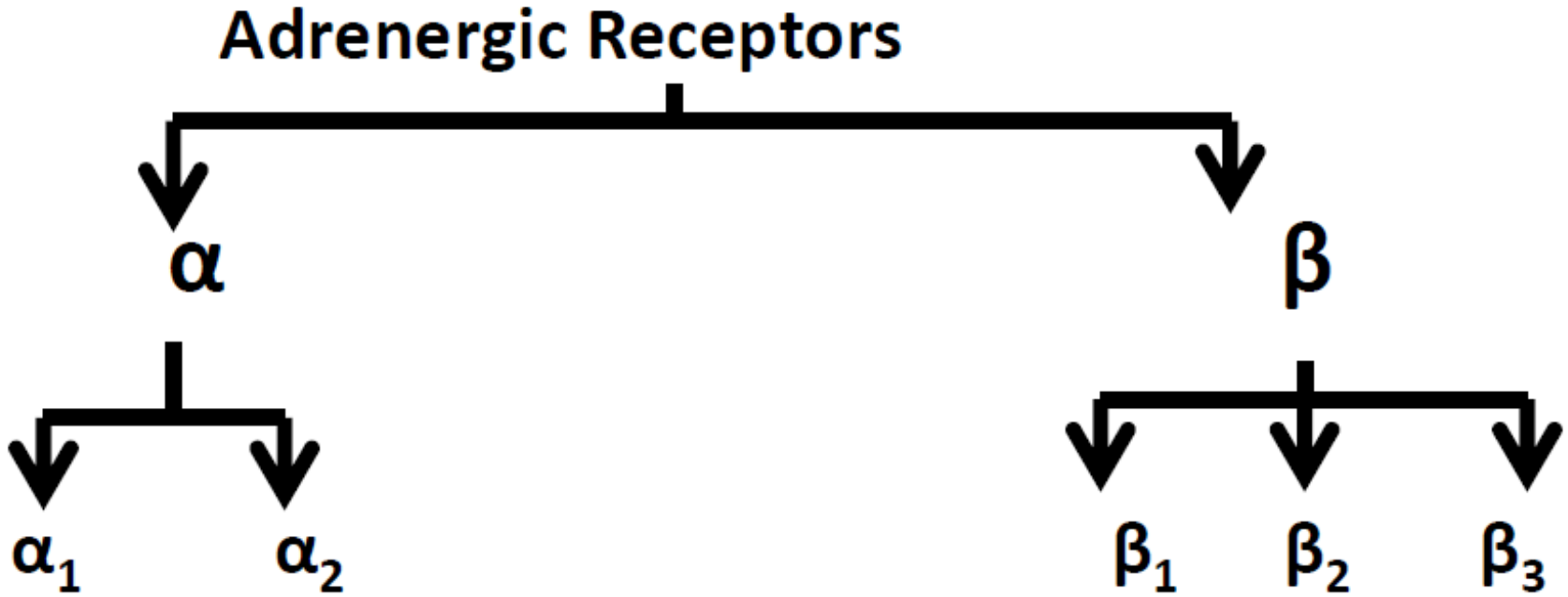
- Part of NA leaking out from vesicles into the cytoplasm and axonal transport is first attacked by **MAO**

- Diffused into circulation is first acted upon by catechol-o-methyl transferase (**COMT**) in the liver and other tissues



Adrenergic drugs (Sympathomimetics)

- These are drugs with actions like that of ADR or of sympathetic stimulation.
- Direct sympathomimetics
- They act directly as agonists on α and/or β adrenoceptors
  ADR, NA, isoprenaline (Iso), phenylephrine, methoxamine, oxylometazoline, salbutamol
- Indirect sympathomimetics
- They act on adrenergic neuron to release NA which then acts on the adrenoceptors tyramine, amphetamine
- Mixed action sympathomimetics
- They act directly as well as indirectly ephedrine, dopamine, mephentermine



Differences between α and β adrenergic receptors

	α	β
1. Rank order of potency of agonists	Adr ≥ NA > Iso	Iso > Adr > NA
2. Antagonist	Phenoxybenzamine	Propranolol
3. Effector pathway	K^+ channel ↑	Ca^{2+} channel ↑

Mechanism of action

- The peripheral actions of CAs are mediated by α, β receptors depending on the predominant receptor type present in a given tissue

