Sympathomimetic drugs (Adrenergic agonists)

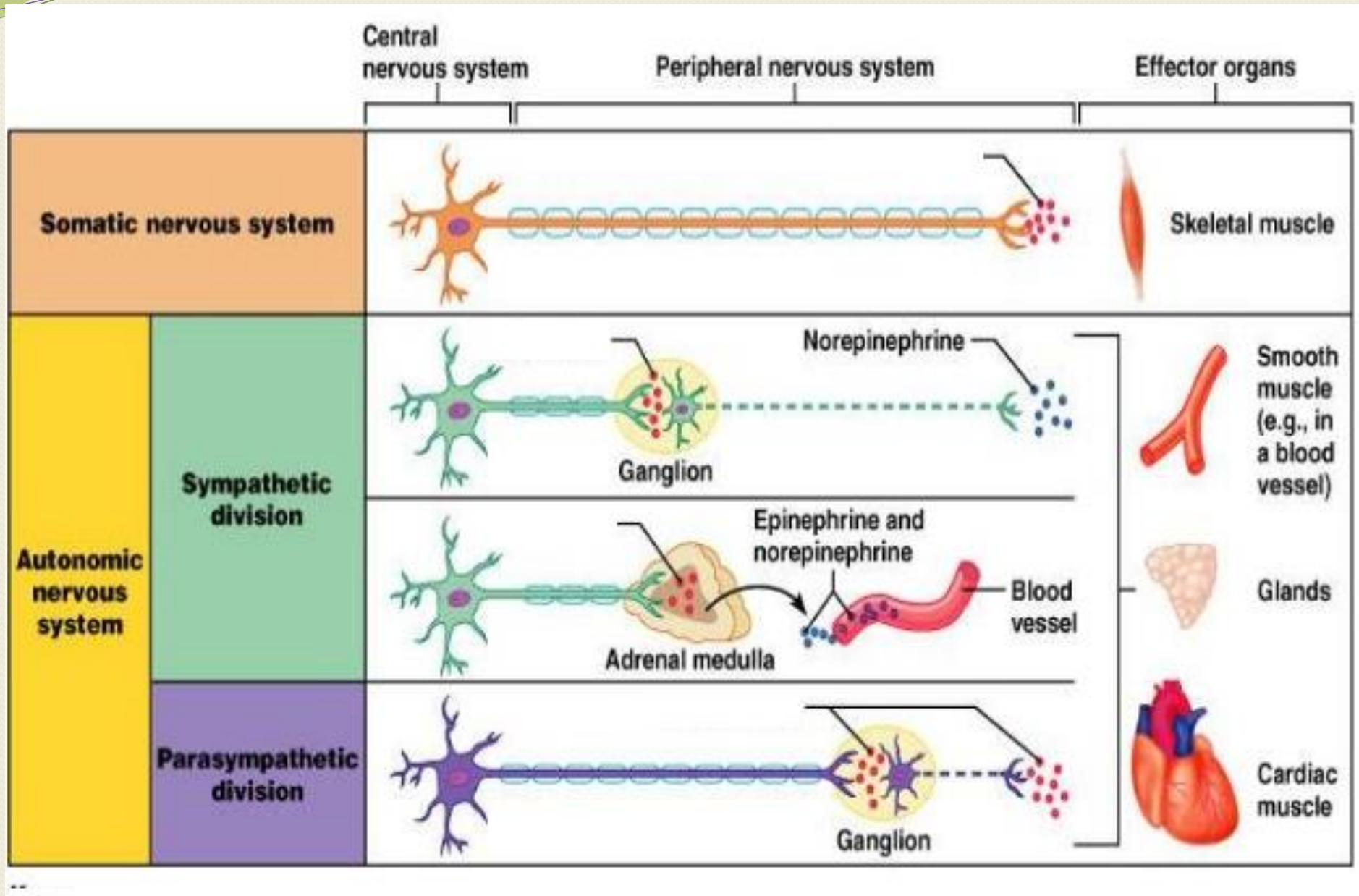
Prof. Hanan Hagar
Pharmacology Department
College of Medicine

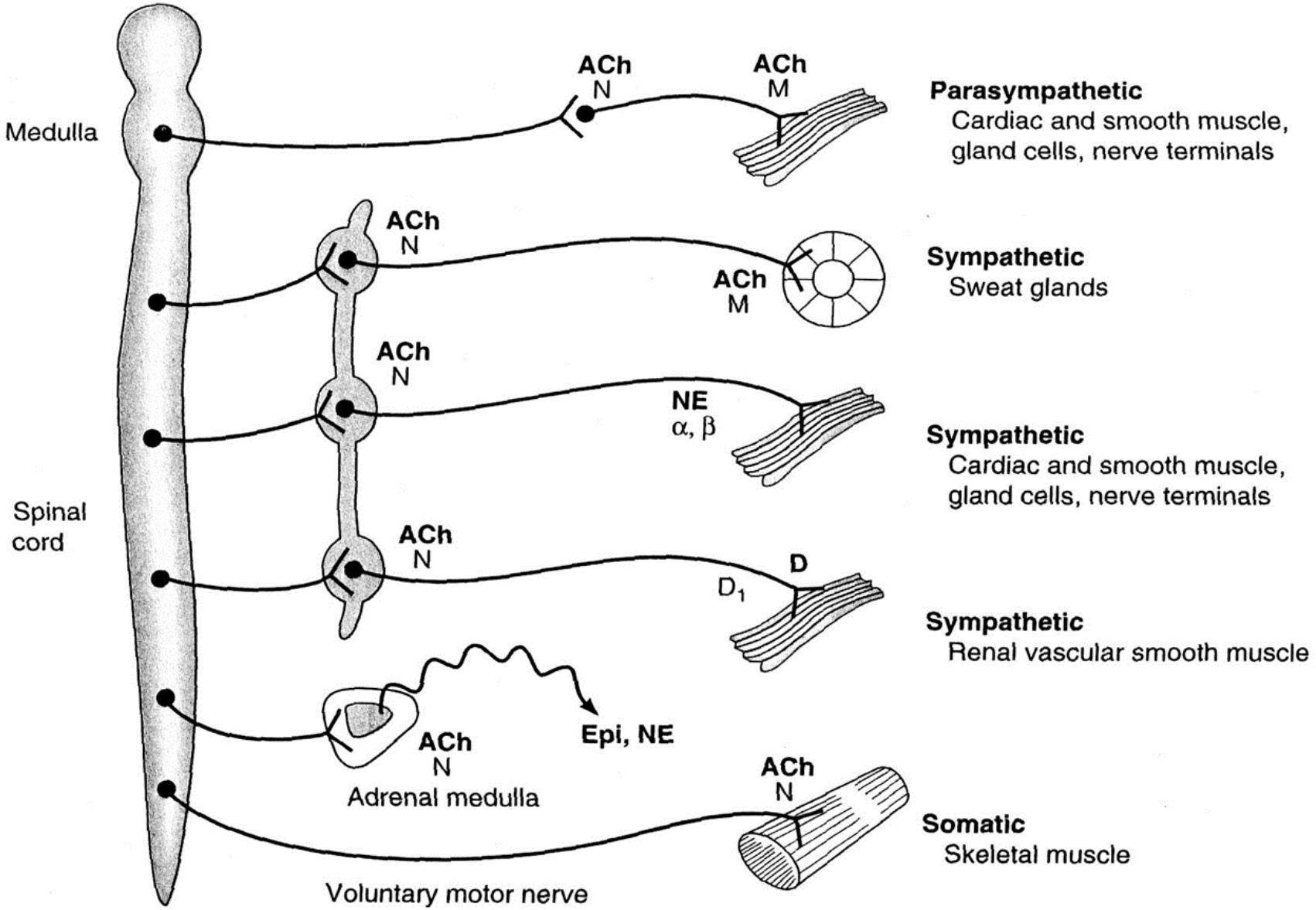
ILOS

- Classify adrenergic agonists according to chemical structure, receptor selectivity and mode of action.

