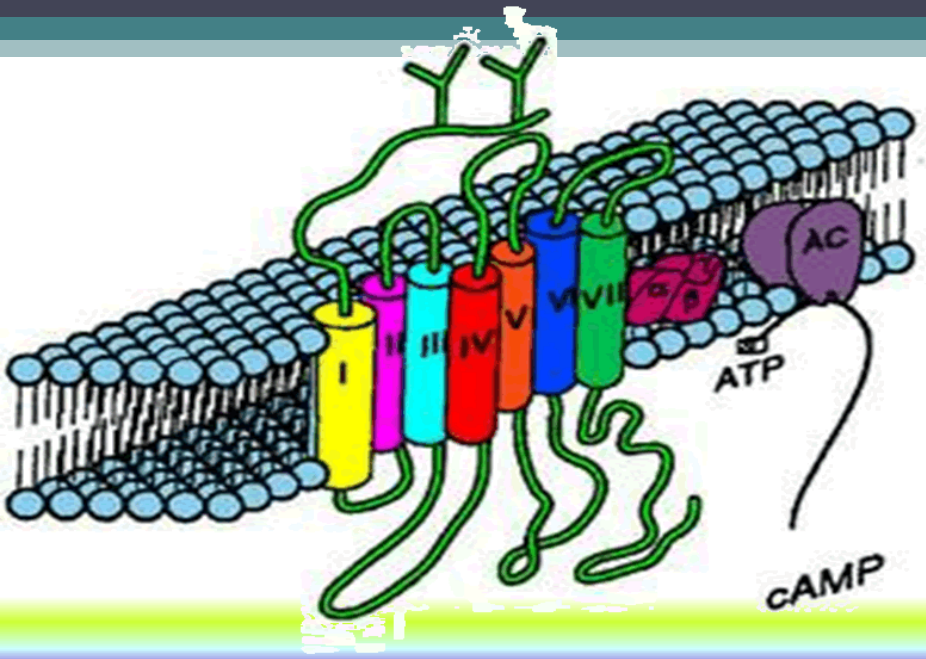
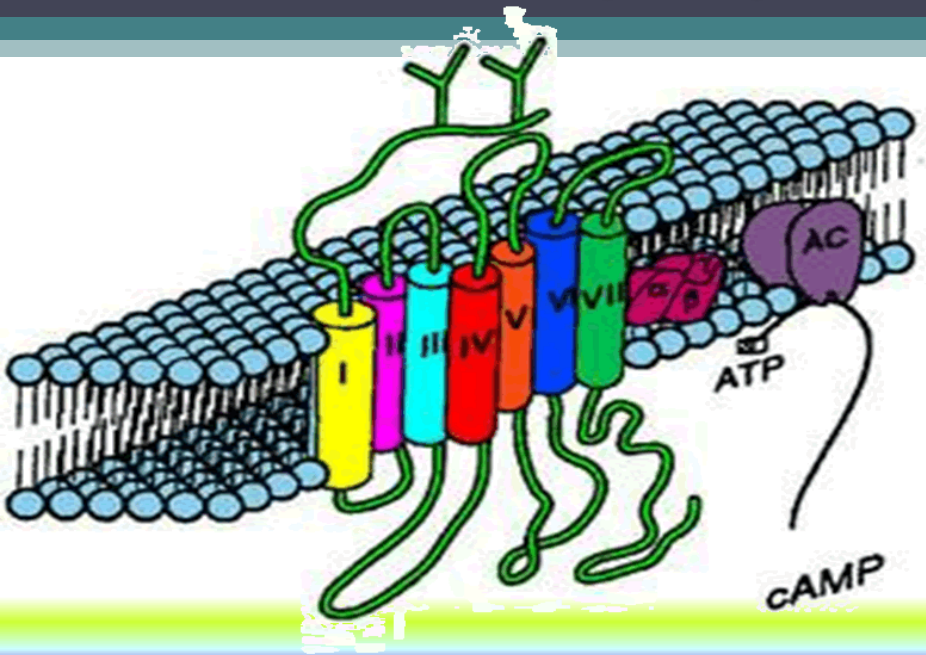
Adrenergic agonist: PHARMACOLOGY OF SNS



ADRENERGICS STIMULANTS [AGONISTS]

Direct Sympathomimetics
Indirect Sympathomimetics
Dual Sympathomimetics



ADRENERGIC STIMULANTS

According to chemistry; **Catecholamines;** Natural; NE, E, Dopamine
Synthetic; Isoprenaline

Rapidly acting / Degraded by MOA & COMT
Sparse CNS effects / Parenterally administered

Non-Catecholamines; Ephedrine

Delayed action / Resist degradation by MOA
Prominant CNS effects / Orally administered

According to spectrum of action;

Non-Selective;

Norepinephrine, epinephrine, dopamine, isoprenaline, ephedrine,…etc

Selective;

α_1; Phenylephrine
α_2; Clonidine
β_1; Dobutamine
β_2; Salbutamol

ADRENERGIC STIMULANTS

According to mode of action;

Direct; Stimulate adrenergic receptors directly.

