AUTACOIDS

They include:

Aminoacid derivatives	• Histamine • Serotonin
Endogenous peptides	• Kinins, Angiotensin
Fatty acid derivatives	• Eicosanoids
Gas	NO

AUTACOIDS

ILOS

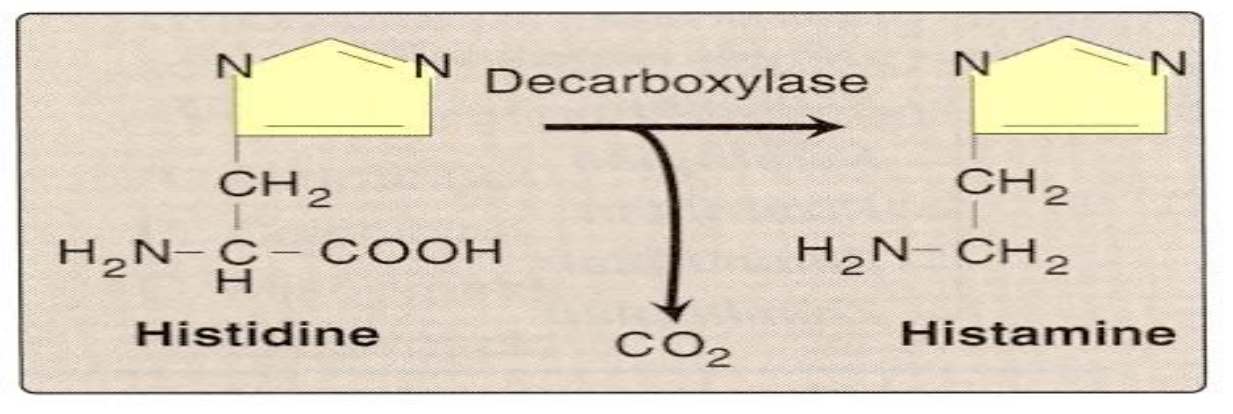
To describe the synthesis, receptors & functions of histamine, 5-HT, eicosanoids, nitric oxide, angiotensin, & kinins

To study the agents which enhance or block their effects.

1 – Histamine

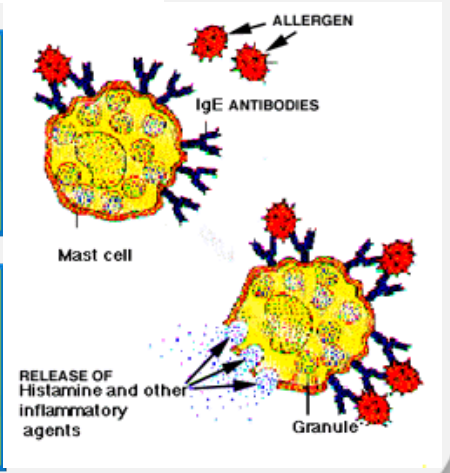
HISTAMINE

Synthesis:- from L- histidine



Stored in mast cells, basophils, lung, intestinal mucosa

Release:- during allergic reaction, inflammatory reaction



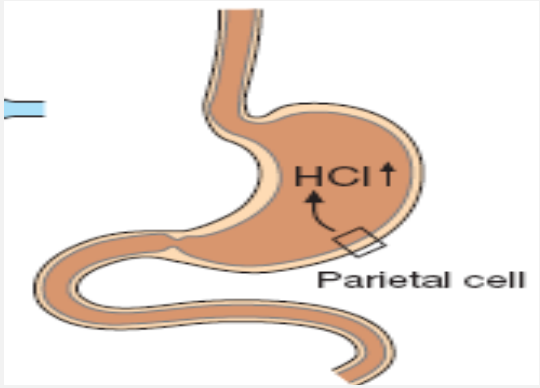
HISTAMINE RECEPTORS

Receptor Type	Major Tissue Locations	Major Biologic Effects
H_1	Smooth muscle, Endothelial cells, Brain	Acute **allergic** responses
H_2	Gastric parietal cells, Cardiac muscle, Mast cells, Brain	Secretion of **gastric acid** & **increase in *COP**
H_3	Central nervous system	Neurotransmission
H_4	Mast cells, Eosinophils, T-cells	Regulating immune responses

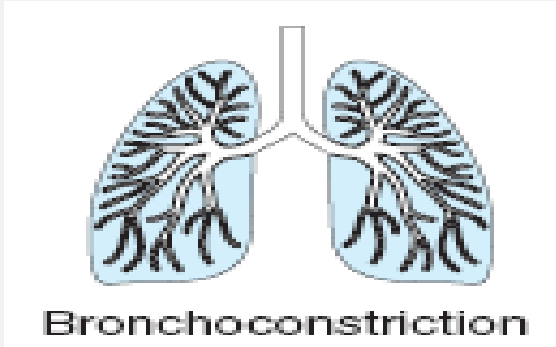
* COP: cardiac output

ACTIONS

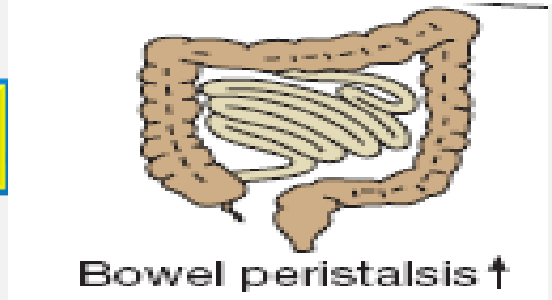
Histamine stimulates gastric acid secretion, through H_2- receptors



Stimulation of H_1- receptors contract smooth muscles, bronchioles, uterus



Increases bowel peristalsis



ACTIONS OF HISTAMINE

Slow IV or SC injection causes flushing of skin, raise temperature, edema, increase blood flow to the periphery, increase heart rate & COP (through increasing Ca^{2+} influx)

Rapid IV bolus injection induces a fall in blood pressure, an increase in CSF pressure, headache, due to dilation of blood vessels

Intradermal injection causes itching.

HISTAMINE RECEPTOR BLOCKERS

Physiological antagonist: epinephrine

HISTAMINE H_1 RECEPTOR ANTAGONISTS :

First generation

Diphenhydramine, Promethazine

Second generation

Cetirizine, Fexofenadine.

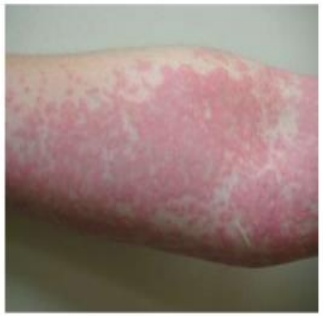
HISTAMINE H_1 RECEPTOR BLOCKERS

First generation

Has a sedating effect

Clinical uses:

- Allergic rhinitis
- Urticaria
- Insomnia
- Motion sickness



Urticaria

HISTAMINE H_1 RECEPTOR BLOCKERS

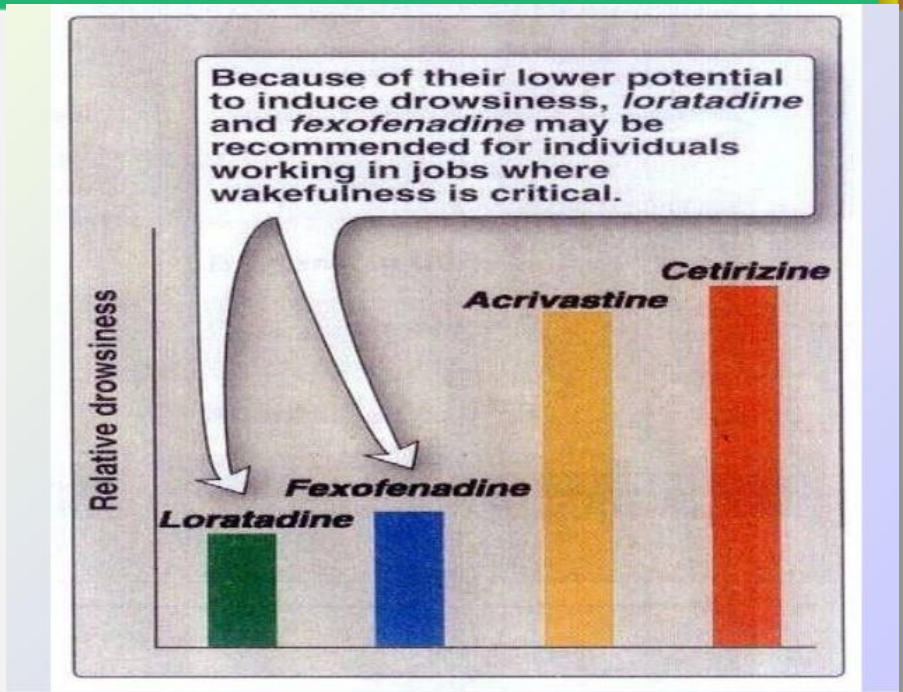
Second generation

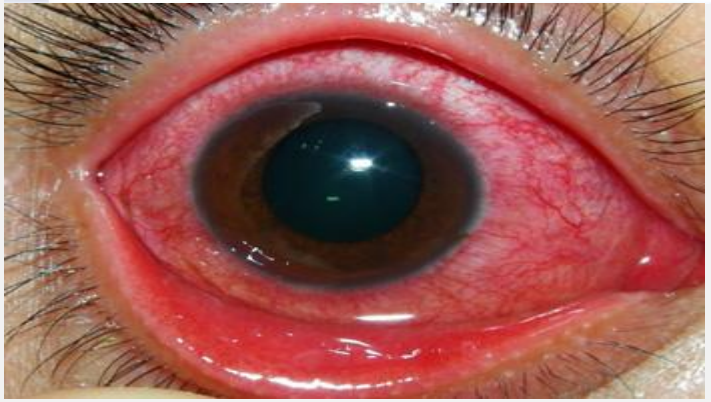
Non-sedating effect

Clinical uses

Allergic conditions such as:-

- Allergic rhinitis
- Conjunctivitis
- Urticaria.