- Discuss pharmacodynamic actions, adverse effects, indications and contraindications of adrenergic agonists

ADRENERGIC DRUGS

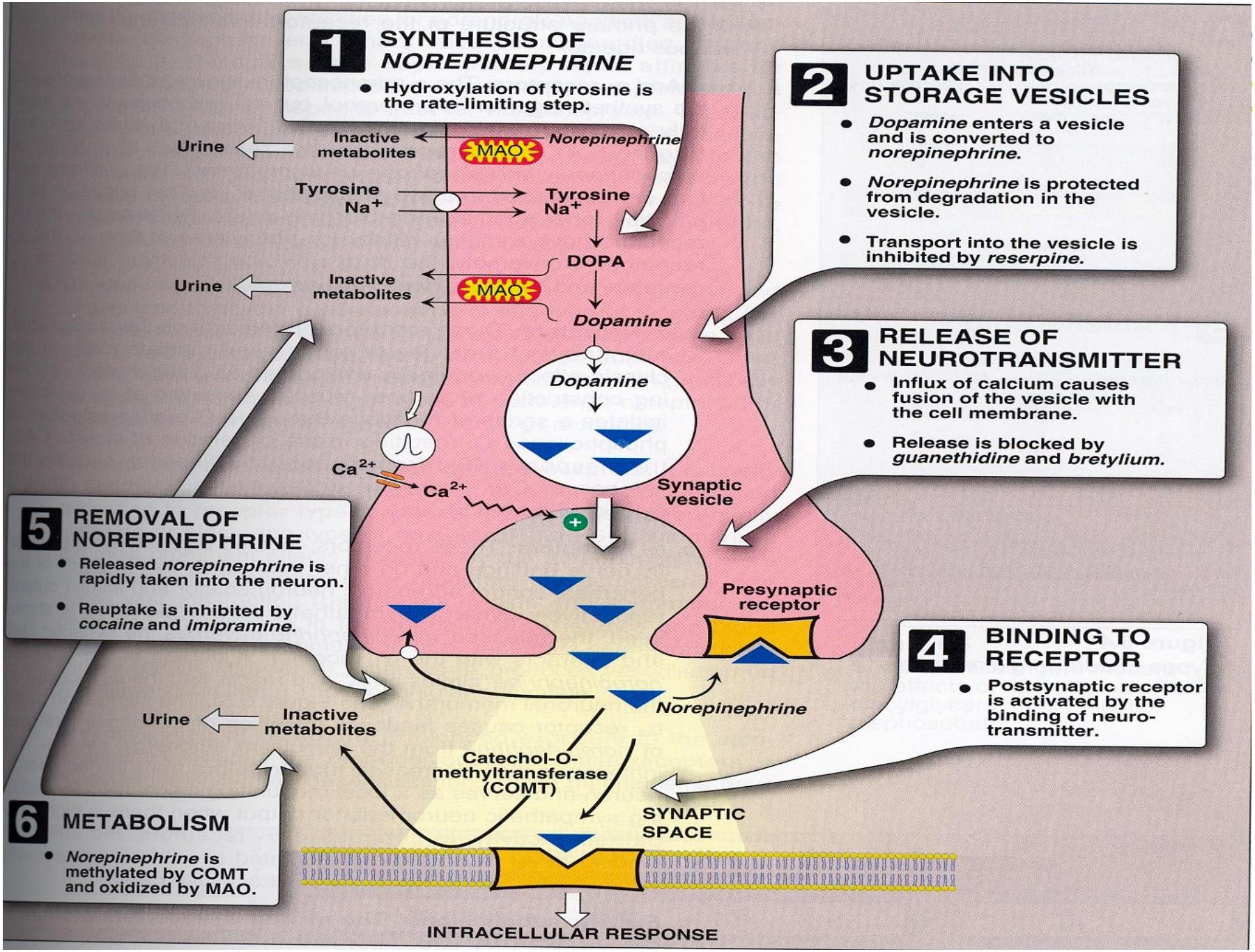



Medulla
Spinal cord
ACh N
ACh M
Parasympathetic
Cardiac and smooth muscle, gland cells, nerve terminals
ACh N
ACh M
Sympathetic
Sweat glands
ACh N
NE α, β
Sympathetic
Cardiac and smooth muscle, gland cells, nerve terminals
ACh N
D D1
Sympathetic
Renal vascular smooth muscle
ACh N
Epi, NE
Adrenal medulla
ACh N
Somatic
Skeletal muscle
Voluntary motor nerve

Adrenergic transmission

1) Synthesis of norepinephrine
2) Storage of norepinephrine
3) Release of norepinephrine
4) Binding to post synaptic receptors
5) **Ending of action** by

- Neuronal reuptake into neuron
- Monoamine oxidase (MAO) in neuronal mitochondria
- Catechol -O-methyl transferase (COMT) in synaptic space


1 SYNTHESIS OF NOREPINEPHRINE
Hydroxylation of tyrosine is the rate-limiting step.
Urine
Inactive metabolites
MAO
Norepinephrine
Tyrosine
Na+
Tyrosine
Na+
DOPA
Urine
Inactive metabolites
MAO
Dopamine
Dopamine
2 UPTAKE INTO STORAGE VESICLES
Dopamine enters a vesicle and is converted to norepinephrine.
Norepinephrine is protected from degradation in the vesicle.
Transport into the vesicle is inhibited by reserpine.
3 RELEASE OF NEUROTRANSMITTER
Influx of calcium causes fusion of the vesicle with the cell membrane.
Release is blocked by guanethidine and bretylium.
Ca2+
Ca2+
Synaptic vesicle
5 REMOVAL OF NOREPINEPHRINE
Released norepinephrine is rapidly taken into the neuron.
Reuptake is inhibited by cocaine and imipramine.
Presynaptic receptor
4 BINDING TO RECEPTOR
Postsynaptic receptor is activated by the binding of neuro-transmitter.
Norepinephrine
Urine
Inactive metabolites
Catechol-O-methyltransferase (COMT)
SYNAPTIC SPACE
6 METABOLISM
Norepinephrine is methylated by COMT and oxidized by MAO.
INTRACELLULAR RESPONSE

Adrenergic receptors

α-adrenoceptors : Subtypes (α_1 & α_2)

β-adrenoceptors : Subtypes (β_1 , β_2 & β_3)

α_1 β_1 β_2 β3 located postsynaptically

α_2 β_2 are located Presynaptically

α-adrenoceptors

Subtypes (α_1 & α_2)

α1 are excitatory in function except in GIT (Inhibition)

- **Present in smooth muscles.**
- **Contraction of radial muscle of eye → mydriasis**
- **Contraction of pregnant uterus.**
- **Vasoconstriction of skin & peripheral blood vessels →↑peripheral resistance → hypertension.**
- **Contraction of sphincters in GIT& urinary bladder .**
- **Relaxation of GIT muscles.**
- **↑ Glycogenolysis.**

Pre-synaptic α_2-adrenoceptors

Inhibition of norepinephrine

(negative feed back mechanism).

Pre-synaptic β_2 Receptors:

↑ Release of norepinephrine (NE)

(Positive feed back mechanism).

β-adrenoceptors

Subtypes (β_1 , β_2 & β_3)

β_1 excitatory in function, mainly in heart

Juxtaglomerular cells of the kidney

- ↑ heart rate: + chronotropic effect (Tachycardia)
- ↑ force of contraction : + inotropic effect
- ↑ conduction velocity: + dromotropic effect
- ↑ blood pressure
- ↑ renin release

β2 is inhibitory in function present mainly in smooth muscles

- **Relaxation** of skeletal & coronary blood vessels (vasodilatation).
- **Relaxation** of bronchial smooth muscles.
- **Relaxation** of GIT muscles **(constipation).**
- **Relaxation** of urinary bladder.
- **Relaxation** of the uterus **(Delay premature labor)**
- Increase blood glucose level (**(hyperglycemia)**
  - ↑ glucagon release from pancreas
  - ↑ liver & muscle glycogenolysis
- Tremor of skeletal muscles

β3

In adipose tissue →↑ lipolysis →↑ free fatty acids.

Sympathetic actions

- **Mydriasis (dilatation of eye pupil)**
- **Increase heart rate (tachycardia).**
- **Bronchodilation**
- **Inhibit peristalsis of GIT and secretion.**
- **Relaxation of GIT muscles (constipation).**
- **Relaxation of urinary bladder.**
- **Relaxation of the uterus (Delay premature labor)**
- **Increase conversion of glycogen to glucose (hyperglycemia)**

Classification of sympathomimetics (according to chemistry)

Catecholamines

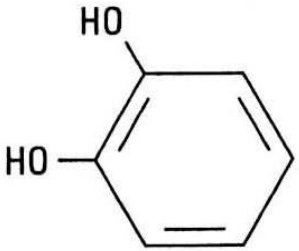
- have catechol ring
- water soluble (polar)
- Can not be given orally.
- Can not cross BBB
- inactivated by COMT & MAO in GIT
- short half-life.