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

Indirect; Release of NE from presynaptic stores at adrenergic nerve terminals

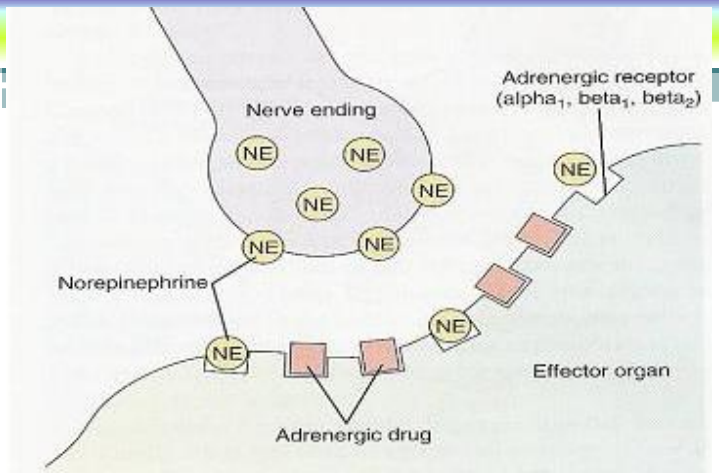
e.g. amphetamine

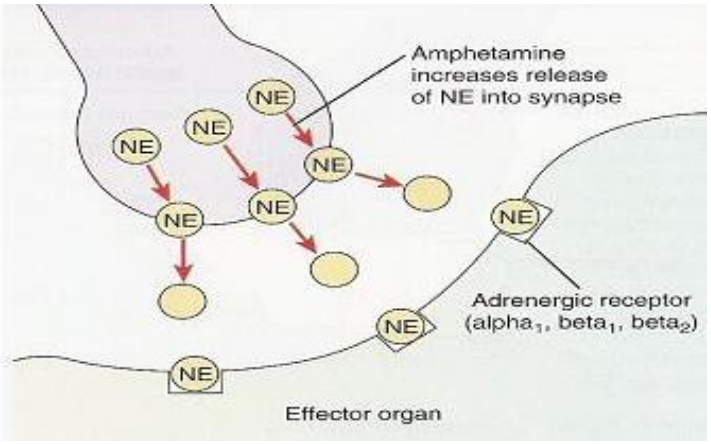
Or Inhibit uptake → ↑its availability in synapse.

