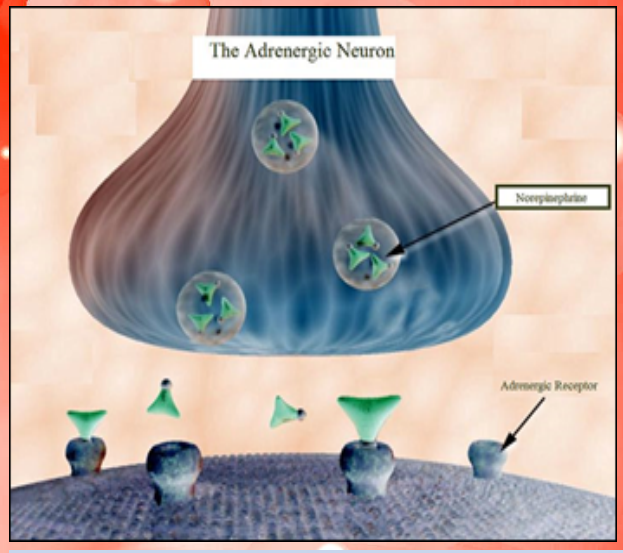
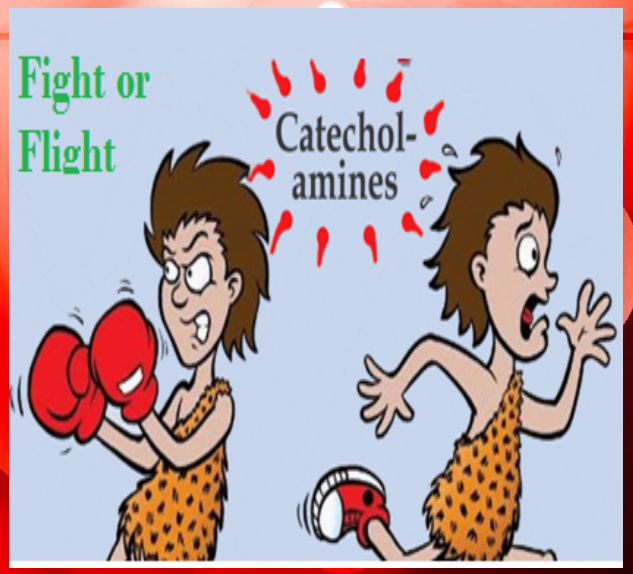
ADRENERGIC AGONISTS

ILOS

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

Discuss pharmacodynamic actions, ADRs, indications and contraindications of adrenergic agonists