Adrenaline, Noradrenaline
Dopamine
Dobutamine
Isoprenaline

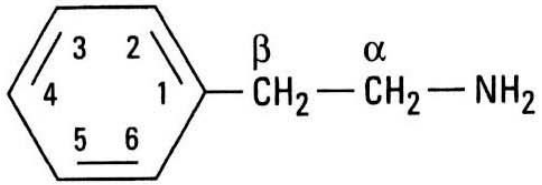
Non-catecholamines

- Lack catechol ring
- Lipid soluble
- Effective orally.
- Cross well BBB
- Prominent CNS effects
- Not metabolized by COMT or MAO
- Long half-life.

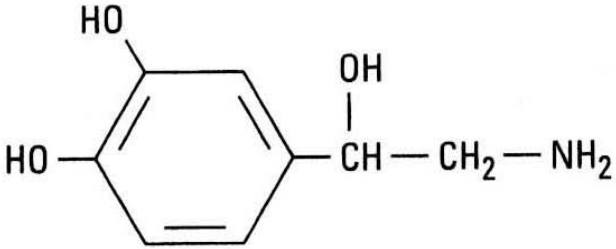
ephedrine, amphetamine, phenylephrine.



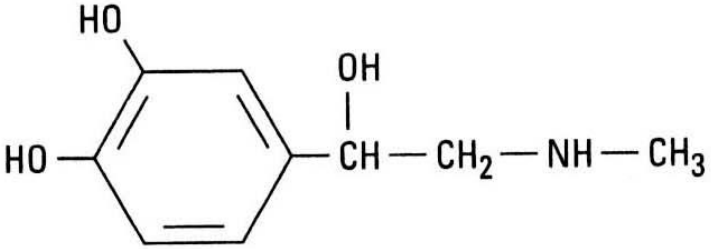
Catechol



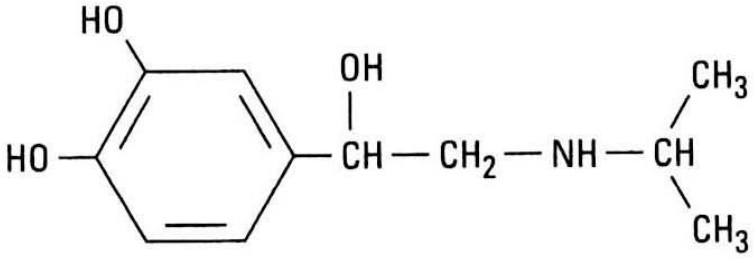
Phenylethylamine



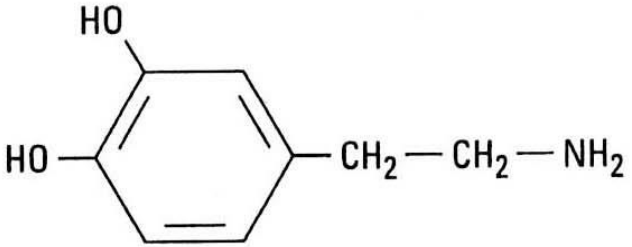
Norepinephrine



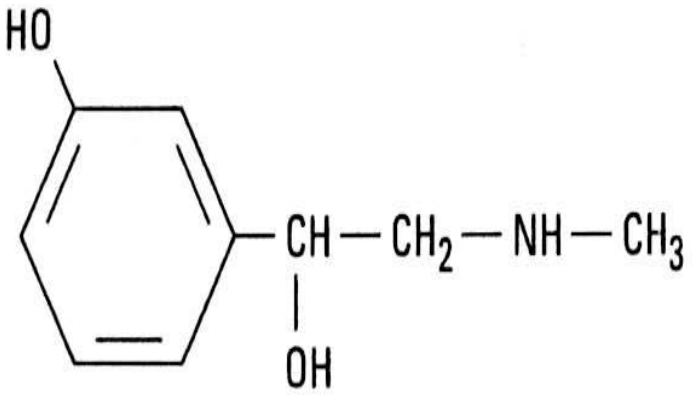
Epinephrine



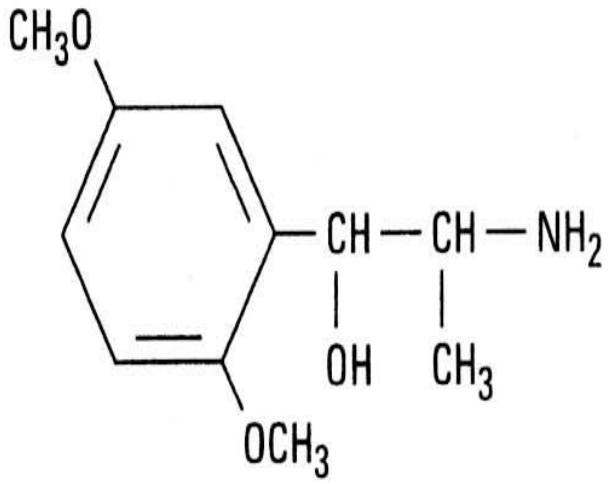
Isoproterenol



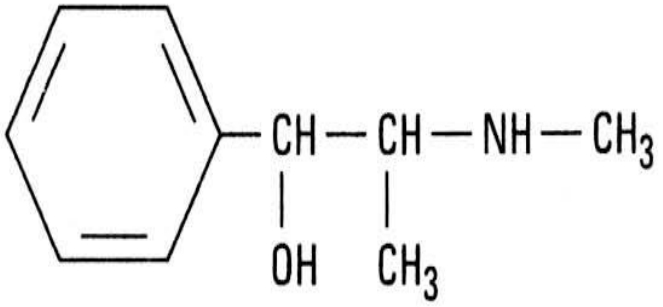
Dopamine



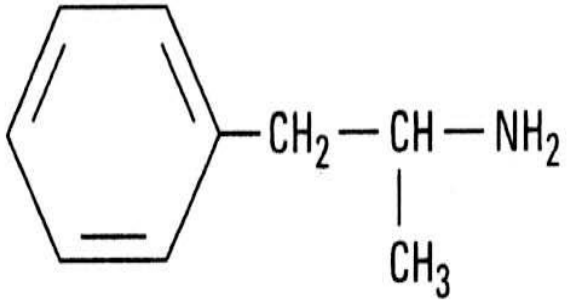
Phenylephrine



Methoxamine



Ephedrine



Amphetamine

Some examples of noncatecholamine sympathomimetic drugs.

Classification of sympathomimetics

Sympathomimetics

Direct acting

Direct actions on receptors e.g.