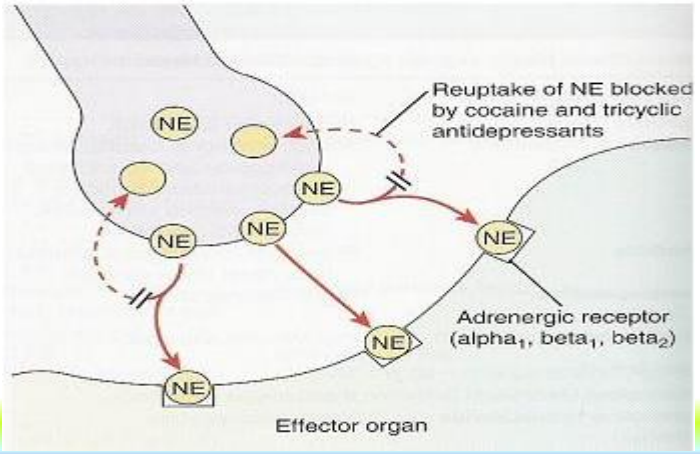
e.g. Cocaine & antidepressants

Dual; Direct and indirect stimulation of adrenergic receptors

e.g. ephedrine, pseudoephedrine

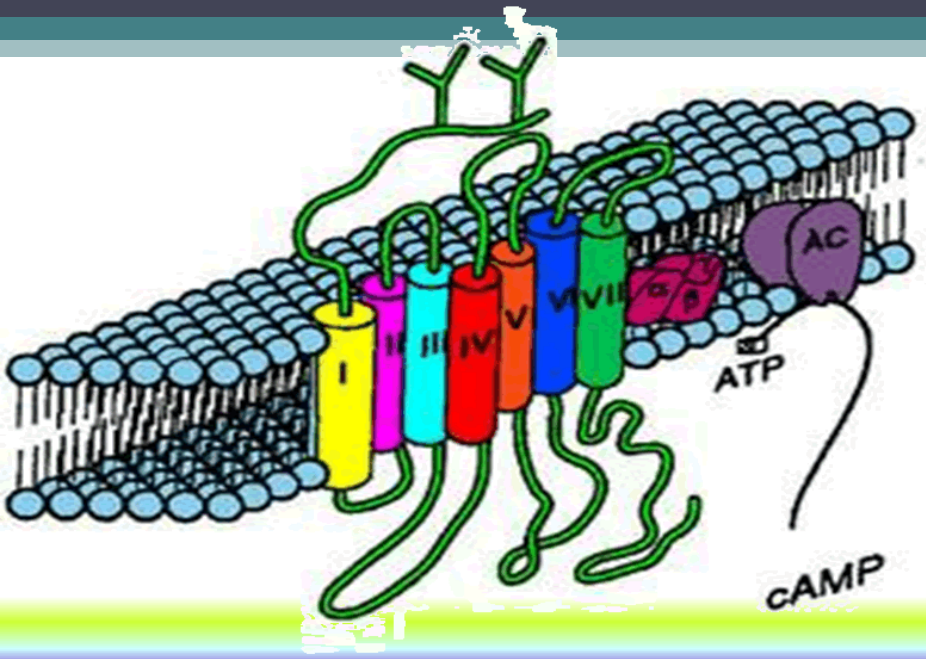






ADRENERGICS AGONISTS

Direct Sympathomimetics



ADRENERGIC STIMULANTS

DIRECT Acting Sympathomimetics

ADRENALINE

Naturally released from adrenal medulla ➔ 2ndry to stress, hunger, fear
Inactivated by intestinal enzymes, so given parentral & by inhalation
Acts on all ADR; β =/> α .

Pharmacological actions➔

- Heart ➔ inotropic, chronotropic, dromotropic (↑excitability)(β_1)
- BP ➔↑ systolic (β_1) / diastolic ↓ ➔ low dose (β_2) & ↑ ➔high dose (α_1)
- Vascular SMC; constrict skin + peripheral (α_1) / dilate coronary+skeletal (β_2)
- Non vascular SMC;
  - Lung ➔ bronchiodilatation (β_2)
  - Pregnant uterus ➔ tocolytic (β_2)
  - Eye ➔ mydriasis (α_1) / ➔ no effect on accommodation or intraocular P
- CNS ➔little, headache, tremors & restlessness

ADRENALINE

Indications

Used locally; as haemostatic (in epistaxsis) & as decongestant (α_1) !!!
with local anesthetics ➔ to ↓its 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 parentally ➔ bronchodilatation (β_2) + ➔ ↓mucosal edema (α_1)
  N.B. Selective β_2 are better in asthma by inhalation
- In cardiac arrest ➔ direct but now through central line
  N.B. Selective β_1 are better

ADRENALINE

ADRs

- 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 decongestion

Contraindications

- CHD, hypertension, peripheral arterial disease.
- Hyperthyroidism.
- Closed-angle glaucoma (ciliary relaxation ↓ filtration angle → ↑ IOP

ADRENERGIC STIMULANTS

Direct Acting Sympathomimetics

NOREPINEPHRINE = NORADRENALINE

It is naturally released from postganglionic adrenergic fibres

Not used much 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

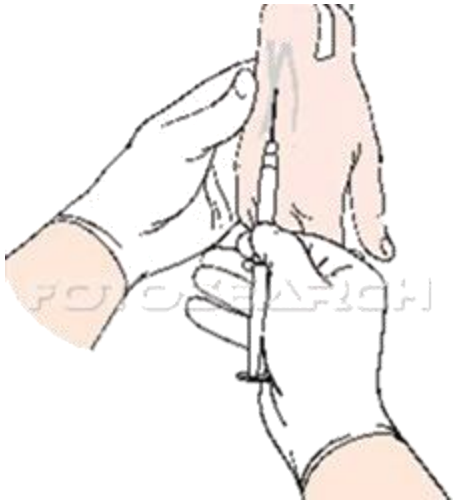
Indications

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)