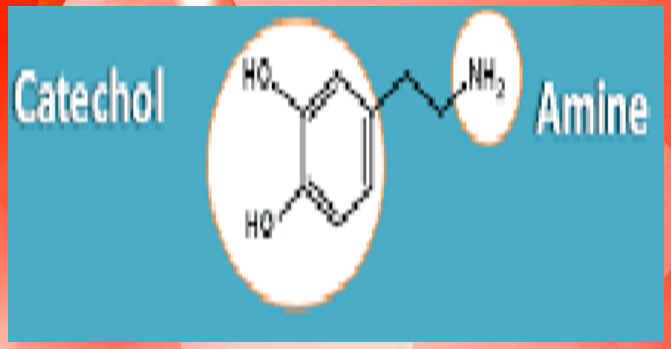




ADRENERGIC AGONISTS

Classification

i-According to chemical structure



A- Catecholamines

1- Natural — Noradrenaline, adrenaline, dopamine

2-Synthetic — Isoprenaline

Degraded by MAO& COMT/Little CNS effects / Parenterally administered

B- Non Catecholamines — Ephedrine

Resist degradation by MAO/ Prominent CNS effects / Orally administered

ADRENERGIC AGONISTS

ii-According to receptor selectivity

1-Selective

α_1; Phenylephrine

α_2; Clonidine

β_1; Dobutamine

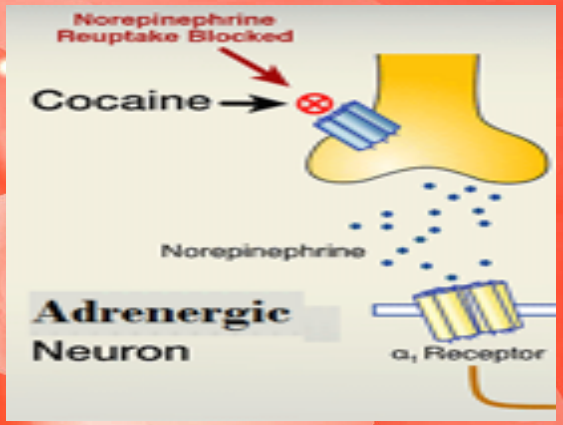
β_2; Salbutamol

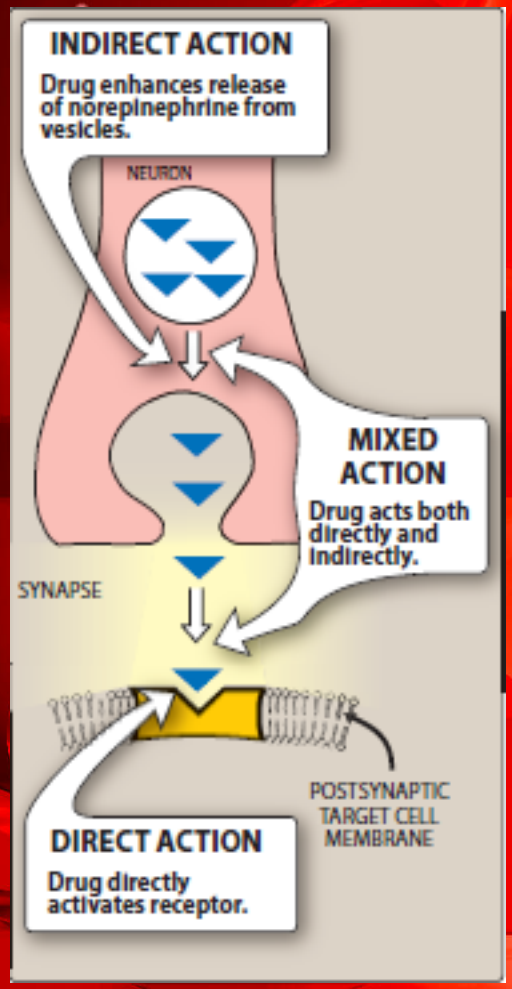
2-Non- selective

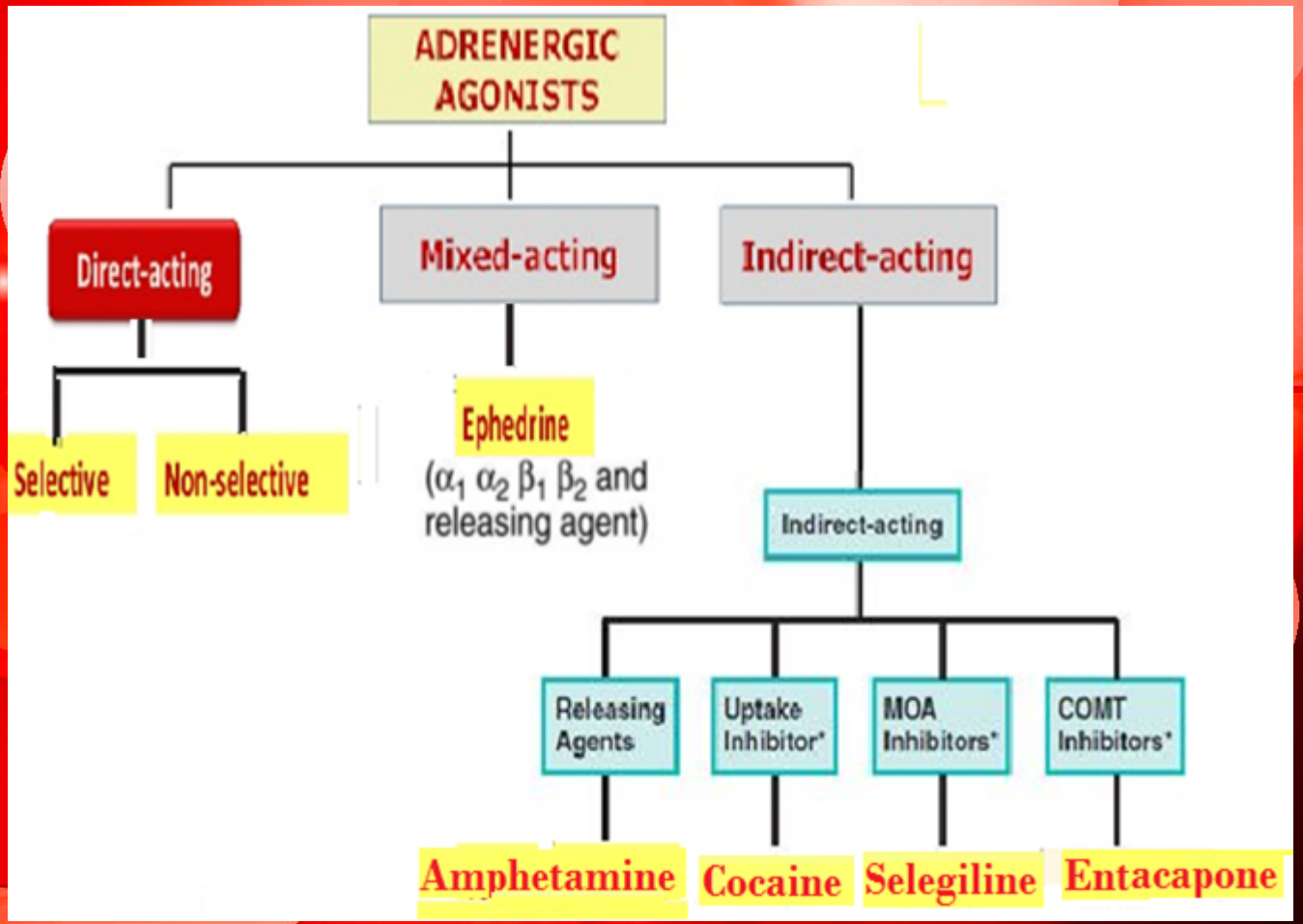
Noradrenaline, adrenaline, dopamine, isoprenaline, ephedrine

