Sympathomimetic drugs (Adrenergic agonists)

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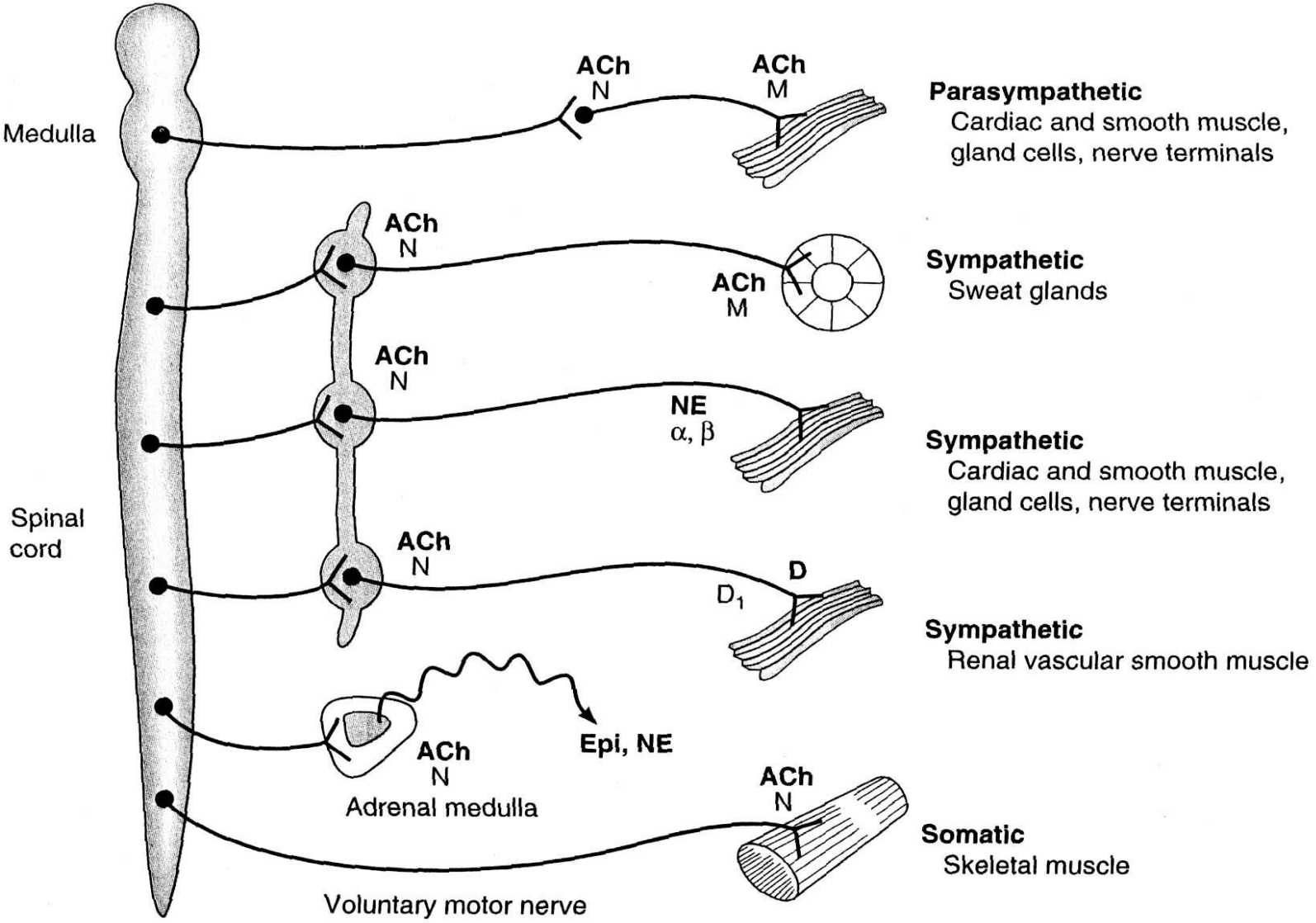
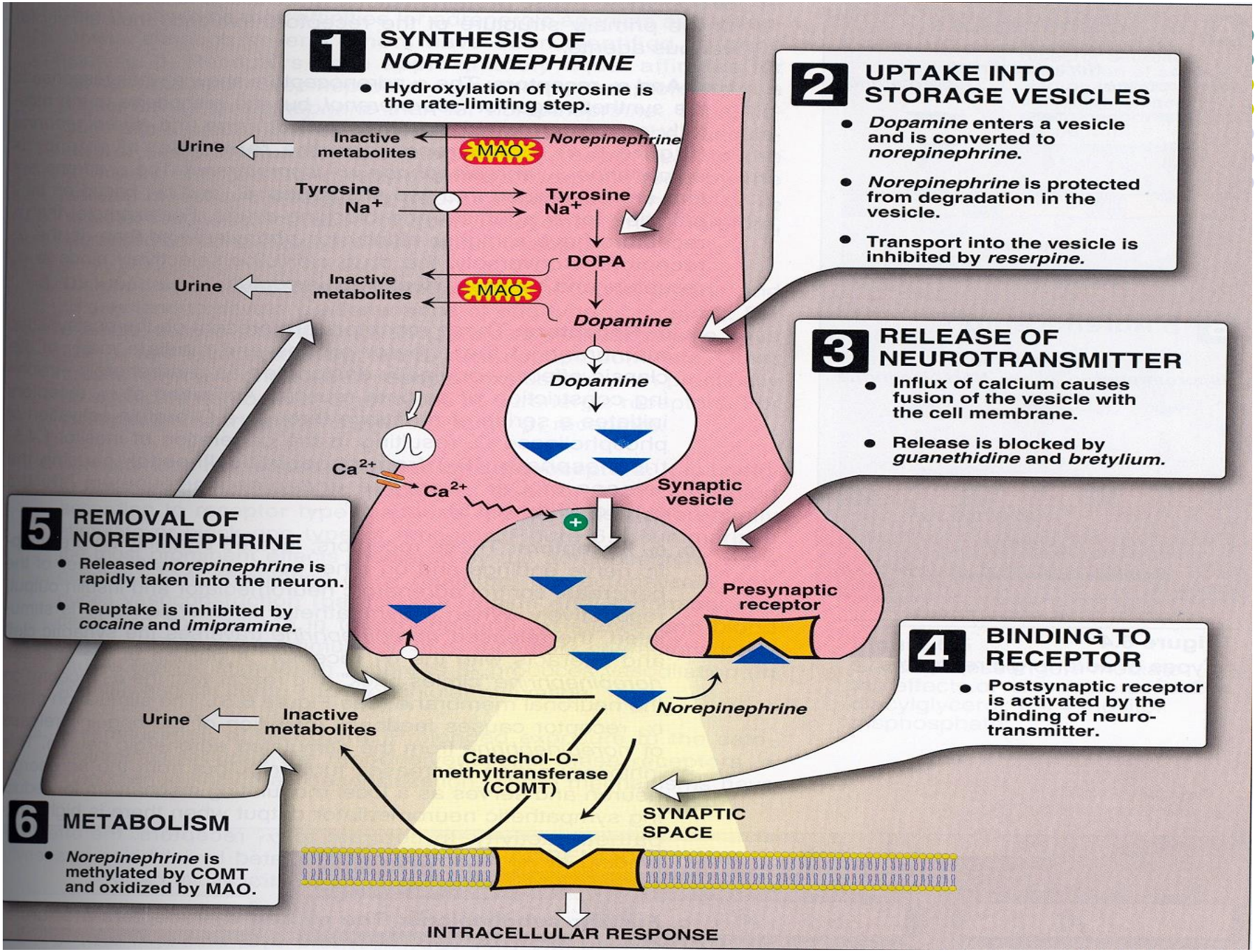

