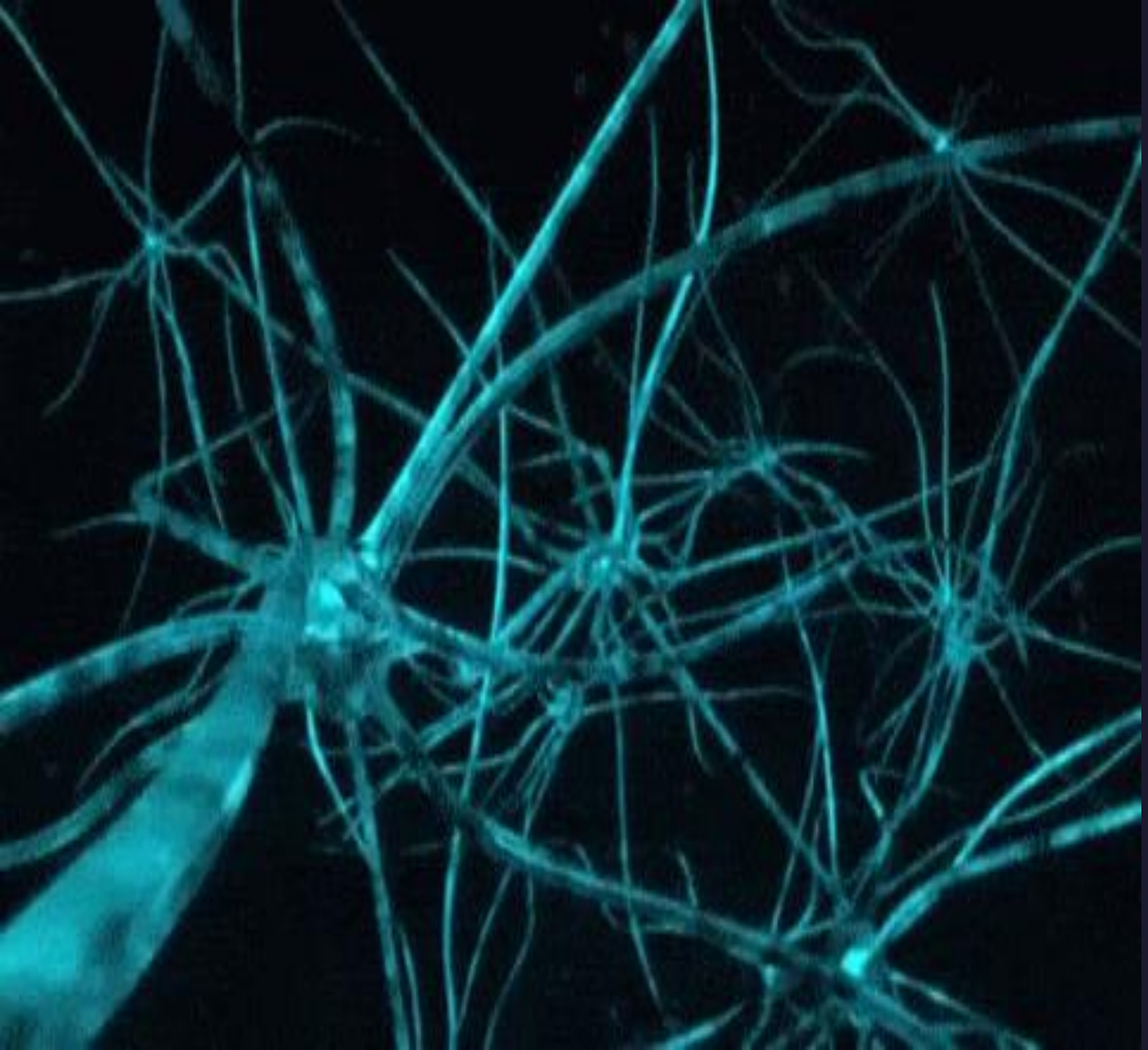


Adrenergic Drugs

Dr Sara Adil
BDS, MSc

Agenda

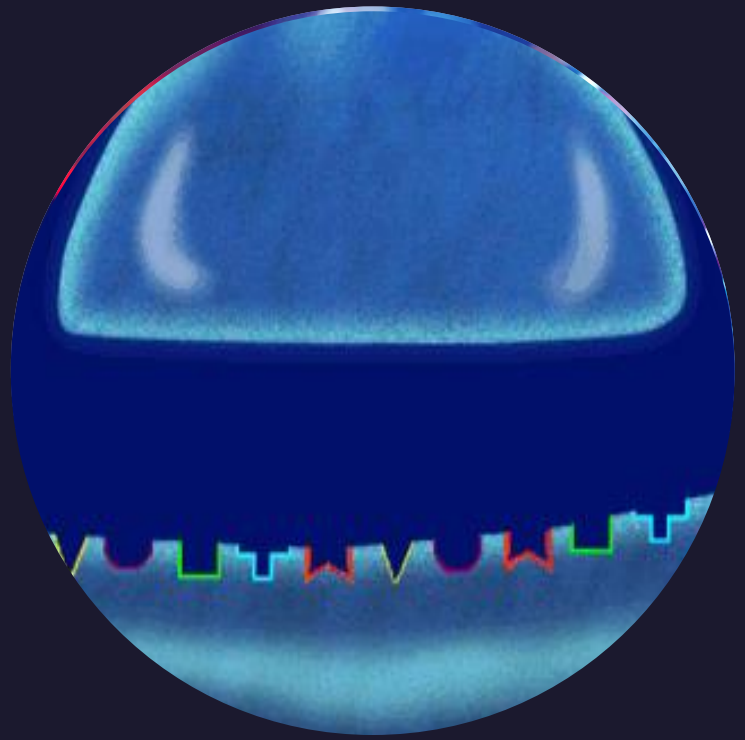
Adrenergic receptors

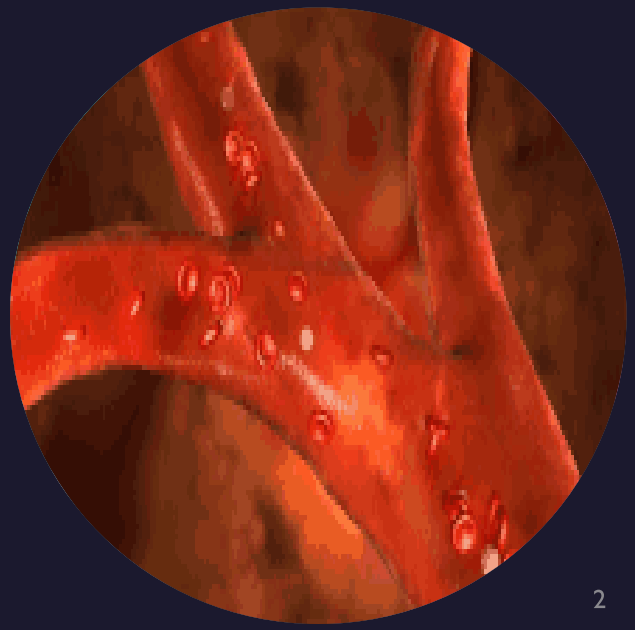
Adrenergic Neurotransmitters

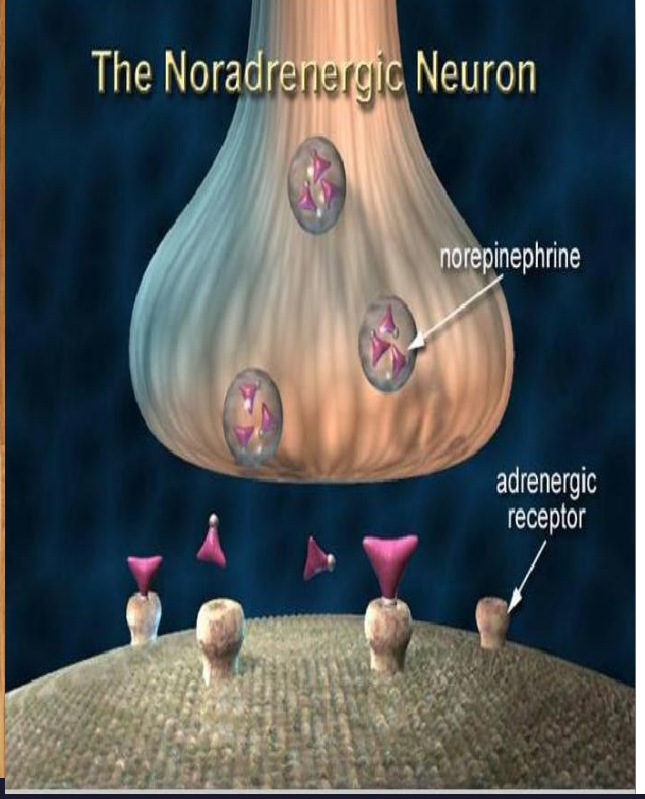
Classification of Adrenergic Drugs

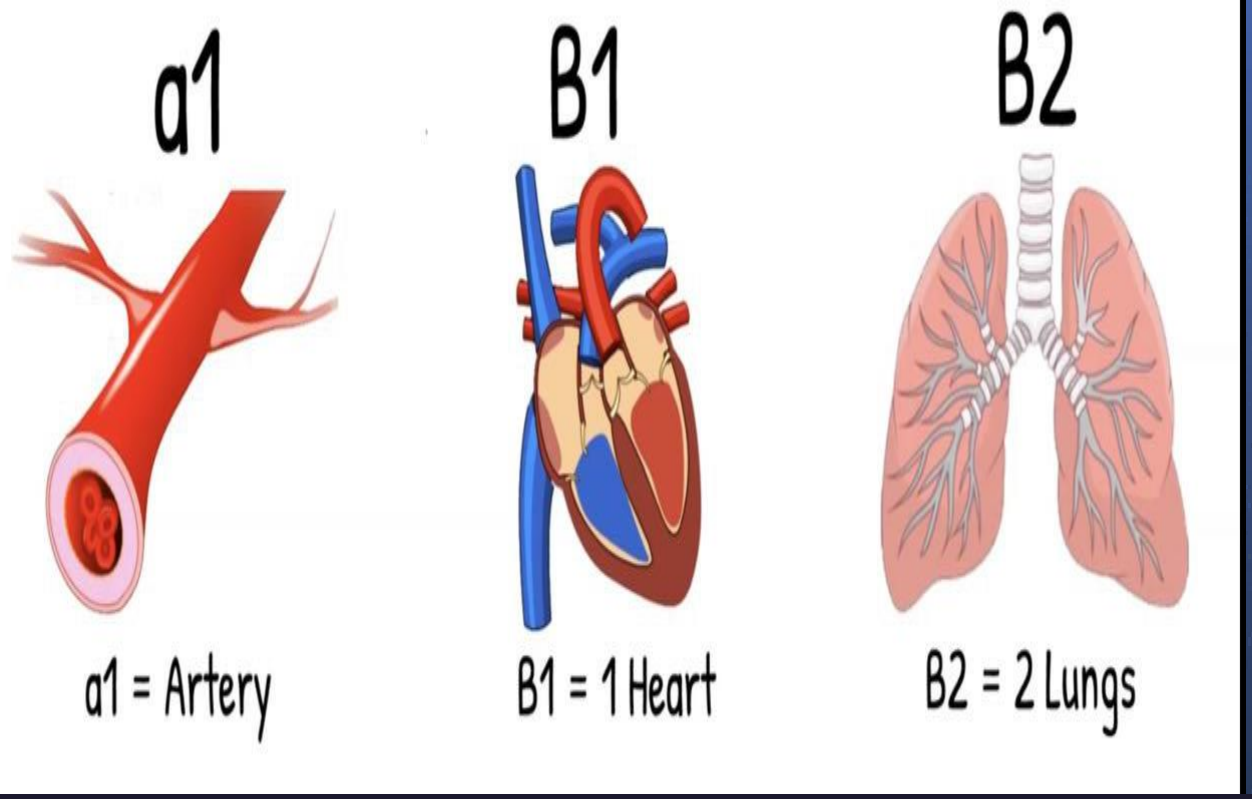
Adrenergic Agonist

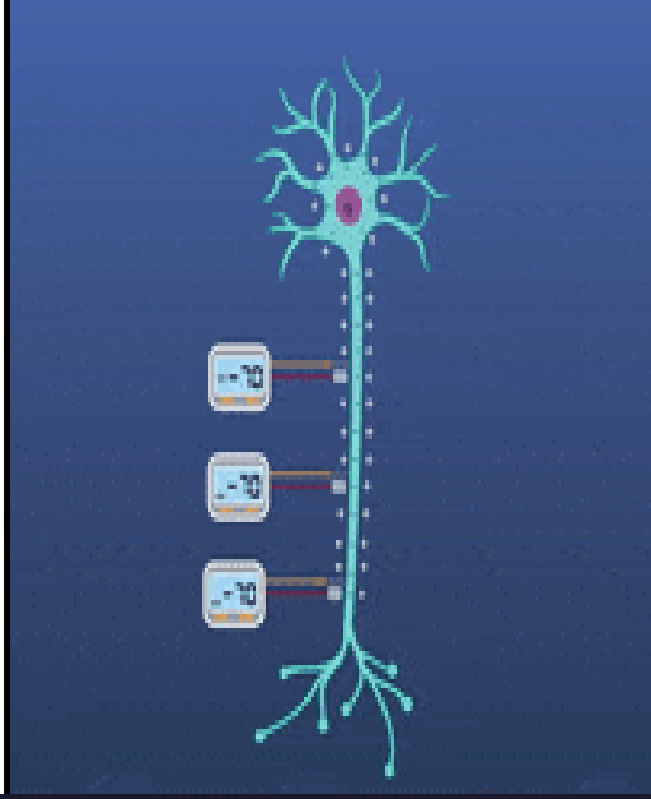