ADRENERGIC STIMULANTS

Direct Acting Sympathomimetics

ISOPRENALINE

It is synthetic ; show no presynaptic uptake nor breakdown by MOA ➔ longer action. Acts on $\beta > > \alpha$

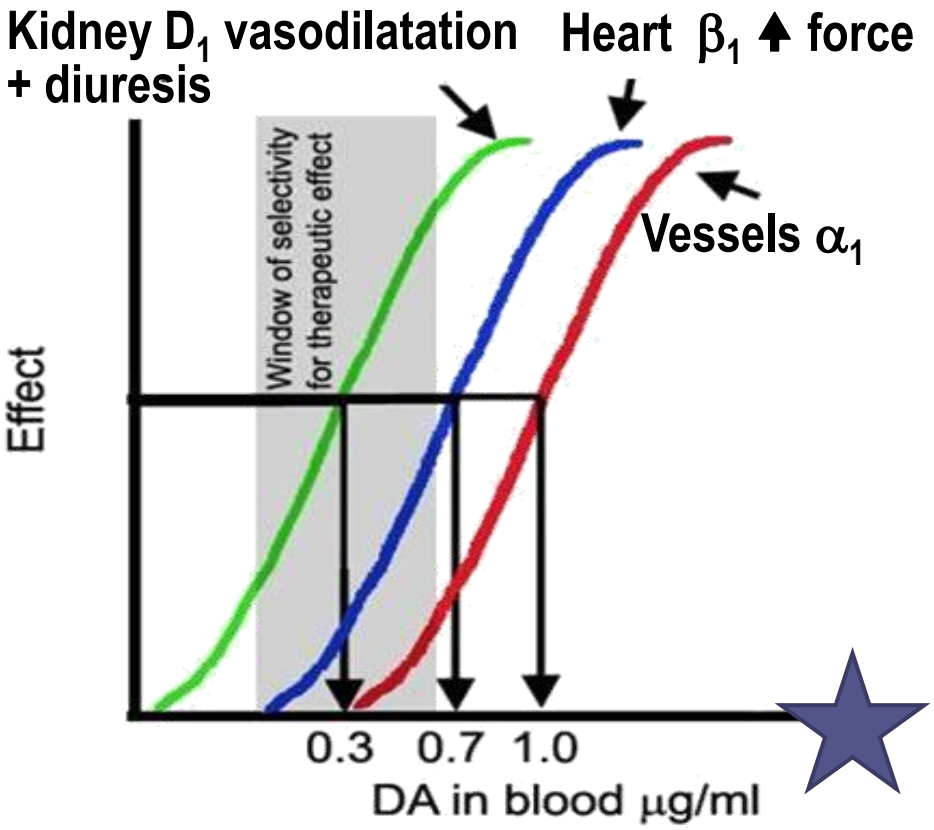
10 times > broncho-dilatation ➔Was used by inhalation in acute asthma

Used in cardiac arrest but contraindicated in hyperthyroidism & CHD

DOPAMINE

- It is a natural CNS transmitter.
- Released from postganglionic adrenergic fibres (> renal vessels)
- Releases NE from postganglionic adrenergic fibres