Epinephrine
Norepinephrine
Dopamine
Dobutamine
Isoprenaline
Phenylephrine

Indirect acting

release NA from nerve endings
e.g. Amphetamine &Tyramine

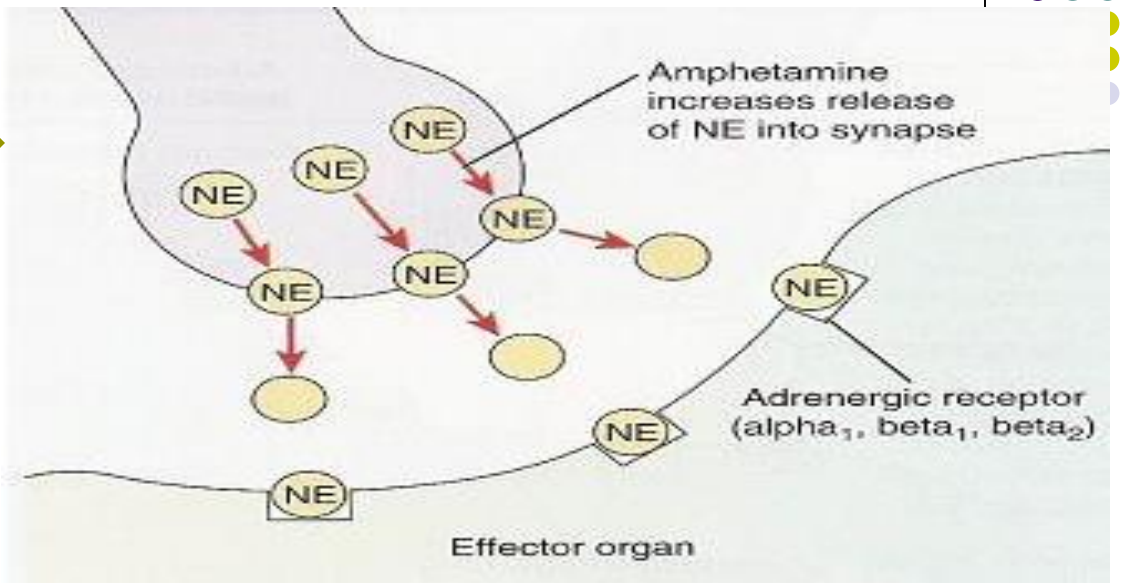
Or Inhibit NA uptake
e.g. cocaine

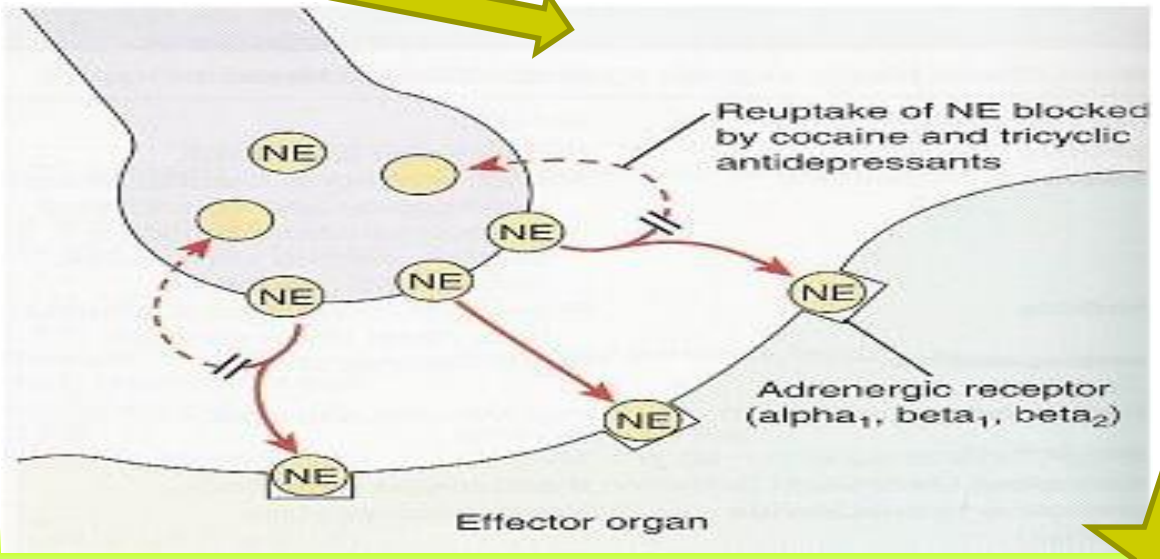
Dual acting

e.g. Ephedrine
pseudoephedrine

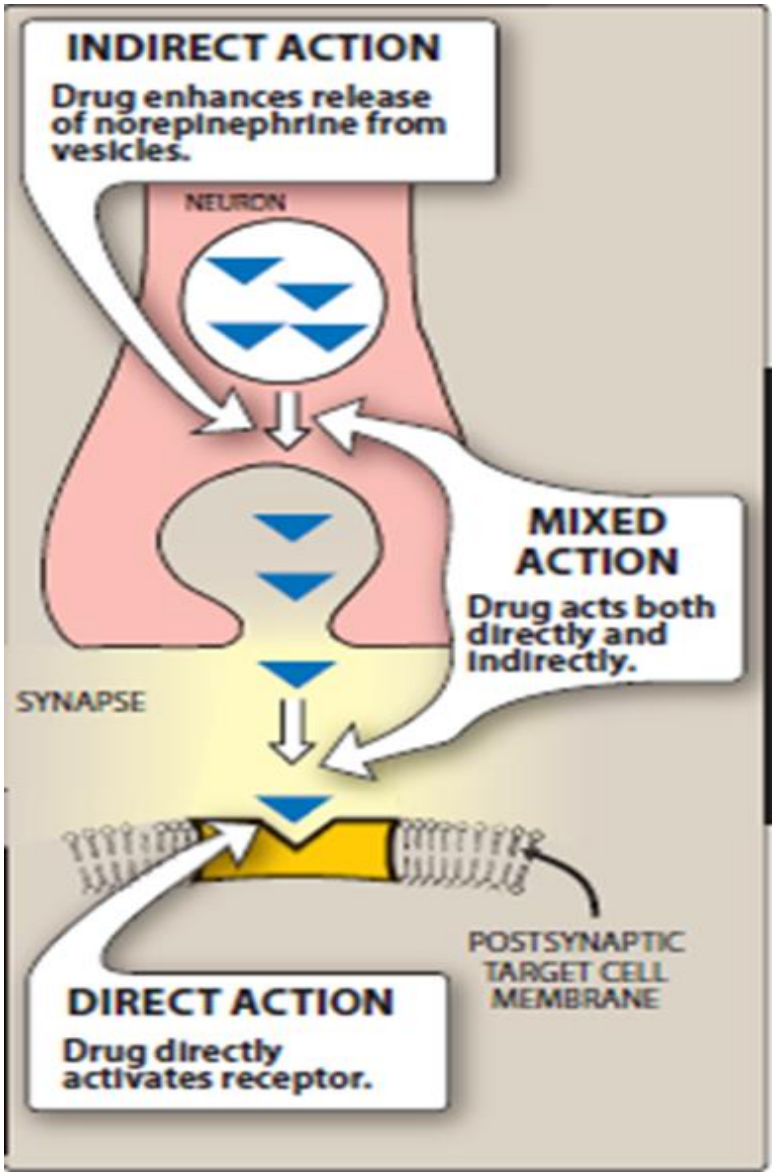
ADRENERGIC STIMULANTS

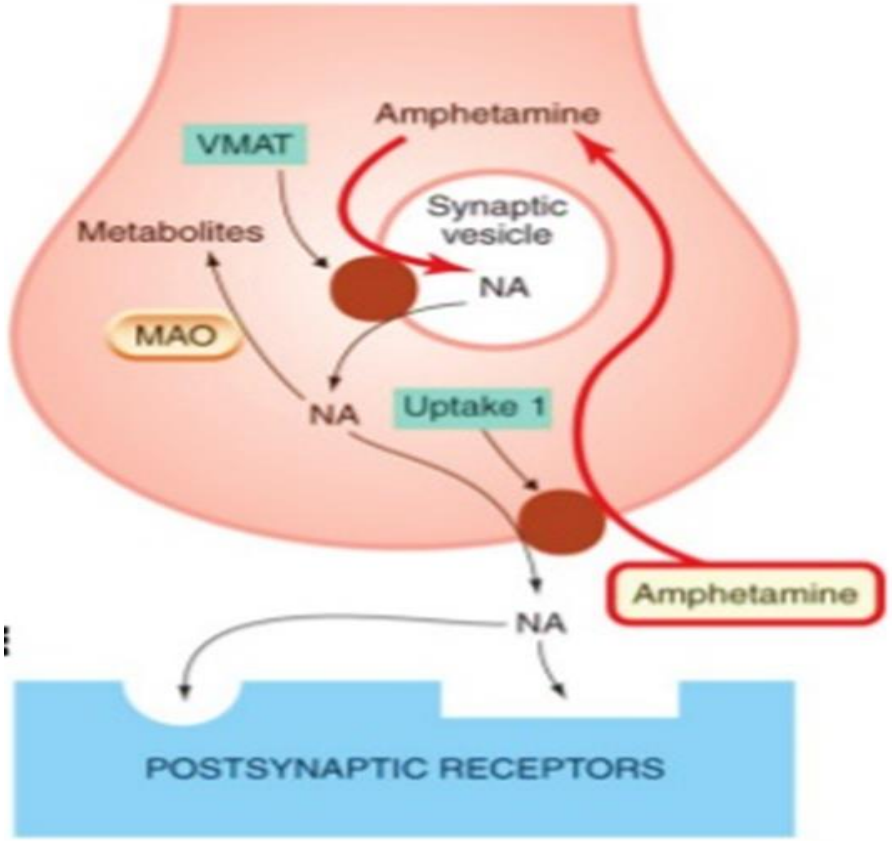
Indirect;
e.g. amphetamine
e.g. Cocaine

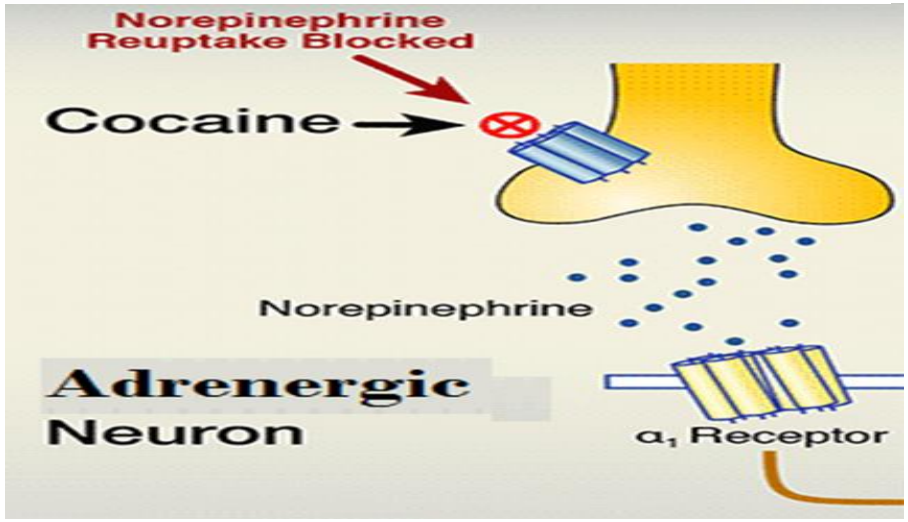




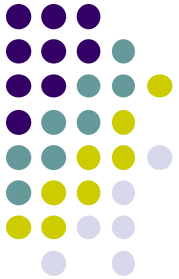
ADRENERGIC STIMULANTS







Classification of sympathomimetics
(according to spectrum of action)