Adrenergic Antagonist











Introduction

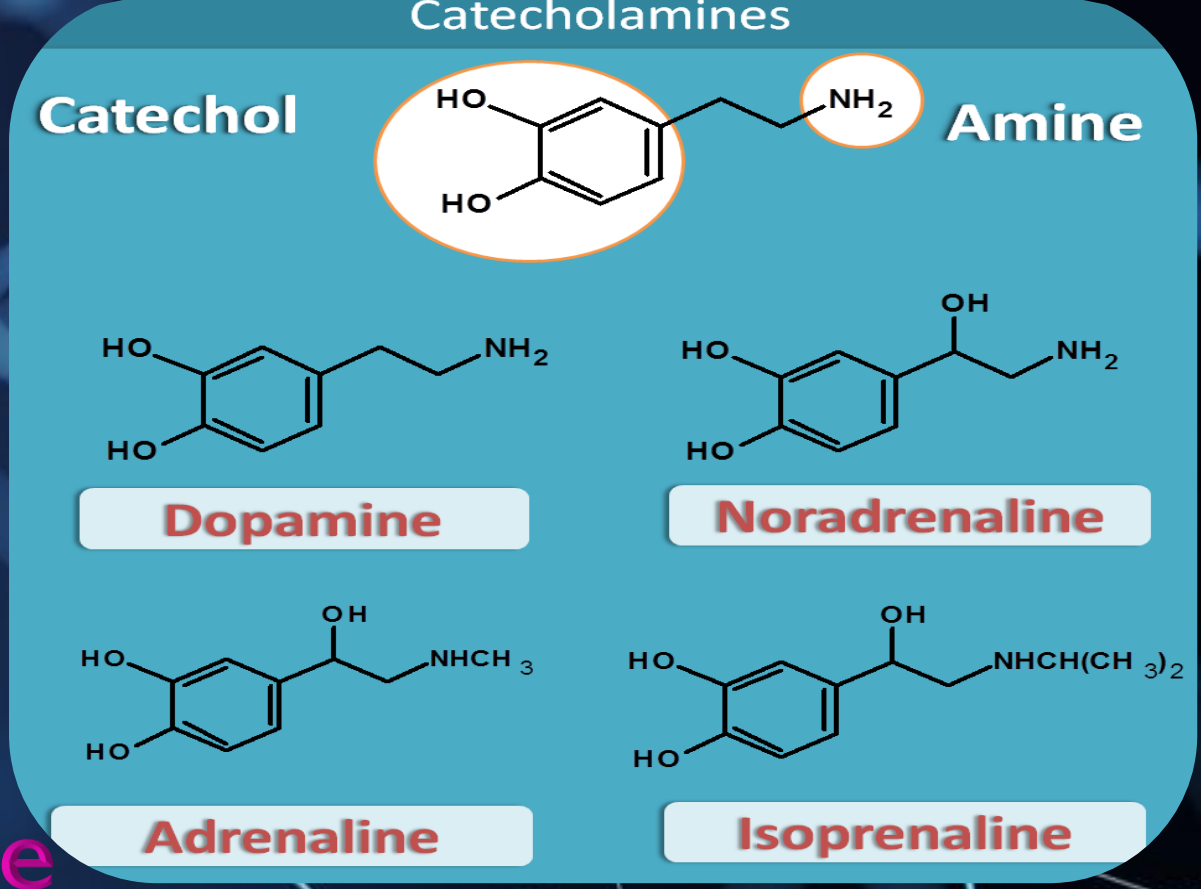
- The **adrenergic drugs** affect **adrenoceptors** that are stimulated by **norepinephrine (noradrenaline)** or **epinephrine (adrenaline).**
- Drugs that **activate** adrenergic receptors are termed **sympathomimetics**, and drugs that **block** the activation of adrenergic receptors are termed **sympatholytic**.

