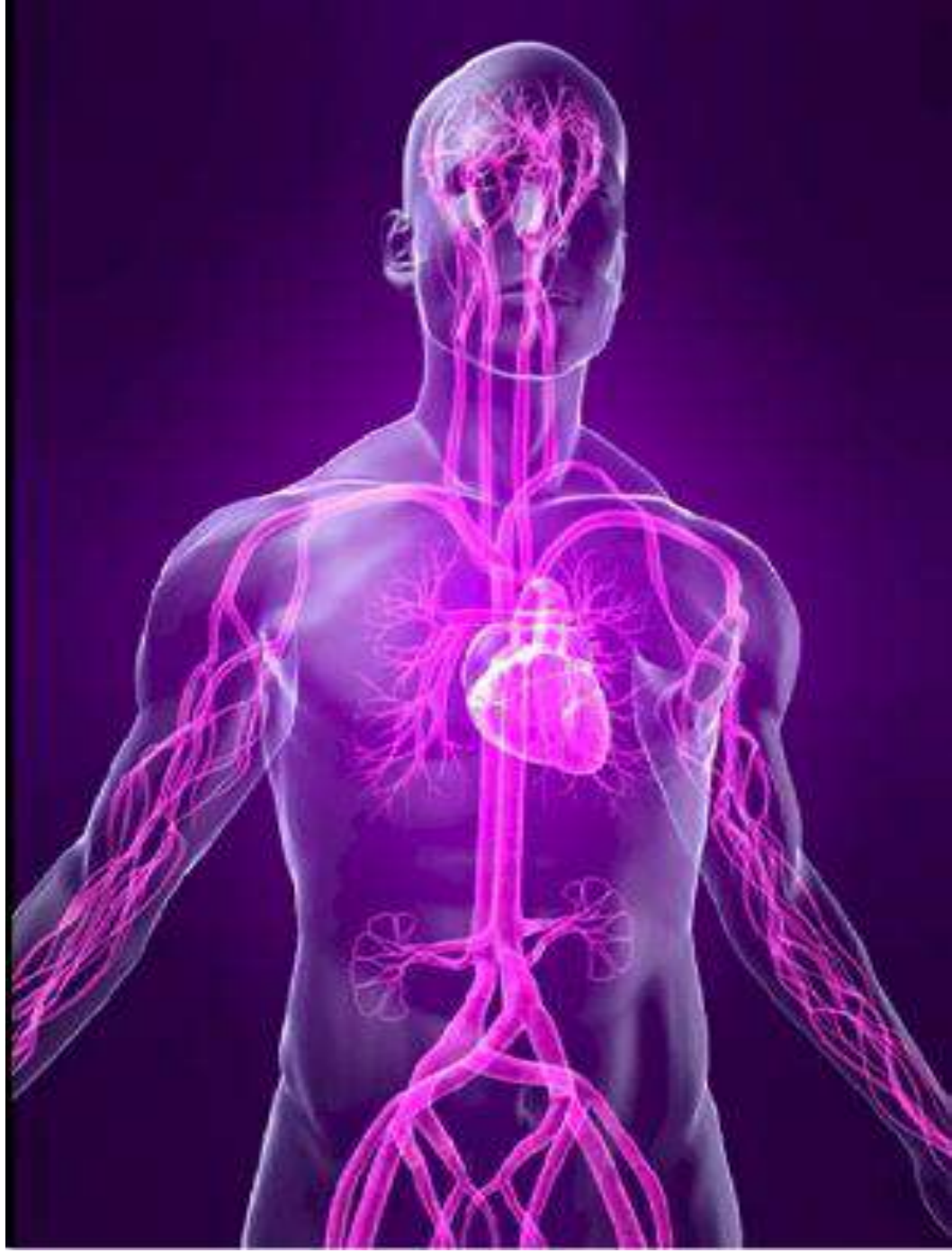
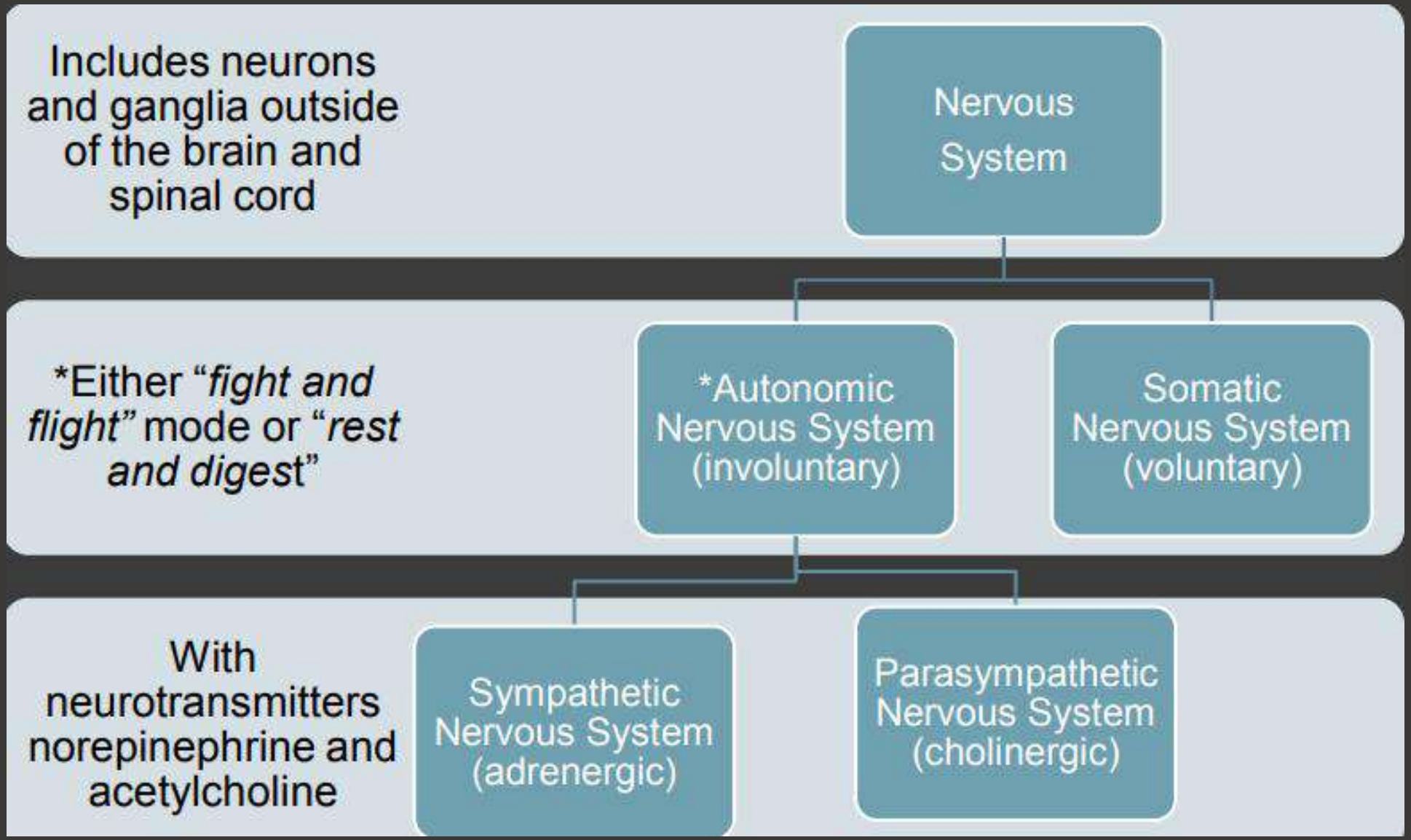
Adrenergic Drugs

