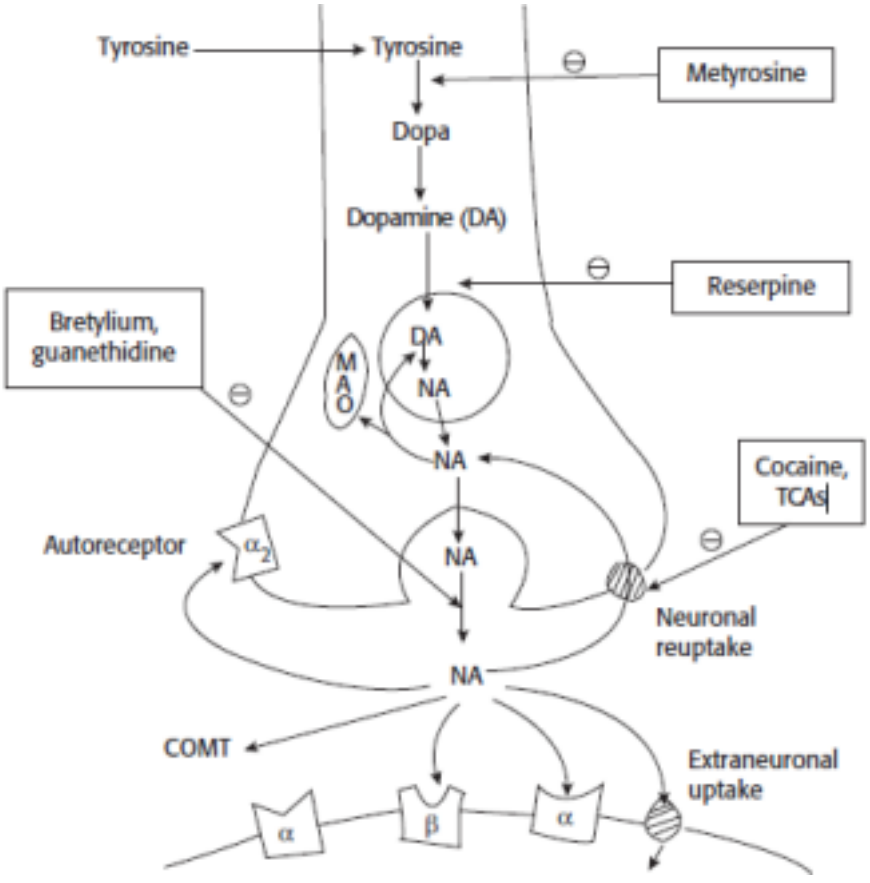
Lec.9 PHARMACOLOGY Dr. Hanadi H. Al-Khafagy Adrenergic Transmission

The transmitter in the sympathetic system is noradrenaline (NA; norepinephrine). Nerves that synthesize, store and release NA are called adrenergic (sympathetic) nerves.

Synthesis of catecholamines begins with the amino acid tyrosine, which is transported into the adrenergic neuron by active transport. In the neuronal cytosol, tyrosine is converted to DOPA by tyrosine hydroxylase and DOPA to dopamine by DOPA decarboxylase. Dopamine enters the storage vesicles of the nerve terminal by active transport, where it is converted to NA by the enzyme dopamine hydroxylase (this enzyme is present only in the storage vesicles); the NA formed gets stored in the vesicles. In the adrenal medulla, NA is further converted to adrenaline by N-methyltransferase. Small quantities of NA are released continuously into the synaptic cleft and large quantities during nerve stimulation.



Three processes are involved in the termination of action of released NA in the synaptic cleft (fate of released NA in the synaptic cleft):

Norepinephrine may
1) diffuse out of the synaptic space and enter the systemic circulation, 2) be metabolized to inactive metabolites by catechol-O-methyltransferase (COMT) in the synaptic space, or
3) undergo reuptake back into the neuron. Reuptake of norepinephrine into the presynaptic neuron is the primary mechanism for termination of its effects.

