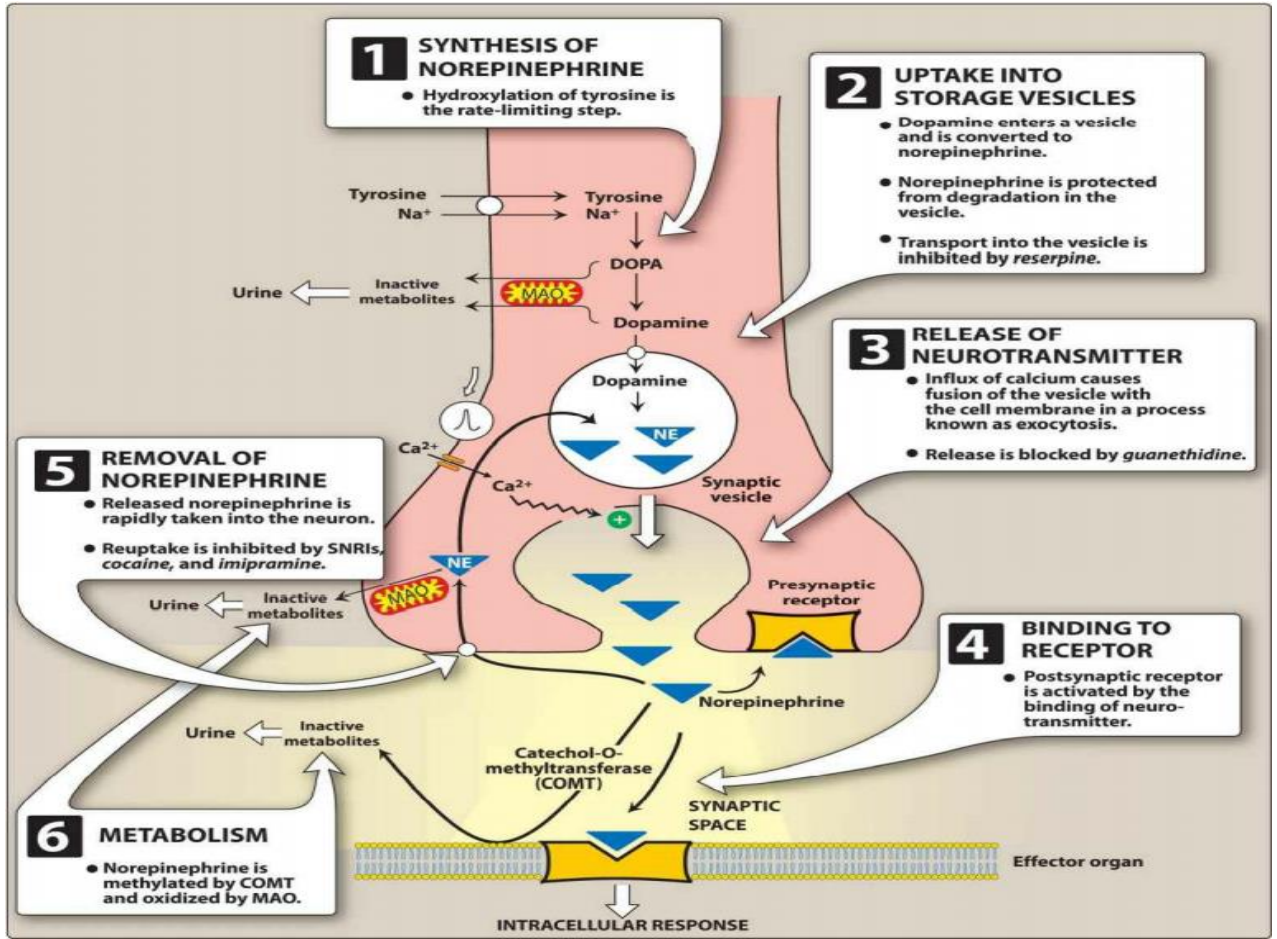
Adrenergic Agonists

Dr. Hasan Falah Alwash

The Adrenergic Neuron

Adrenergic neurons release norepinephrine as the primary neurotransmitter. These neurons are found in the central nervous system (CNS) and in the sympathetic nervous system, where they serve as links between ganglia and the effector organs.