Dentistry Collage Dr. Khetam Alhilali

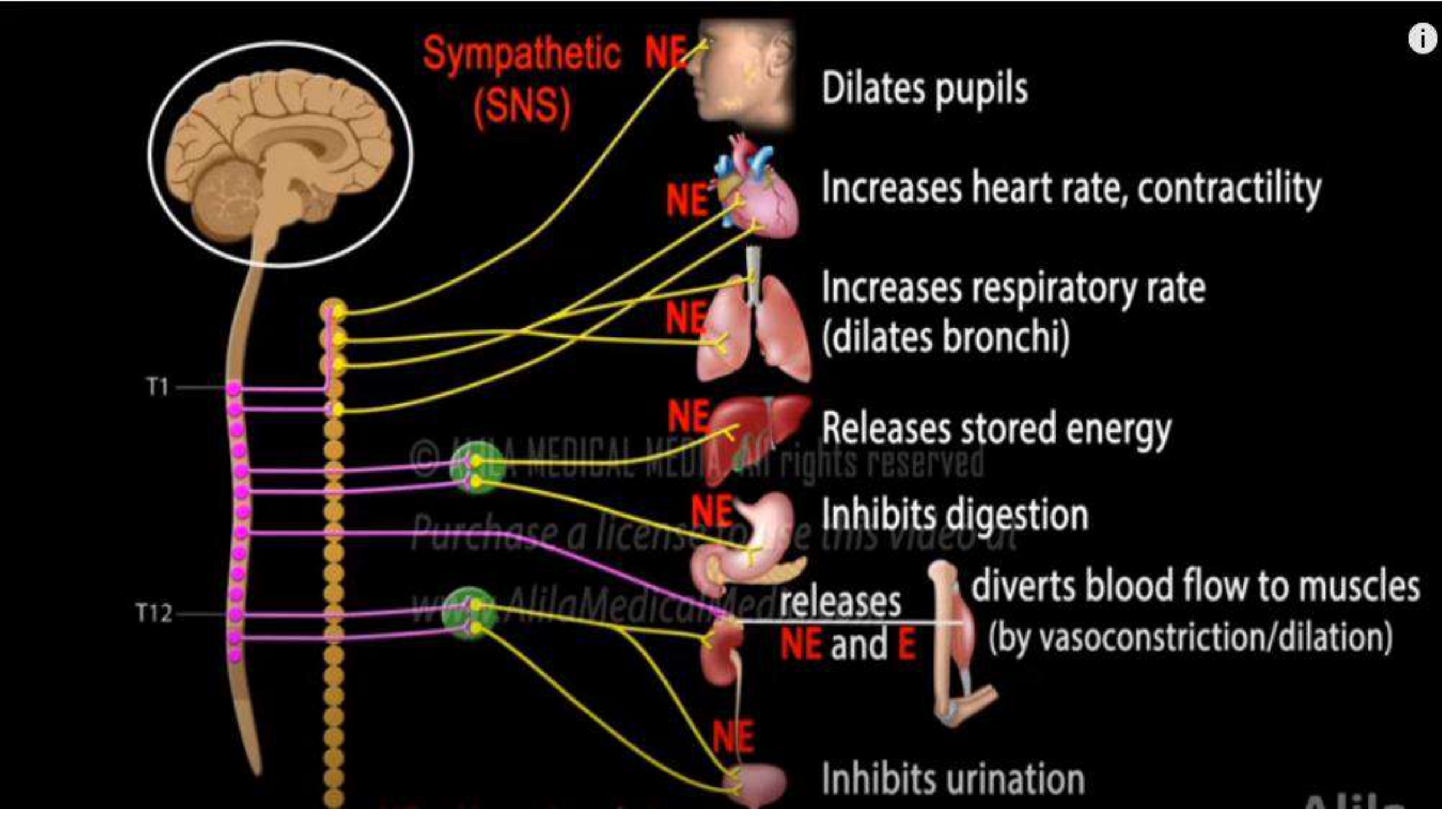


Nervous system



Adrenergic system

- Important regulator of the activities of heart and peripheral vasculature, especially in responses to exercise and stress
- Drugs that mimic the actions of epinephrine are called **sympathomimetic drugs or adrenergic drugs**


Sympathetic (SNS)
NE
Dilates pupils
NE
Increases heart rate, contractility
NE
Increases respiratory rate
(dilates bronchi)
NE
Releases stored energy
T1
NE
Inhibits digestion
T12
releases
NE and E
diverts blood flow to muscles
(by vasoconstriction/dilation)
NE
Inhibits urination

- The **autonomic** nervous system **(ANS)** works to keep the body's against internal and external **homeostasis** changes in the environment which alter the body's internal functions (e.g., blood pressure regulation, urinary excretion, water balance, and digestive functions).