ADRENERGIC AGONISTS

iii-According to mode of Action





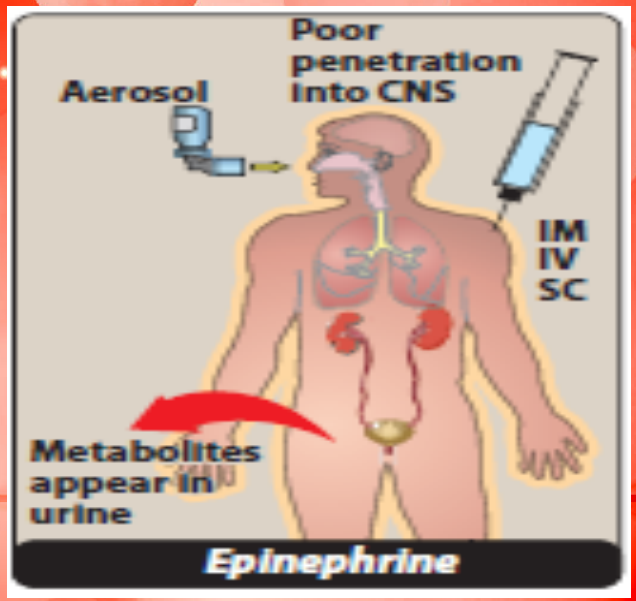


DIRECT- ACTING ADRENALINE

Naturally released from adrenal medulla
➔ secondary to stress, hunger, fear

Inactivated by intestinal enzymes, so given parenterally or by inhalation

Acts on all adrenergic receptors; β =/> α



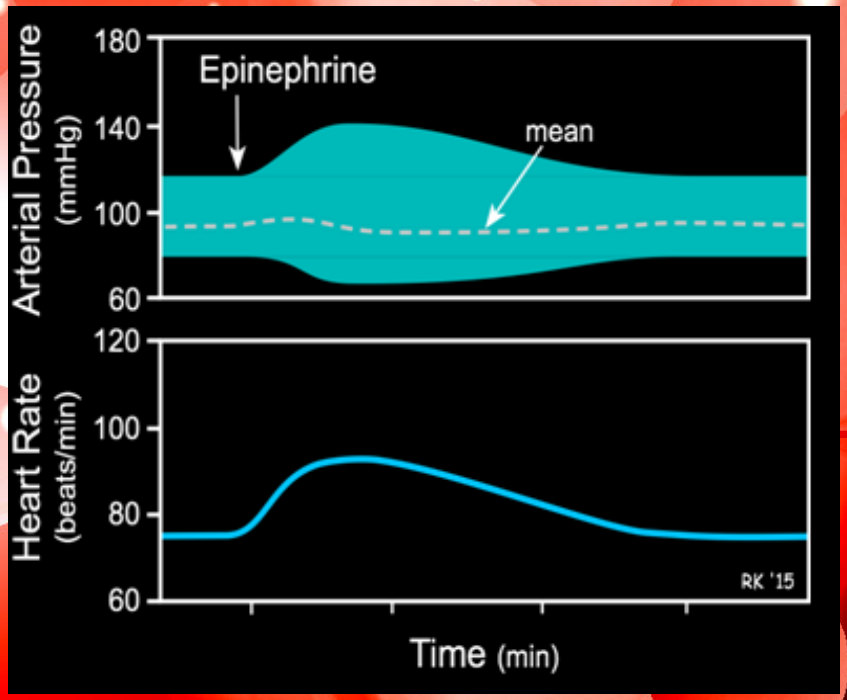
Lung ➔ bronchiodilatation (β_2)
Pregnant uterus ➔ tocolytic (β_2), Eye ➔ mydriasis (α_1)
CNS ➔little, headache, tremors & restlessness

ADRENALINE

PHARMACOLOGICAL ACTIONS

Heart ➔ +inotropic, chronotropic, dromotropic (⬆excitability)(β_1)

- BP ➔ ⬆ systolic (β_1) / ⬇ diastolic . Low dose (β_2) , high dose (α_1)