Medulla
Spinal cord
ACh N
ACh M
Parasympathetic
Cardiac and smooth muscle, gland cells, nerve terminals
ACh N
ACh M
Sympathetic
Sweat glands
ACh N
NE α, β
Sympathetic
Cardiac and smooth muscle, gland cells, nerve terminals
ACh N
D D1
Sympathetic
Renal vascular smooth muscle
ACh N
Epi, NE
Adrenal medulla
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
Ca2+
Ca2+
Synaptic vesicle
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.
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.
Urine
Inactive metabolites
Norepinephrine
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)

α_1 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.

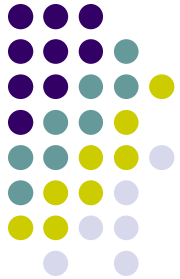
Pre-synaptic α2-adrenoceptors

Inhibition of norepinephrine (negative feed back mechanism).

Pre-synaptic β2 Receptors: ↑ release of NE
(Positive feed back mechanism).

β-adrenoceptors

Subtypes (β_1 , β_2 & β_3)



β_1 excitatory in function, mainly in heart

- ↑ 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.
- 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 action)

Direct-acting: direct stimulation of adrenergic receptors

e.g. adrenaline, noraderanaline, dopamine, isoprenaline, salbutamol phenylephrine, methoxamine, naphazoline, clonidine, dobutamine….etc

Indirect-acting:

↑ NA release from pre-synaptic adrenergic nerve endings.

e.g. amphetamine

Or Inhibit NA uptake

e.g. Cocaine & antidepressants

Mixed (Dual acting):

Direct and indirect stimulation of adrenergic receptors

e.g. ephedrine, pseudoephedrine.

Sympathomimetics

Direct acting sympathomimetics

Direct actions on receptors e.g.