- **Adrenergic agonists** are autonomic nervous system drugs that stimulate the adrenergic receptors of the sympathetic nervous system (SNS), either directly (by reacting with receptor sites) or indirectly (by increasing norepinephrine levels).

- An adrenergic agonist is also called a **sympathomimetic** because it stimulates the effects of SNS.

- **Adrenergic agonists** are further classified into three: alpha- and beta-adrenergic agonists, alpha-specific adrenergic agonists, and beta-specific adrenergic agonists.

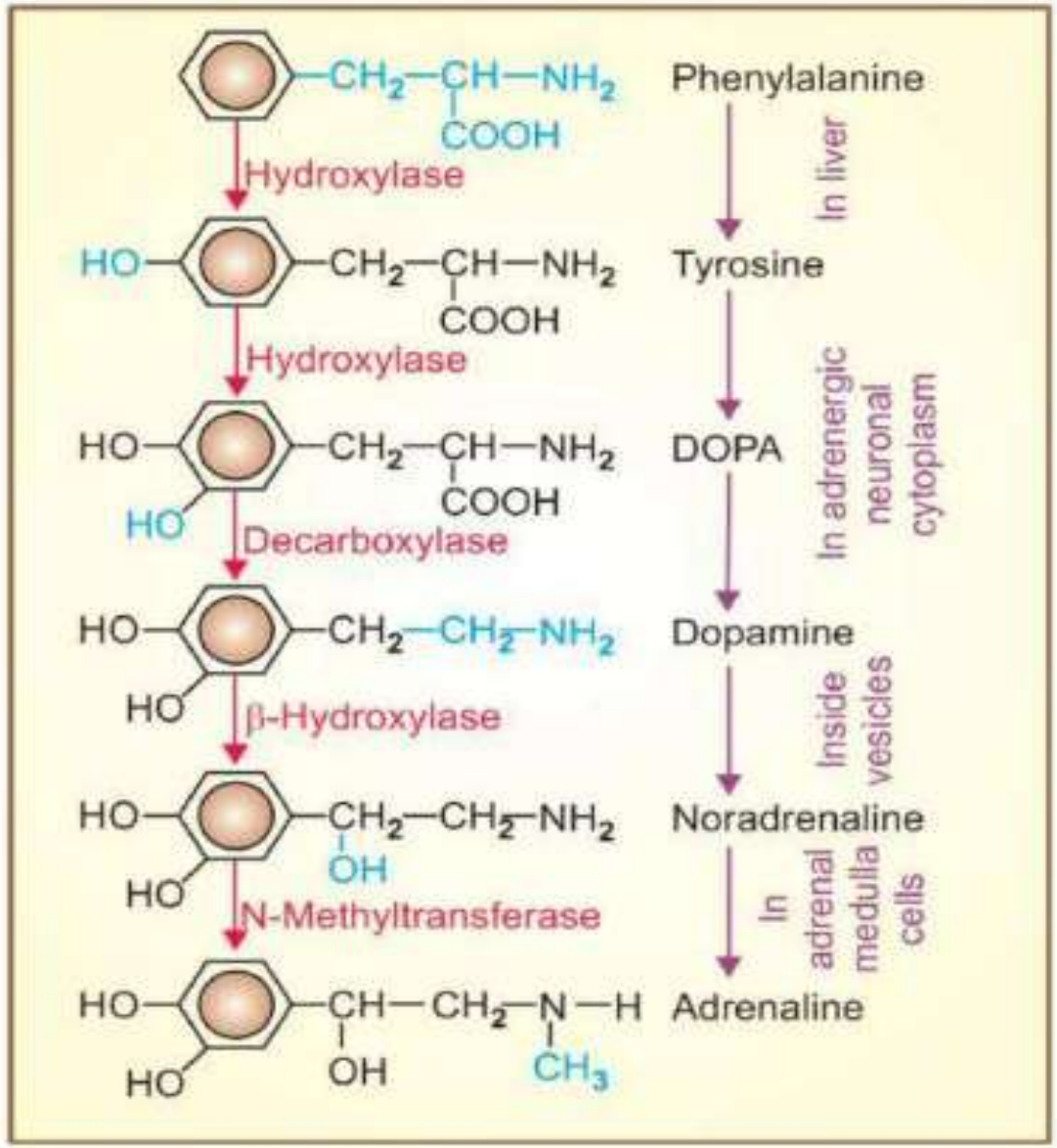
- **Adrenergic Neurotransmission: Introduction to the Neurotransmitters**
  - Norepinephrine: transmitter released at most postganglionic sympathetic terminals
  - Dopamine: major CNS neurotransmitter of mammalian extrapyramidal system and some mesocortical and mesolimbic neuronal pathways.
  - Epinephrine: most important hormone of the adrenal medulla