Vascular SMC:- Constricts skin & peripheral vessels (α_1) . Dilates coronary & skeletal vessels (β_2)

ADRENALINE

INDICATIONS

Used locally; as haemostatic (in epistaxsis) & as decongestant (α_1)

With local anesthetics ➔ to reduce absorption, toxicity & bleeding from incision

Used systemically for treatment of:-

Allergic reactions ➔ drug of choice in anaphylactic shock as it is the physiological antagonist of histamine ➔ ↑ BP & cause vasoconstricton

- In status asthmatics ➔ given parenterally ➔ bronchodilatation (β_2) + ➔ ↓mucosal edema (α_1)

- In cardiac arrest ➔ direct but now through central line

N.B. Selective β_1 agonists are preferred

ADRENALINE

ADRS

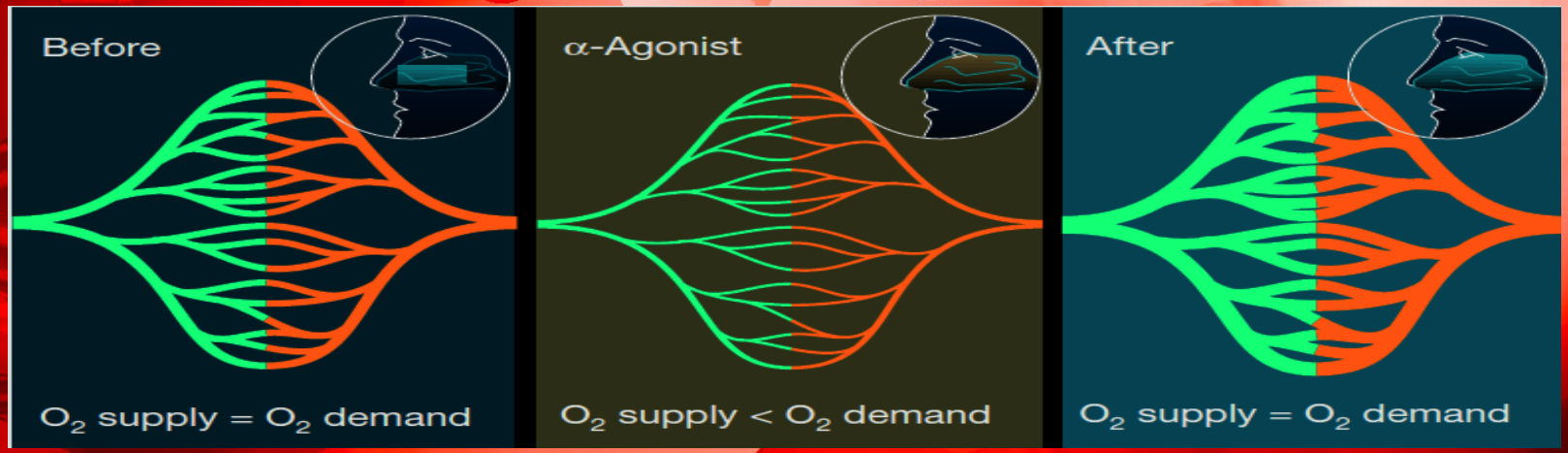
Tachycardia, palpitation, arrhythmias, angina pains

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 decongestion

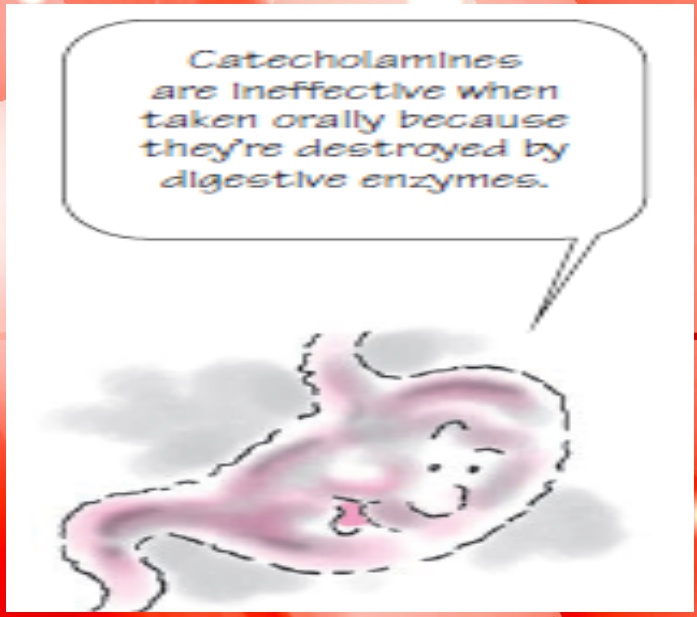


ADRENALINE

CONTRINDICATIONS

- Coronary heart disease, hypertension, peripheral arterial disease.