Adrenergic Receptors

α_1- α_2

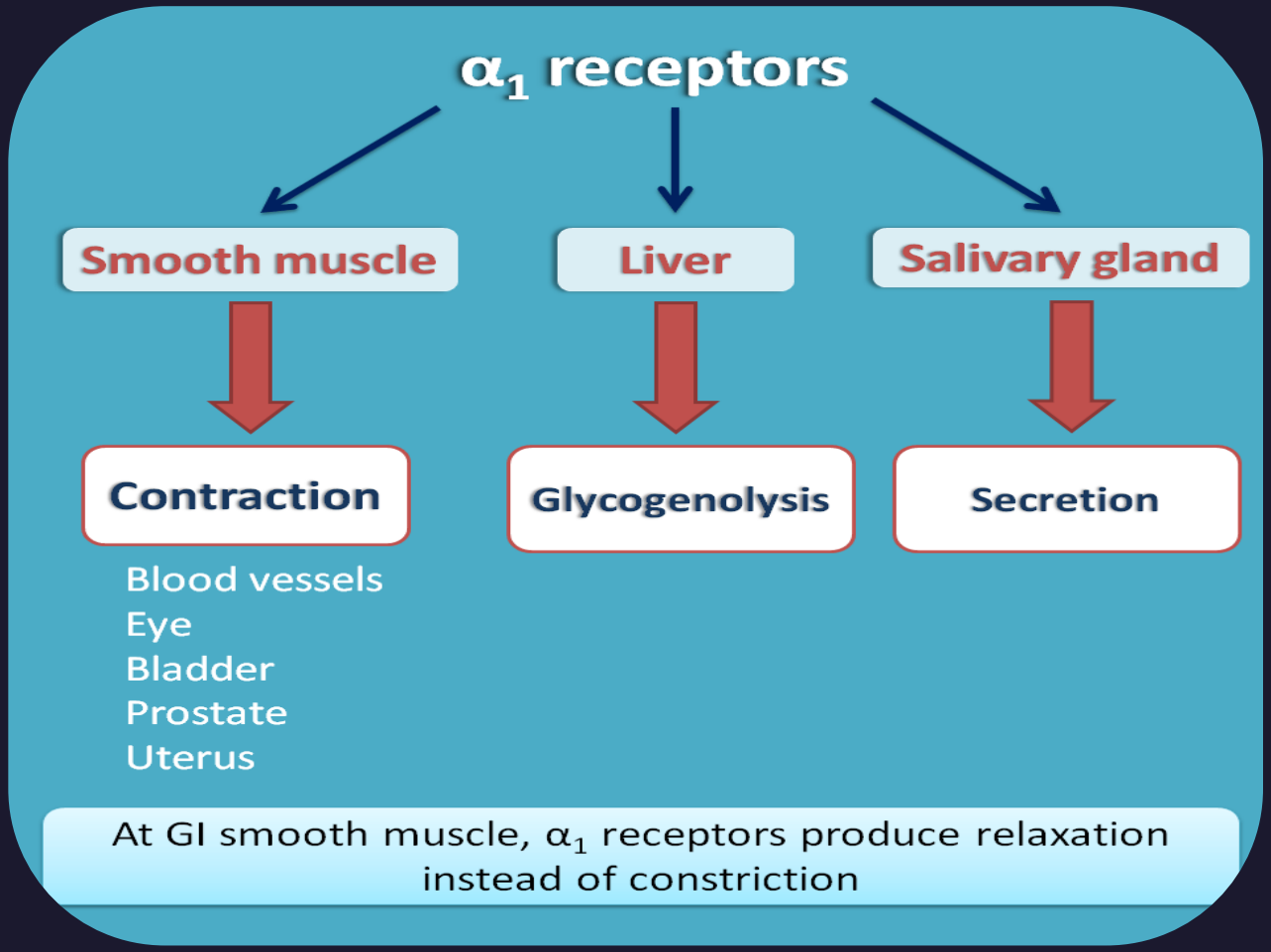
β_1- β_2- β_3

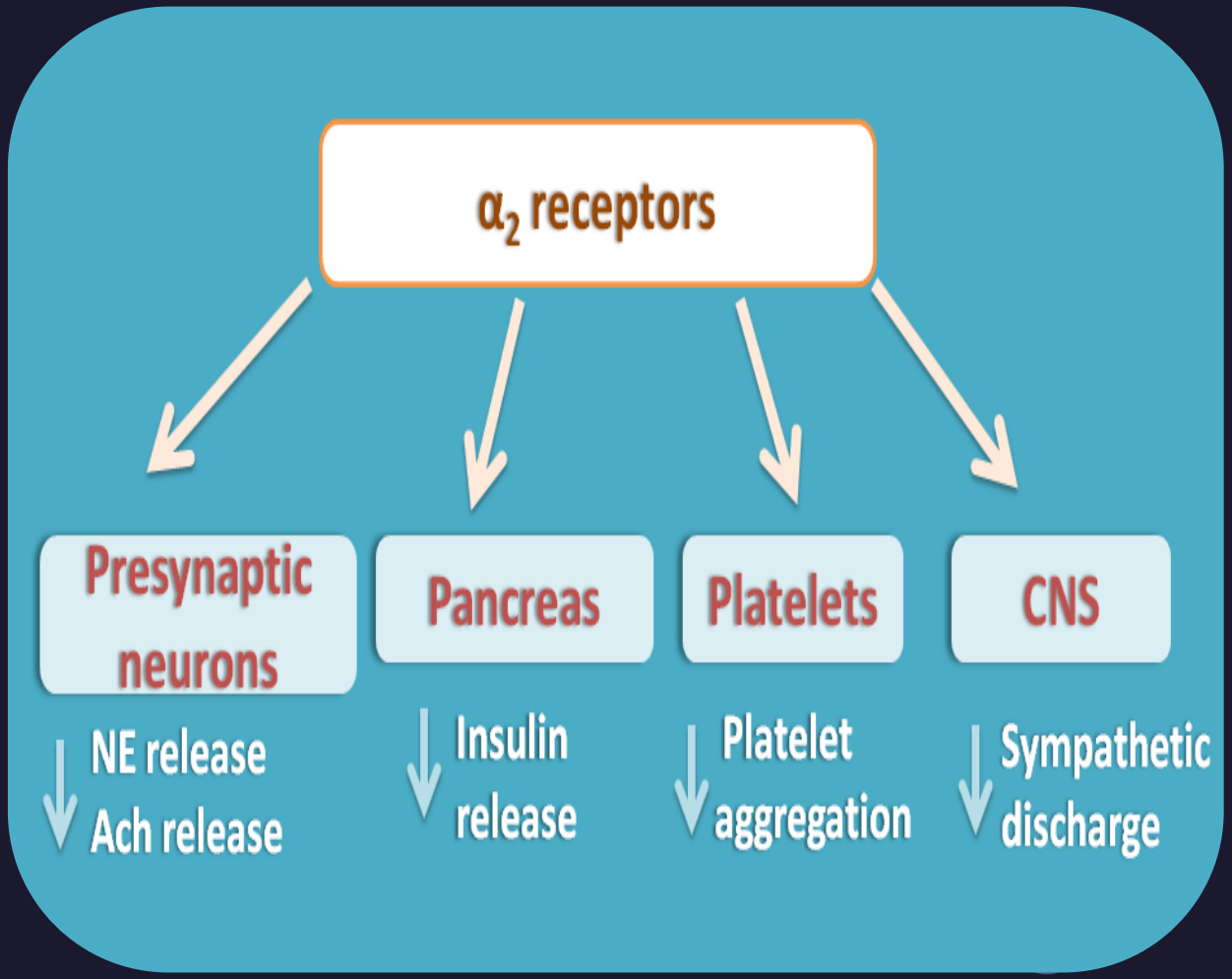
Adrenergic Neurotransmitters



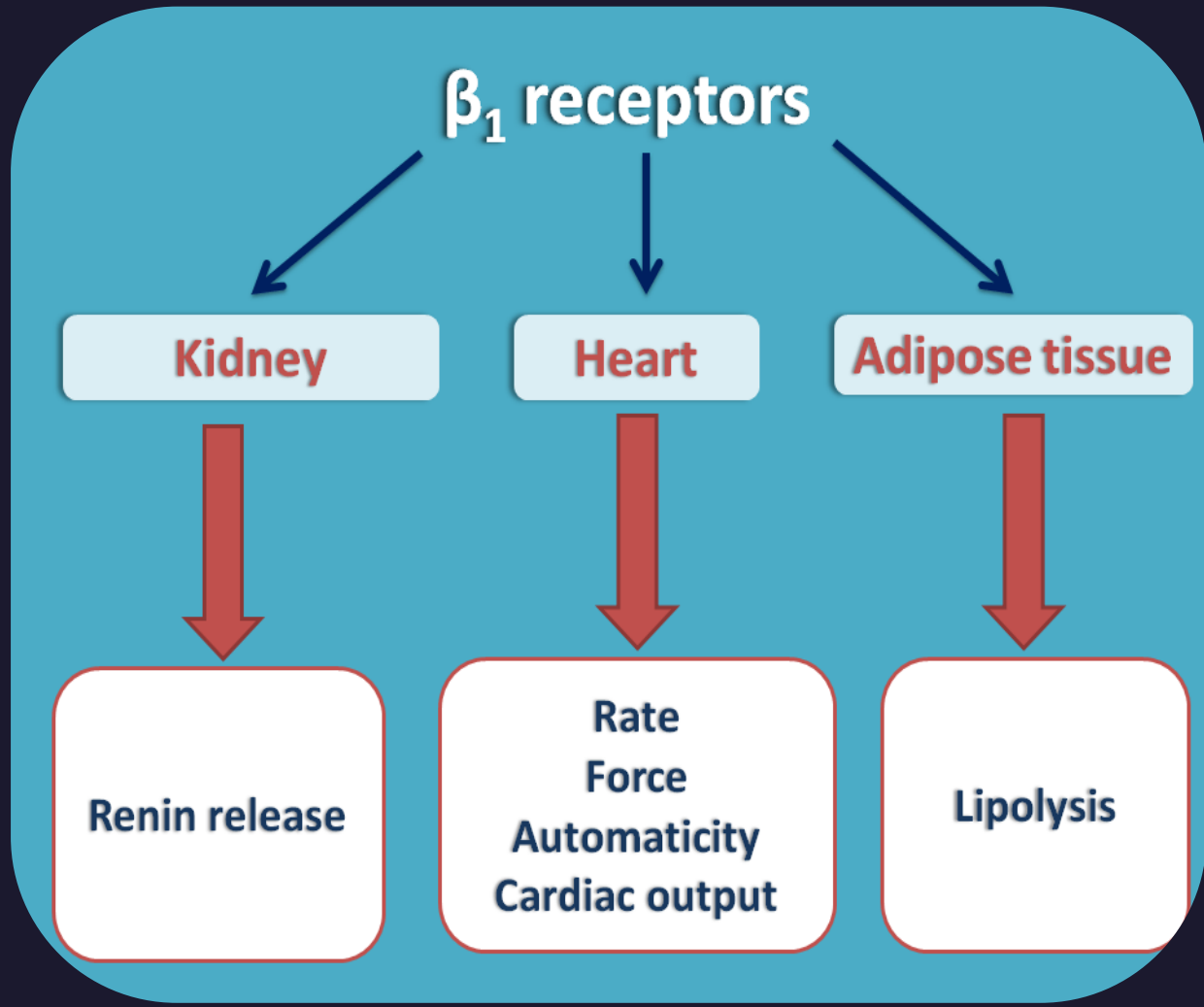
- Epinephrine/ Adrenaline
- Norepinephrine/ Noradrenaline