Adr :	$\alpha_1 + \alpha_2 + \beta_1 + \beta_2$
NA:	$\alpha_1 + \alpha_2 + \beta_1$ but no β_2 action
Iso:	$\beta_1 + \beta_2$ but no α action

Drugs that affect Autonomic Nervous System will affect:

- Heart
- Blood Vessels
- Pancreas
- Ureters
- Bladder
- Eyes
- Pupils
- Lacrimal Gland
- Lung Airways
- Brain

Therapeutic classification of adrenergic drugs

I. Pressor agents

NA, Phenylephrine, Ephedrine, Methoxamine, and DA

II. Cardiac stimulants

ADR, Dobutamine and Iso

III. Bronchodilators

Iso, Terbutaline, Salbutamol, Bambuterol (Albuterol), Salmeterol, and Formoterol

IV. Nasal decongestants

Phenylephrine, Naphazoline, Pseudoephedrine, and Oxymetazoline

V. CNS stimulants

Amphetamine, Methamphetamine, and Dexamphetamine

VI. Uterine relaxant and vasodilators

Ritodrine and Terbutaline

Heart

- All cardiac actions are predominantly β1 receptor-mediated
- When BP rises markedly, reflex bradycardia occurs due to stimulation of the vagal tone
- ADR increases heart rate by increasing the automaticity of SA node
- It also activates latent pacemakers in AV node
- Force of cardiac contraction is increased
- Cardiac output and oxygen consumption of the heart are markedly enhanced

Blood vessels

- Both vasoconstriction (α)and vasodilatation (β2) can occur depending on the drug, its dose, and vascular bed.
- Constriction predominates in cutaneous, mucous membranes, and renal beds. Vasoconstriction occurs through both α1 and α2 receptors.
- Dilatation predominates in skeletal muscles, the liver, and coronaries
- The direct effect on cerebral vessels is not prominent

Lung

- ADR and Iso but not NA are potent bronchodilators (β2) when the bronchi are constricted.
- ADR can directly stimulate the respiratory center (RC), but this action is seldom manifest at clinically used doses
- Bronchial asthma
- Adrenergic drugs, especially β2 stimulants, are the primary drugs for the relief of reversible airway obstruction

Selective β 2 agonists

- **Salbutamol, terbutaline, and its long-acting prodrug bambuterol, salmeterol, formoterol, and ritodrine**
- They cause bronchodilation, vasodilation, and uterine relaxation without producing significant cardiac stimulation
- Salbutamol has a β2:β1 action ratio of about 10.
- They are primarily used in **bronchial asthma**
- Occasionally ritodrine is employed to depress uterine contractions and delay premature labor
- The most important side effect is muscle tremor

Administration

- CAs are orally inactive because they are rapidly degraded by COMT in the intestinal wall and liver
- ADR is administered systematically by s.c. or i.m. injection in a dose of 0.2–0.5 mg, (lasts 0.5–2 hours)
- **In dental practice**, it should not be used as a local vasoconstrictor added to local anesthetics for dental anesthesia.

Contraindication

- ADR is contraindicated in hypertensive, hyperthyroid, and angina patients
- ADR mixed local anesthetic should **NOT** be used in dental anesthesia
- It should not be given to patients receiving β blockers (a marked rise in BP can occur)
- Certain anesthetics (chloroform, halothane) sensitize the heart to the arrhythmic action of ADR.

Adrenergic antagonists (Adrenoblockers)

These are drugs that antagonize the action of ADR and related drugs

They are competitive antagonists at α or β or both receptors

α blockers

General effects of α blockers

- Blockade of vasoconstrictor α1 also α2 receptors ↓ peripheral resistance and causes pooling of blood (Hypovolemia) → ↓ venousreturn and cardiac output → ↓ BP
- They inhibit adrenergic responses mediated by α receptors without affecting β receptors
- Nonequilibrium α blockade could not be reversed by large concentrations of ADR
- This implies that mass-action equilibration between agonist and antagonist is prevented (nonequilibrium α blockade)
- This blockade is produced only by specific compounds having the ability to form stable covalent bonds at α site

Classification of α blockers

- **Nonequilibrium type**
  - β Haloalkylamines, Phenoxybenzamine

- **Equilibrium type** (nonselective and competitive)
- **Ergot alkaloids**
  - Ergotamine and Ergotoxine
- **Hydrogenated ergot alkaloids**
  - Dihydroergotamine (DHE) and Dihydroergotoxine
- **Imidazolines**
  - Tolazoline and Phentolamine
- **α1 selective**
  - Prazosin, Terazosin, Doxazosin,Tamsulosin and Alfuzosin
- **α2 selective**
  - Yohimbine