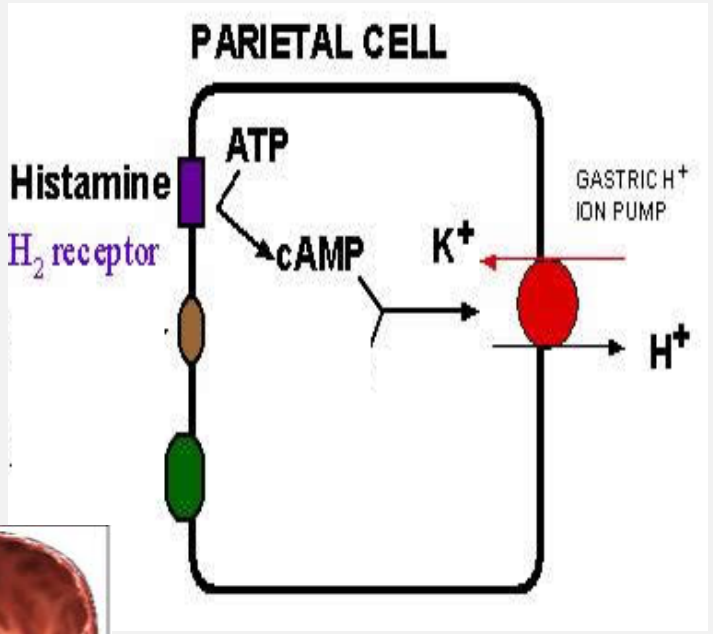


H2- RECEPTOR BLOCKERS

Histamine plays an important role in the formation & secretion of HCl by the activity of H2 receptors

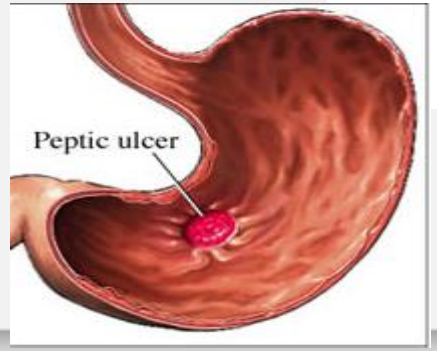
Blockers of H2 receptors inhibit gastric acid secretion

e.g. Cimetidine



Used for treatment of:

- **Gastritis**
- **Peptic ulcers**



H3- RECEPTOR BLOCKERS

e.g. Betahistine

It produces dilatation of blood vessels in inner ear

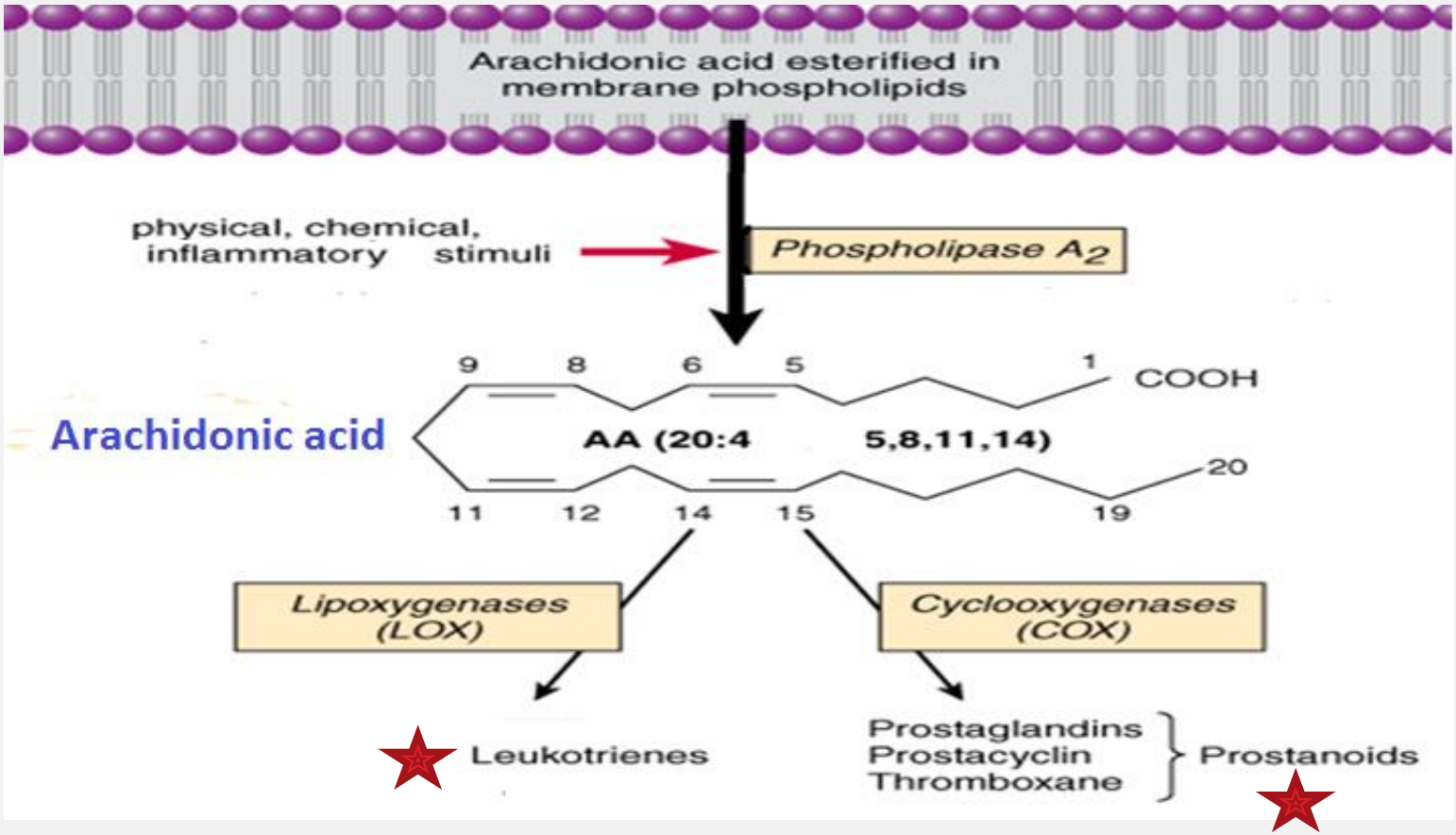
Used in treatment of :
Vertigo of Ménière's disease & other **balance disturbances** of vestibular origin

Side effects:
May produce headache & insomnia.