- Dopamine

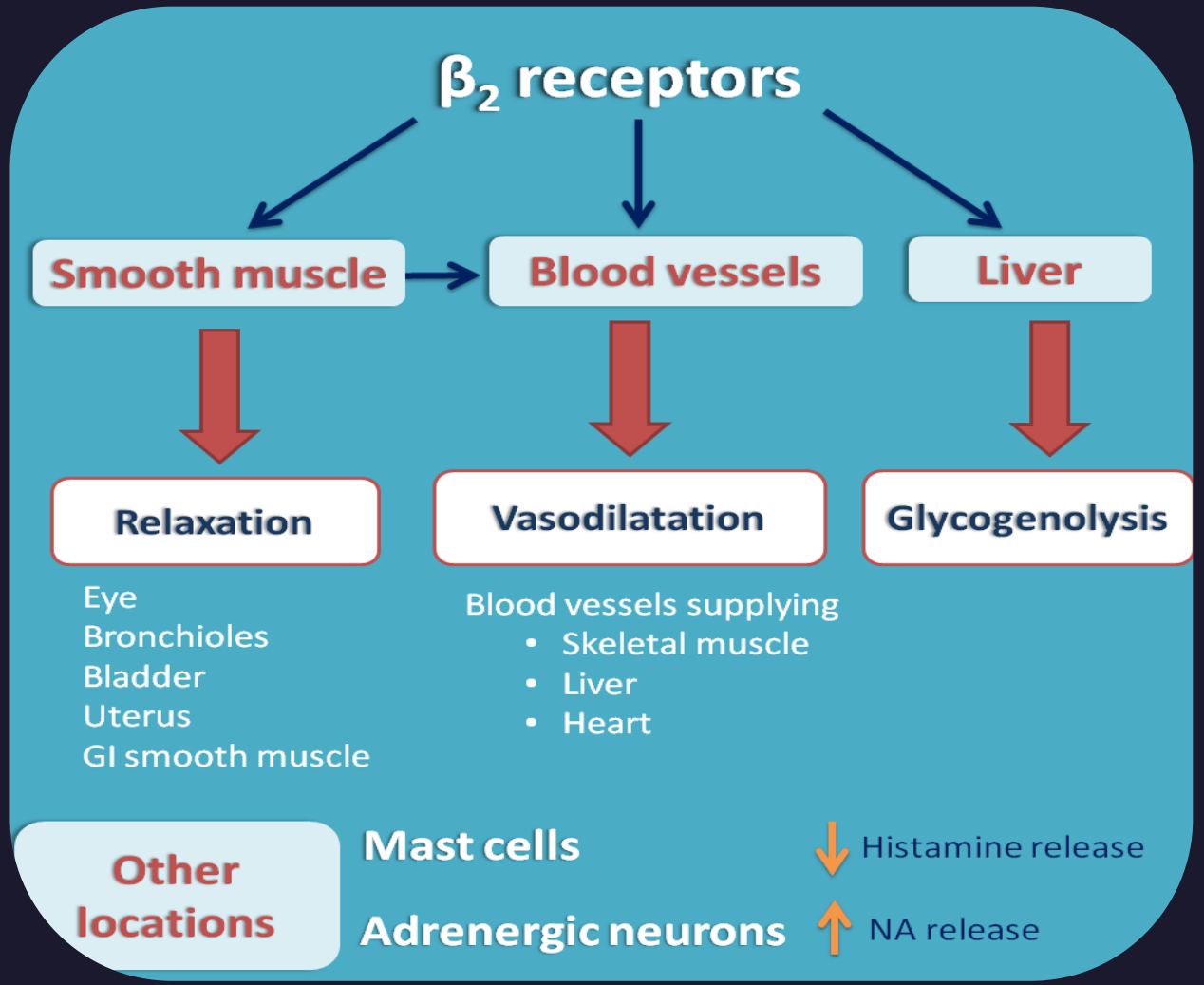
α Adrenergic Receptors

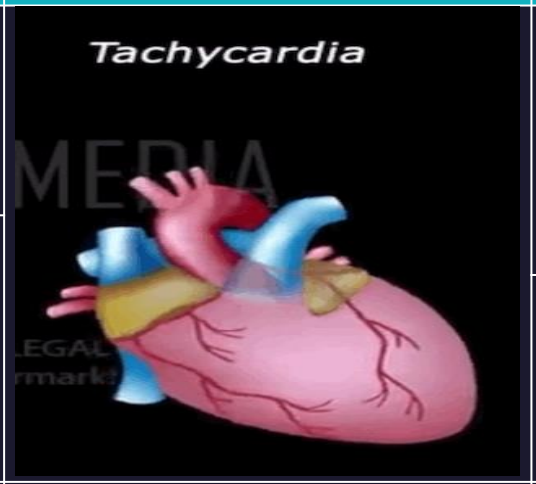
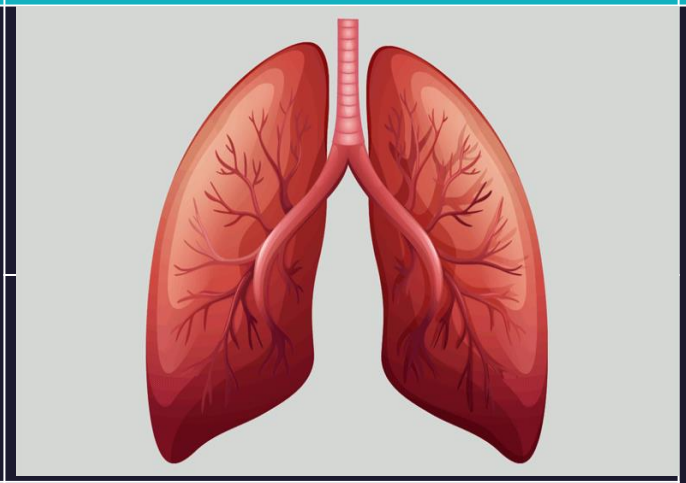
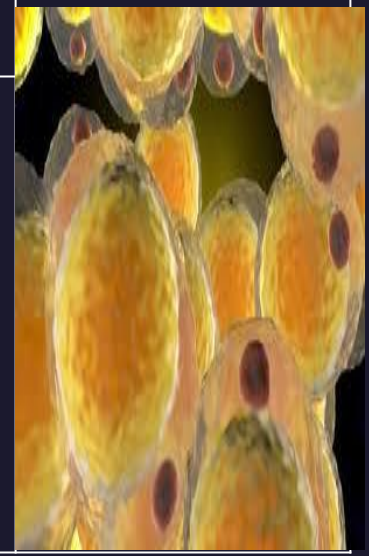
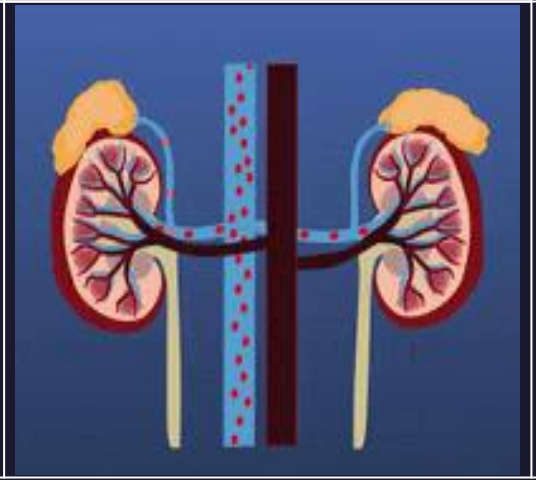