A. Neurotransmission at adrenergic neuron



B. Adrenergic receptors (adrenoceptors)

- Two main families of receptors, designated α and β, are classified based on response to the adrenergic agonists epinephrine, norepinephrine, and isoproterenol.
- Both the α and β receptor types have a number of specific receptor subtypes.

1. α-Adrenoceptors

- α-adrenergic, involving constriction of smooth muscle

a. α1 Receptors These receptors are present on the postsynaptic membrane of the effector organs

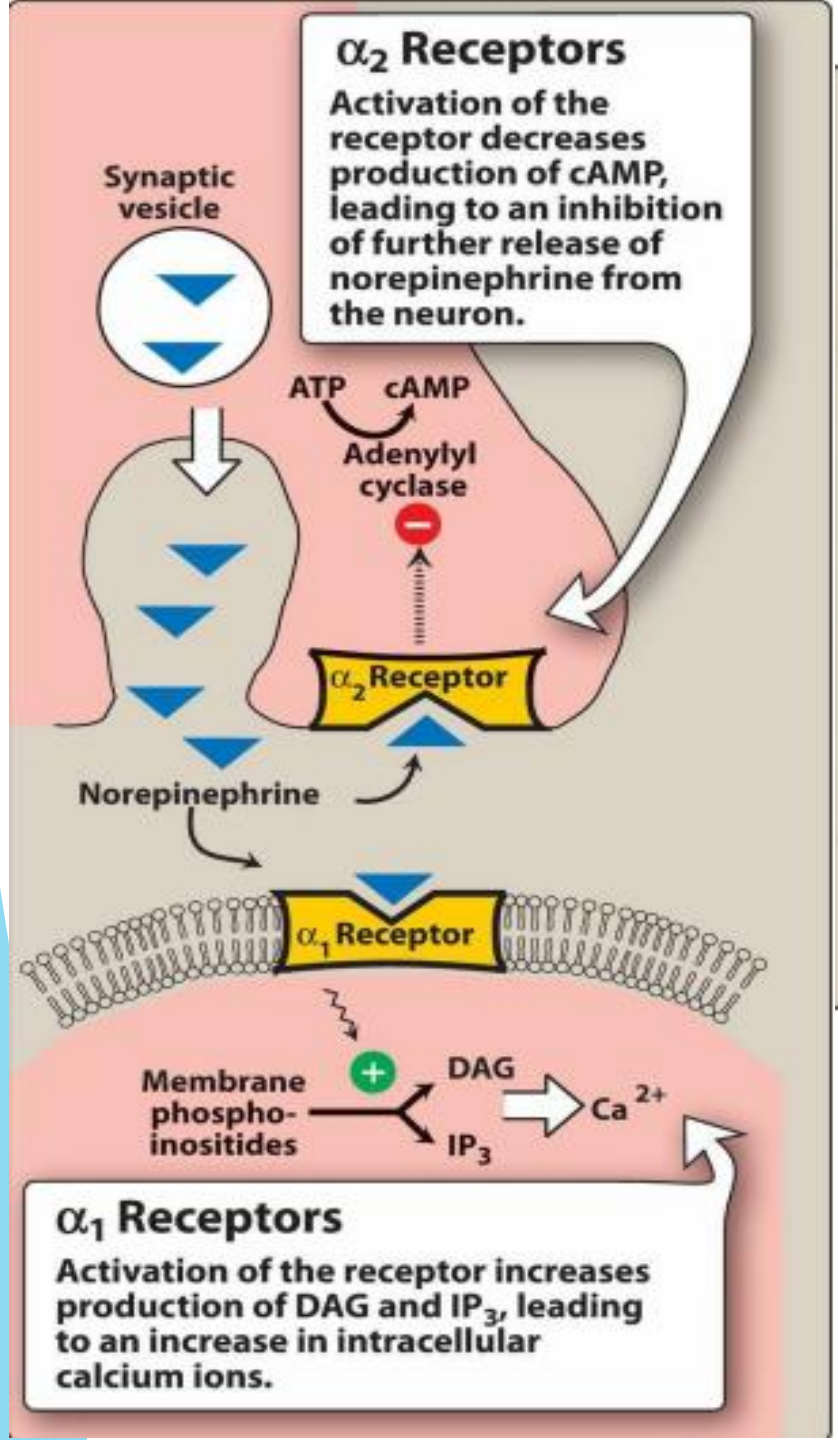
b. α2 Receptors These receptors are located primarily on sympathetic presynaptic nerve endings and control the release of norepinephrine