Epinephrine
Norepinephrine
Isoprenaline
Phenylephrine

Indirect acting sympathomimetics

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

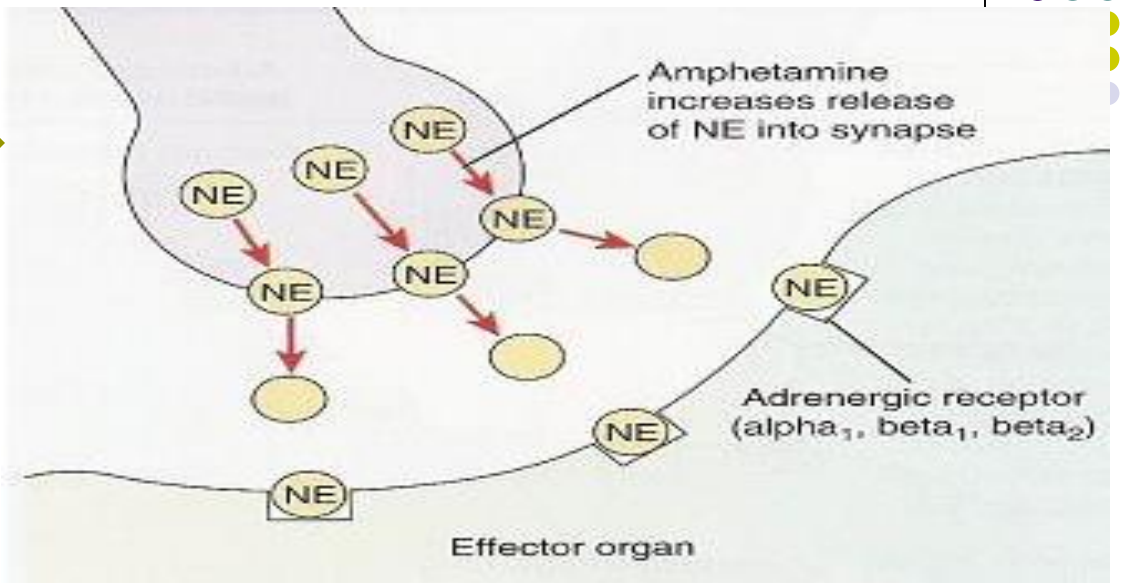
Or Inhibit NA uptaker
e.g. cocaine

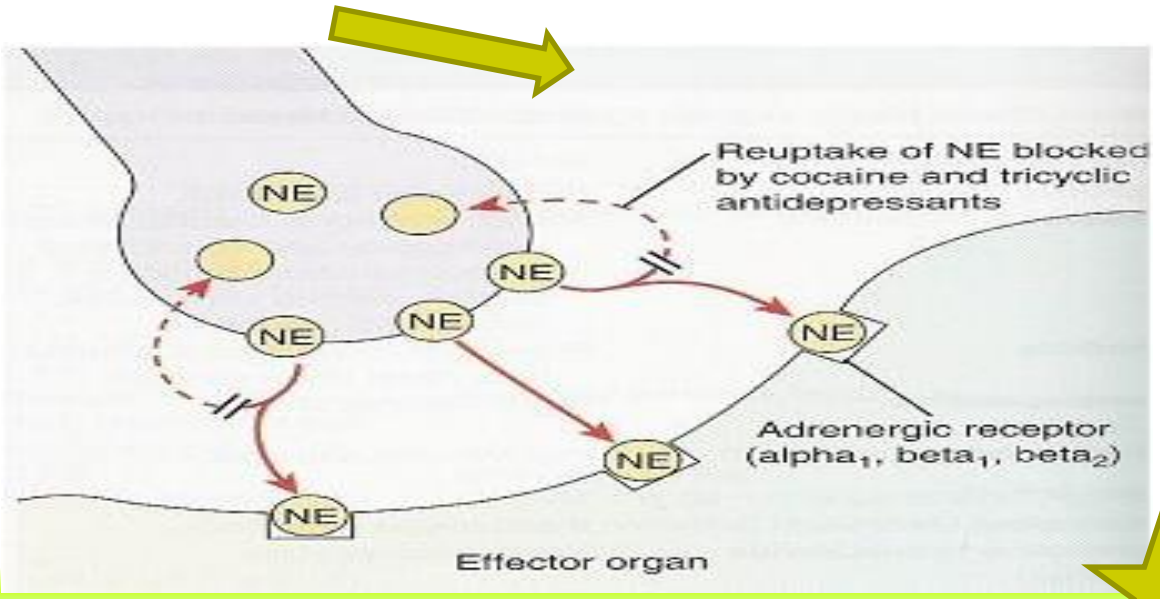
Dual acting

e.g. Ephedrine

ADRENERGIC STIMULANTS

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





Classification of sympathomimetics (according to chemistry)

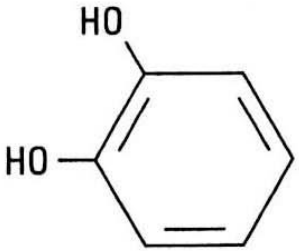
Catecholamines

- have catechol ring
- water soluble (polar)
- Not effective orally.
- Poor penetration into CNS
- inactivated by COMT & MAO in GIT
- short half-life.
- e.g. adrenaline, noradrenaline, dopamine isoprenaline,

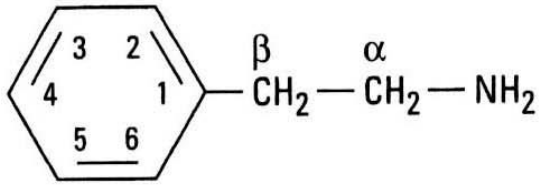
Non-catecholamines

- Lack catechol ring
- Lipid soluble
- Effective orally.
- Cross well BBB
- Prominent CNS effects
- Not inactivated by COMT in gut wall
- Long half-life.
- E.g.

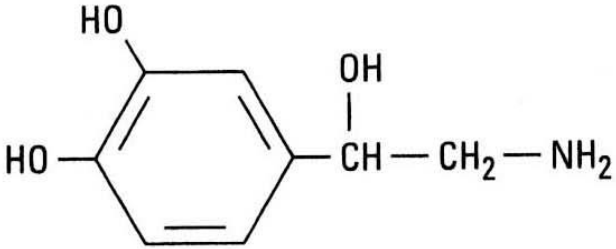
Ephedrine, amphetamine, phenylephrine.