Adrenergic receptors (adrenoceptors)

In the sympathetic nervous system, several classes of adrenoceptors can be distinguished pharmacologically. Two main families of receptors, designated α and β.

Both the α and β receptor types have a number of specific receptor subtypes.

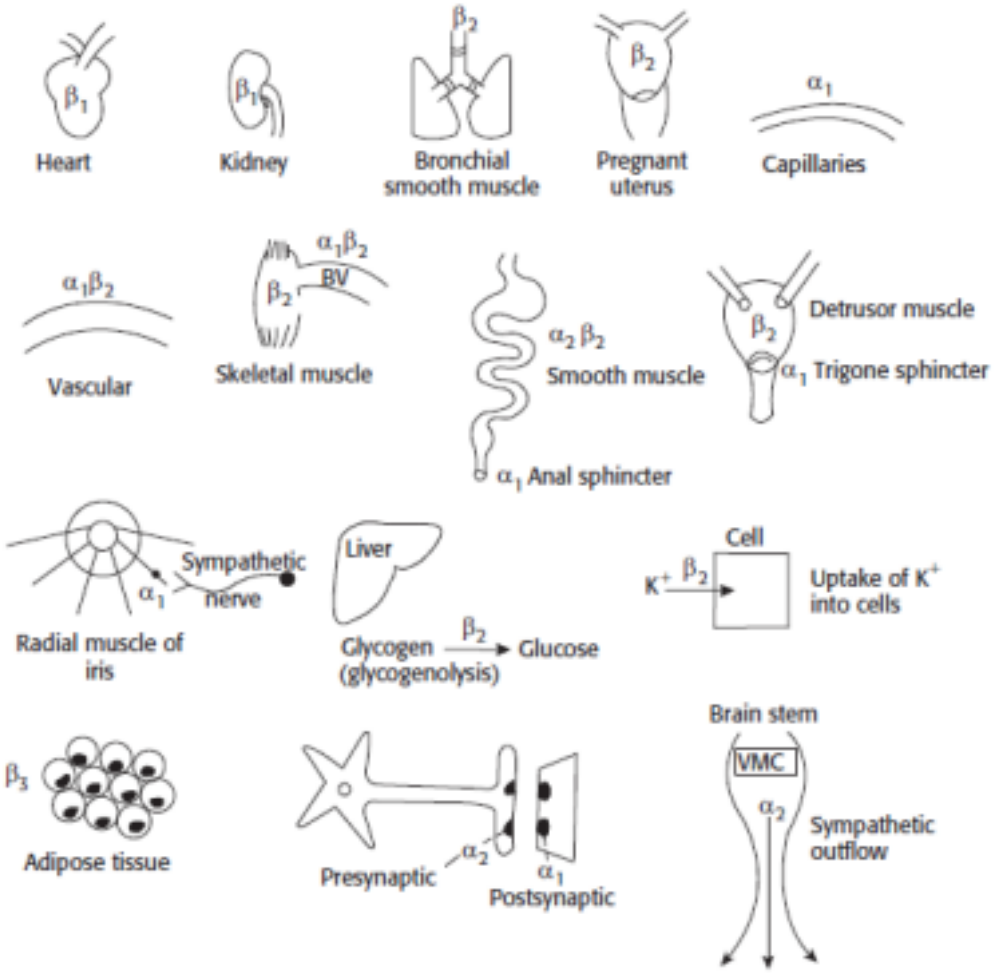
α_1 β_1

α β β_2

α_2 β_3

The α_1 and α_2 receptors are further divided into α_{1A}, α_{1B}, α_{1C}, and α_{1D} and into α_{2A}, α_{2B}, and α_{2C}. This extended classification is necessary for understanding the selectivity of some drugs. For example, tamsulosin is a selective α_{1A} antagonist that is used to treat benign prostatic hyperplasia. The drug has fewer cardiovascular side effects because it targets α_{1A} subtype receptors found primarily in the urinary tract and prostate gland and does not affect the α_{1B} subtype found in the blood vessels.