β Adrenergic Receptors





α1	α2	β1	β2	β3
Blood vessel (contraction)	CNS			Adipose tissue
	Pre-synaptic neuron ↓ NA release			
S.M of GIT (relaxation)	Platelets	Kidney- juxta glomerular cells	Blood vessels of skeletal muscle & coronary A. (Vasodilation)	
S.M of Bladder, uterus Eye, Prostatic urethra (contraction)	Pancreas		S.M of GIT Bladder, Eye, uterus (Relaxation)	

Classification of Adrenergic Drugs

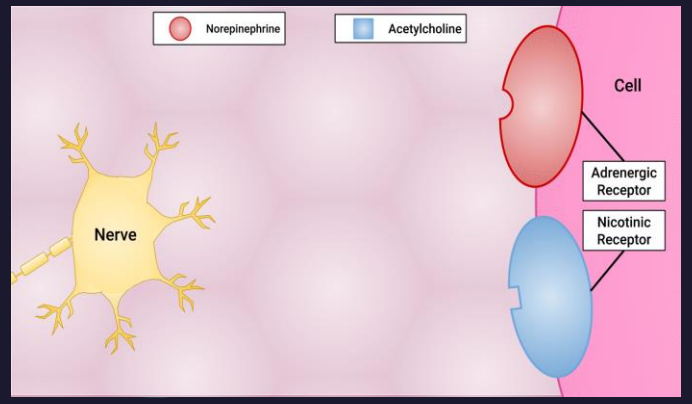
Classification

Based on the mechanism of action, adrenergic agonists are classified to…

1

Direct-acting Agonists

- They directly bind to & activate adrenoceptors.
- Epinephrine, Norepinephrine.



2

Indirect-acting Agonists

- They ↑ adrenergic transmission indirectly by

a. Displace norepinephrine from the storage vesicle Amphetamine,

b. Inhibit norepinephrine re-uptake Tricyclic antidepressant, Cocaine.

c. Inhibit metabolism, MAO inhibitor

3

Mixed-action Agonists

- Both stimulate adrenoceptors directly and enhance the release of norepinephrine from the adrenergic neuron.
- **Ephedrine, pseudoephedrine**.

Catecholamines VS Non-catecholamines

CATECHOLAMINES

- like epinephrine, norepinephrine, isoproterenol, and dopamine
- metabolized by catechol-O methyltransferase (COMT) and monoamine oxidase (MAO)
- Short-half live
- Cannot use orally
- Cannot cross blood-brain barrier (polar)

NON-CATECHOLAMINES

- like phenylephrine, ephedrine, and amphetamine.
- they don't → have a prolonged duration of action
- longer half lives
- Can use orally
- Can cross the BBB (lipid soluble).

Direct-acting Agonists

Epinephrine/ Adrenaline

- Epinephrine interacts with both **α** and **ß** receptors.
- At low doses – β2 effects (vasodilation) on the vascular system predominate,
- At high doses – α1 effects (vasoconstriction) are strongest.

ACTIONS

1. Cardiovascular:

- Strengthens the contractility of the myocardium (positive inotropic: β 1 action)
- Increases heart rate of contraction (positive chronotropic: β 1 action)

Direct-acting Agonists

Epinephrine/ Adrenaline

Activates **β1** receptors in the **kidney** to cause **renin release**.

- ❑ Constricts arterioles in the skin, mucous membranes, and viscera (α1 effects),
- ❑ dilates vessels going to the liver and skeletal muscle (β 2 effects).

The cumulative effect of adrenaline is

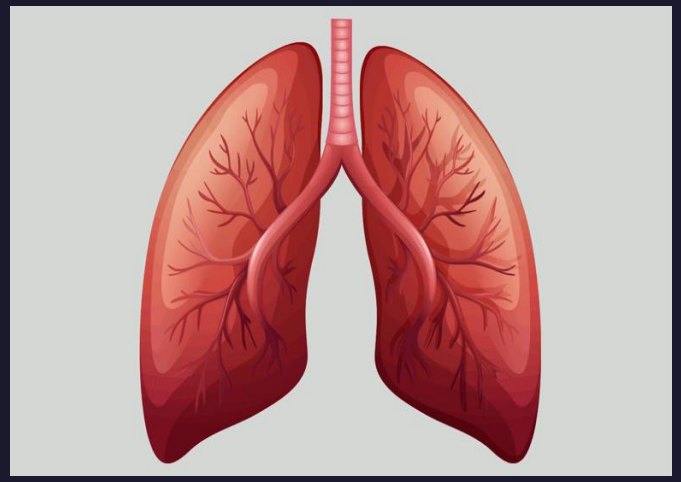
- An increase in systolic blood pressure SBP
- Slight decrease in diastolic pressure DBP

Direct-acting Agonists

Epinephrine/ Adrenaline

ACTIONS

2. Respiratory: powerful bronchodilation by acting directly on bronchial smooth muscle (β2 action).



2. Hyperglycemia: Epinephrine has a significant hyperglycemic effect (↑ blood glucose) because of

- ✓increased glycogenolysis in the liver (β2 effect),
- ✓increased release of glucagon (β2 effect),
- ✓decreased release of insulin (α2 effect).

Epinephrine/ Adrenaline Pharmacokinetics

1. Epinephrine has a rapid onset
2. short duration of action.

Because it is rapidly metabolized by MAO and COMT

- The preferred route is intramuscular (I.M at the anterior thigh) due to rapid absorption.
- In emergency situations, epinephrine is given intravenously (IV) for the most rapid onset of action.
- It may also be given subcutaneously, by endotracheal tube,
- by inhalation.

Epinephrine: Therapeutic uses:

a. Acute Bronchospasm (acute asthma)
b. Anaphylactic shock
c. Cardiac arrest:
d. As an adjunct to local anesthesia in dentistry.

Local Anaesthetics (L.A): Local anaesthetic solutions in dentistry may contain low concentrations (for example, 1:100,000 parts) of epinephrine to:

I. increases the duration of local anaesthesia (L.A) action,
II. Reduce systemic toxicity of L.A
III. reduce bleeding as well

Direct-acting Agonists

Norepinephrine/ Noradrenaline

- Is selective for α receptor (α1=α2 > β1).
- Norepinephrine causes both systolic and diastolic blood pressures increase due to intense vasoconstriction of most vascular beds (α1 effect).

Direct-acting Agonists

Isoproterenol:

- a direct-acting synthetic catecholamine that stimulates both β1, β2 receptors.
- Heart: increasing heart rate, contractility, and cardiac output (β1)
- also dilates the arterioles of skeletal muscle (β2 effect), resulting in decreased peripheral resistance
- **Lungs: a potent bronchodilator** (β2 effect).

Direct-acting Agonists

Dopamine:

- Stimulate both (α, β receptors).
- In addition, **D1** and **D2** dopaminergic receptors in renal vascular beds, where binding of dopamine produces **vasodilation**..
- **Dopamine is the drug of choice for cardiogenic and septic shock and is given by continuous infusion.**

Non-catecholamines adrenergic agonists

- like phenylephrine, ephedrine, and amphetamine.
- they don't metabolize by COMT or MOA
- have a prolonged duration of action
- Can use orally
- Can cross the BBB (lipid soluble).

α1-Agonist
α2-Agonist

Phenylephrine/ α1-Agonist

- Is a direct-acting synthetic adrenergic agonists
- Binds primarily to α1 receptors.
- Phenylephrine is a vasoconstrictor that raises both systolic and diastolic blood pressures.
- Uses

1. as a nasal decongestant
2. Ophthalmic solutions for mydriasis.

Direct-acting Agonists

Clonidine: α2 agonist

- Clonidine acts centrally on presynaptic α2 receptors to produce inhibition of sympathetic vasomotor centres, decreasing sympathetic outflow to the periphery.

- **Uses:**

1. as centrally acting anti-hypertensive drugs.
2. To reduce withdrawal symptoms of opiates, tobacco smoking, and benzodiazepines.