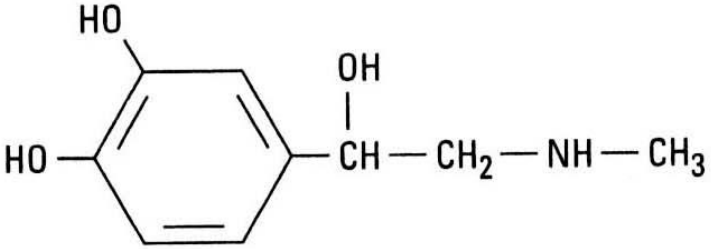
Catechol



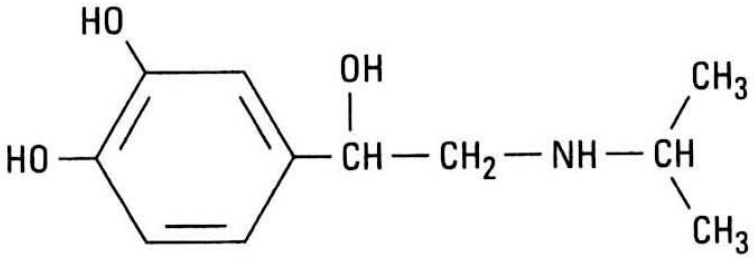
Phenylethylamine



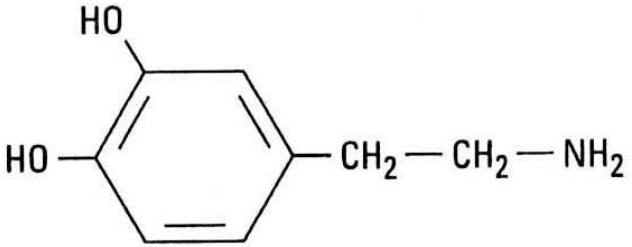
Norepinephrine



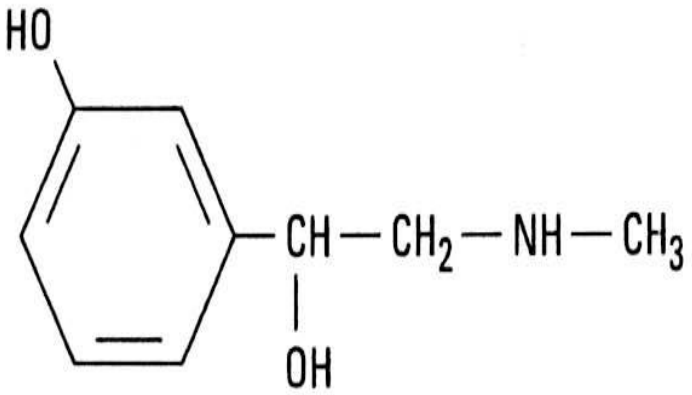
Epinephrine



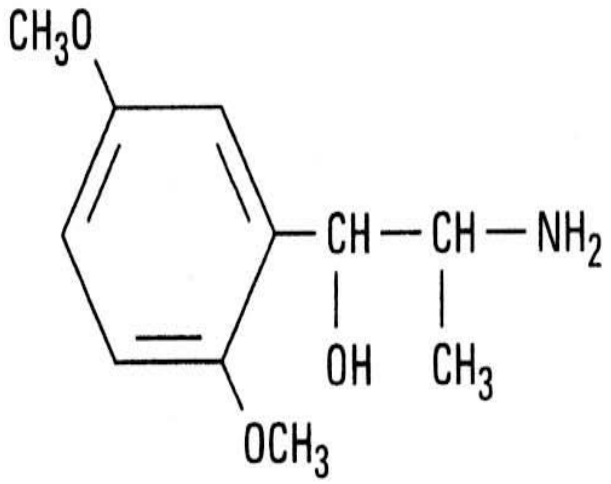
Isoproterenol



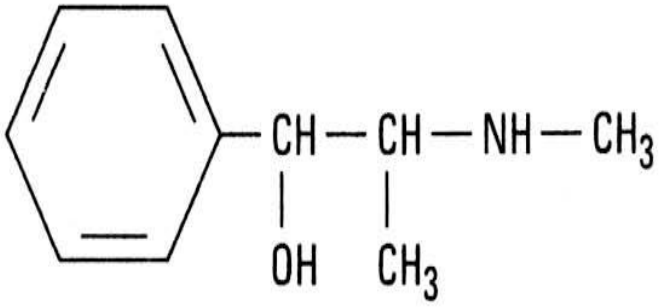
Dopamine



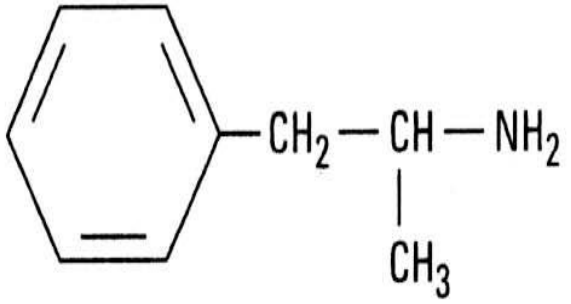
Phenylephrine



Methoxamine



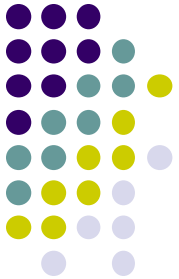
Ephedrine



Amphetamine

Some examples of noncatecholamine sympathomimetic drugs.