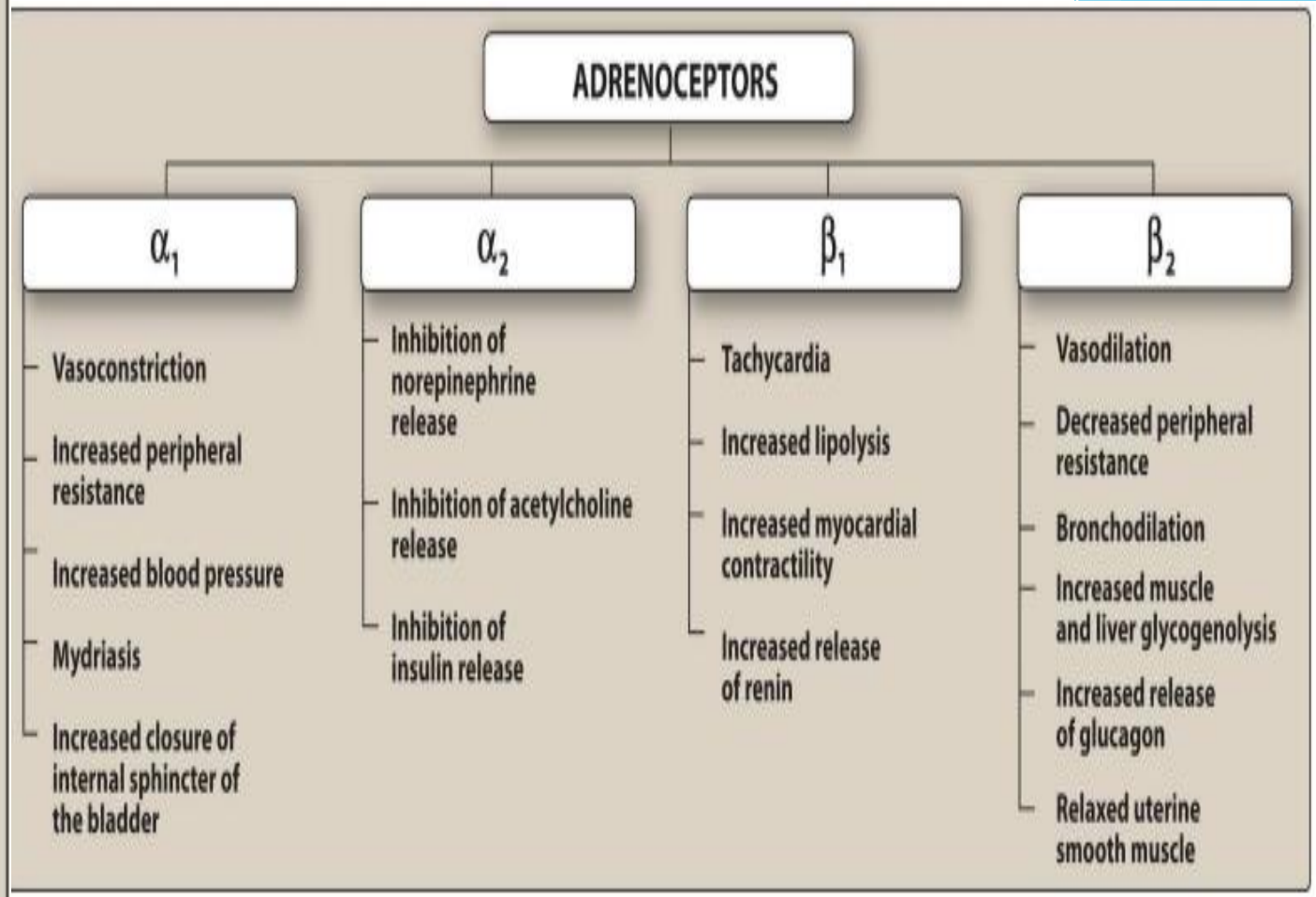
2. β-Adrenoceptors

*Stimulation of β1 receptors characteristically causes cardiac stimulation (increase in heart rate and contractility),

*stimulation of β2 receptors produces vasodilation (in skeletal muscle vascular beds) and smooth muscle relaxation.