Adrenergic system

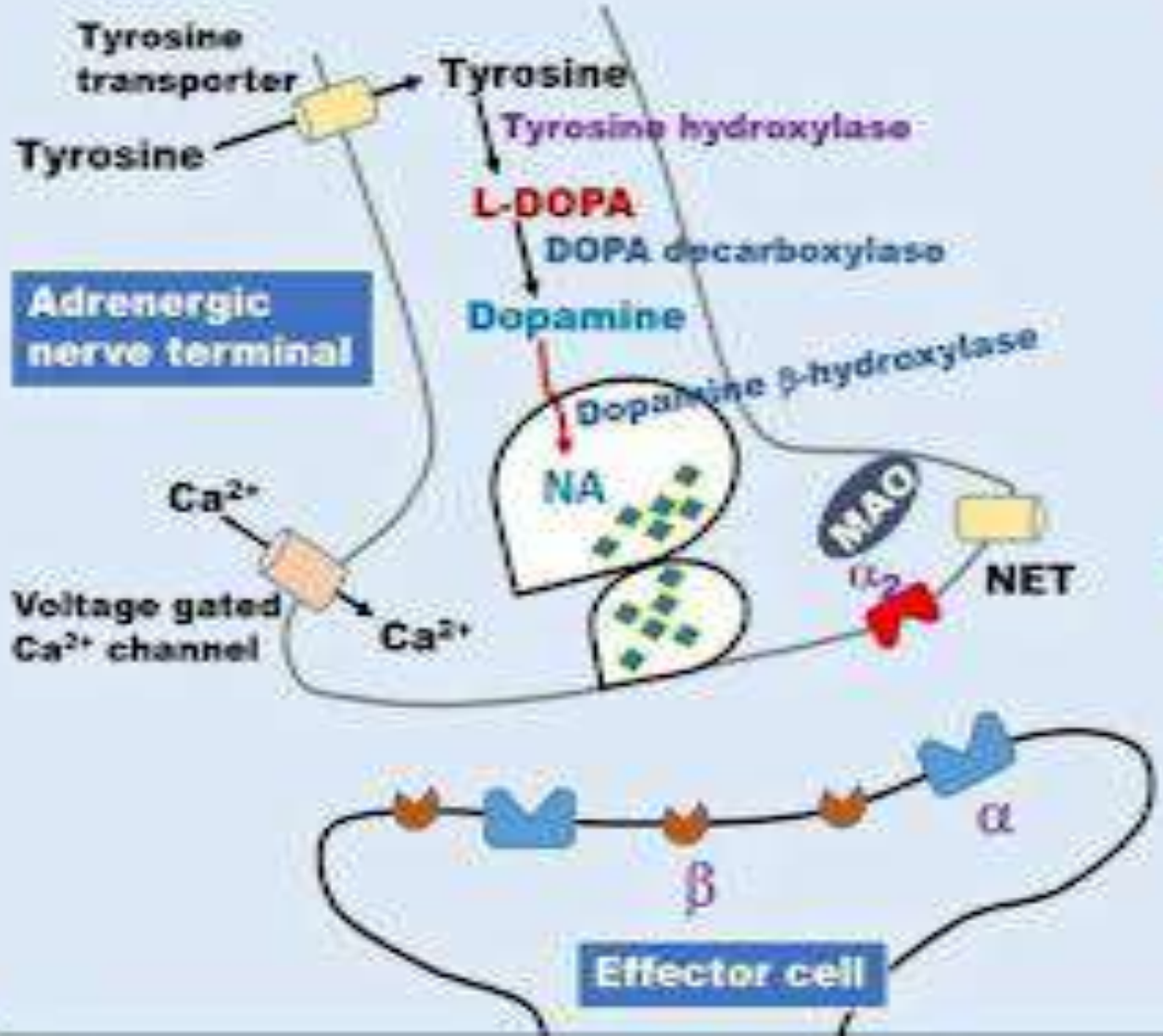
- **Adrenergic transmission**
  - *Noradrenaline/ Norepinephrine:* It is a transmitter at postganglionic sympathetic sites (except sweat glands, hair follicles and some vasodilator fibres) *and in certain areas of brain.*
  - *Adrenaline/ Epinephrine:* It is secreted by adrenal medulla and may have a transmitter role in the brain.
  - *Dopamine:* It is a major transmitter in basal ganglia, limbic system, CTZ, anterior pituitary, etc.

Adrenergic system

- ***Steps in the synthesis of catecholamines (CAs)***
  - **Synthesis of CAs**
  - **Storage of CAs**
  - **Release of CAs**
  - **Uptake of CAs**
  - **Metabolism of CAs**



Adrenergic Neurotransmission



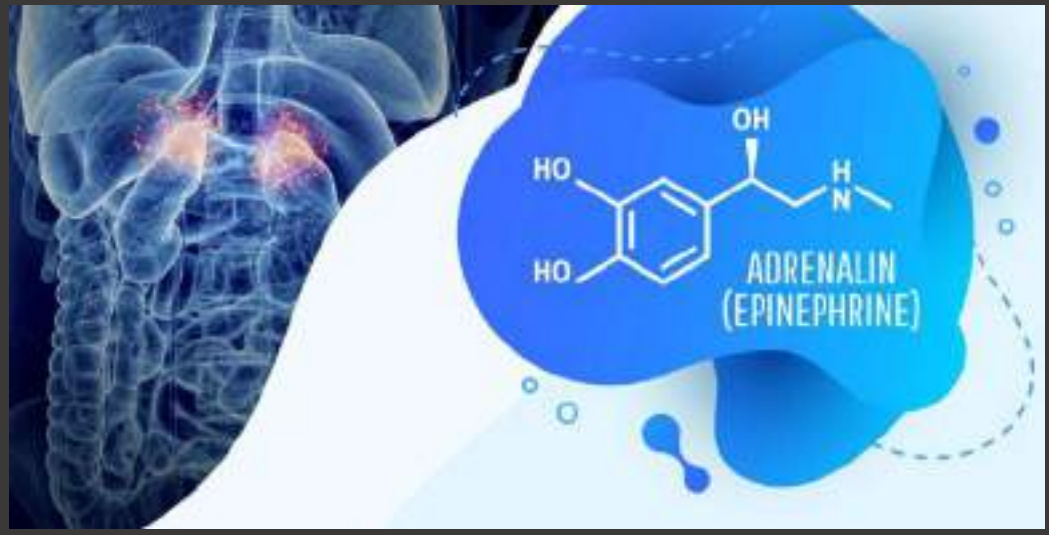
Steps in the synthesis of **Catecholamines (CAs)**

- Synthesis of CAs
- Storage of CAs
- Release of CAs
- Uptake of CAs
- Metabolism of CAs