Hyperthyroidism



- Closed-angle glaucoma
- (Iris relaxation ↓ filtration angle → ↑ IOP

NORADRENALINE

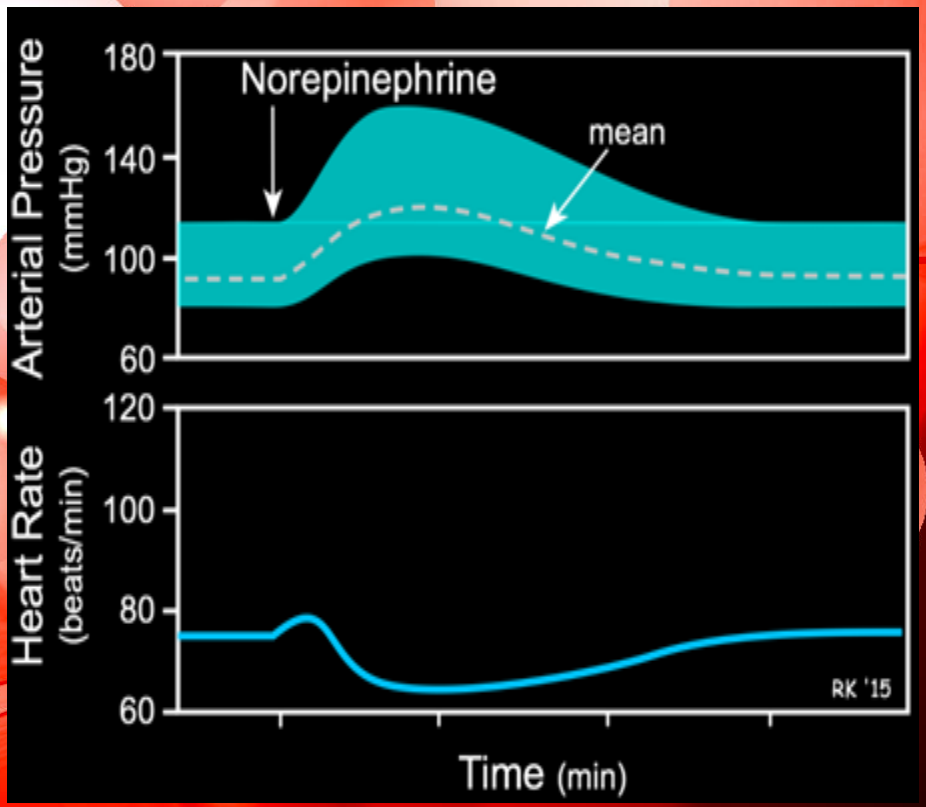
It is naturally released from postganglionic adrenergic fibers

Not much used therapeutically ➔ severe vasoconstriction

Acts on $\alpha > \beta_1$

Only administered IV - Not IM or Subcutaneous ➔necrosis

It ↑ BP [systolic & diastolic] ➔ reflex bradycardia *(vagal stimulation)* ➔ CO not much changed



NORADRENALINE

INDICATIONS

Used systemically; hypotensive states

In spinal anesthesia, in septic shock if fluid replacement and inotropics fail

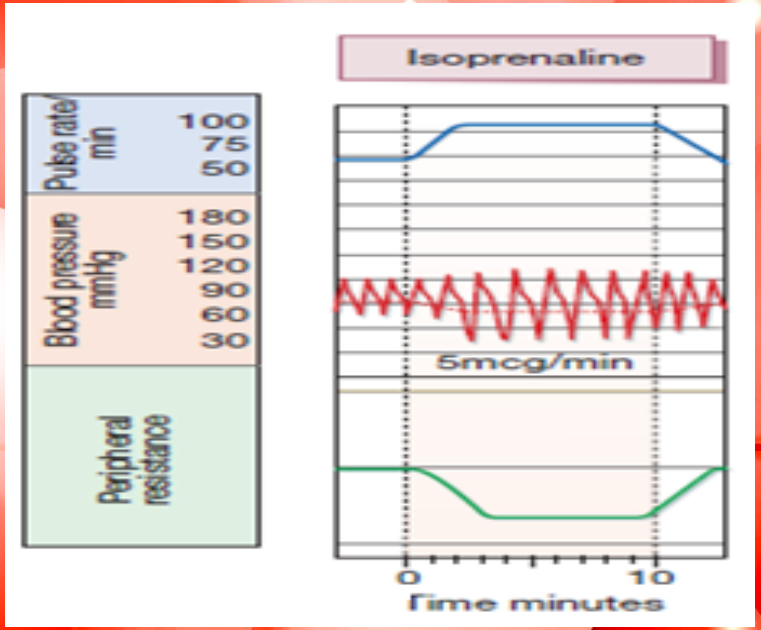
Used topically; as a local haemostatic with local anesthetic
(< tachycardia & irritability & > necrosis & sloughing)

ISOPRENALINE

It is synthetic ; show no presynaptic uptake nor breakdown by MA O ➔ longer action.