- The side effects include: lethargy, sedation, constipation and xerostomia

Dobutamine:/ β1-Agonist

- Is a selective β1 agonist. (heart)
- Increases cardiac rate and output but without increasing oxygen consumption of the myocardium, a major advantage over other sympathomimetic drugs.
- Uses.

- Congestive heart failure
- Cardiogenic shock.

Salbutamol and Salmeterol/ β2-Agonist

- Is a selective β2 agonist. (lung)
- Uses:

- Bronchial asthma
- Chronic obstructive coronary disease (COPD).

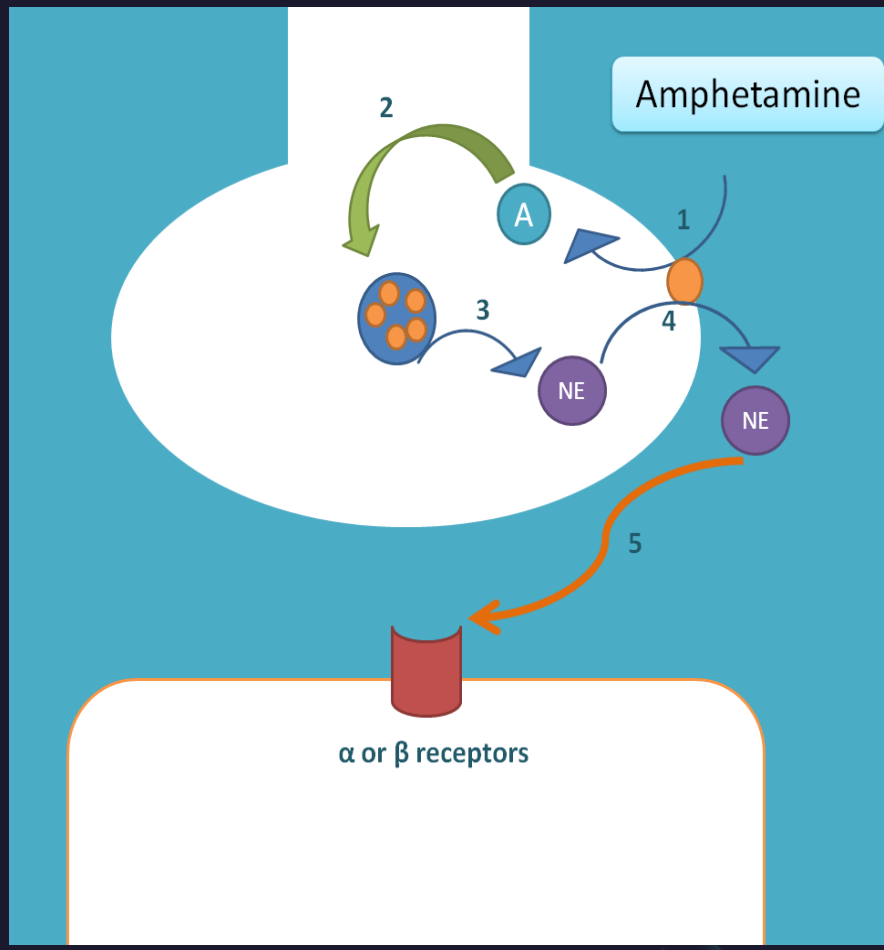
Indirect-Acting Adrenergic Agonists

Act by stimulating the release, inhibiting the reuptake, or inhibiting the degradation of epinephrine or norepinephrine.
so

They potentiate the effects of epinephrine or norepinephrine produced endogenously but do not directly affect postsynaptic receptors (Amphetamine, tyramine, and cocaine).

Amphetamine:

- Is an **indirect-acting adrenergic drug** that causes the release of stored norepinephrine,
- its main effect is **CNS stimulation** ⟶ **Euphoria** ⟶ **addiction (drug abuse).**
- **Therapeutic uses:** in attention deficit hyperactivity disorder (ADHD), CNS stimulatory effects, suppression of appetite.

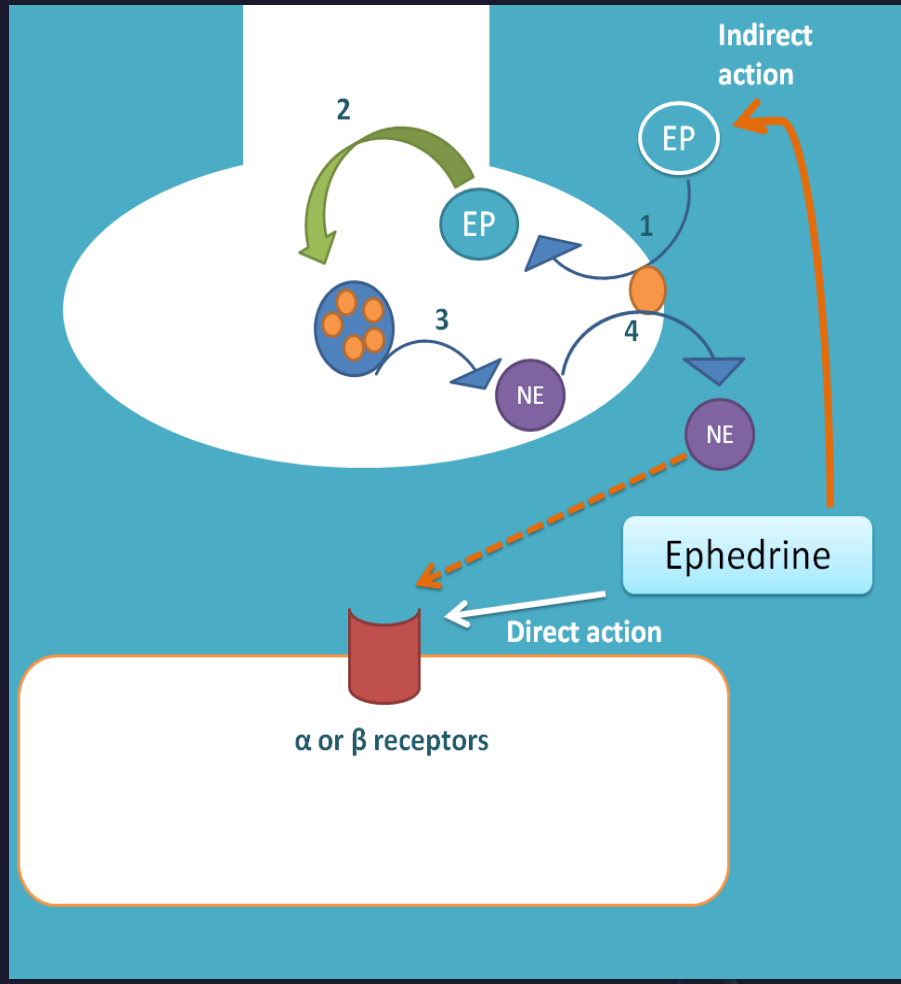


Cocaine

- Block re-uptake of catecholamine at the adrenergic nerve terminal.
- Cocaine can affect:
  - **CNS:** general stimulation, euphoria, dysphoria, followed by depression. (drug abuse)
  - **CVS:** in small doses, it causes bradycardia, and at higher doses tachycardia; vasoconstriction; and myocardial infarction.
  - Can cause **local anaesthesia** by blocking Na+ channels.

Ephedrine and pseudoephedrine:

- Mixed-Action Adrenergic Agonists.
- They not only enhance the release of stored norepinephrine from nerve endings but also directly stimulate both **α and β** receptors.
- Thus, a wide variety of adrenergic actions ensue that are similar to those of **epinephrine**, although less potent.



Ephedrine and pseudoephedrine:

- Since Ephedrine produces a mild stimulation of the CNS. This increases alertness decreases fatigue and prevents sleep, It also improves athletic performance.
- Since Ephedrine can enter CNS and produces **euphoria** → **drug abuse**
- **Oral pseudoephedrine is primarily used as nasal decongestant.**

The way to get started is to quit talking and begin doing.