Non-selective adrenergic agonists

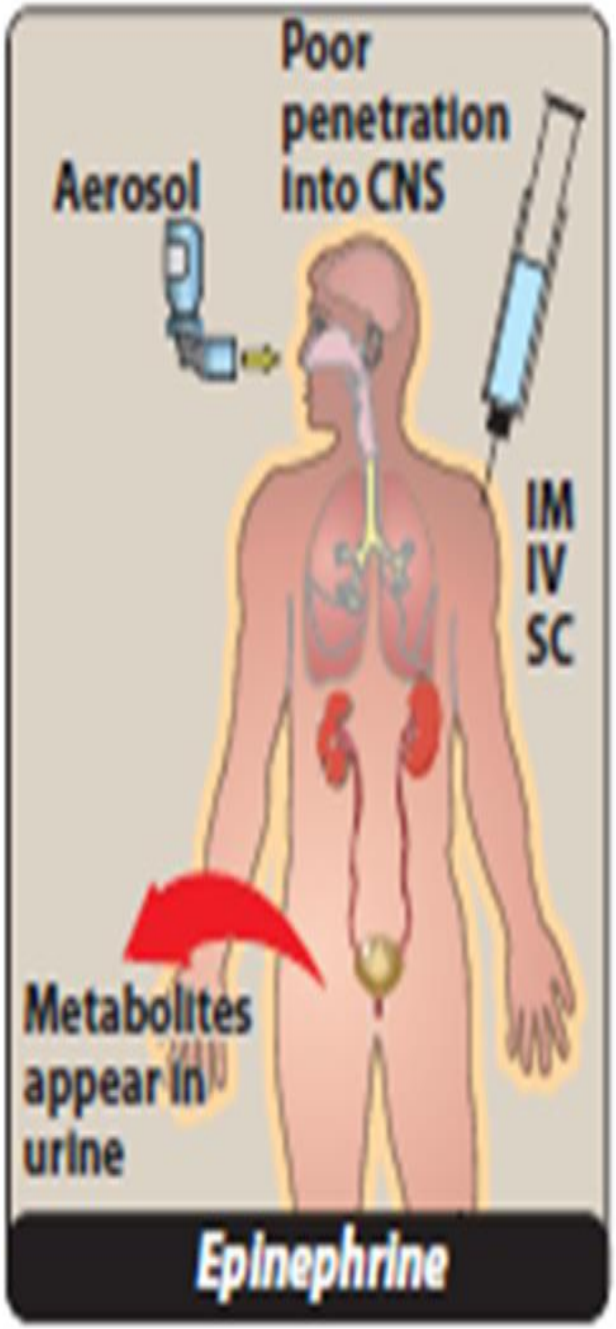
- Adrenaline (α1, α2 , β1 , β2, β3)
- Noradrenaline (α1, α2 , β1)
- Isoprenaline (β1, β2, β3)
- Dopamine (D1, β1, α1)

Selective agonists

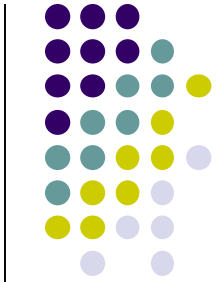
- Phenylephrine (α1)
- α -Methyldopa - clonidine (α2)
- Dobutamine (β1)
- Salbutamol, terbutaline, ritoderine (β2)

Adrenaline (α1, α2 , β1 , β2, β3)

- Natural released from adrenal medulla ➔ secondary to stress, hunger, fear
- Direct acting catecholamine
- Fast onset of action
- short duration of action.
- Not effective orally (inactivated by intestinal enzymes).
- Given I.V, S.C, inhalation.
- Non-selective agonist
- α1, α2 , β1 , β2, β3



Pharmacological actions of adrenaline



Eye → mydriasis (α_1)

Lung → bronchodilatation (β_2)

GIT → ↓motility (β_2) / contract sphincter (α_1)

Bladder : relaxation of detrusor muscle (β_2)

contraction of sphincter (α_1)

Pregnant uterus → relaxation tocolytic effect (β_2)

Metabolism

↓insulin (α_2) , ↑glucagon (β_2)

↑ liver glycogenolysis + skeletal muscle glycolysis (β_2)

↑ adipose lipolysis (β_3)

CNS →little, headache, tremors & restlessness

Pharmacological actions of adrenaline

- **Heart** → + inotropic, chronotropic, dromotropic (β_1)
- **BP** →↑ systolic (β_1) (α_1) / diastolic ↓ (β_2)
- **Blood vessels (Vascular smooth muscle cells):**

vasoconstriction of skin & peripheral vessles (α_1)

Vasodilatation skeletal vessels and coronaries ($\beta 2$)

USES

Locally:

- **Haemostatic (control bleeding):**
  Nasal pack in epistaxis and in dental practice.
- **combined with local anesthetic (LA) to:**
  - ↓ bleeding from the incision, ↓ absorption of L.A, ↓ side effects.
  - ↑duration of action

Systemically:

- **In acute asthma** ➔ S.C., inhalation, emergency
  bronchodilatation (β_2) + ↓mucosal edema (α_1).
- **Anaphylactic shock (Hypersensitivity reactions)** is the drug of choice as it is the physiological antagonist of histamine (↑ BP & bronchodilation).
- **Cardiac arrest** (i.v.) ➔ direct but now through central line
  - *N.B. Selective β_1 agonists are preferred*

ADRENALINE

Adverse effects

- Tachycardia, palpitation, arrhythmias, angina pains
- Headache, weakness, tremors, anxiety and restlessness.
- Hypertension → cerebral hemorrhage and pulmonary edema.
- Coldness of extremities → tissue necrosis and gangrene if extravasations
- Nasal stuffiness: rebound congestion if used as decongestant.

Contraindications

- coronary heart diseases (CHD), Ischemic heart disease
- Arrhythmia, Myocardial infarction
- Hypertension, peripheral arterial disease.
- Hyperthyroidism.
- Closed-angle glaucoma (ciliary relaxation ↓ filtration angle) → ↑ IOP

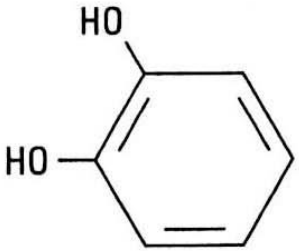
NOREPINEPHRINE = NORADRENALINE

- natural released from postganglionic adrenergic fibers
- Direct acting catecholamine
- mainly on α adrenoceptors (α1, α2, β1).
- Severe vasoconstriction α1
- Weak action on β2
- Increase force of contraction but decrease H.R.
- Reflex bradycardia
- Only administered IV - Not IM or S.C. ➔necrosis

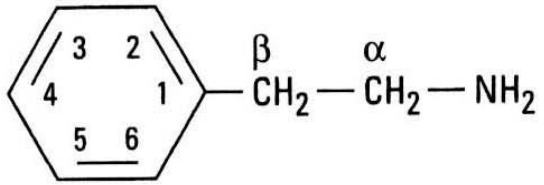
Uses:

Hypotensive states (in septic shock if fluid replacement and inotropics fail).

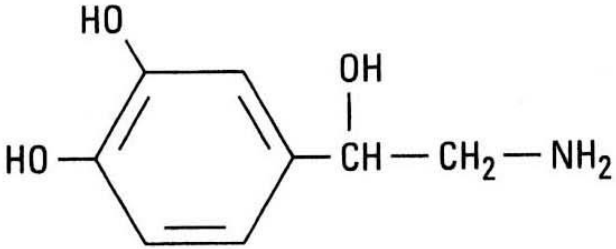
As a local hemostatic with local anesthetic.