As a generalization, stimulation of α_1 receptors characteristically produces vasoconstriction (particularly in skin and abdominal viscera) and an increase in total peripheral resistance and blood pressure. Stimulation of β_1 receptors characteristically causes cardiac stimulation (increase in heart rate and contractility), whereas stimulation of β_2 receptors produces vasodilation (in skeletal muscle vascular beds) and smooth muscle relaxation. β_3 Receptors are involved in lipolysis (along with β_1), and also have effects on the detrusor muscle of the bladder.



Desensitization of receptors

Prolonged exposure to the catecholamines reduces the responsiveness of these receptors, a phenomenon known as desensitization. Three mechanisms have been suggested to explain this phenomenon:

1) sequestration of the receptors so that they are unavailable for interaction with the ligand;

2) down-regulation, that is, a disappearance of the receptors either by destruction or by decreased synthesis; and

3) an inability to couple to G-protein, because the receptor has been phosphorylated on the cytoplasmic side.

Adrenergicagonists (Sympathomimetics): The sympathomimetic drugs mimic the effects of sympathetic nerve stimulation. **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 from the adrenal medulla. Examples of direct-acting agonists include epinephrine, norepinephrine, isoproterenol, dopamine, and phenylephrine.

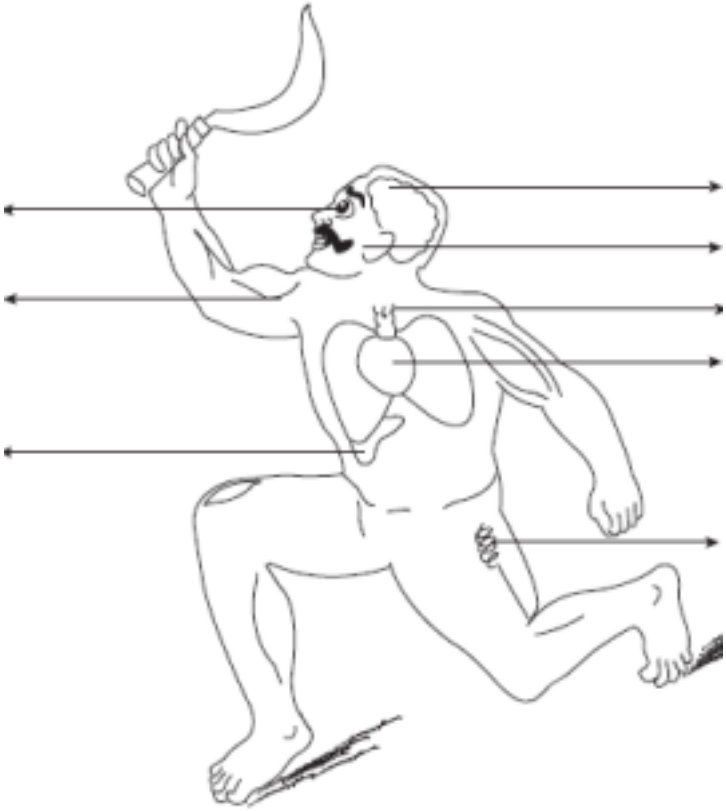
2. Indirect-acting agonists:

These agents may block the reuptake of norepinephrine or cause the release of norepinephrine from the cytoplasmic pools or vesicles of the adrenergic neuron. The norepinephrine then traverses the synapse and binds to α or β receptors. Examples of reuptake inhibitors and agents that cause norepinephrine release include cocaine and amphetamine, respectively.