Acts on β > > α

Slightly ↑systolic pressure, ↓diastolic pressure ,↓PVR, ↑HR



Produce broncho-dilatation ➔Was used by inhalation in acute asthma

Used in cardiac arrest but contraindicated in hyperthyroidism & CHD

DOPAMINE

It is a natural CNS transmitter

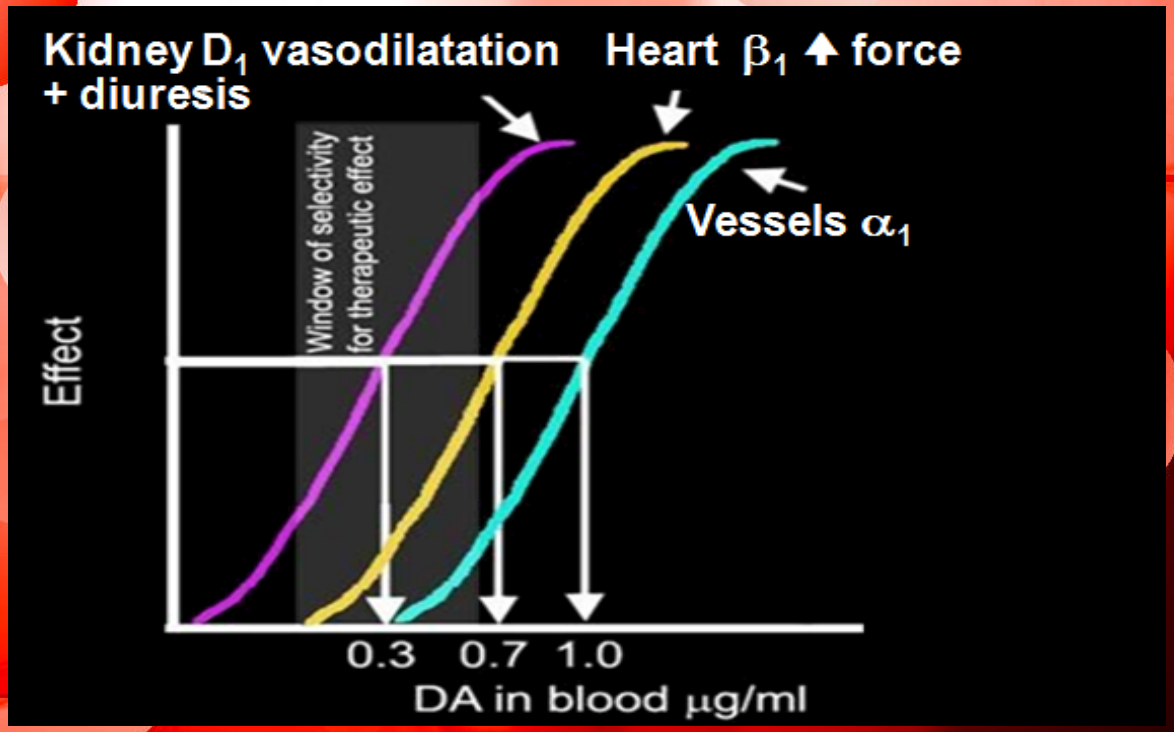
Released from postganglionic adrenergic fibers (> renal vessels)

Releases NE from postganglionic adrenergic fibers

Acts on $D_1 > \beta_1 > \alpha_1$

On BP ➔ According to dose; first ↓ D_1 then ↑ due to β_1 followed by α_1 effect

On heart ➔ Inotropic, no chronotropic effect



DOPAMINE

Indications

- Given parenterally by continuous infusion
- It is the drug of choice in treatment of SHOCK → septic, hypovolaemic (after fluid replacement), cardiogenic. It ↑ BP & CO (β_1), without causing renal impairment (D_1)
- Can be given in acute heart failure (HF) but dobutamine is prefered

DOBUTAMINE

It is synthetic. Given IV.

Acts on $\beta_1 > \beta_2 > \alpha_1$

On heart ➔ Inotropic with little chronotropic effect

On BP ➔ No or little ↓ in therapeutic dose (β_1 & β_2 counterbalance + no α_1)

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

It is synthetic, noncatecholamine

Given orally & has prolonged duration of action

Systemically; Pressor agent in hypotensive states. *Infusion.* Acts as *selective* α_1 Peaks in 20 min. $t_{½}$ 30 min

Terminate atrial tachycardia *(reflex bradycardia)*

Nasal decongestant. *Oral*

Topically; Local Haemostatic, with Local anesthesia.