Acts on $D_1 > \beta_1 > \alpha_1$

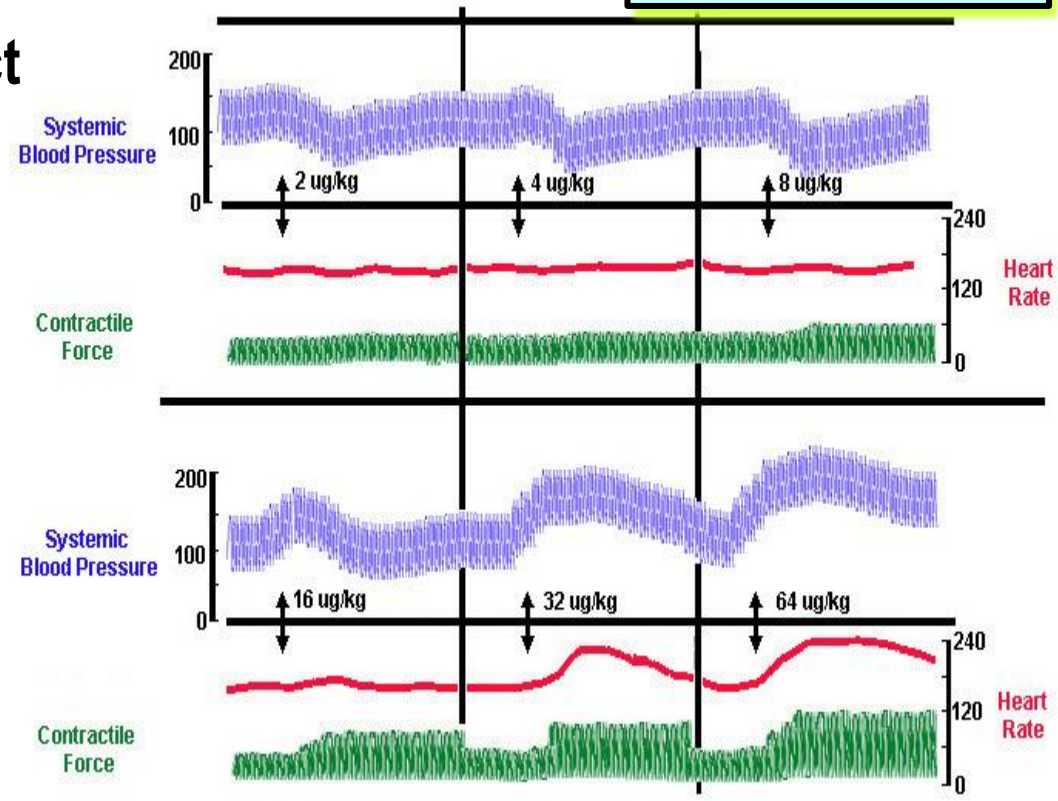


ADRENERGIC STIMULANTS

Direct Acting Sympathomimetics

DOPAMINE

On heart ➔
Inotropic, no chronotropic effect
On BP ➔ According to dose;
first ↓ D_1
then ↑ due to β_1
followed by α_1 effect



- Given parentrally by infusion

Indications

- 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 better dobutamine

ADRENERGIC STIMULANTS

Direct Acting Sympathomimetics

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)

Indications

- Given parentrally 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

ADRENERGIC STIMULANTS

Direct Acting Sympathomimetics

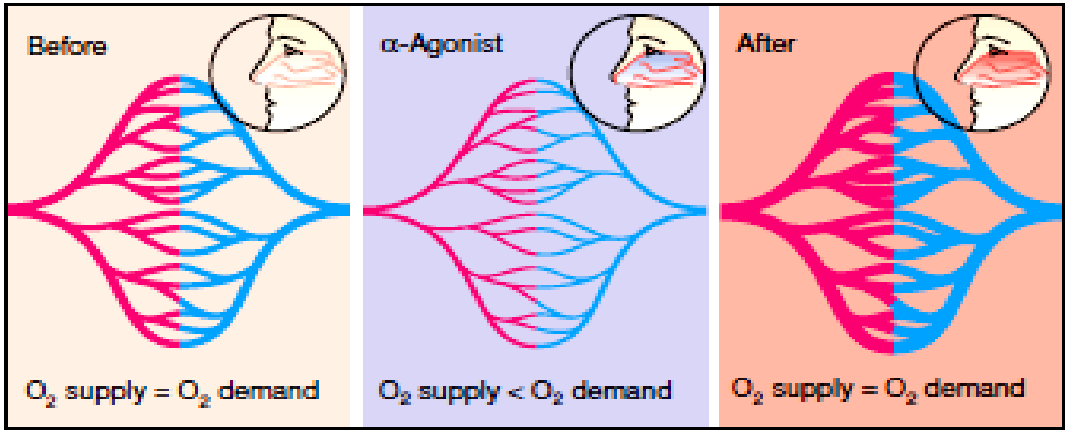
Nasal & Ocular Decongestants

PHENYLETHYLAMINES

- Pseudoephedrine
- Phenylephrine
- Methoxamine

IMIDAZOLINE

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



Used for treatment of nasal stuffiness

But can cause Rebound nasal stuffiness

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

- *N.B. Brimonidine is an imidazoline → α_2 agonist used in glucoma*

ADRENERGIC STIMULANTS

Direct Acting Sympathomimetics

PHENYLPHERINE

It is synthetic, noncatecholamine.
Given orally & has prolonged duration of action.
Acts as *selective* α_1

MIDODRINE

Peaks in 20 min.
$t_{½}$ 30 min.