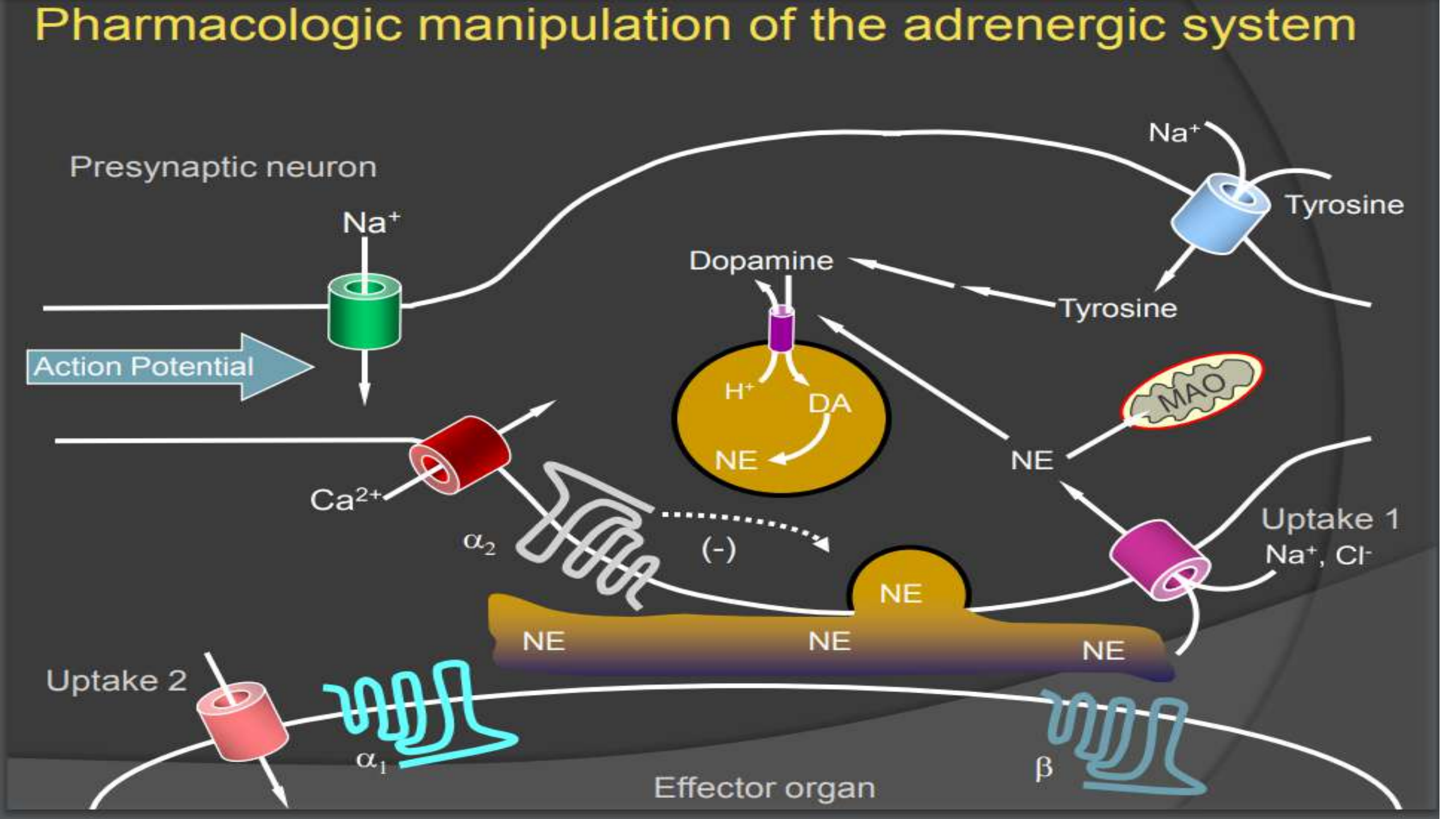
COMT

Introduction

- Epinephrine, also called adrenaline, hormone that is secreted mainly by the medulla of the adrenal glands and that functions primarily to increase cardiac output and to raise glucose levels in the blood.
- Epinephrine typically is released during acute stress, and its stimulatory effects fortify and prepare an individual for either “fight or flight”
- Epinephrine is closely related in structure to norepinephrine, differing only in the presence of a methyl group on the nitrogen side chain.



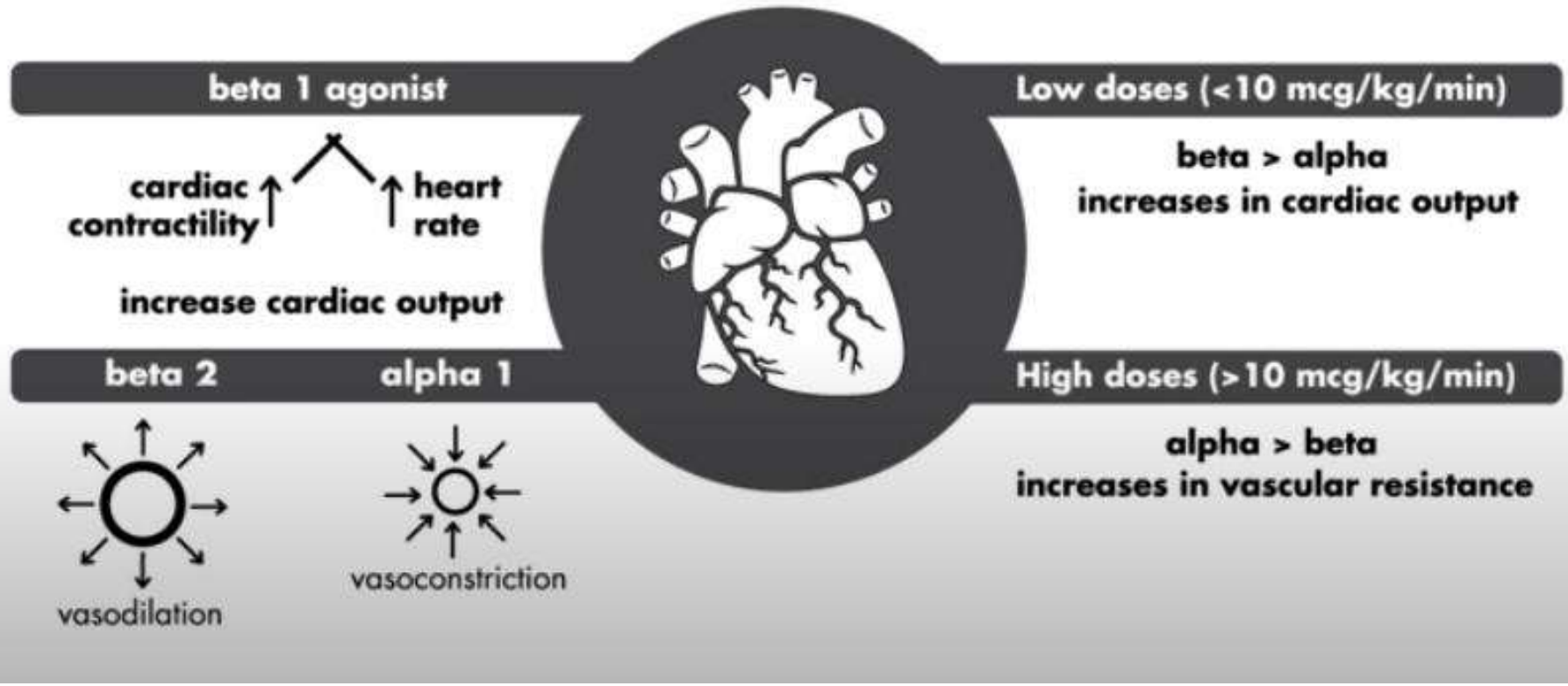
Pharmacologic manipulation of the adrenergic system