*β3 Receptors are involved in lipolysis (along with β1), and also have effects on the detrusor muscle of the bladder


α2 Receptors
Activation of the receptor decreases production of cAMP, leading to an inhibition of further release of norepinephrine from the neuron.
Synaptic vesicle
ATP
cAMP
Adenylyl cyclase
α2 Receptor
Norepinephrine
α1 Receptor
Membrane phospho-inositides
DAG
IP3
Ca 2+
α1 Receptors
Activation of the receptor increases production of DAG and IP3, leading to an increase in intracellular calcium ions.

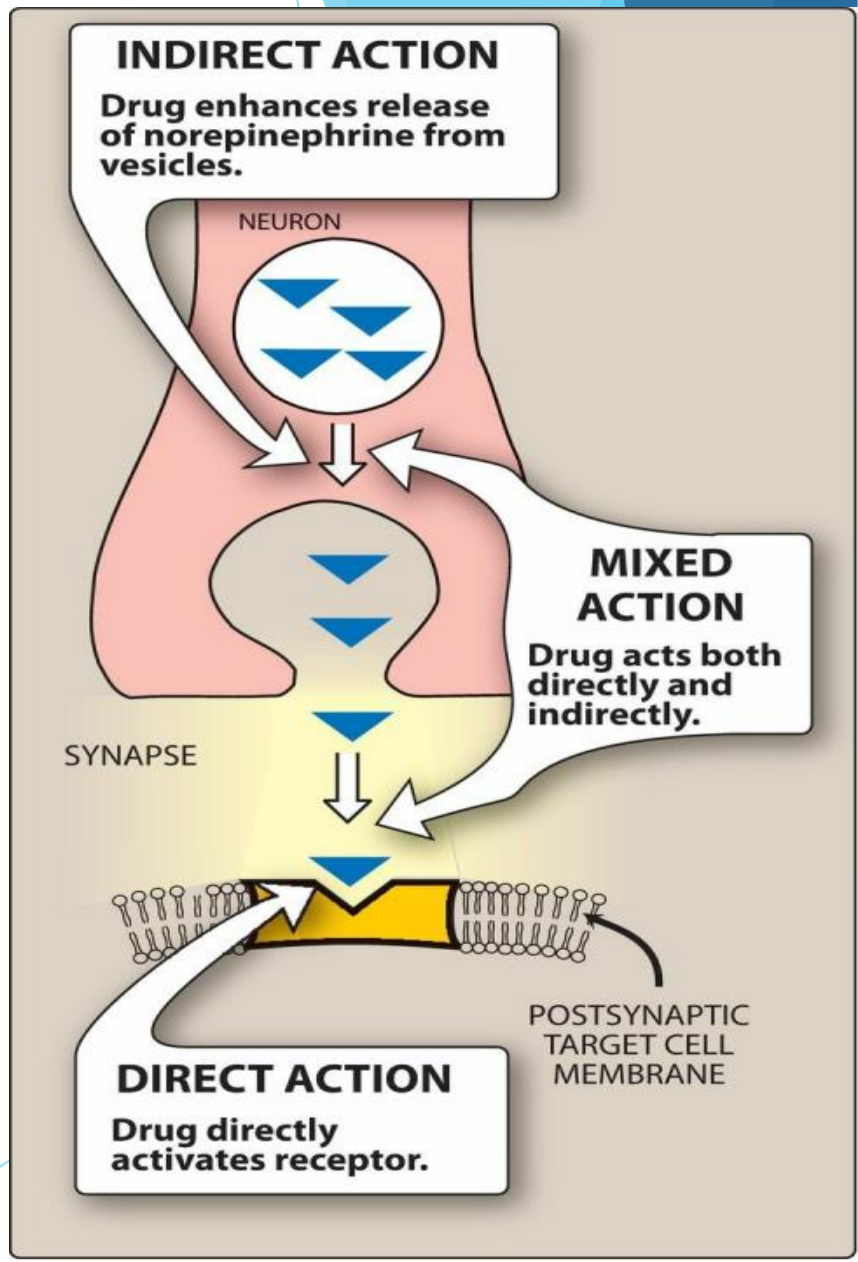

ADRENOCEPTORS
α1
Vasoconstriction
Increased peripheral resistance
Increased blood pressure
Mydriasis
Increased closure of internal sphincter of the bladder
α2
Inhibition of norepinephrine release
Inhibition of acetylcholine release
Inhibition of insulin release
β1
Tachycardia
Increased lipolysis
Increased myocardial contractility
Increased release of renin
β2
Vasodilation
Decreased peripheral resistance
Bronchodilation
Increased muscle and liver glycogenolysis
Increased release of glucagon
Relaxed uterine smooth muscle