In Hypotension

On heart ➔ reflex bradycardia
On BP ➔ ↑ due to vasoconstriction (α_1)

Indications

- **Systemically:** Pressor agent in hypotensive states. *Infusion*
  Terminate atrial tachycardia *(reflex bradycardia)*
  Nasal decongestant. *Oral*
- **Topically:** Local Haemostatic, with Local anesthesia.
  Decongestant (*nasal & ocular)*
  Mydriatic *(no cycloplegia so facilitate eye examination)*

ADRENERGIC STIMULANTS

Direct Acting Sympathomimetics

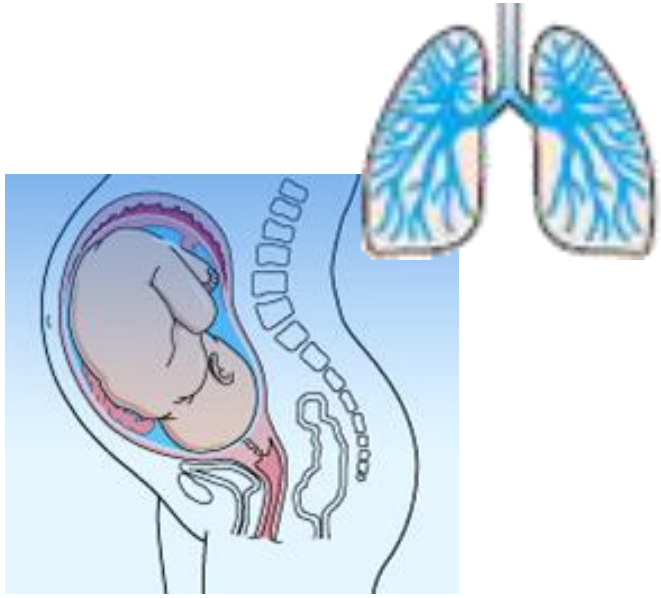
SALBUTAMOL

It is synthetic. Given orally, by inhalation or parentral.
Acts *selectively* on β_2 ➔ on bronchi. *Hardly effect on heart (β_1)*
Bronchodilater ➔ asthma & chronic obstructive airway disease (COPD)

- *N.B. Because $t_{1/2}$ is 4 hrs longer acting preparations exist ; Salmeterol & Formoterol*

Other selective β_2 agonists :

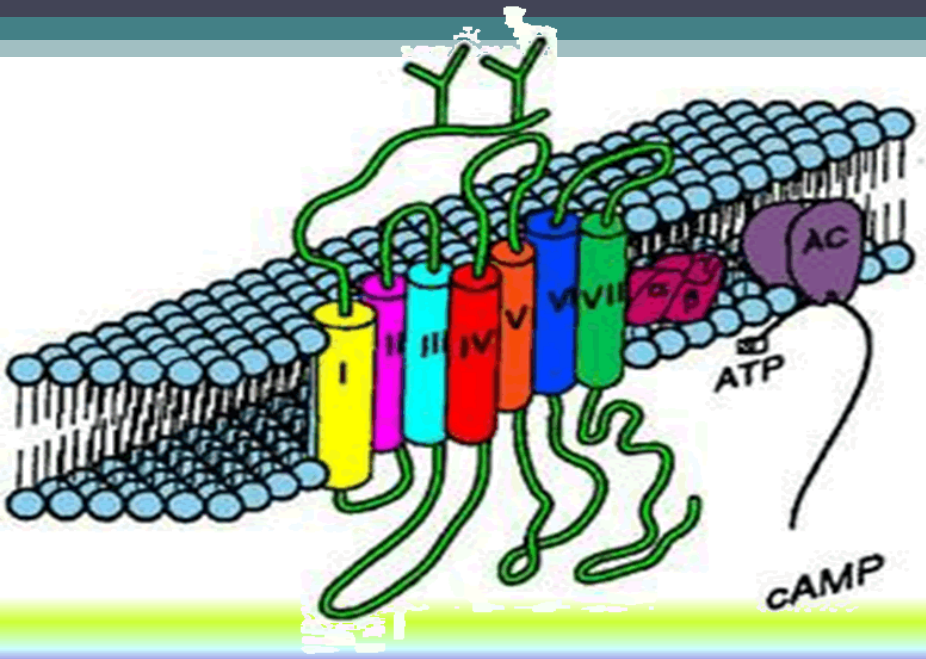
Terbutaline; Bronchodilator & Tocolytic



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

ADRENERGICS STIMULANTS [AGONISTS]