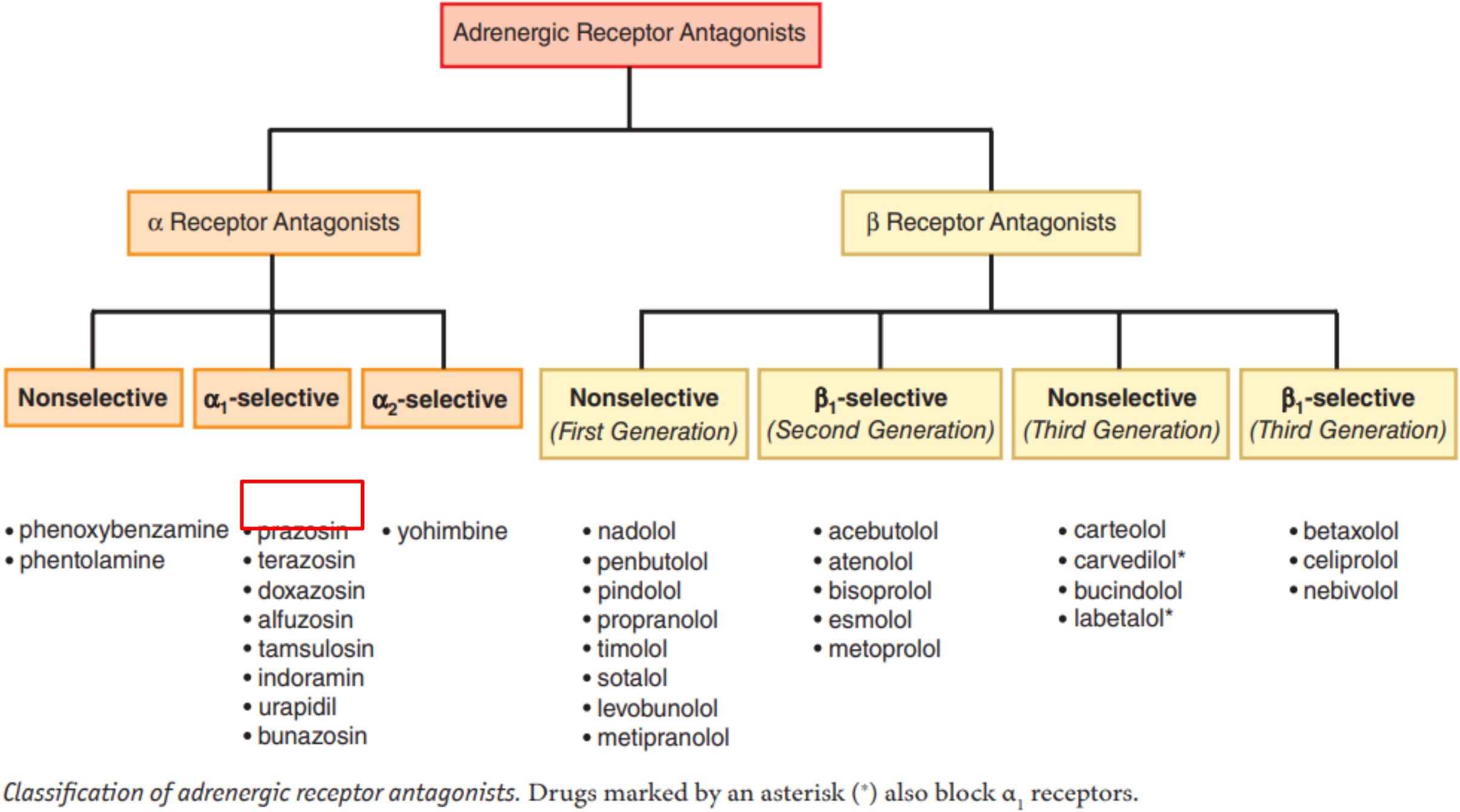
Walt Disney

Adrenergic Antagonists

- also called adrenergic blockers or sympatholytic drugs.
- They bind to adrenoceptors but do not trigger the usual effects.
- The adrenergic antagonists are classified

✓ β blockers
✓ α blockers
✓ Drug act pre-synaptically

a. Storage inhibitor (reserpine)
b. Release inhibitor (guanethidine)



Classification of adrenergic receptor antagonists. Drugs marked by an asterisk (*) also block α_1 receptors.

α-Adrenergic blocking agents:

Phenoxybenzamine:

- Non –selective α blocker (α1, α2)
- Irreversible blocker, long-acting (4 days)

- Uses: pheochromocytoma (Phenoxybenzamine + propranolol)

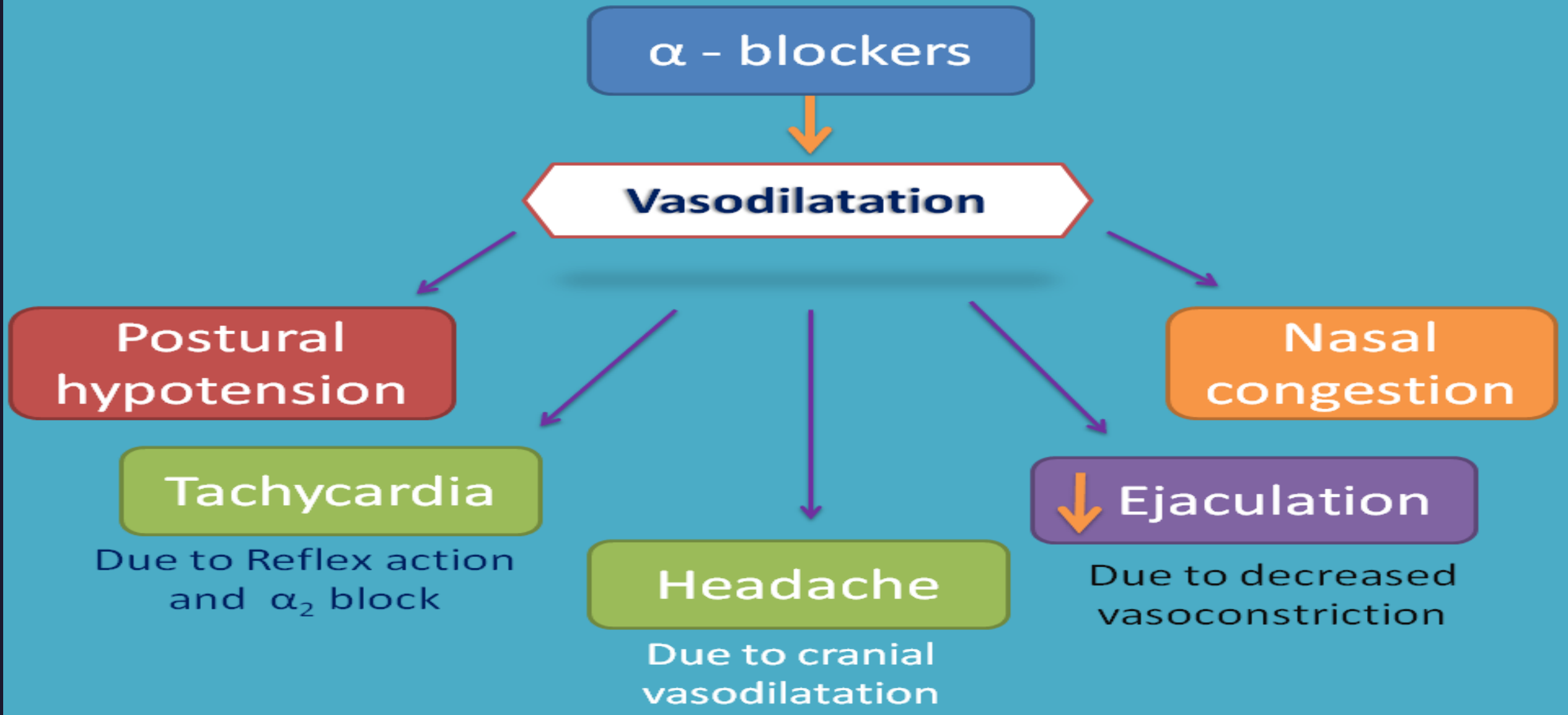
α-Adrenergic blocking agents:

Prazosin

- Selective α_1 blocker

- Uses:
- hypertension
- acute heart failure
- Benign prostate hypertrophy

Non-selective α blockers – Side effects



DRUG SUMMARY TABLE: Adrenoceptor Blockers

Subclass	Mechanism of Action	Clinical Applications
Nonselective α blockers		
Phentolamine	Competitive pharmacologic antagonism at α receptors	Pheochromocytoma, antidote to overdose of α agonists
Phenoxybenzamine	Irreversible (covalent) binding to α receptors	Pheochromocytoma, carcinoid, mastocytosis, Raynaud's phenomenon
Alpha$_1$-selective blockers		
Prazosin	Competitive antagonism at α_1 receptors	Hypertension, benign prostatic hyperplasia
Doxazosin, terazosin: like prazosin; longer duration of action (12–24 h)		
Tamsulosin, silodosin: like prazosin, approved only for benign prostatic hyperplasia		
Alpha$_2$-selective blockers		
Yohimbine	Competitive antagonism at α_2 receptors	Obsolete use for erectile dysfunction • research use

Adrenergic β Antagonists

- Non-selective β1 and β2 antagonists (e.g. propanolol, Nadalol, Timolol, Pindolol).
- β1-selective blocker (e.g. Metoprolol, Atenolol,Bisoprlol, Esmolol, Acebutolol, Betaxolol).
- Non-selective or selective β-blockers with vasodilating effect (due to α1-blocking effect) Labetalol and carvedilol: (Antagonists of both α and β)

Therapeutic uses of β-blockers

1. **Hypertension:** β-Blockers are useful for all grades of hypertension. These drugs are preferred especially in patients with **coexisting angina**, **myocardial infarction** or **cardiac arrhythmias**.
2. **Angina pectoris and MI**: By reducing myocardial O2 demand by decreasing heart rate, myocardial contractility and blood pressure.
3. **Atrial arrhythmias**

Therapeutic uses of β-blockers

1. **Congestive cardiac failure:** Chronic use of β-blockers such as carvedilol, metoprolol and bisoprolol has shown to reduce the mortality rate in chronic heart failure.
2. **Pheochromocytoma:** β-Blockers are used to control the cardiac manifestations of pheochromocytoma but should not be given alone.
3. **Glaucoma:** By decreasing the IOP. Timolol is the most frequently used β-blocker in glaucoma.