Classification of sympathomimetics
(according to spectrum of action)



Non-selective adrenergic agonists

- Adrenaline (α1, α2 , β1 , β2, β3)
- Nor adrenaline (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 (α , β)

- Natural, catecholamine
- Non-selective agonist α1, α2 , β1 , β2 , β3
- Fast onset of action & Short duration of action.
- Not effective orally (inactivated by intestinal enzymes).
- Given I.V, S.C, inhalation.

Pharmacological actions

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

vasoconstriction of b.v. in skin + peripheral (α_1)

Vasodilatation of b.v.of skeletal muscles and coronaries β2

Eye → mydriasis (α_1) / → no effect on accommodation

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 (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

USES

Locally:

- **Haemostatic (control bleeding):**

  Nasal pack in epistaxis and in dental practice.

- **combined with local anesthetic to:**
  - ↓ absorption of L.A. & ↑duration of action
  - ↓ side effects of local anesthetic.
  - ↓ bleeding from the incision.

Systemically:

- **In acute asthma S.C., inhalation, emergency**

  bronchodilatation (β_2) + ↓mucosal edema (α_1).

- **Anaphylactic shock (Hypersensitivity reactions) is the drug of choice given S.C. as it is the physiological antagonist of histamine (↑ BP & bronchodilation).**

- **Cardiac arrest** (i.v.).

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
- Nasal stuffiness: rebound congestion if used as decongestant.

Contraindications

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

NOREPINEPHRINE = NORADRENALINE

- Catecholamine, non-selective agonist
- mainly on α adrenoceptors (α1, α2, β1).
- Weak action on β2
- Severe vasoconstriction α1
- Increase force of contraction but decrease H.R.
- Reflex bradycardia
- Only administered IV - Not IM or S.C. ➔necrosis

Uses:

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

As a local haemostatic with local anesthetic.

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

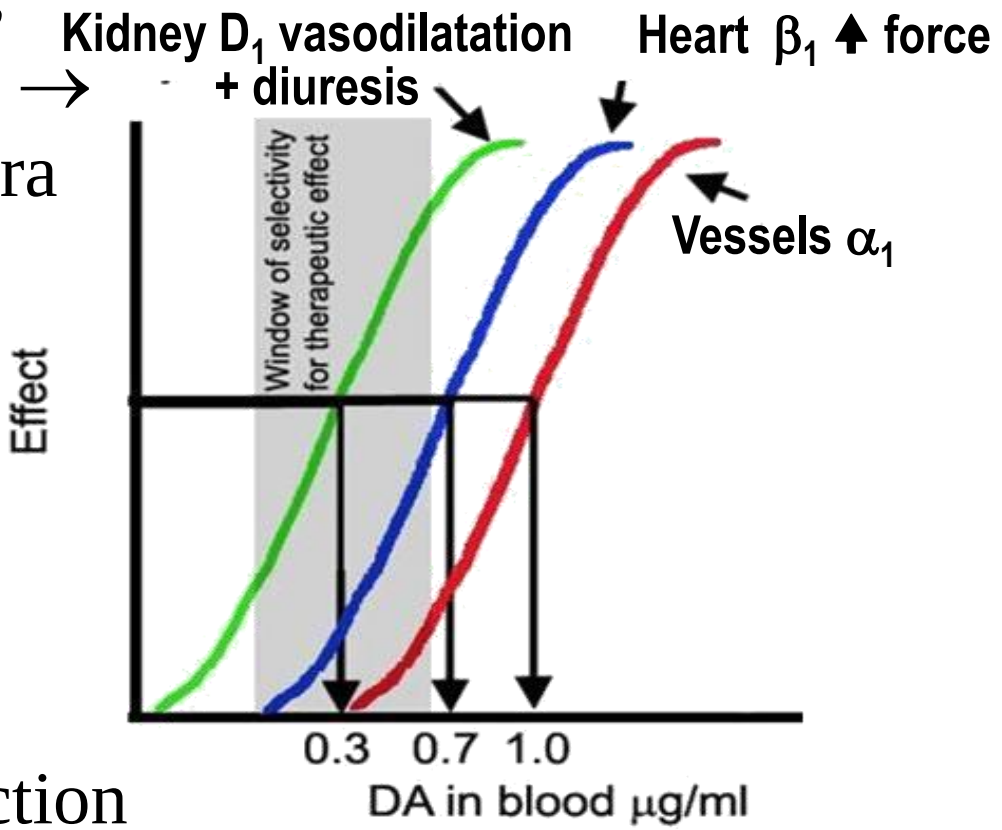
Dopamine ($D_1 > \beta_1 > \alpha_1$)