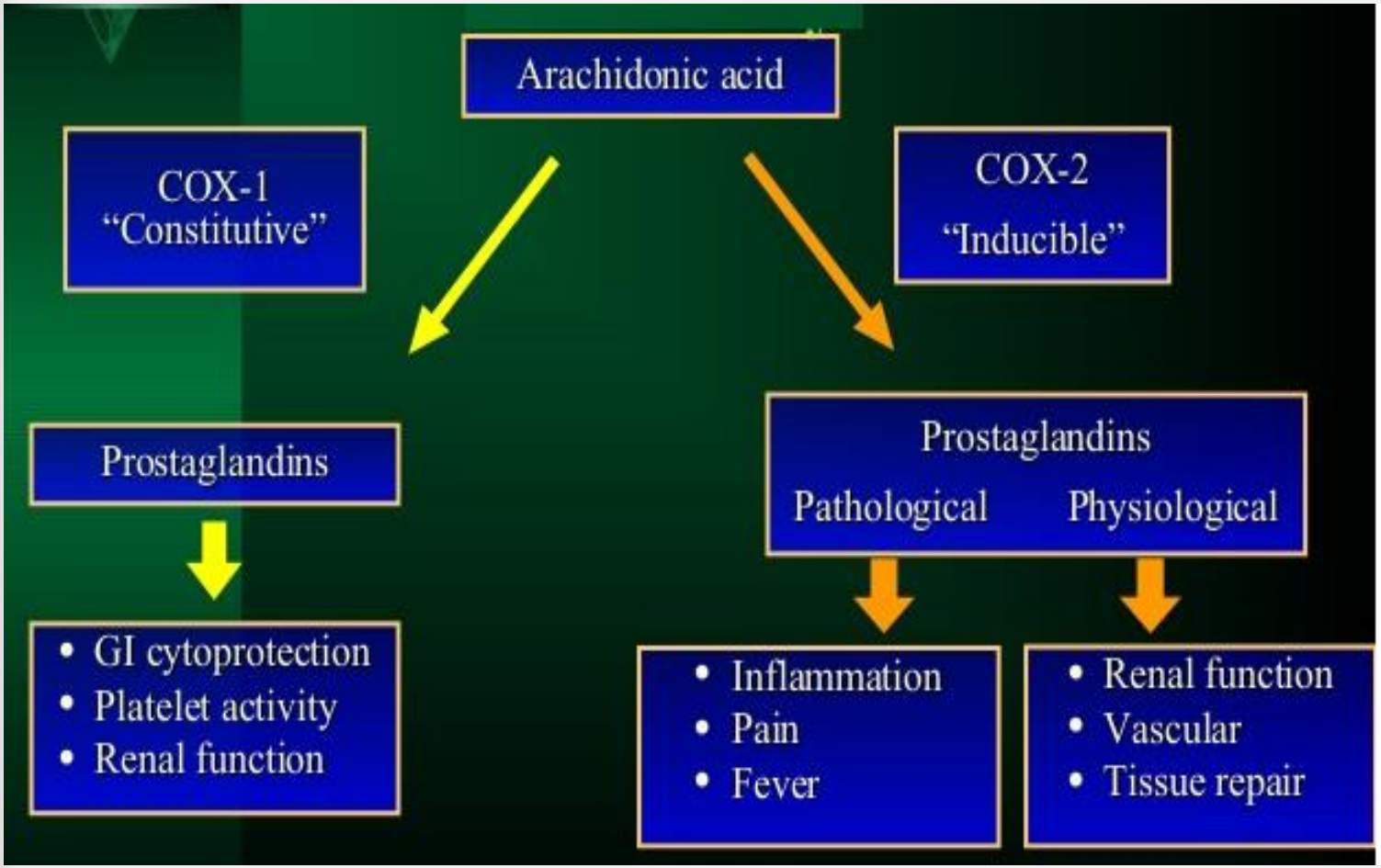
2- Eicosanoids

EICOSANOIDS

SYNTHESIS



COX ISOZYMES



ACTIONS OF PROSTAGLANDINS

They are pro-inflammatory

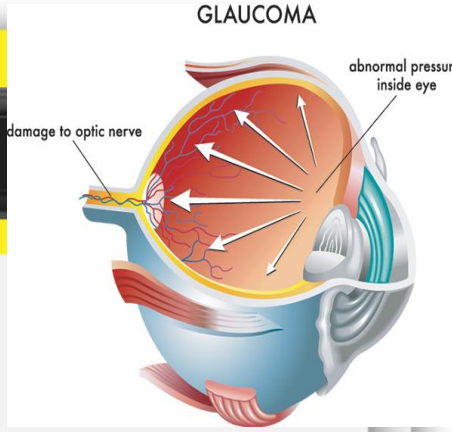
Cause vasodilatation of vascular smooth muscle

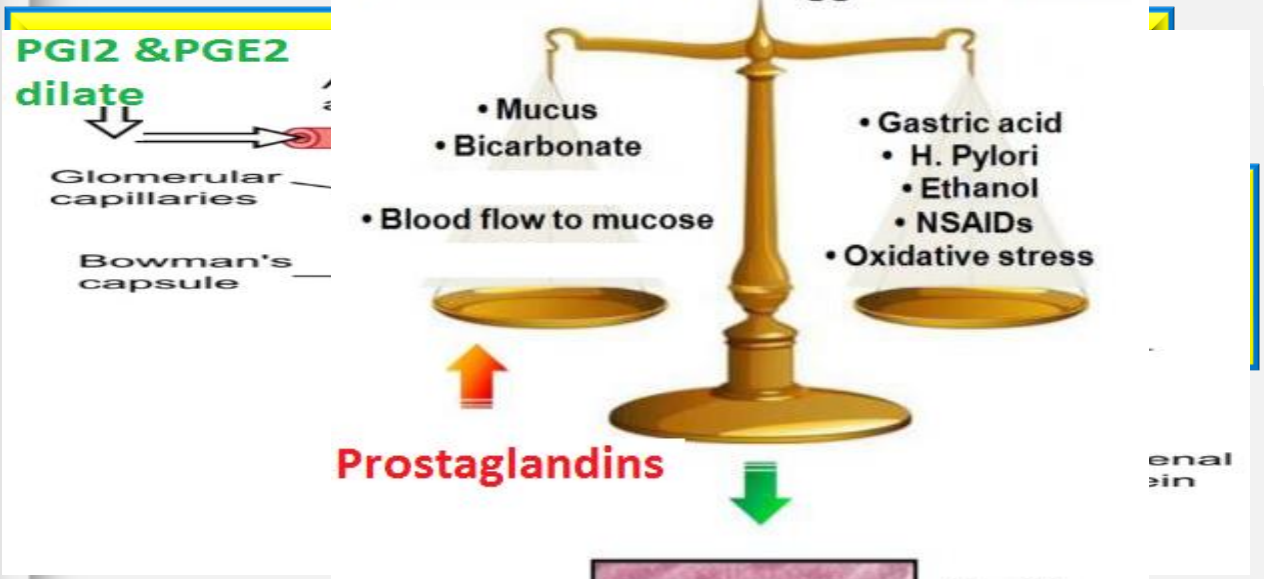
Inhibition of platelets aggregation (high PG conc) / increase platelet aggregation (low PG conc)

Sensitize neurons to cause pain

Induce labor.

ACTIONS OF PROSTAGLANDINS

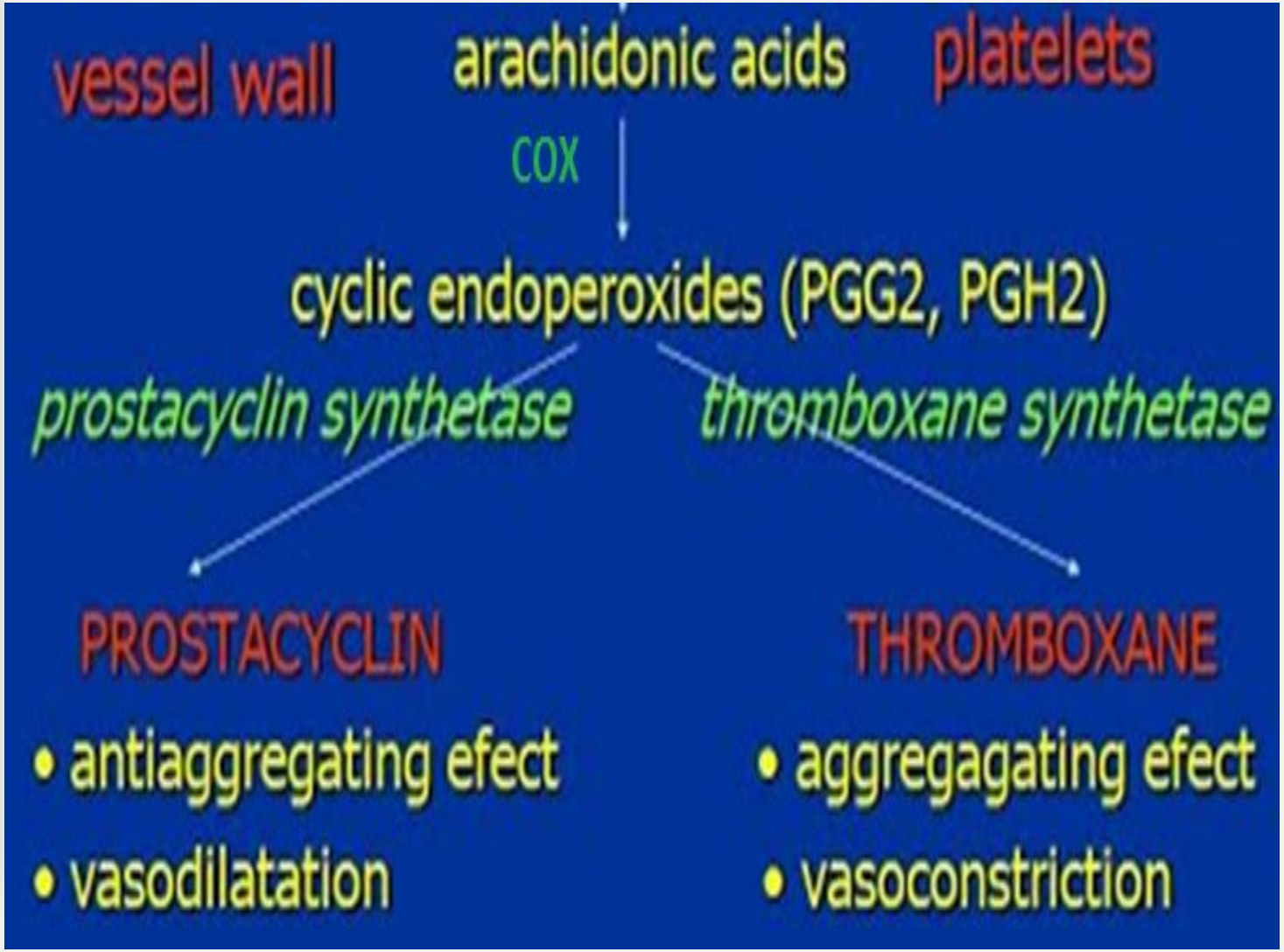




Acts on k ular filtration

Acts on parietal cells of stomach to protect gastric mucosa.