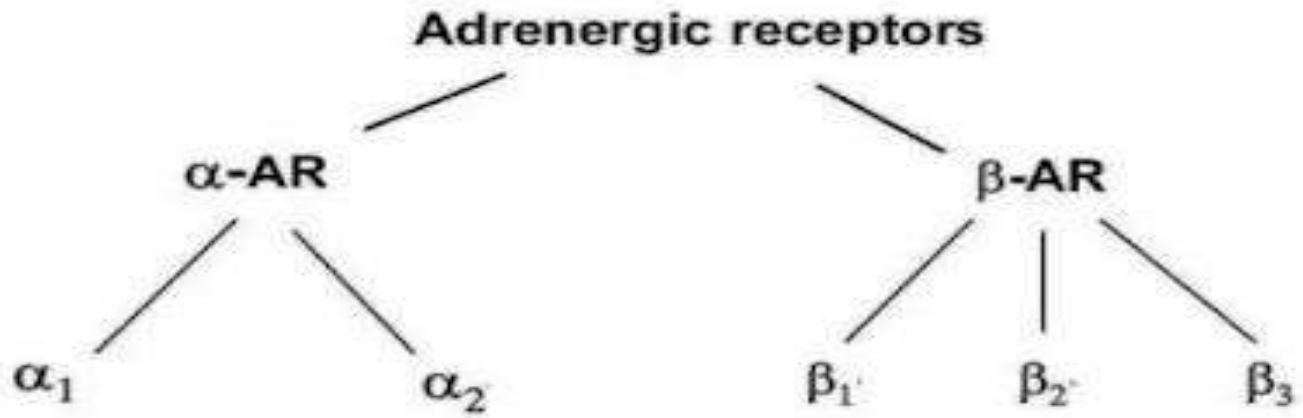
Epinephrine

beta 1 (β_1) beta 2 (β_2) & alpha 1 (α_1)

Dose dependent alpha-1 response



They are all G-protein-coupled receptors. Adrenergic receptors come in two varieties.

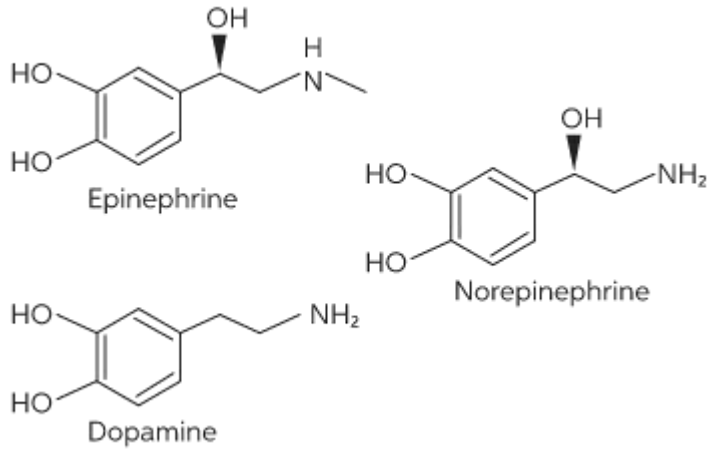


Distribution of Adrenergic Receptor

Receptor type	Tissue location
α1	Arterioles (coronary, visceral, cutaneous), veins, internal sphincters, Iris dilator muscle.
α2	Presynaptic membrane, pancreas, veins, adipose tissue, GIT sphincters, salivary glands.
β1	Heart (SA node, atrial muscle, AV node, ventricles), kidney(JG apparatus), Adipose tissue.
β2	Arterioles(muscular), veins, bronchi (muscles), liver, pancreas, uterus , Iris constrictor muscle.
β3	Adipose tissue, urinary bladder.