TISSUE	RECEPTOR TYPE	ACTION	OPPOSING ACTIONS
Heart			
• Sinus and AV	β_1	↑ Automaticity	Cholinergic receptors
• Conduction pathway	β_1	↑ Conduction velocity, automaticity	Cholinergic receptors
• Myofibrils	β_1	↑ Contractility, automaticity	
Vascular smooth muscle	β_2	Vasodilation	α-Adrenergic receptors
Bronchial smooth muscle	β_2	Bronchodilation	Cholinergic receptors
Kidneys	β_1	↑ Renin release	α_1-Adrenergic receptors
Liver	β_2, α_1	↑ Glycogenolysis and gluconeogenesis	—
Adipose tissue	β_1, β_3	↑ Lipolysis	α_2-Adrenergic receptors
Skeletal muscle	β_2	↑ Increased contractility Potassium uptake; glycogenolysis Dilates arteries to skeletal muscle Tremor	—
Eye-ciliary muscle	β_2	Relaxation	Cholinergic receptors
GI tract	β_2	↓ Motility	Cholinergic receptors
Gall bladder	β_2	Relaxation	Cholinergic receptors
Urinary bladder detrusor muscle	β_2, β_3	Relaxation	Cholinergic receptors
Uterus	β_2	Relaxation	Oxytocin

Characteristics of Adrenergic Agonists

- Mechanism of action of adrenergic agonists

1. Direct-acting agonists These drugs act directly on α or β receptors, producing effects similar to those that occur following stimulation of sympathetic nerves or release of epinephrine
2. Indirect-acting agonists These agents may block the reuptake of norepinephrine or cause the release of norepinephrine from the cytoplasmic pools or vesicles of the adrenergic neuron
3. Mixed-action agonists Ephedrine and its stereoisomer, pseudoephedrine, both stimulate adrenoceptors directly and enhance release of norepinephrine from the adrenergic neuron



Direct-Acting Adrenergic Agonists

A. Epinephrine

*Therapeutic uses :

1. Bronchospasm
2. Anaphylactic shock
3. Cardiac arrest
4. Local anesthesia :Epinephrine greatly increases the duration of local anesthesia by producing vasoconstriction at the site of injection. Epinephrine also reduces systemic absorption of the local anesthetic
5. Intraocular surgery Epinephrine is used in the induction and maintenance of mydriasis during intraocular surgery.

*.Adverse effects Epinephrine can produce adverse CNS effects that include anxiety, fear, tension, headache, and tremor. Epinephrine can also induce pulmonary edema

B. Norepinephrine

- Therapeutic uses Norepinephrine is used to treat shock (for example, septic shock), because it increases vascular resistance and, therefore, increases blood pressure. It has no other clinically significant uses.
- Adverse effects These are similar to epinephrine. In addition, norepinephrine is a potent vasoconstrictor and may cause blanching and sloughing of skin along an injected vein.

C. Isoproterenol

stimulates both ß1 - and ß2 - adrenergic receptors. Its nonselectivity is a disadvantage and the reason why it is rarely used therapeutically

stimulation of the heart (ß1 effect), increasing heart rate, contractility, and cardiac output

. Isoproterenol is also a potent bronchodilator (ß2 effect)

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	Anaphylactic shock Cardiac arrest 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 For relief of eye redness
Phenylephrine	α_1	As a nasal decongestant Raise blood pressure Treatment of paroxysmal supraventricular tachycardia
Clonidine	α_2	Treatment of hypertension
Albuterol *Metaproterenol* *Terbutaline*	β_2	Treatment of bronchospasm (short-acting)
Arformoterol *Formoterol* *Indacaterol* *Salmeterol*	β_2	Treatment of bronchospasm (long-acting)
Amphetamine	α, β, CNS	As a CNS stimulant in treatment of children with ADHD, narcolepsy, and for appetite control
Ephedrine *Pseudoephedrine*	α, β, CNS	Raise blood pressure As a nasal decongestant