PROSTACYCLIN VERSUS THROMBOXANE



CLINICAL USES OF PGS ANALOGS

Carboprost (PGF): Induce abortion in first trimester

Latanoprost (PGF): Glaucoma

Misoprostol (PGE1): Peptic ulcer

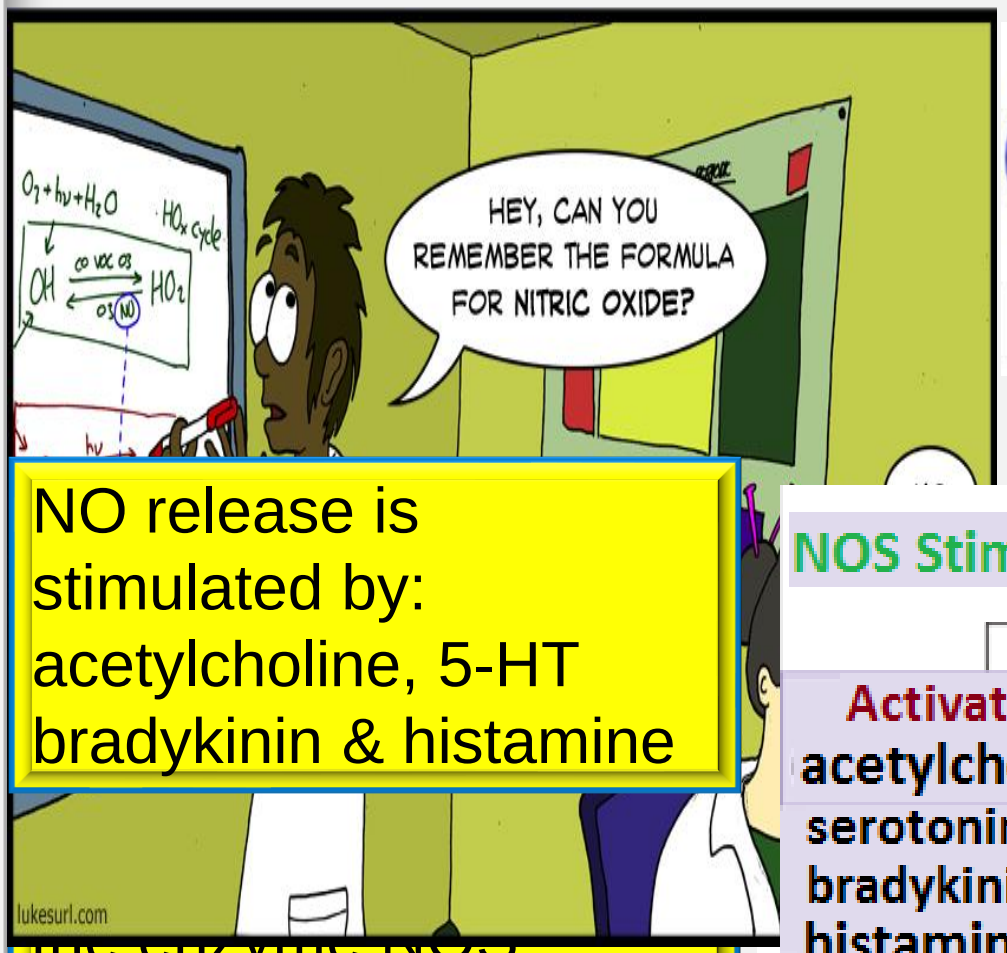
Alprostadil (PGE1): Erectile dysfunction

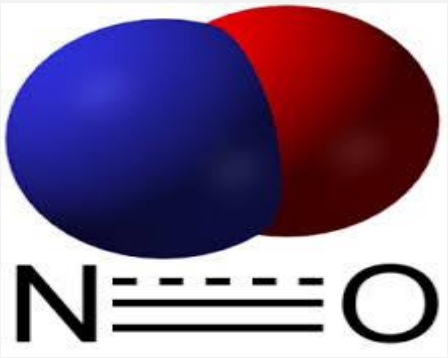
Zileuton (lipoxygenase inhibitor): Asthma

Zafirlukast (leukotriene receptor blocker): Bronchial asthma.

3- Nitric oxide

NITRIC OXIDE





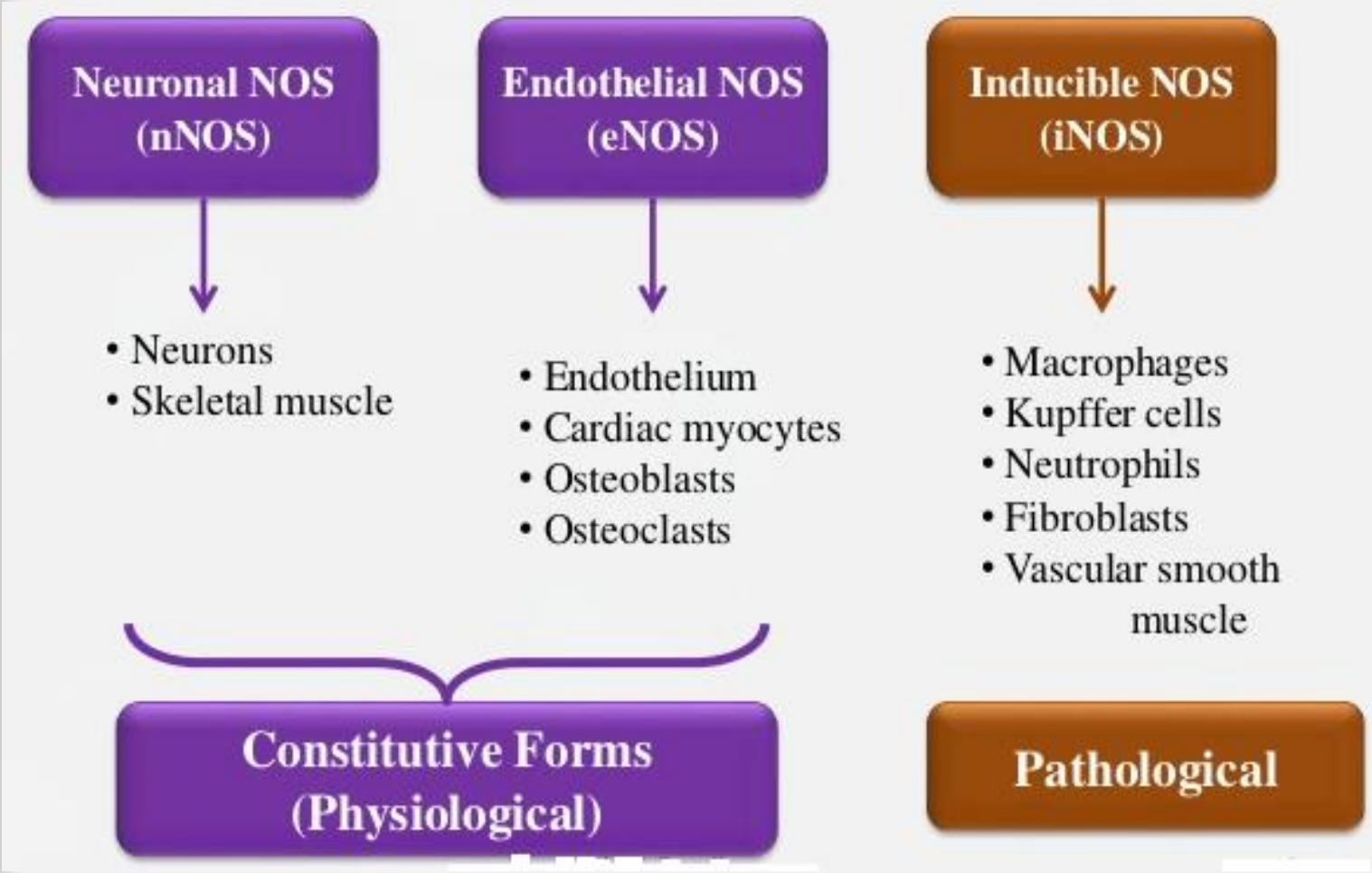
NO release is stimulated by: acetylcholine, 5-HT bradykinin & histamine

the enzyme NOS.

NOS Stimulants & Inhibitors

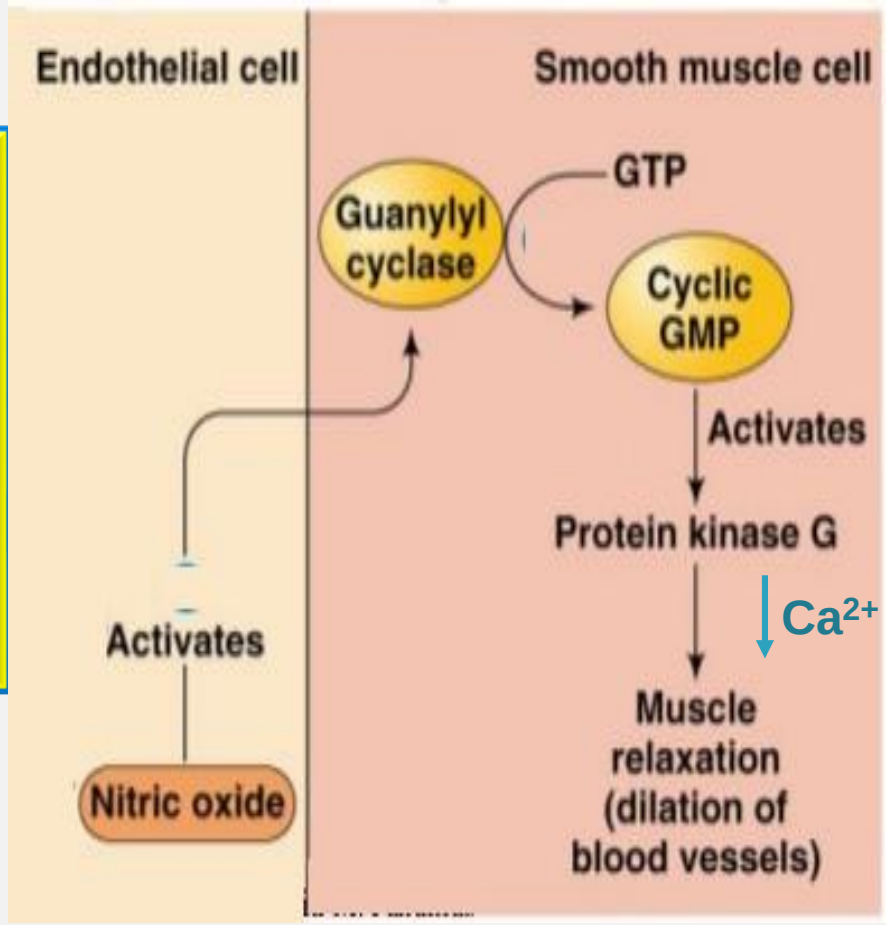
Activators	Inhibitor
acetylcholine serotonin, bradykinin histamine	hemoglobin