Nasal & Ocular Decongestants

Used for treatment of nasal stuffiness . But can cause Rebound nasal stuffiness

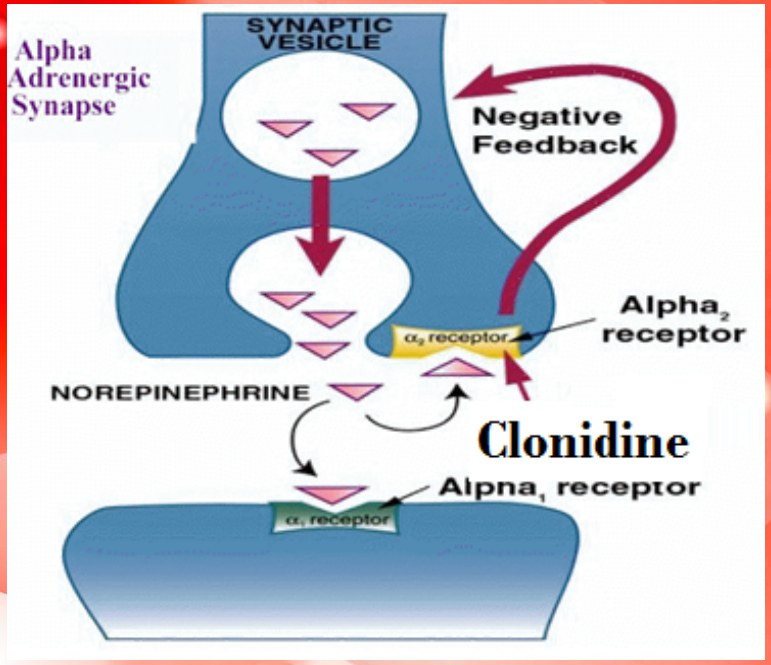
Mydriatic *(no cycloplegia so facilitate eye examination)*

CLONIDINE

It is synthetic, imidazoline

Given orally or as patch

Acts *selectively* on presynaptic α_2



↓ BP ➔ *by action on (α_2) at nucleus tractus solitarius to ↓ sympathetic outflow to heart & vessels.* ➔ Antihypertensive agent

Brimonidine is an imidazoline ➔ α_2 agonist used in glaucoma

SALBUTAMOL

It is synthetic. Given orally, by inhalation or parenteral.

Acts *selectively* on β_2 ➔ on bronchi. *Little effect on heart (β_1)*

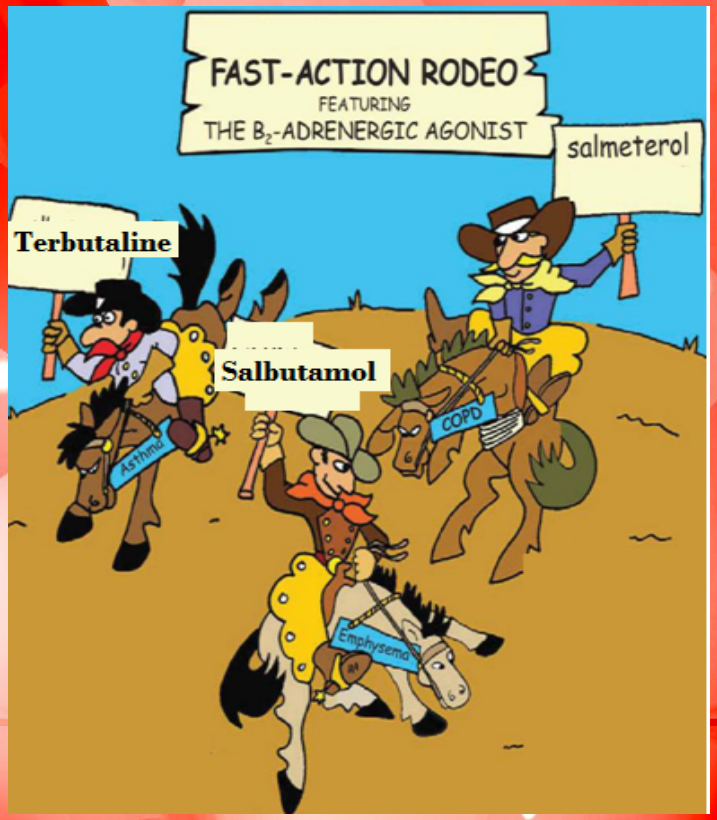
Bronchodilater ➔ asthma & chronic obstructive airway disease (COPD)

Because $t_{1/2}$ is 4 hrs longer acting preparations exist ; Salmeterol & Formoterol

Other selective β_2 agonists :

Terbutaline; Bronchodilator & Tocolytic

Ritodrine; Tocolytic ➔ postpone premature labour *(labour that begins before the 37th week of gestation)*



INDIRECTLY-ACTING SYMPATHOMIMETIC AMINES

AMPHETAMINE

It acts indirectly; Releasing NE from adrenergic nerve endings > Blocking of its reuptake