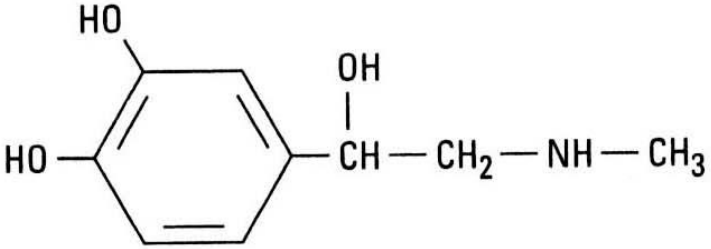
Catechol



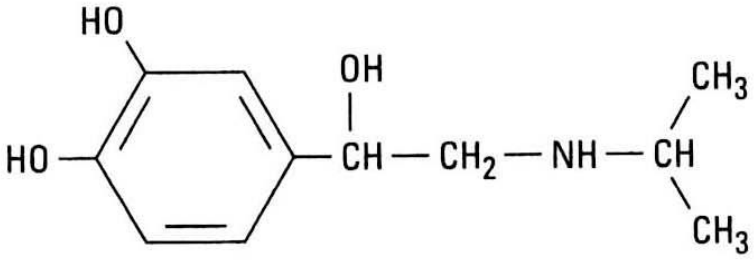
Phenylethylamine



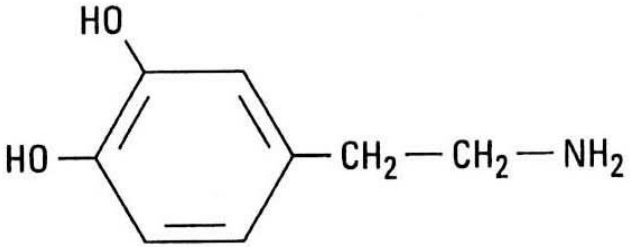
Norepinephrine



Epinephrine



Isoproterenol



Dopamine

Isoprenaline

- A synthetic, direct acting catecholamine
- **Longer effect** (no reuptake-no destruction by MAO)
- non-selective β agonist (β1, β2 & β3)
  β1 + inotropic effect, + chronotropic effect, increase cardiac output (CO).
- β2 Vasodilatation of blood vessels of skeletal muscles and coronaries.
- β2 Bronchodilatation .
- β2 Relaxation of uterus.
- β2 Hyperglycemia
- β3 lipolysis

Uses:

- Used mainly in cardiac arrest (Parenteral).
- Rarely in acute attack of asthma (inhalation).

Contraindicated in hyperthyroidism & CHD

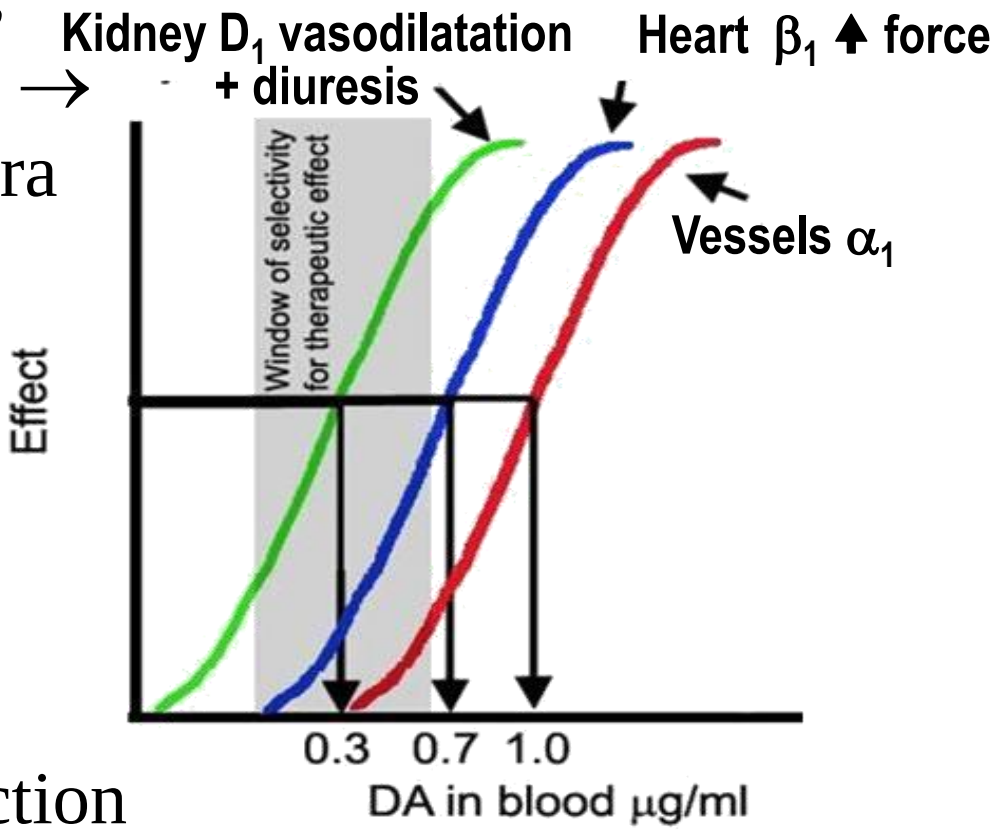
Dopamine ($D_1 > \beta_1 > \alpha_1$)

- Natural CNS neurotransmitter.
- Direct acting, catecholamine
- Given parenterally via continuous infusion

Low dose: dopaminergic receptors D_1

vasodilatation of mesenteric, coronary, renal blood vessels → improves blood flow to viscera

Has diuretic action



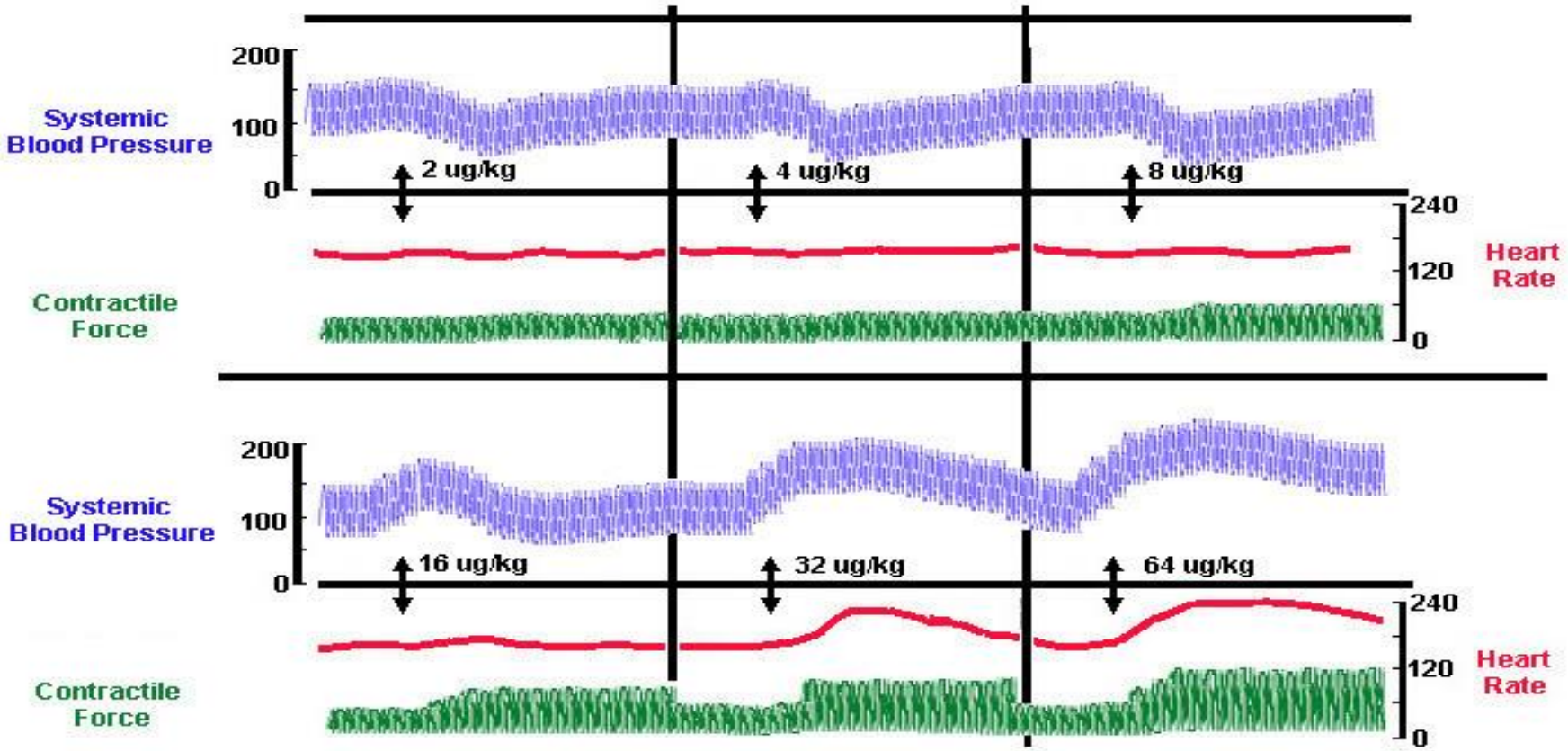
Intermediate dose (β1)