ISOFORMS OF NOS



NO MECHANISM OF ACTION

Combining with haem in guanylate cyclase, activating the enzyme, increasing cGMP & thereby lowering $[Ca^{2+}]_i$

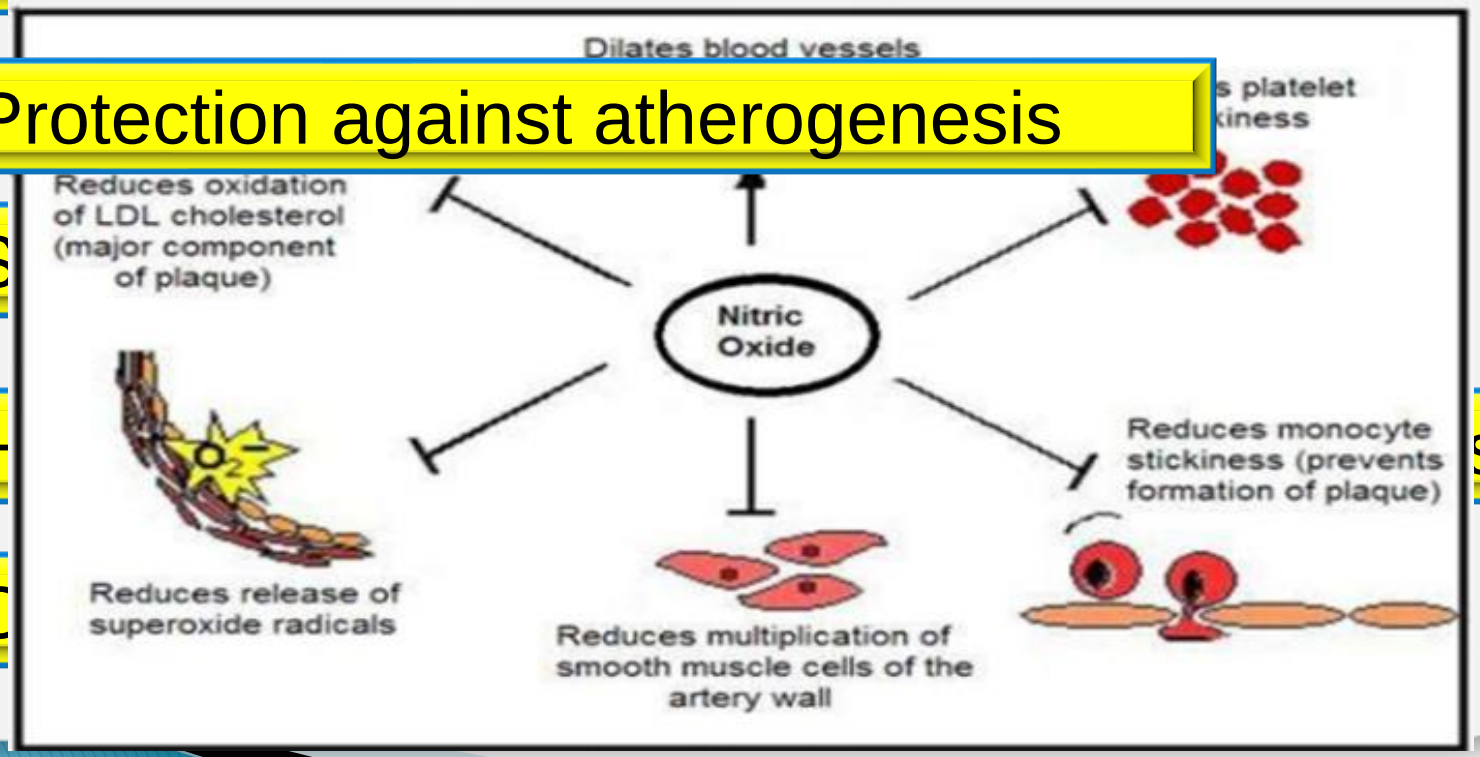


ACTIONS OF NO

Inhibition of platelet & monocyte adhesion & aggregation

Inhibition of smooth muscle proliferation

Protection against atherogenesis



ACTIONS OF NOS

nNOS	eNOS	iNOS
• Long Term Potentiation • Cardiac function, Peristalsis, Sexual arousal	• Vascular tone, Insulin secretion, Airway tone, Regulation of cardiac function and angiogenesis • Embryonic heart development	• In response to attack by parasites, bacterial infection and tumor growth • Causes septic shock, autoimmune conditions

NO IN THERAPEUTICS

Endothelial NO production is reduced in patients with diabetes, hypertension & atherosclerosis

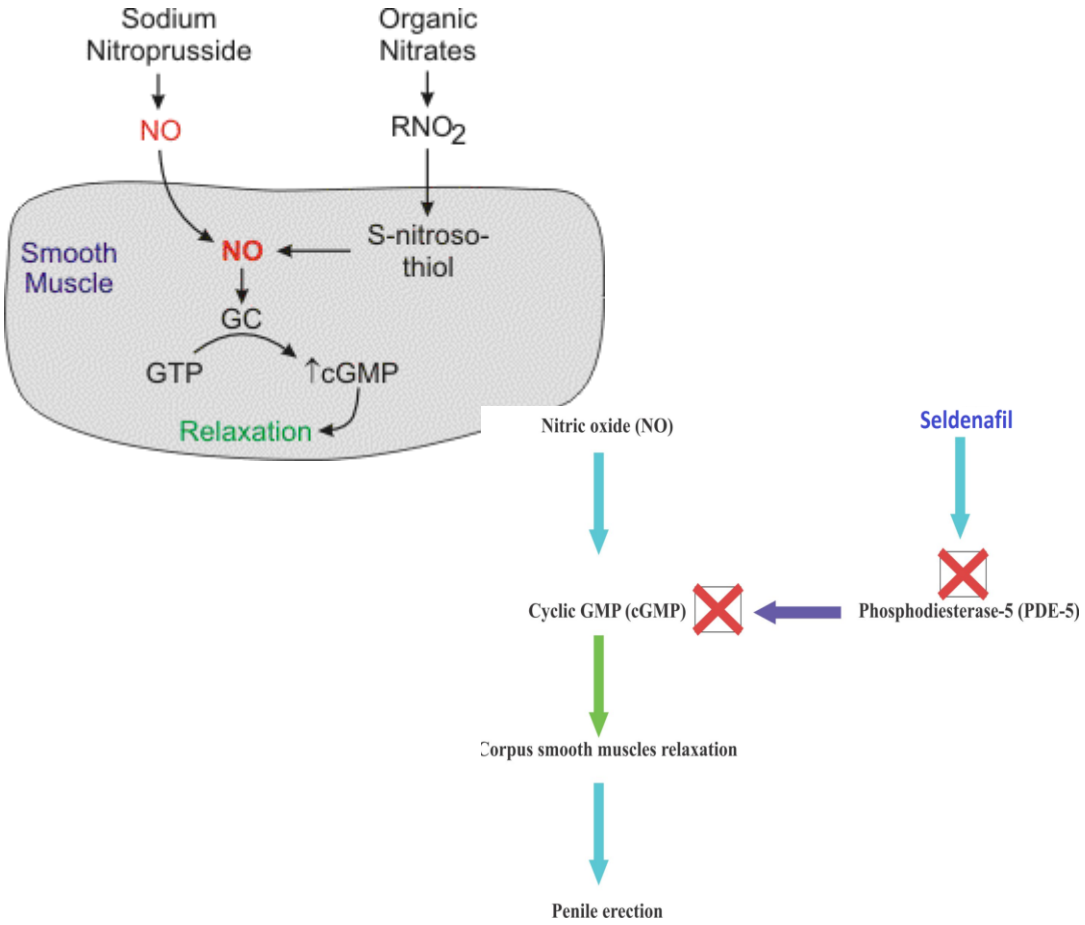
Overproduction of NO occurs in neurodegenerative diseases (e.g. Parkinsonism) & in septic shock

NO donors have well established therapeutic uses e.g. in hypertension & angina pectoris

NO is used in critical care to treat pulmonary hypertension in neonates

NO is used in patients with right ventricular failure secondary to pulmonary embolism

Sildenafil potentiates the action of NO on corpora cavernosa smooth muscle.
It is used to treat erectile dysfunction.