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

Low dose: dopaminergic receptors D_1

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

Has diuretic action



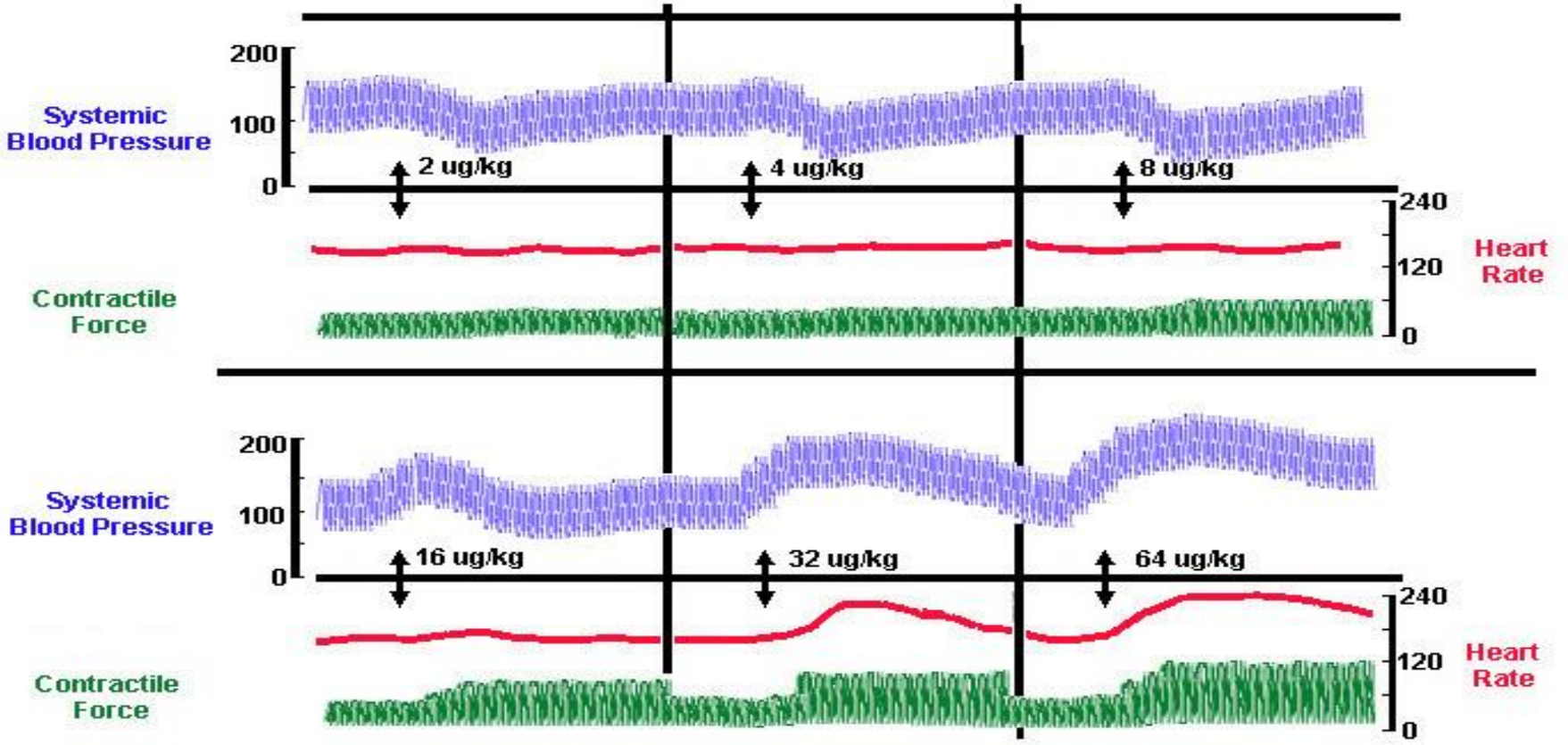
Intermediate dose (β1)

+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:**
  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 better dobutamine**

Dobutamine

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

Uses:

- **short term management of cardiac decompensation after cardiac surgery, in acute myocardial infarction (AMI) & heart failure.**

Phenylephrine (selective α1)

- A synthetic **non catecholamine, direct acting**
- Not inactivated by COMT, longer duration of action
- Vasoconstriction ,↑ increased both systolic & diastolic blood pressure, hypertension, reflex bradycardia.