+ve inotropic

+ve chronotropic effects

High dose (α1): vasoconstriction

On heart : Inotropic, chronotropic effect
On BP ➔ According to dose
First ↓ D_1
then ↑ due to β_1
followed by α_1 effect



Uses

- **Cardiogenic shock:**

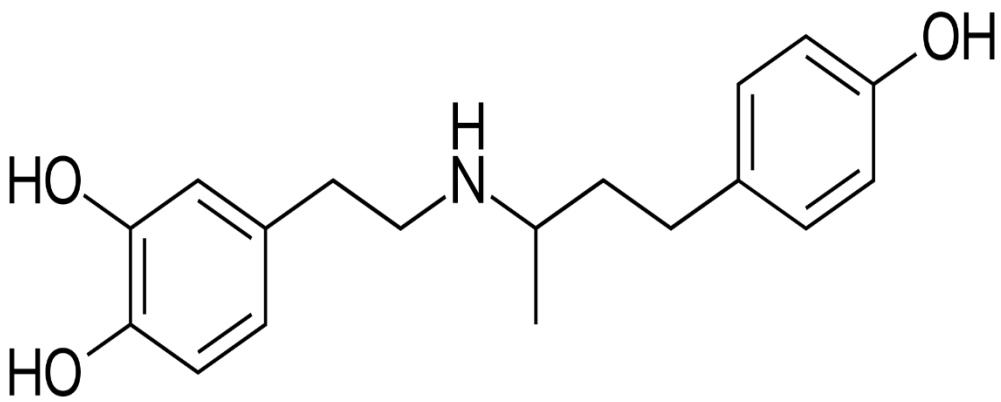
  It is the drug of choice in SHOCK➔ septic hypovolemia or cardiogenic (I.V infusion)

  ⬆ BP & CO (β_1), without causing renal impairment (D1)

- **Can be given in acute heart failure (HF) but dobutamine is preferrable**

Dobutamine

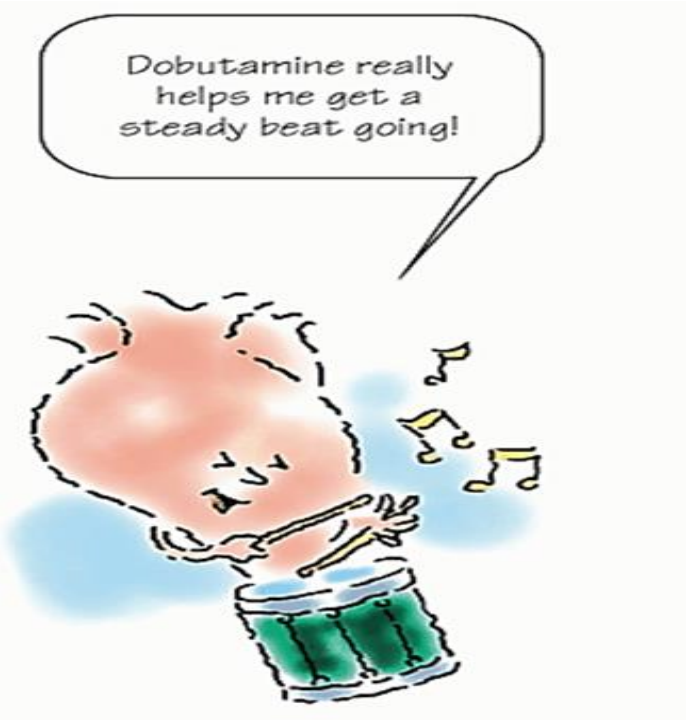
- Synthetic.
- Direct acting, catecholamine
- Metabolized by COMT
- Short duration, given by intravenous infusion
- Selective β_1–receptor agonist.
- Positive inotropic effect with little chronotropic effect
- increase heart contractility, increases cardiac output.



Uses of Dobutamine

- Given parenterally by infusion for short term management of cardiac decompensation after cardiac surgery, in acute myocardial infarction (AMI) & HF

- It is preferred because it does not ↑ oxygen demand



Phenylephrine (selective α1)

- A synthetic **non catecholamine, direct acting**
- Given orally
- Not inactivated by COMT, longer duration of action
- Mydriasis, vasoconstriction ,↑ increased both systolic & diastolic blood pressure, hypertension **(pressor effect)**
- reflex bradycardia (Terminate atrial tachycardia).

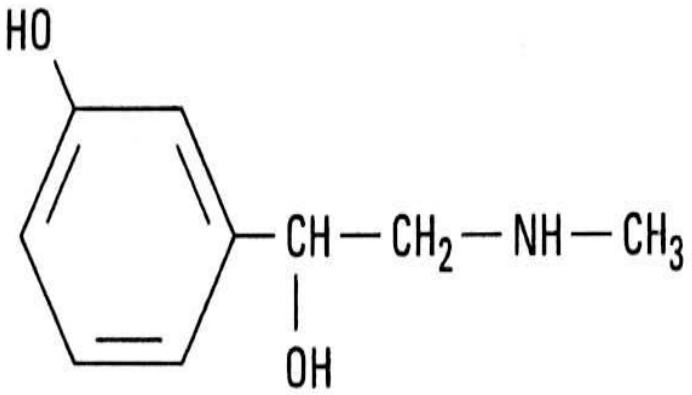
Uses:

Mydriatic: In ophthalmic solutions to facilitate eye examination.
Vasopressor agent: by infusion in hypotensive states
Nasal and ocular decongestant: in allergic rhinitis, cold as nasal or eye drop.
Local Hemostatic with local anesthesia
Adverse effect: hypertension

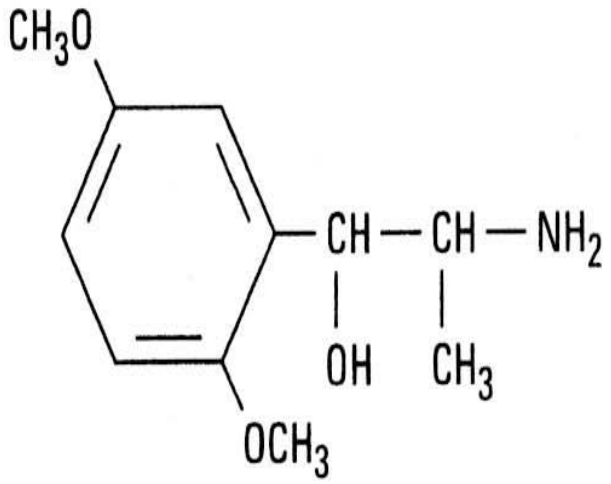
Midodrine

peaks in 20 min, duration 30 min

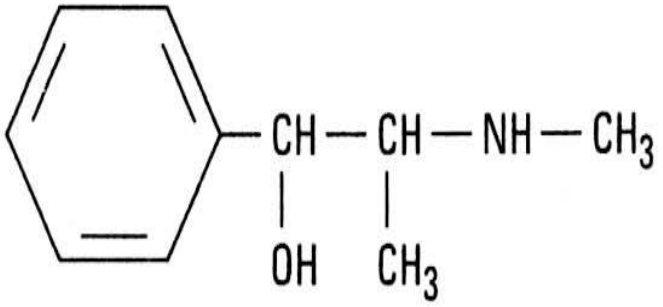
used mainly in orthostatic hypotensive states.



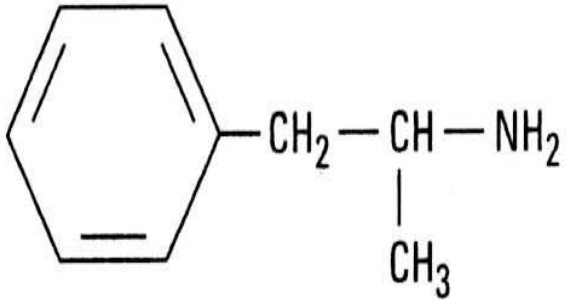
Phenylephrine



Methoxamine



Ephedrine

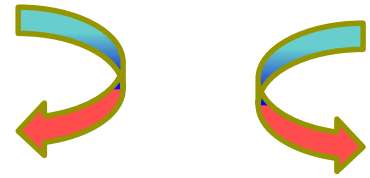


Amphetamine

Some examples of noncatecholamine sympathomimetic drugs.