Sodium Nitroprusside
Organic Nitrates
NO
RNO2
Smooth Muscle
NO
S-nitroso-thiol
GC
GTP
↑cGMP
Relaxation
Nitric oxide (NO)
Seldenafil
Cyclic GMP (cGMP)
Phosphodiesterase-5 (PDE-5)
Corpus smooth muscles relaxation
Penile erection

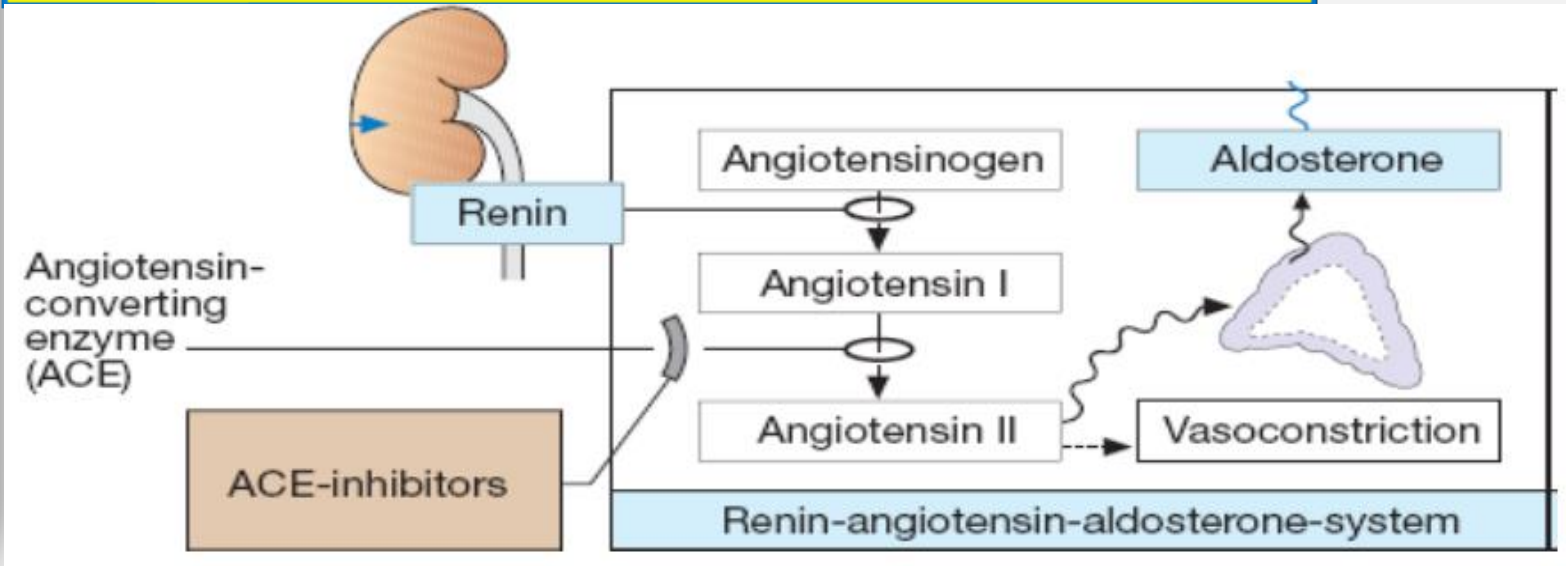
4- Angiotensin

ANGIOTENSIN

Biosynthesis

Renin released from the kidney converts angiotensinogen to Ag I

ACE converts Ag I to Ag II



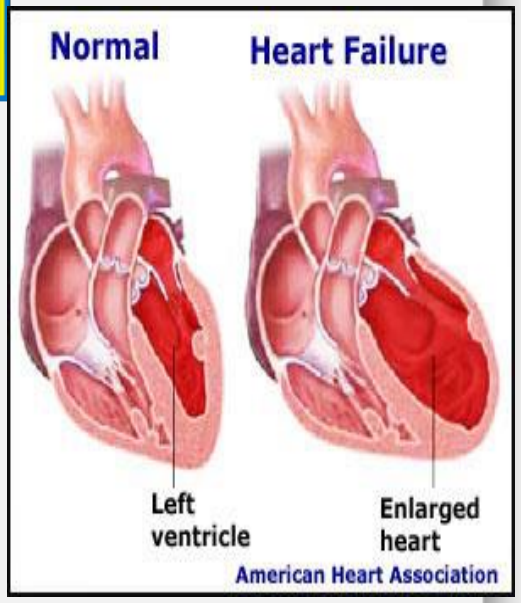
ACTIONS OF ANGIOTENSIN II

Promotes vasoconstriction directly or indirectly by releasing NA & AD

Increases force of contraction of the heart by promoting Ca^{2+} influx

- Increases aldosterone release → sodium & water retention

- Causes hypertrophy of vascular & cardiac cells & increases synthesis & deposition of collagen by cardiac fibroblasts (remodeling).



ANGIOTENSIN INHIBITORS

ACE inhibitors:
e.g. Captopril

Angiotensin receptor blockers (ARBs):
e.g. Losartan.

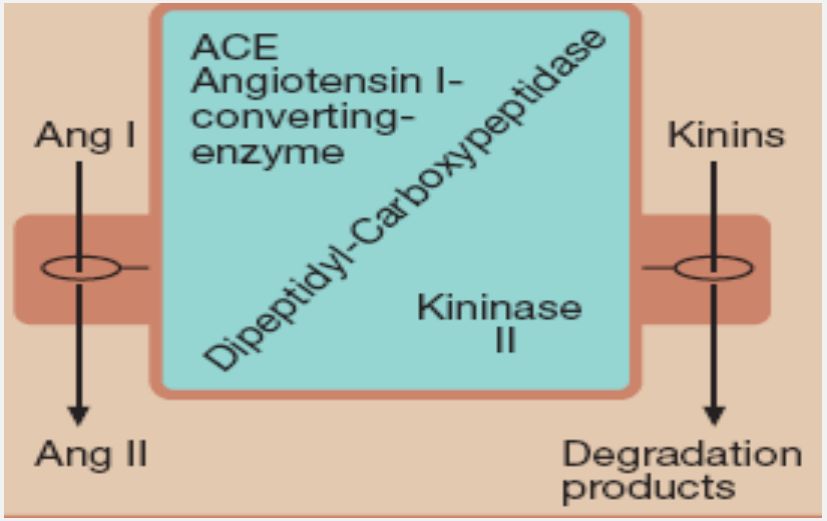
"No, taking an ACE inhibitor won't hurt your poker game."

ACE INHIBITORS

Cause a fall in blood pressure in hypertensive patients especially those with high rennin levels

CLINICAL USES:

- Hypertension
- Cardiac failure
- Following myocardial infarction.

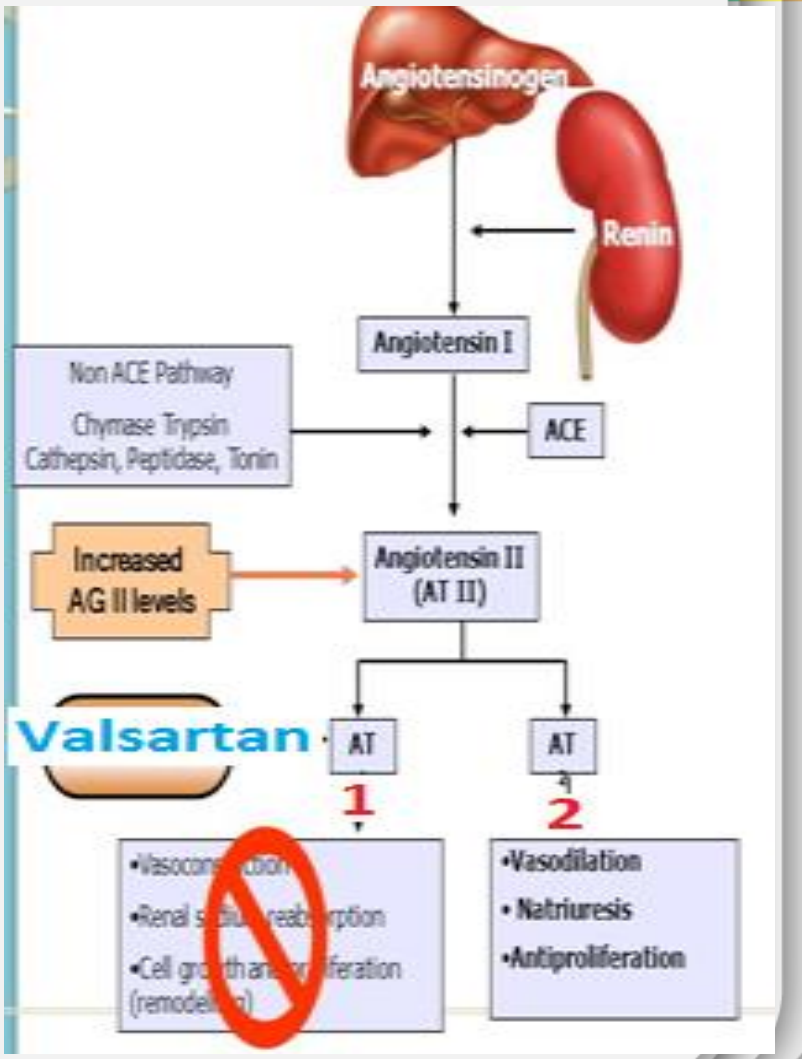


ANGIOTENSIN RECEPTOR BLOCKERS

Angiotensin receptors AT_1 & AT_2

AT_1 receptors predominate in vascular smooth muscle, mediate most of the known actions of Ang, coupled to G proteins & DAG