Therapeutic uses of β-blockers

1. **Prophylaxis of migraine:** Propranolol, atenolol and metoprolol are effective in reducing the frequency of migraine headaches. The mechanism is not known.

2. **Hyperthyroidism:** The signs and symptoms of hyperthyroidism such as tachycardia, palpitation, tremor, anxiety, etc. are reduced due to the blockade of β-receptors. **Propranolol** is used in thyroid storms.

3. **Essential tremors:** **Oral propranolol**

4. **Acute anxiety states:** β-Blockers are useful in controlling the symptoms of acute anxiety such as palpitation, tachycardia, tremor, sweating,

Nonselective a blockers			
Propranolol	Competitive block of β receptors, local anesthetic effect	Angina, arrhythmias (treatment and prophylaxis), hypertension, thyrotoxicosis, tremor, stage fright, migraine	
Timolol, betaxolol, others: lack local anesthetic action; useful in glaucoma *Pindolol:* partial agonist action; possibly safer in asthma *Nadolol:* like propranolol but longer action (up to 24 h) and less CNS effect			
$Beta_1$-selective blockers			
Atenolol	Competitive block of β_1 receptors	Hypertension, angina, arrhythmias	
Esmolol: IV agent for perioperative and thyroid storm arrhythmias, hypertensive emergency *Metoprolol:* like atenolol, oral, shown to reduce mortality in heart failure *Nebivolol:* oral β_1-selective blocker with additional nitric oxide–dependent vasodilating action			
$Beta_2$-selective blockers			
Butoxamine	Competitive block of β_2 receptors	**None • research use only**	—
Alpha + beta blockers			
Labetalol	Four isomers; 2 bind and block both α and β receptors	Hypertension, hypertensive emergencies (IV)	
Carvedilol: like labetalol, 2 isomers; shown to reduce mortality in heart failure			

CATECHOLAMINES

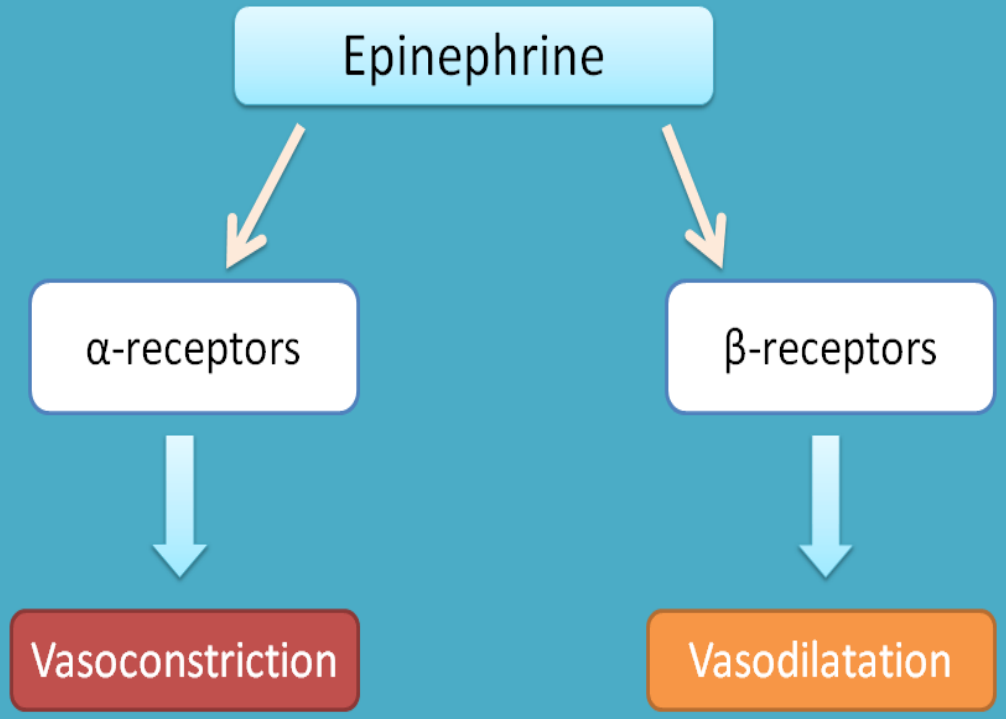
- Rapid onset of action
- Brief duration of action
- Not administered orally
- Do not penetrate the blood–brain barrier

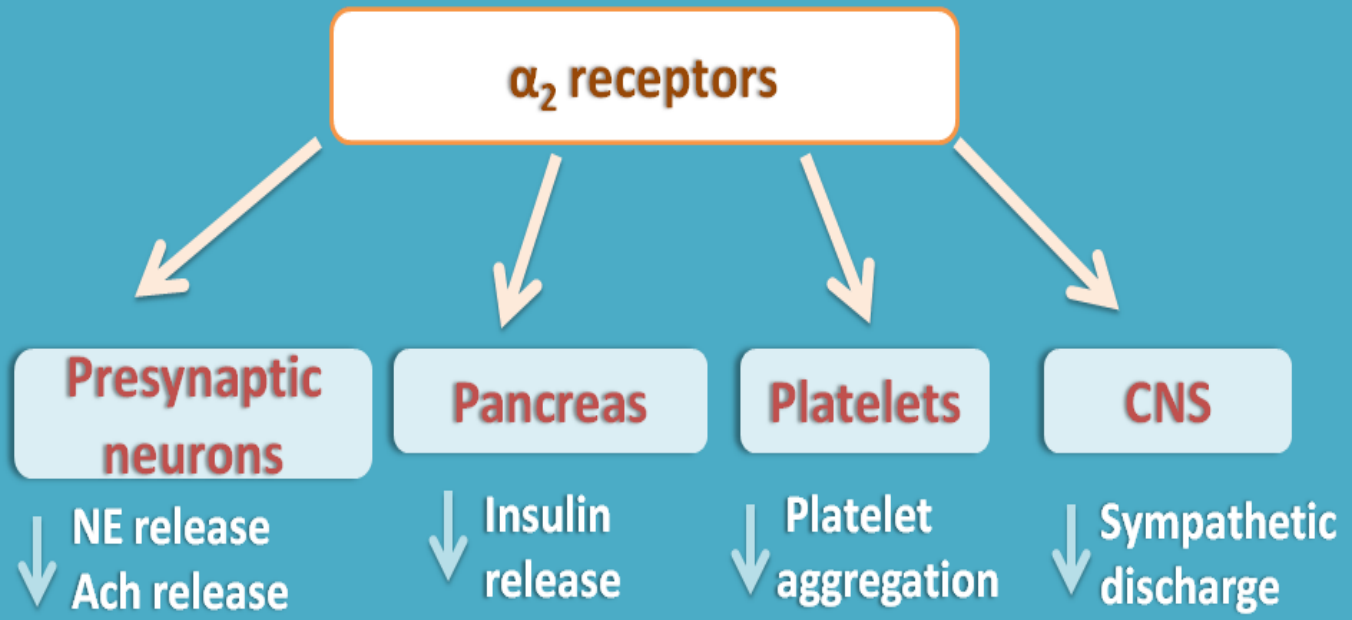
NONCATECHOL–AMINES

Compared to catecholamines:

- Longer duration of action
- All can be administered orally or via inhalation

DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
Epinephrine	α_1, α_2 β_1, β_2	Acute asthma Anaphylactic shock In local anesthetics to increase duration of action
Norepinephrine	α_1, α_2 β_1	Treatment of shock
Isoproterenol	β_1, β_2	As a cardiac stimulant
Dopamine	Dopaminergic α_1, β_1	Treatment of shock Treatment of congestive heart failure Raise blood pressure
Dobutamine	β_1	Treatment of acute heart failure
Oxymetazoline	α_1	As a nasal decongestant
Phenylephrine	α_1	As a nasal decongestant Raise blood pressure Treatment of paroxysmal supraventricular tachycardia
Clonidine	α_2	Treatment of hypertension
Albuterol *Terbutaline*	β_2	Treatment of bronchospasm (short acting)
Salmeterol *Formoterol*	β_2	Treatment of bronchospasm (long acting)
Amphetamine	α, β, CNS	As a CNS stimulant in treatment of children with attention deficit syndrome, narcolepsy, and for appetite control
Ephedrine *Pseudoephedrine*	α, β, CNS	As a nasal decongestant Raise blood pressure


Epinephrine
α-receptors
β-receptors
Vasoconstriction
Vasodilatation


α2 receptors
Presynaptic neurons
Pancreas
Platelets
CNS
NE release
Ach release
Insulin release
Platelet aggregation
Sympathetic discharge

Summary

Thank You

Dr. Sarah Adil