Indirect Sympathomimetics



ADRENERGIC STIMULANTS

INDIRECT Acting Sympathomimetics

AMPHETAMINE

It acts indirectly;
Releasing NE from adrenergic nerve endings > Blocking of its reuptake
Because it depletes vesicles from stored NE ➔ tachyphylaxsis

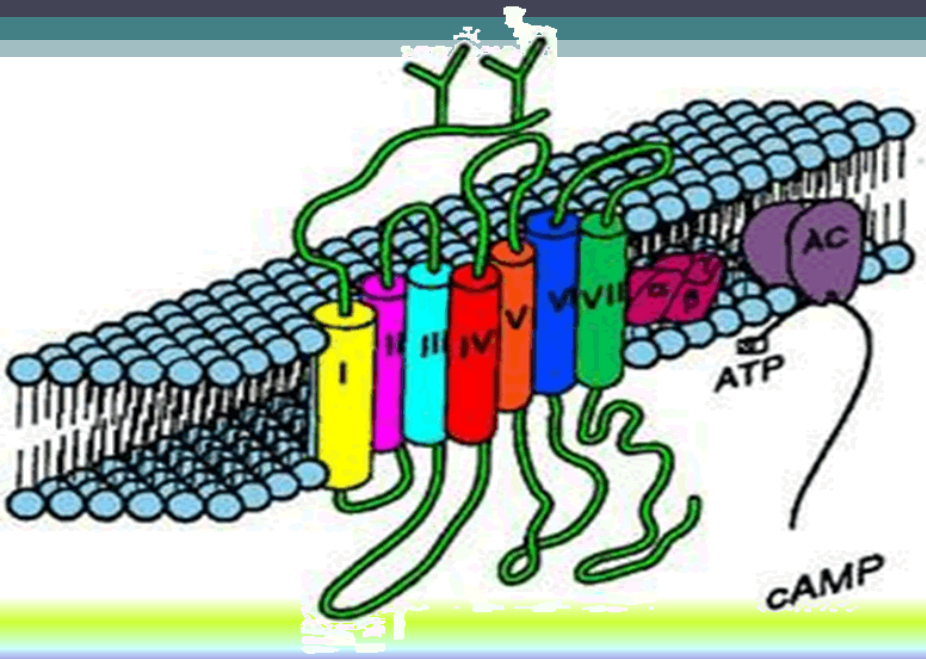
Absorbed orally, not destroyed by MAO, excreted mostly unchanged (↑ *by acidification of urine)*

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
↑ euphoria ➔ causes its abuse…..
↓ Weight ➔ ↓ appetite
↑ increase energy expenditure

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

ADRENERGICS STIMULANTS [AGONISTS]

Dual Sympathomimetics



ADRENERGIC STIMULANTS

DUAL Acting Sympathomimetics

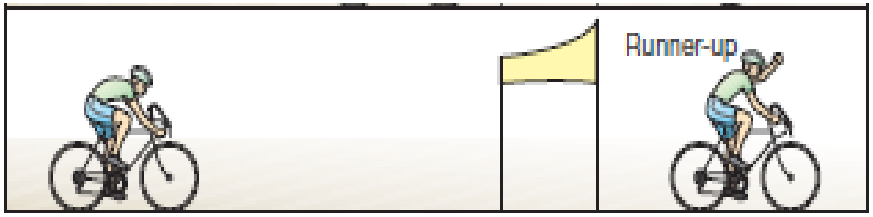
EPHEDRINE

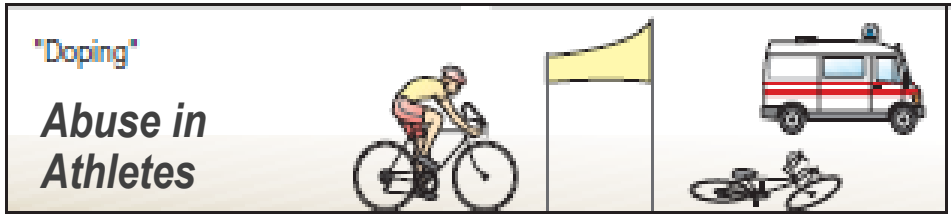
Plant alkaloid, synthetic, mixed sympathomimetic;
Prolonged direct action on receptors ➔ receptor down regulation
Release NE from adrenergic nerve endings ➔depletes stores
➔ tachyphylaxsis

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

Acts on α& β
+ > facilitation of neuromuscular transmission & 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.