Similar uses to ACEI

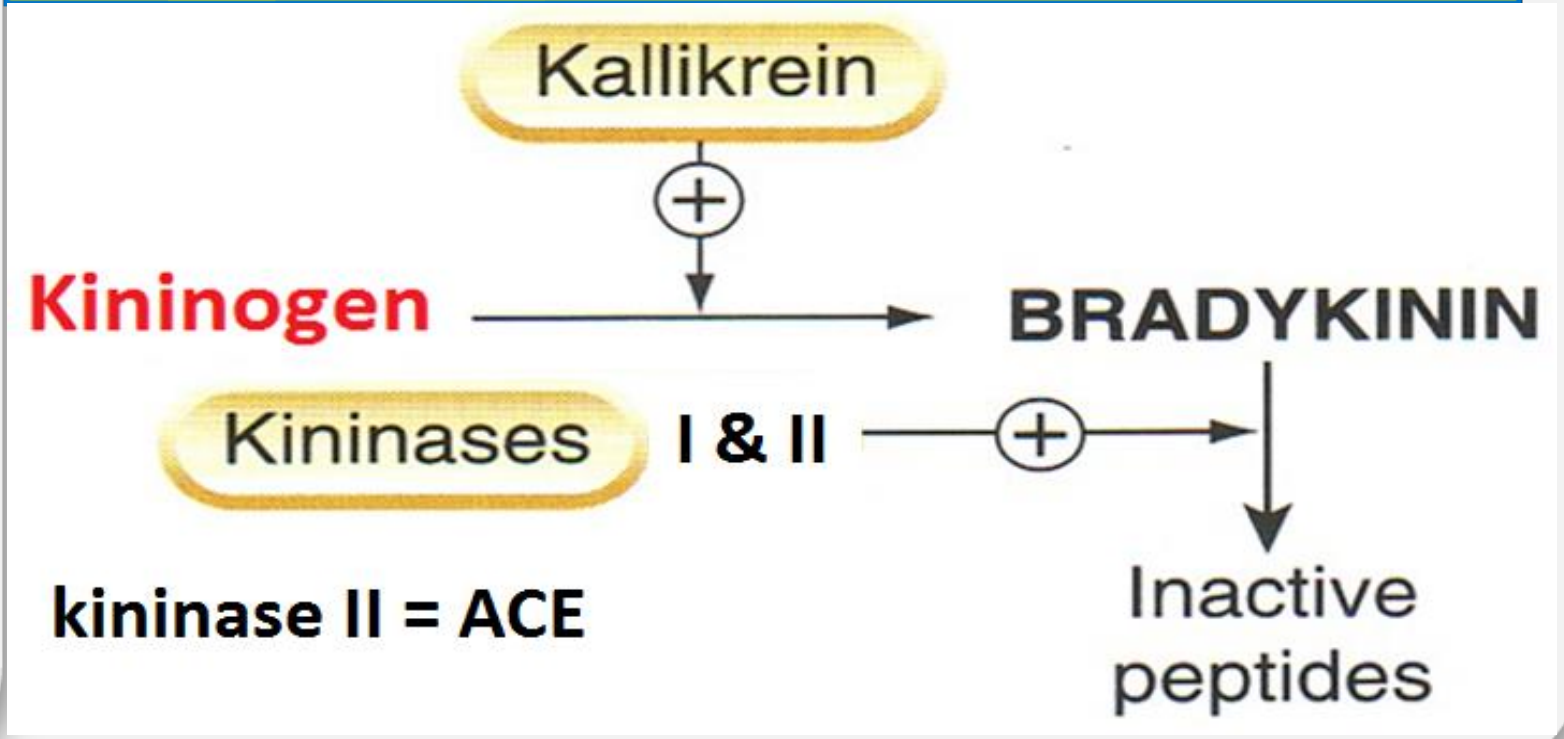


5- Kinins

KININS

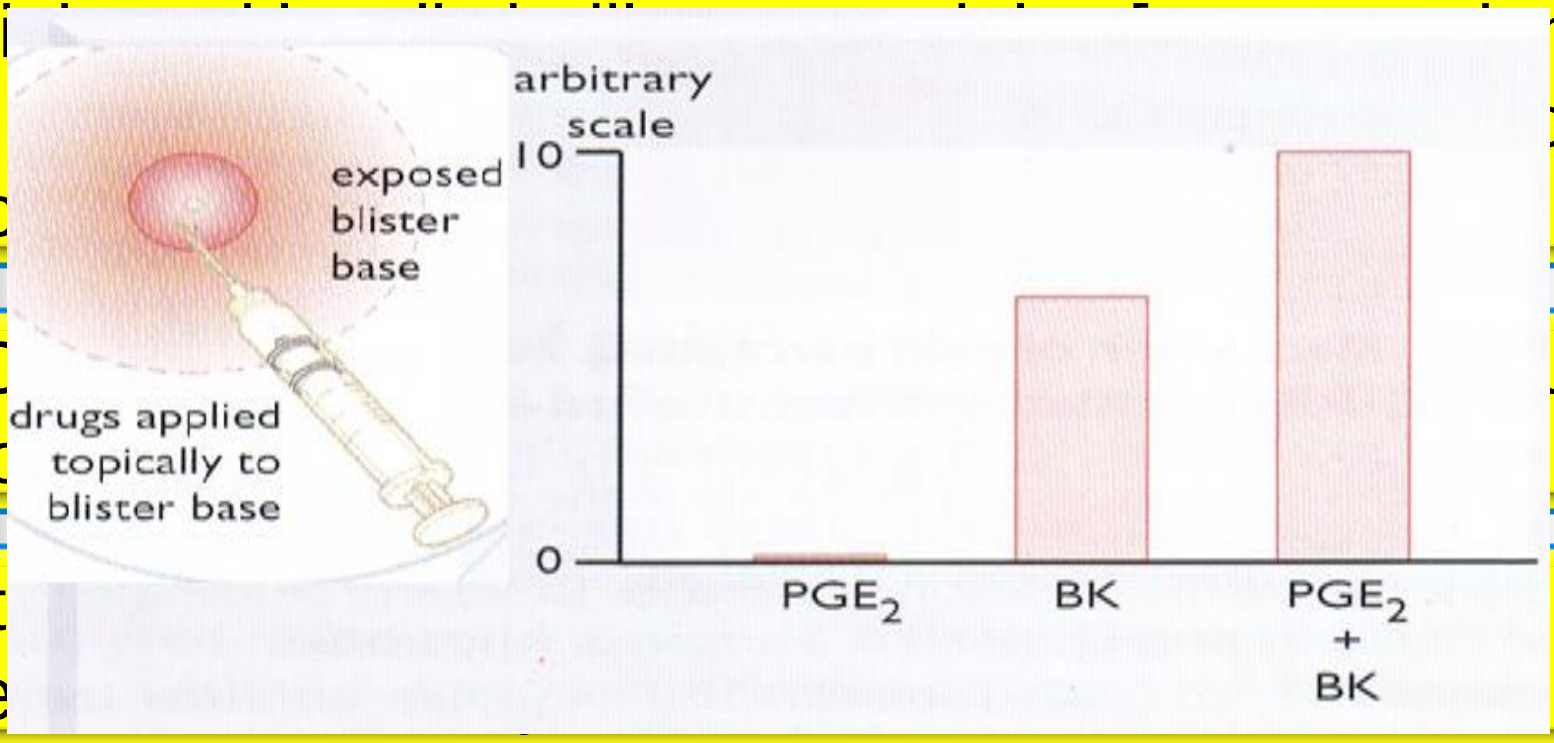
Are Bradykinin & kallidin

Bradykinin is formed by proteolytic cleavage of circulating proteins (kininogens)



ACTIONS OF BRADYKININ

- Causes pain, this effect is potentiated by PG. Has a role in inflammation



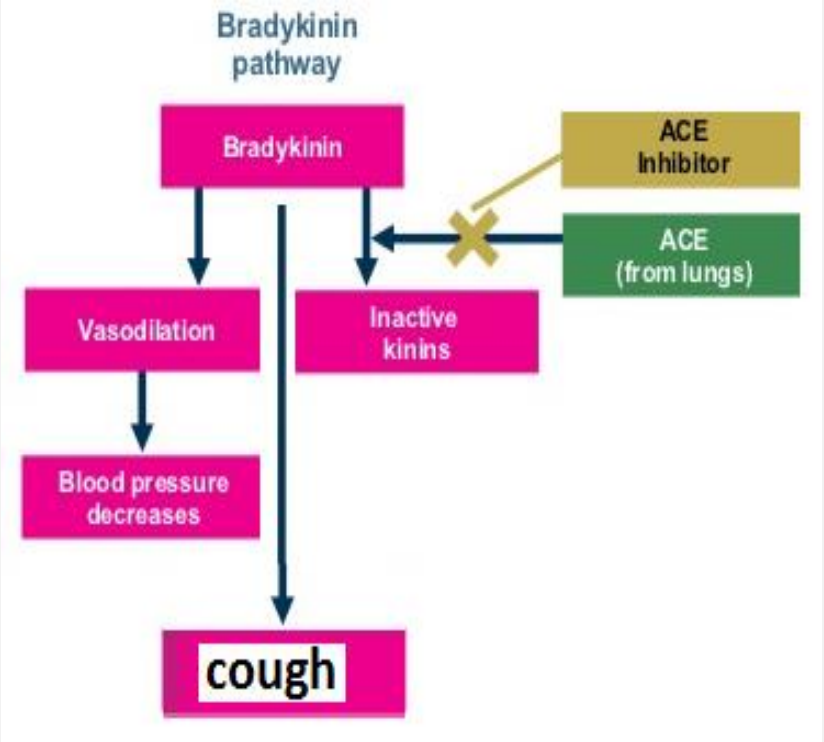
RECEPTORS & CLINICAL USES

- Receptors B_1 & B_2 (both are G protein-coupled receptors)
- B_1 inducible under condition of inflammation
- B_1 receptor has low affinity to bradykinin
- plays a significant role in inflammation & hyperalgesia
- B_2 constitutive
- High affinity to bradykinin & mediates the majority of its effects.