ADRENERGIC STIMULANTS
Direct Acting Sympathomimetics

Nasal & Ocular Decongestants



PHENYLETHYLAMINES

- Phenylephrine
- Pseudoephedrine
- Methoxamine

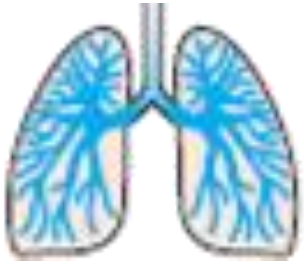
IMIDAZOLINE

- Naphazoline
- Oxymetazoline HCl (Afrin)
- Xylometazoline HCl (Otrivine)

Selective β_2 agonists

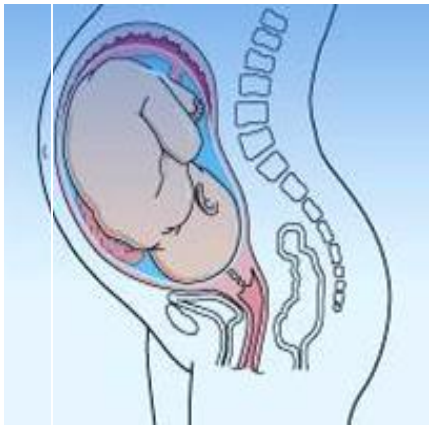
Salbutamol

- selective β2 agonists, non catecholamines
- orally or by inhalation or injection.
- Produces bronchodilation
- **Used for acute attack of asthma & COPD.**



Ritodrine

- Selective β2 agonist, non catecholamines.
- orally or by injection
- Is a tocolytic drug (relaxation of uterus).
- **Used in premature labor** ➔ postpone premature labor (begins before the 37th week of gestation)



- **Terbutaline Bronchodilator & Tocolytic**

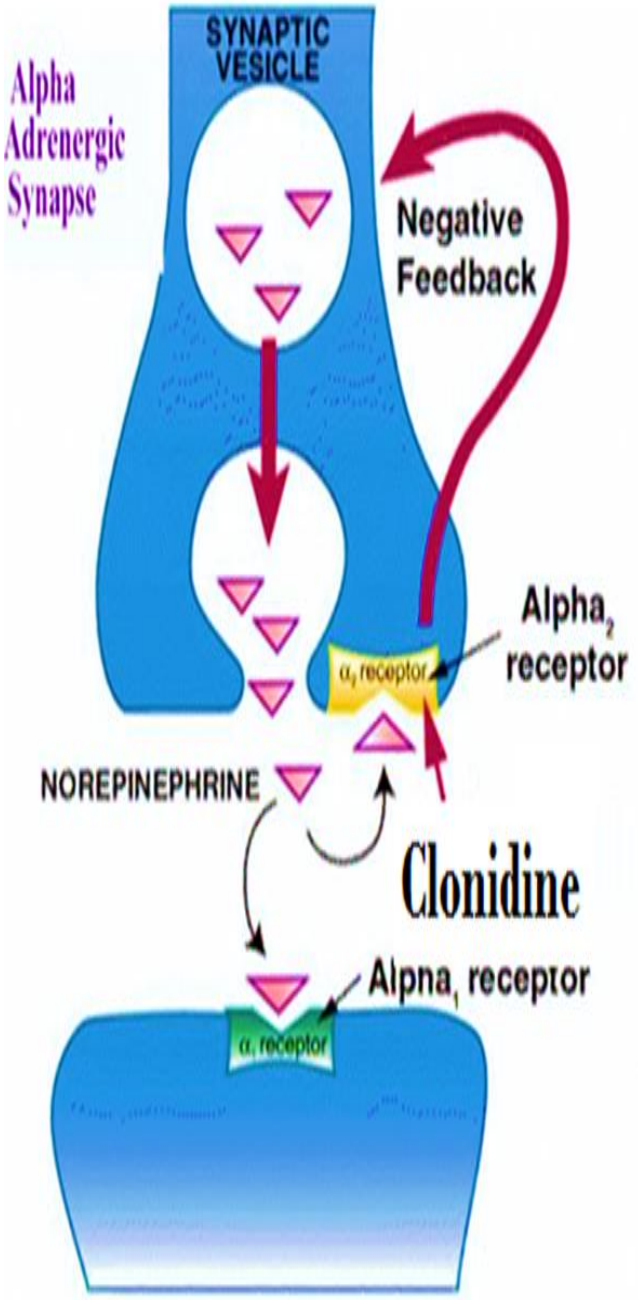
Clonidine selective α_2

- Synthetic
- Given orally or as patch.
- a presynaptic α_2 **agonist**.
- acts centrally (α_2) to↓ sympathetic outflow to heart & vessels.
- Inhibit sympathetic vasomotor centers.
- Used as antihypertensive in essential hypertension to lower BP.

Brimonidine

α_2 **agonist** used in **glaucoma**

(reduce aqueous humor production by the ciliary body)



ADRENERGIC STIMULANTS
Indirect acting sympathomimetics

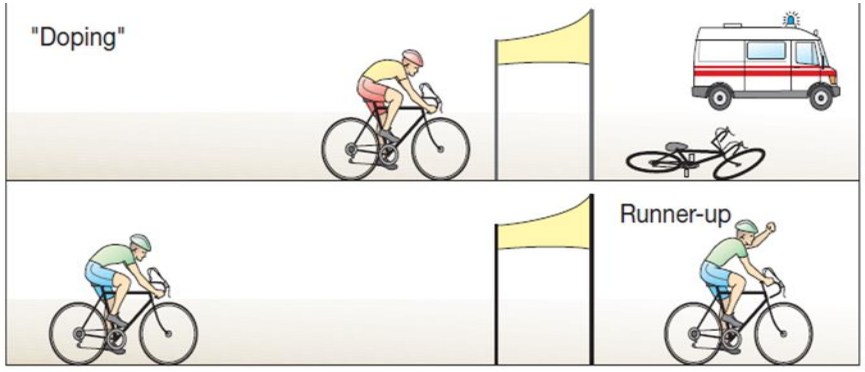
Amphetamine α& β

- Synthetic, non-catecholamine.
- Given orally, long duration
- Excreted mostly unchanged (↑ by acidification of urine)
- Acts indirectly, it depletes vesicles from stored NE
  → tachyphylaxis
- **has CNS stimulant effects**; mental alertness, wakefulness, concentration & self-confidence followed by depression & fatigue on continued use
- ↑ **euphoria** → causes its abuse
- ↓ Weight → ↓ appetite ↑ increase energy expenditure
- No more used therapeutically → induces psychic & physical dependence and psychosis.

ADRENERGIC STIMULANTS
DUAL Acting Sympathomimetics

Ephedrine (α & β)

- Plant alkaloid, synthetic, non-catecholamine
- Orally, not destroyed by enzymes ➔ prolonged action
- Has mixed action , **direct** action on receptors
- **Indirect** by releasing NE from adrenergic endings ➔ depletes stores ➔ Tachyphylaxis
- has **CNS stimulant effects** (less than amphetamine)
- No more therapeutically used ➔ but is abused by athletes and prohibited during games.



Pseudoephedrine

- Produce vasoconstriction of blood vessels, mainly those located in the nasal passages, pseudoephedrine causes a decrease in the symptoms of nasal congestion.
- Used as nasal & ocular decongestant & in flu remedies.

SUMMARY FOR USES OF Sympathomimetics

- **Agents specifically indicated for hypotension**

  Midodrine, Phenylephrine, Norepinephrine, Phenylpropanolamine

- **Agents specifically indicated for cardiogenic shock➔ Acute Hear Failure**

  Dobutamine, Dopamine, Epinephrine

- **Agents specifically indicated for shock**

  Dopamine, Norepinephrine

- **Agents specifically indicated for cardiac arrest**

  (Dobutamine, Epinephrine, Norepinephrine)

- **Agents specifically indicated for bronchial asthma**

  Salbutamol, Salmeterol, Formoterol, Terbutaline, Isoprenaline

- **Agents specifically indicated for premature labour**

  Ritodrine, Terbutaline

- **Agents specifically indicated for nasal decongestion**

  Pseudoephedrine, Phenylephrine

Agents specifically abused in sports → Ephedrine, Amphetamine