Types and Structure of Catecholamine Hormone

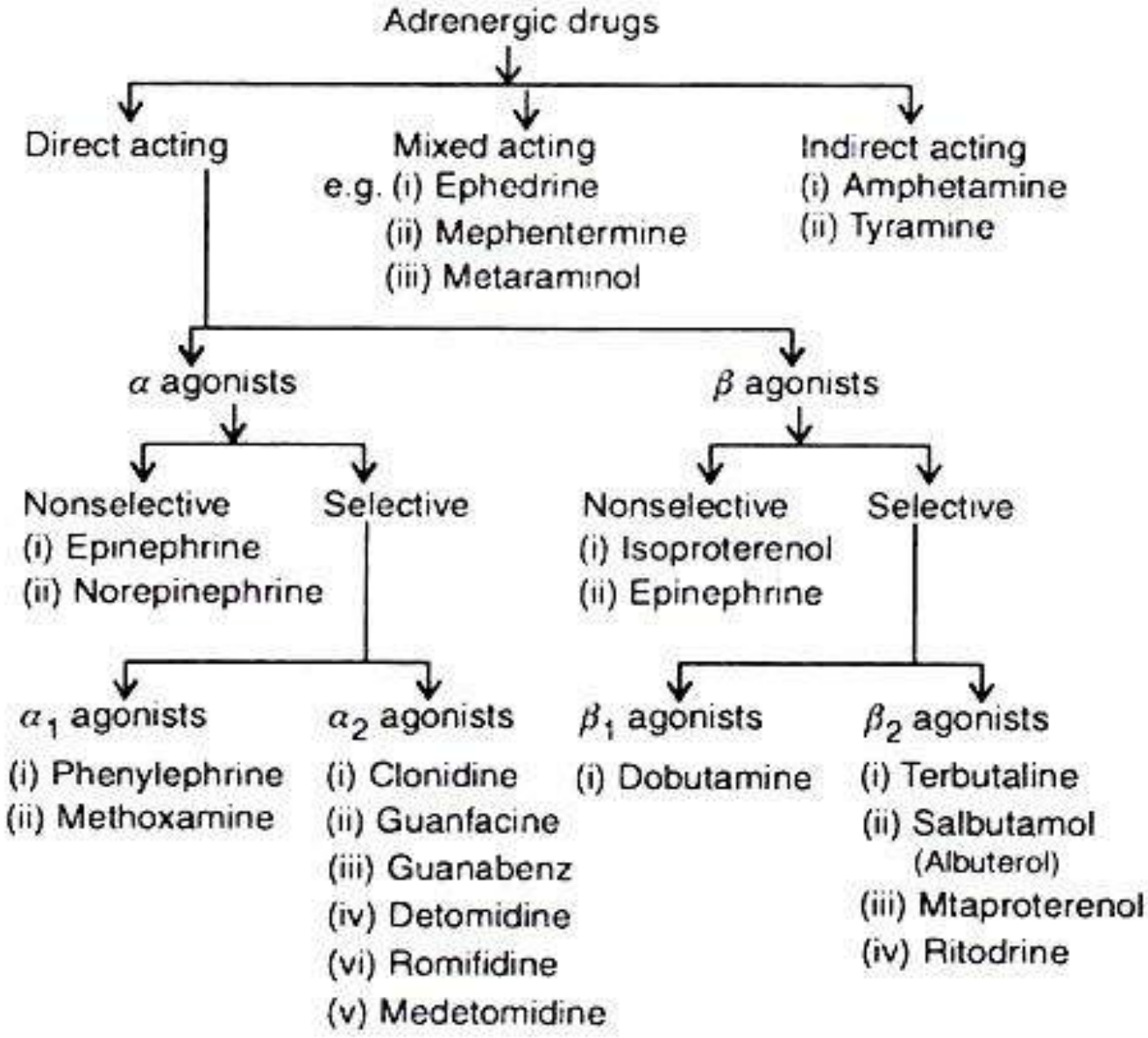
- Catecholamine is a monoamine organic compound consisting of a catechol group (1,2dihydroxybenzene), and a side-chain amine group.
- Catecholamines include three organic compounds:
- Norepinephrine, epinephrine, and dopamine.
- The catecholamines will have a structure of benzene ring with two hydroxyl groups, attached to an amine group through an ethyl chain.



Classification of Adrenergic Drugs:

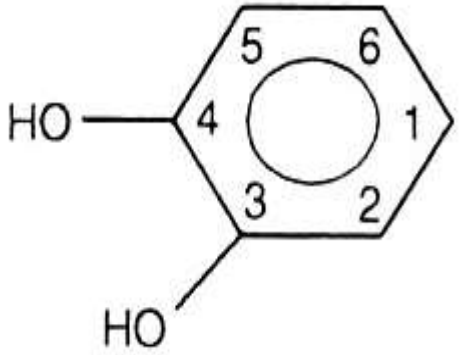
- **(A) On the Basis of Mechanism of Action:**

- Direct acting drugs act directly on adrenergic receptors to elicit responses.
- Indirect acting drugs act by releasing norepinephrine from adrenergic nerve endings. Mixed acting drugs act by both direct and indirect mechanisms.



B. On the Basis of Chemical Structure:

Catecholamines are the drugs which have catechol nucleus in their structures.



Adrenergic drugs

Catecholamines
e.g. (i) Epinephrine
(ii) Norepinephrine
(iii) Dopamine
(iv) Isoproterenol

Nonecatechlamine
e.g. (i) Phenylephrine
(ii) Ephedrine
(iii) Amphetamine
(iv) Methamphetamine
(v) Metaraminol
(vi) Tyramine

Adrenergic Drugs - Classification

I. Directly Acting Sympathomimetics

Catecholamines

Endogenous

- **Epinephrine** (α1+ α2+ β1 + β2 and weak β3action)
- **Norepinephrine** (α1 + α2 + β1 + β3but no β2 action)
- **Dopamine** (D1+D2+ β1with little α action)

Synthetic

- **Isoprenaline** (β1 + β2+ β3but no αaction)
- **Dipivefrine**(prodrug of epinephrine)
- **Dobutamine** (mainly β1action little α1 action)
- **Fenoldopam** (selective D1 agonist)

Non Catecholamines

- **α1 selective agonists**
  Phenylephrine, Naphazoline Oxymetazoline, Xylometazolne
- **α2 selective agonists**
  Clonidine, Apraclonidine Brimonidine , α-methyldopa
- **β1 selective agonists**
  Prenalterol
- **β2 selective agonists**
  Salbutamol, Terbutaline