Uses:

Nasal decongestant topically, nasal drops in allergic rhinitis, cold

Vasopressor agent: hypotension & terminate atrial tachycardia (reflex bradycardia).

Local Haemostatic with local anesthesia

Mydriatic: In ophthalmic solutions to facilitate eye examination.

Adverse effects: Hypertension

Midodrine peaks in 20 min, duration 30 min, used in hypotensive states.

ADRENERGIC STIMULANTS
Direct Acting Sympathomimetics

Nasal & Ocular Decongestants

PHENYLETHYLAMINES

- Phenylephrine
- Pseudoephedrine
- Methoxamine

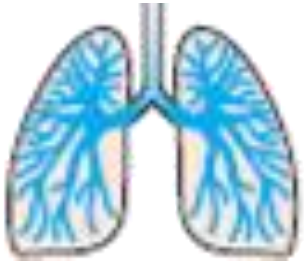
IMIDAZOLINE

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

Selective β_2 agonists

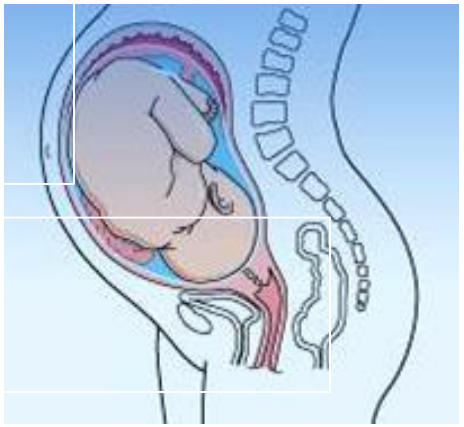
Salbutamol

- 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** orally and injection to treat **premature labor.**



Terbutaline Bronchodilator & Tocolytic

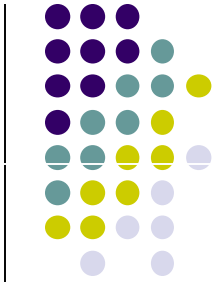
Clonidine selective α2

- synthetic, imidazoline
- Given orally or as patch.
- Is a presynaptic α_2 **agonist**.
- Acts centrally (a2) at nucleus tractus solitaries to ↓ sympathetic outflow to heart & vessels.
- Inhibit sympathetic vasomotor centers.
- Used as antihypertensive in essential hypertension to lower BP.

Brimonidine

is an imidazoline → α_2 **agonist** used in **glaucoma**

ADRENERGIC STIMULANTS
Indirect acting sympathomimetics



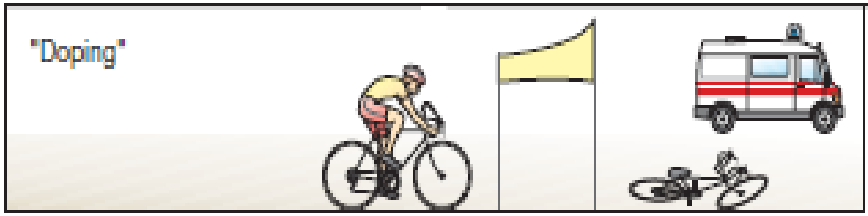
Amphetamine α& β

- Synthetic non-catecholamine.
- given orally, longer duration
- Excreted mostly unchanged (↑ by acidification of urine)
- Acts indirectly, it depletes vesicles from stored NE → tachyphylaxsis
- **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, dual acting
- direct action on receptors ➔ down regulation of receptors
- indirect by releasing NE from adrenergic endings ➔ depletes stores
- Tachyphylaxsis
- Orally, not destroyed by enzymes ➔ prolonged action
- has **CNS stimulant effects** (less than amphetamine)
- No more therapeutically used ➔ but is abused by athletes and prohibited during games.



Pseudoephedrine

Dual acting < CNS & pressor effects compared to ephedrine.

Used as nasal & ocular decongestant & in flu remedies.

- **Agents specifically indicated for hypotension**

  Midodrine, Phenylephrine, Norepinephrine, Phenylpropanolamine
- **Agents specifically indicated for cardiogenic shock→AHF**

  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, Naphazoline,

- **Agents specifically abused in sports** → Ephedrine, Amphetamine