Agents specifically indicated for hypotension

Midodrine, Phenylephrine, Norepinephrine,

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

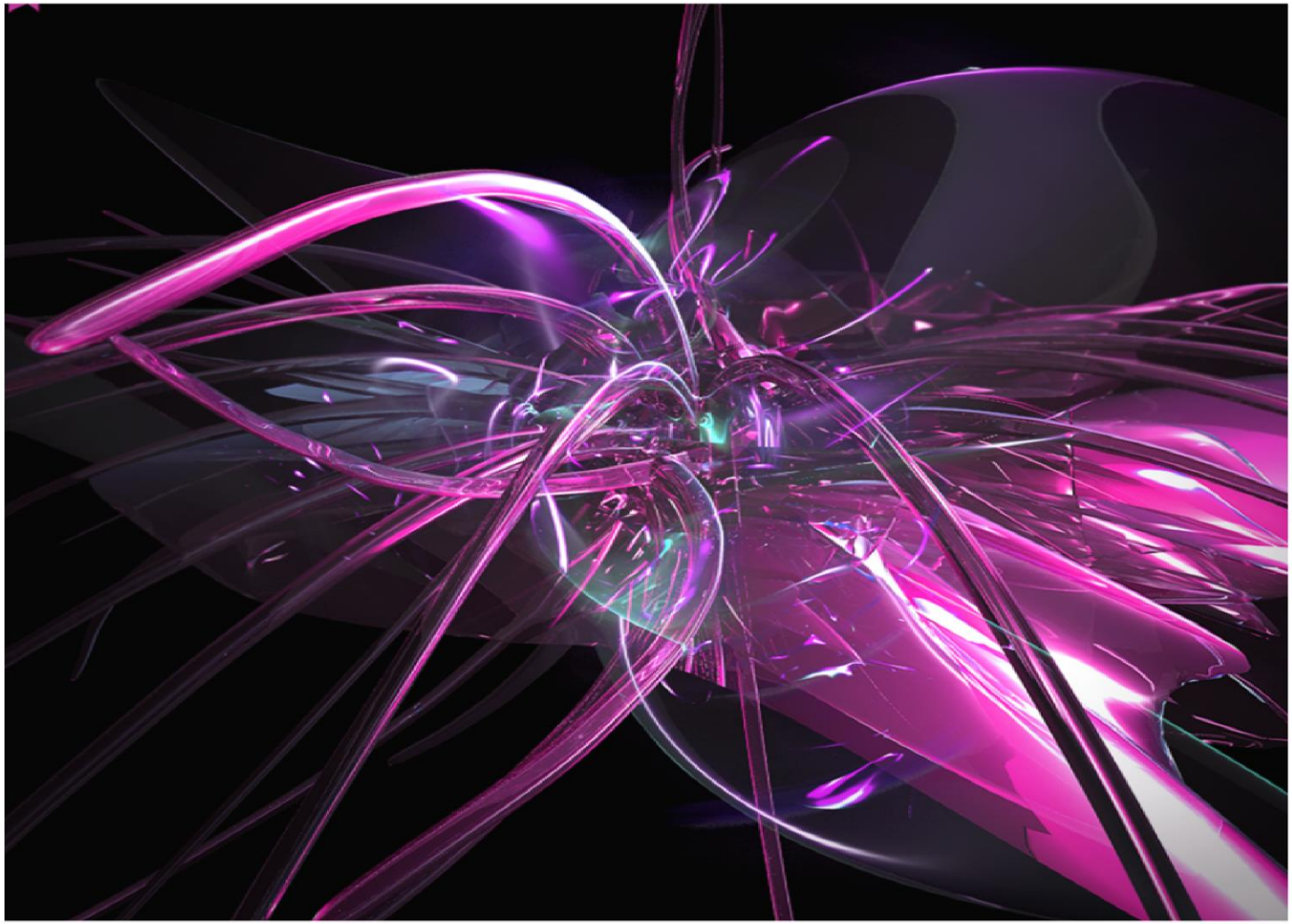
Agents specifically indicated for premature labour

Ritodrine, Terbutaline

Agents specifically indicated for nasal decongestion

Pseudoephedrine, Naphazoline, Oxymetazoline, Phenylephrine, Xylometazoline

Agents specifically abused in sports ➔ Ephedrine, Amphetamine



GOOD LUCK