Adrenergic/ Sympathomimetic drugs

Directly acting drugs

On α –receptors

E.g.. phenylephrine

On β- receptors

Egg. isoprenaline

On both α, β-receptors

Eg. Adrenaline /epinephrine

Indirectly acting drugs

Eg. Tyramine

Mixed acting drugs

Indirect action on low dose, direct action on high dose

Eg. Amphetamine

Dexamphetamine

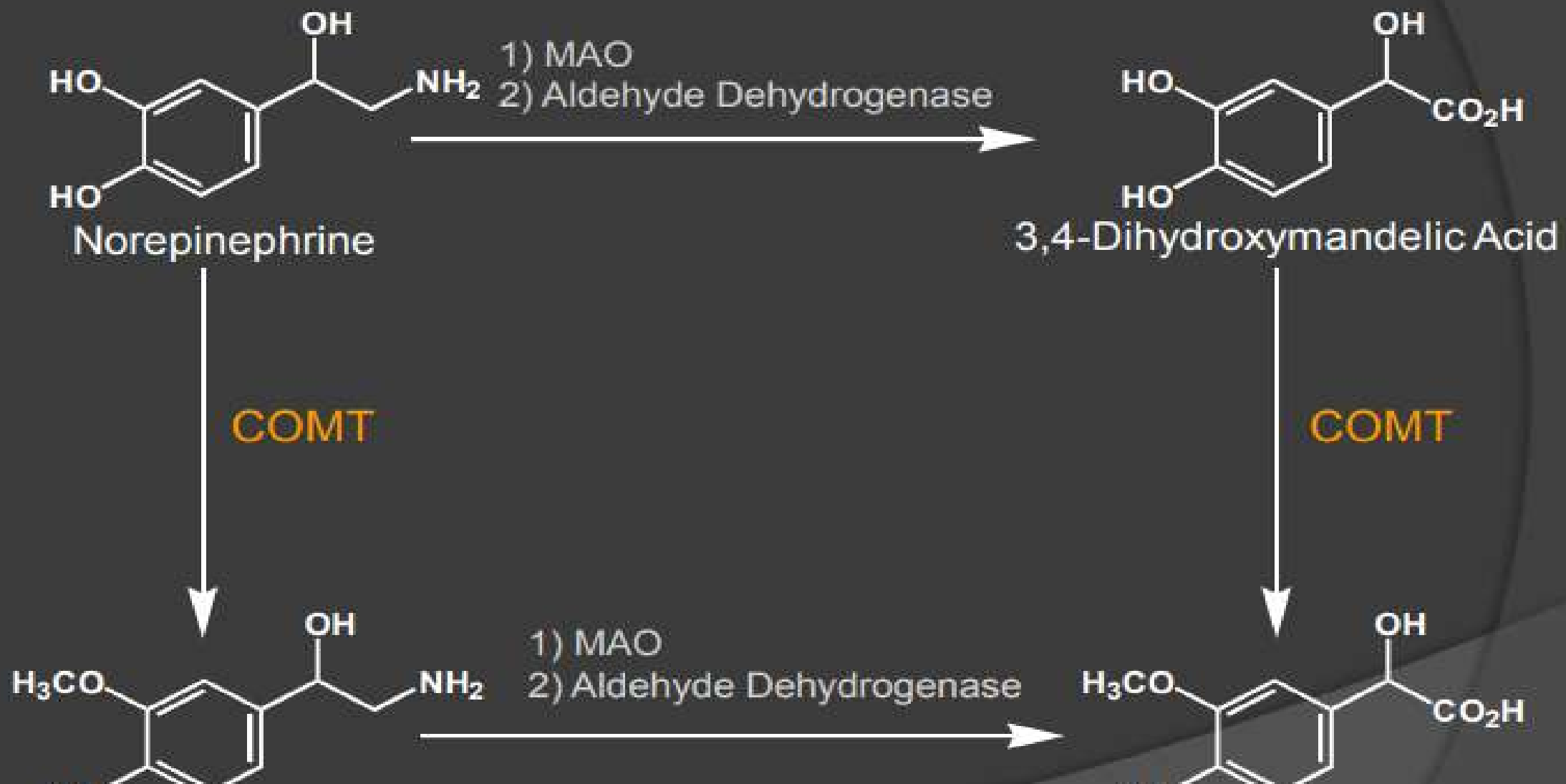
Methamphatamine

Ephedrine

Metabolism of Neurotransmitter

- Catecholamines, both endogenous and exogenous, are primarily metabolized by two enzymes: monoamine oxidase and catechol-O-methyl transferase (COMT).
- MAO is found in cells linked to the surface membrane of mitochondria, which are prevalent in noradrenergic nerve terminals.
- COMT, a widely distributed enzyme found in both neuronal and nonneuronal tissues, operates on catecholamines and their deaminated derivatives generated by MAO activity.
- 3-methoxy-4-hydroxymandelic acid is the primary end metabolite of adrenaline and noradrenaline

Metabolism of norepinephrine



Sympathetic nervous system

Fight or flight response results in:

1. Increased BP
2. Increased blood flow to brain, heart and skeletal muscles
3. Increased muscle glycogen for energy
4. Increased rate of coagulation
5. Pupil dilation

Adrenergic receptors

- Alpha—A1 and A2
- Beta—B1, B2, B3
- Dopamine—subsets D1-5

Review of functions of sympathetic nervous system receptors

- Alpha 1—smooth muscle contraction
- Alpha 2-negative feedback causes less norepinephrine to be released so BP is reduced
- Beta 1—increased heart rate
- Beta 2—bronchodilation
- Beta 3—actual site for lipolysis

Mechanisms of action and effects of adrenergic drugs

- 1. Direct adrenergic drug action
- Affects postsynaptic alpha 1 and beta receptors on target effector organs
- Examples: epinephrine, Isuprel, norepinephrine, phenylephrine

Mechanisms of action cont.

- 2. Indirect adrenergic drug action occurs by stimulation of postsynaptic alpha 1, beta 1 and beta 2 receptors. Cause release of norepinephrine into the synapse of nerve endings or prevent reuptake of norepinephrine.
- Examples include cocaine and TCAs (Tricyclic antidepressants)

- 3. mixed action. Combination of direct and indirect receptor stimulation
- Examples are ephedrine and pseudoephedrine

Indications for use

- Emergency drugs in treatment of acute cardiovascular, respiratory and allergic disorders
- In children, epinephrine may be used to treat bronchospasm due to asthma or allergic reactions
- Phenylephrine may be used to treat sinus congestion

Indications of adrenergics cont.

- Adams Stokes
- Shock
- Inhibition of uterine contractions
- For vasoconstrictive and hemostatic purposes

Contraindications to use of adrenergics

- Cardiac dysrhythmias, angina pectoris
- Hypertension
- Hyperthyroidism
- Cerebrovascular disease
- Distal areas with a single blood supply such as fingers, toes, nose and ears
- Renal impairment use caution

Individual adrenergic drugs

- Epinephrine—prototype
- Effects include: increased BP, increased heart rate, relaxation of bronchial smooth muscle, vasoconstriction in peripheral blood vessels

epinephrine

- Affects both alpha and beta receptors
- Usual doses, beta adenergic effects on heart and vascular smooth muscle will predominate, high doses, alpha adrenergic effects will predominate
- Drug of choice for bronchospasm and laryngeal edema of anaphylaxis with physiologic antagonist to histamine

epinephrine

- Increased glucose, lactate, and fatty acids in the blood due to metabolic effects
- Increased leukocyte and increased coagulation
- Inhibition of insulin secretion

epinephrine

- Excellent for cardiac stimulant and vasoconstrictive effects in cardiac arrest
- Added to local anesthetic
- May be given IV, inhalation, topically
- Not PO

Other adrenergics

- Ephedrine is a mixed acting adrenergic drug. Stimulates alpha and beta receptors. Longer lasting than epinephrine.

- Pseudoephedrine
- Used for bronchodilating and nasal decongestant effects