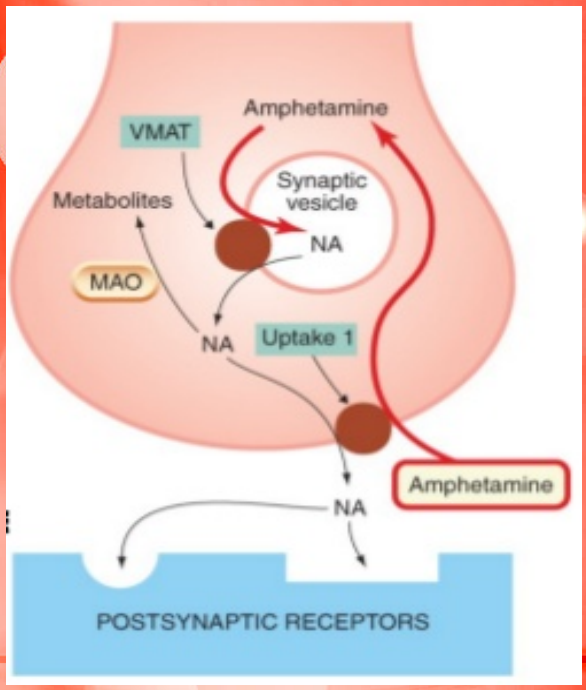
Because it depletes vesicles from stored NE ➔ tachyphylaxsis

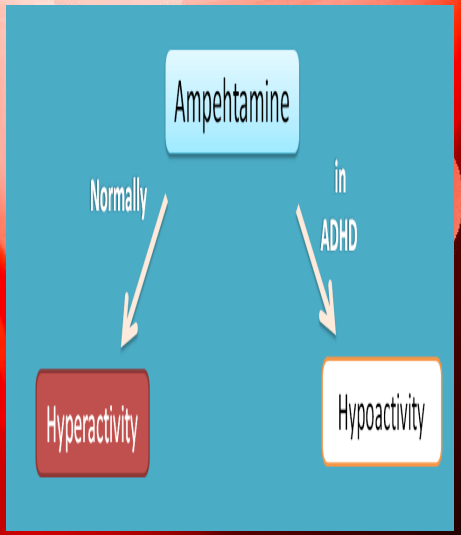
Absorbed orally, not destroyed by MAO, excreted mostly unchanged (⬆*by acidification of urine)*

Acts on α& β ➔ similar to epinephrine but has CNS stimulant effects; mental alertness, wakefulness, concentration & self-confidence / followed by depression & fatigue on continued use

⬇ Weight ➔ ⬇ appetite ⬆ increase energy expenditure

No more used therapeutically ➔ induces psychic & physical dependence and psychosis + the CVS side effects





MIXED SYMPATHOMIMETICS

EPHEDRINE

Plant alkaloid, synthetic, mixed sympathomimetic

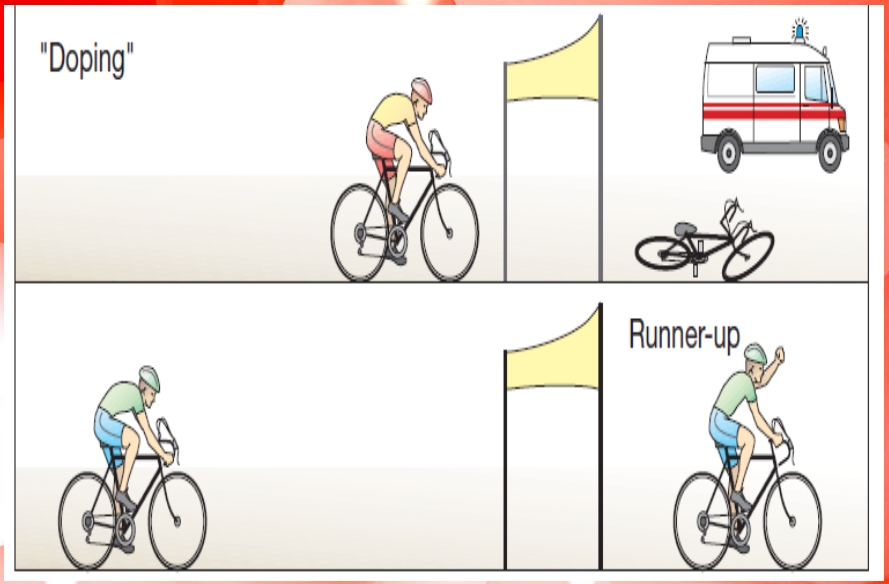
Prolonged direct action on receptors ➔ receptor down regulation

Release NE from adrenergic nerve endings ➔depletes stores ➔ tachyphylaxsis

Absorbed orally, not destroyed by MAO or COMT ➔ prolonged action

MIXED SYMPATHOMIMETICS

EPHEDRINE



Acts on α& β

Facilitation of neuromuscular transmission(mythenia gravis) & retention of urine

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 flue remedies