3. Mixed-action agonists

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

Anger, alert, aggressive



Adipose tissue–lipolysis–energy

Pupillary dilatation (mydriasis)

Increased muscle tone, tremors

Liver–glycogenolysis–more energy

Flushing of the face

Tachypnoea, bronchodilatation

Palpitation–increased cardiac output–increased blood flow to the skeletal muscles

1. Direct-acting agonists:

Epinephrine: It is a catecholamine, which is secreted mainly by adrenal medulla. Adrenaline is a direct acting nonselective adrenergic agonist. Epinephrine (adrenaline) acts on α_1, α_2, β_1, β_2 and β_3 receptors. Actions of epinephrine are: a. Cardiovascular

The major actions of epinephrine are on the cardiovascular system. Epinephrine strengthens the contractility of the myocardium (positive inotrope: β1 action) and increases its rate of contraction (positive chronotrope: β1 action). Therefore, cardiac output increases. These effects increase oxygen demands on the myocardium. Epinephrine activates β1 receptors on the kidney to cause renin release. Renin is an enzyme involved in the production of angiotensin II, a potent vasoconstrictor. Epinephrine constricts arterioles in the skin, mucous membranes, and viscera (α effects), and it dilates vessels going to the liver and skeletal muscle (β2 effects). These combined effects result in a decrease in renal blood flow. Therefore, the cumulative effect is an increase in systolic blood pressure, coupled with a slight decrease in diastolic pressure due to β2 receptor–mediated vasodilation in the skeletal muscle vascular bed.

b. Respiratory

Epinephrine causes powerful bronchodilation by acting directly on bronchial smooth muscle (β2 action). It also inhibits the release of allergy mediators such as histamine from mast cells.

c. Hyperglycemia

Epinephrine has a significant hyperglycemic effect because of increased glycogenolysis in the liver (β2 effect), increased release of glucagon (β2 effect), and a decreased release of insulin (α2 effect).

d. Lipolysis

Epinephrine initiates lipolysis through agonist activity on the β3 receptors of

adipose tissue.

Therapeutic uses of epinephrine (ABCDE)

1. Anaphylactic shock: epinephrine is the life-saving drug in anaphylactic shock. It rapidly reverses the manifestations of severe allergic reactions when given IM. 2. Bronchial asthma: Adrenaline is a powerful bronchodilator and has rapid onset but short duration of action. It is useful for acute attack. Its use has declined because of its dangerous cardiac-stimulant effect. It is given subcutaneously. It can be given by nebulization (as inhalation).

3. Cardiac resuscitation: In the treatment of cardiac arrest due to drowning or electrocution, epinephrine is injected IV along with other supportive measures such as external cardiac massage, as a part of advanced life support.

4. Prolongs the Duration of local anesthesia: epinephrine by its vasoconstrictor effect (α1) delays the systemic absorption of local anesthetic and prolongs the duration of local anesthesia and promotes local hemostasis.

5. Controls Epistaxis and other capillary oozing: Epinephrine is used as a local haemostatic to control bleeding following tooth extraction and during surgical procedures in nose, throat, larynx, etc. because of its vasoconstrictor effect. 6. Intraocular surgery: Epinephrine is used in the induction and maintenance of mydriasis during intraocular surgery.

Adverse effects of epinephrine:

Epinephrine can produce adverse CNS effects that include anxiety, fear, tension, headache, and tremor. It can trigger cardiac arrhythmias, particularly if the patient is receiving digoxin. Epinephrine can also induce pulmonary edema due to increased afterload caused by vasoconstrictive properties of the drug. Patients with hyperthyroidism may have an increased production of adrenergic receptors in the vasculature, leading to an enhanced response to epinephrine, and the dose must be

reduced in these individuals. Inhalation anesthetics also sensitize the heart to the effects of epinephrine, which may lead to tachycardia. Epinephrine increases the release of endogenous stores of glucose. In diabetic patients, dosages of insulin may have to be increased. Nonselective β-blockers prevent vasodilatory effects of epinephrine on β2 receptors, leaving α receptor stimulation unopposed. This may lead to increased peripheral resistance, and increased blood pressure.

Routs of administration:

SC (slow absorption).
IM (rapid absorption).
IV (in emergency: rapid onset of action).
Inhalation (in bronchial asthma).
Intracardiac IC (in resuscitation).

IV and IC routes are very dangerous (must be diluted to 1:10000).

Contraindications:

1. Severe hypertension .
2. Cardiac disease.
3. Thyrotoxicosis.