Natural and hydrogenated ergot alkaloids

- **Ergotamine and ergotoxine** from ergot fungus
- They are partial agonists and antagonists at α, serotonergic and dopaminergic receptors
- They produce long-lasting vasoconstriction more than α blockade
- Their principal use is in migraine
- Hydrogenation reduces vasoconstrictors and increases α blocking activity
- Hydrogenated ergot alkaloids are used for symptoms of mental decline in elderly
- Dihydroergotamine has been used as a cognition enhancer
- The amine alkaloid **ergometrine** has no α blocking activity

Nonselective α blockers -1

- **Phentolamine**
- short acting (in minutes) used for management of pheochromocytoma and control of hypertension due to clonidine withdrawal, cheese reaction
- **Prazosin**
- It is the first of the highly selective α1 blockers with α1:α2 selectivity ratio of 1000:1
- It is primarily used as an anti-hypertensive
- It is also used in benign prostatic hypertrophy (BHP)
- Patients receiving prazosin for hypertension or BPH should not suddenly stand up after being supine **on the dental chair**
- **Terazosin and doxazosin** longer half-life than prazosin suitable for once-daily dosing, particularly in BHP

Nonselective α blockers -2

- **Tamsulosin**
- Is relatively uroselective due to higher affinity for α1A subtype
- It does not cause significant changes in BP or HR at doses that relieve urinary symptoms of BHP
- Its modified-release capsule needs only once-daily dosing
- **Yohimbine**
- An alkaloid from the West African plant *Yohimbehe*
- It is a relatively selective α2 blocker with a short duration of action
- There are no valid indications for the clinical use of yohimbine

Side effects

- Palpitation
- Postural hypotension
- Nasal blockage
- Loose motions
- Fluid retention
- Inhibition of ejaculation and impotence
- α blockers have no effect on adrenergically induced cardiac stimulation, bronchodilatation, or vasodilatation because these are predominantly mediated through β receptors

β blockers

β blockers

- **Nonselective (β1 and β2)**
  - **Without intrinsic sympathomimetic activity**

    Propranolol, Sotalol, Timolol
  - **With intrinsic sympathomimetic activity**

    Pindolol
  - **With additional α blocking property**

    Labetalol, Carvedilol
- **Cardioselective (β1)**
  - Metoprolol, Atenolol, Acebutolol, Celiprolol, Nebivolol

First generation (older, nonselective)	Second generation (β_1 selective)	Third generation (with additional α blocking and/or vasodilator property)
Propranolol	Metoprolol	Labetalol
Timolol	Atenolol	Carvedilol
Sotalol	Acebutolol	Celiprolol
Pindolol	Bisoprolol	Nebivolol
	Esmolol	

Propranolol is described as prototype β blocker, has negative chronotropic and inotropic effects leading to a reduction in cardiac output

Pindolol, Acebutolol partial agonistic (intrinsic sympathomimetic action)

Therapeutic uses-1

- **Hypertension**
- β blockers are relatively mild anti-hypertensives
- All agents are nearly equally effective
- They are one of the first-choice drugs because of good patient acceptability and cardioprotective potential
- **Angina pectoris**
- All β blockers benefit angina of effort
- Taken regularly they decrease the frequency of attacks and increase exercise tolerance
- **Cardiac arrhythmias**
- β blockers suppress adrenergically mediated tachycardias during anesthesia or digitalis induced (IV)

Therapeutic uses-2

- **Migraine**
- Propranolol is the most effective drug for chronic prophylaxis of migraine
- **Anxiety**
- Propranolol exerts an apparent antianxiety effect, especially under conditions that provoke nervousness and panic such as:
  - Post-traumatic stress disorder (PTSD) and specific phobias like **dentophobia (Dental fear)** and unaccustomed public appearance (stage fright)
- **Thyrotoxicosis**
- Propranolol rapidly controls symptoms (palpitation, nervousness, tremor, and sweating) without significantly affecting thyroid status
- It is used pre-operatively while awaiting the response to anti-thyroid drugs/radioactive iodine

Propranolol-drug interactions

- Clinically significant interactions particularly occur with:
- ADR
- Salbutamol
- Clonidine
- Ergot alkaloids
- Iso
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Lidocaine

Thank you