THERAPEUTIC USES

- No current therapeutic use of bradykinin

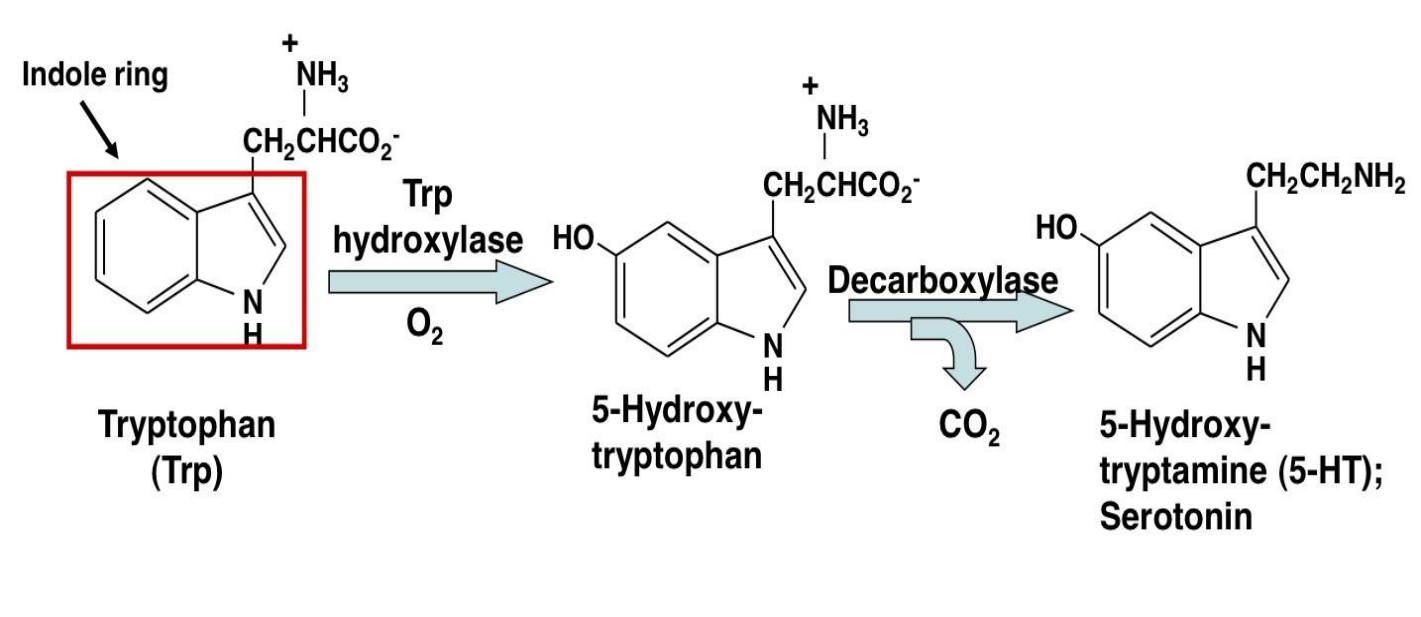
- **Increased** bradykinin is implicated in the therapeutic efficacy & cough produced by ACEIs.



6- Serotonin

SEROTONIN [5HT]

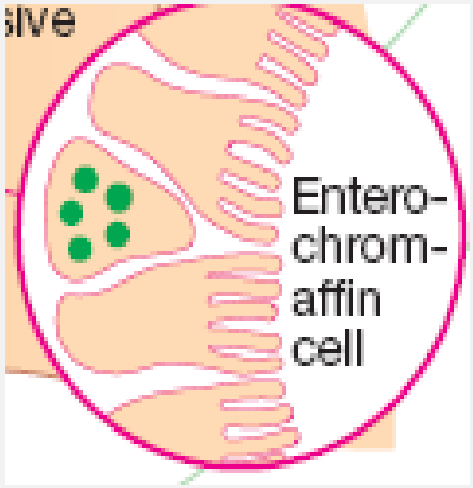
Serotonin is synthesized from the amino acid L-tryptophan



SEROTONIN [5-HT]

DISTRIBUTION

1] Intestinal wall: in chromaffin cells, in neuronal cells in the myenteric plexus

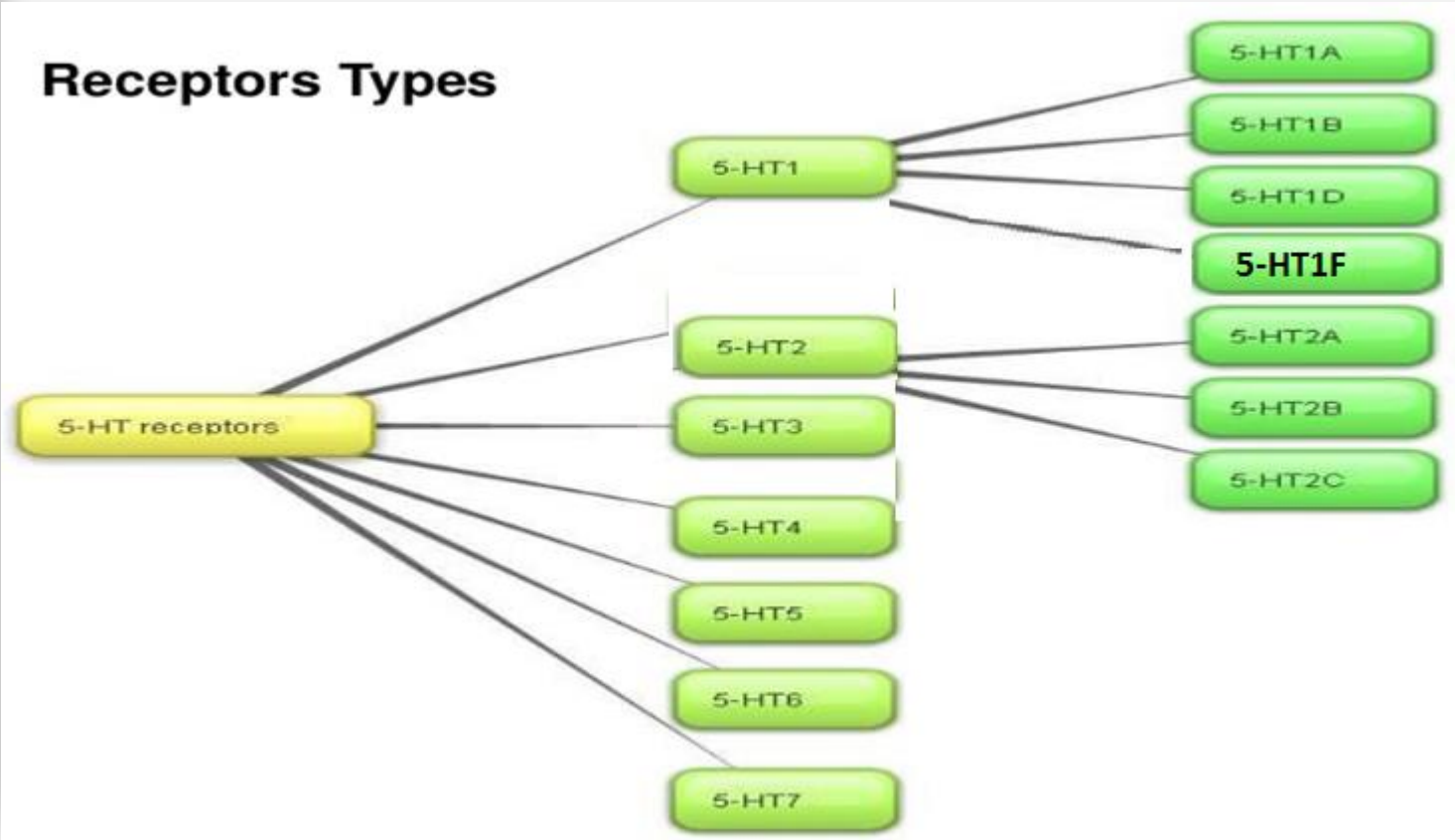


2] Blood, in platelets, released when aggregated, in sites of tissue damage

3] CNS: a neurotransmitter, in midbrain

5-HT

RECEPTORS



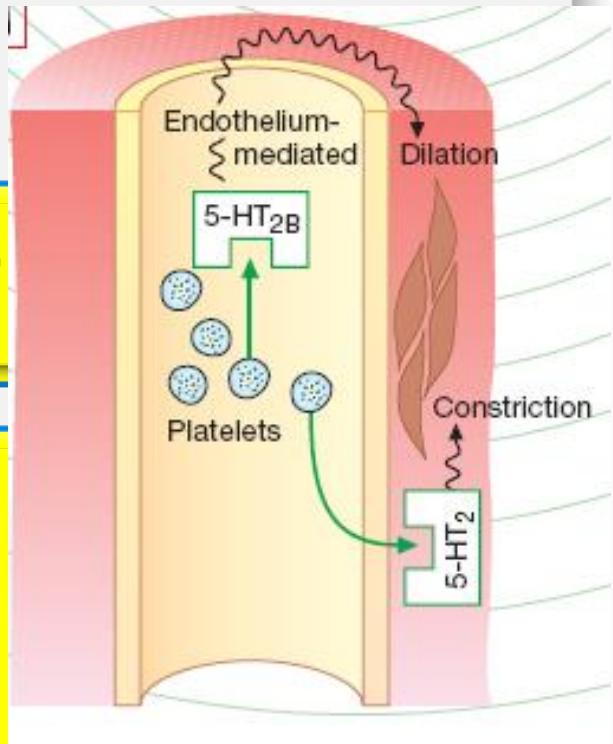
ACTIONS OF 5-HT

GIT: 5-HT increases motility

- Contracts uterus, bronchiole, other smooth muscles

- **Blood vessels**:-
Contracts large vessels by a direct action & relaxes other vessels by releasing NO

Increases capillary pressure & permeability.



5-HT ACTIONS

Platelets:- causes aggregation, aggregated platelets release 5-HT

- **Neuronal terminals**: 5-HT stimulates nociceptive neuron endings → pain

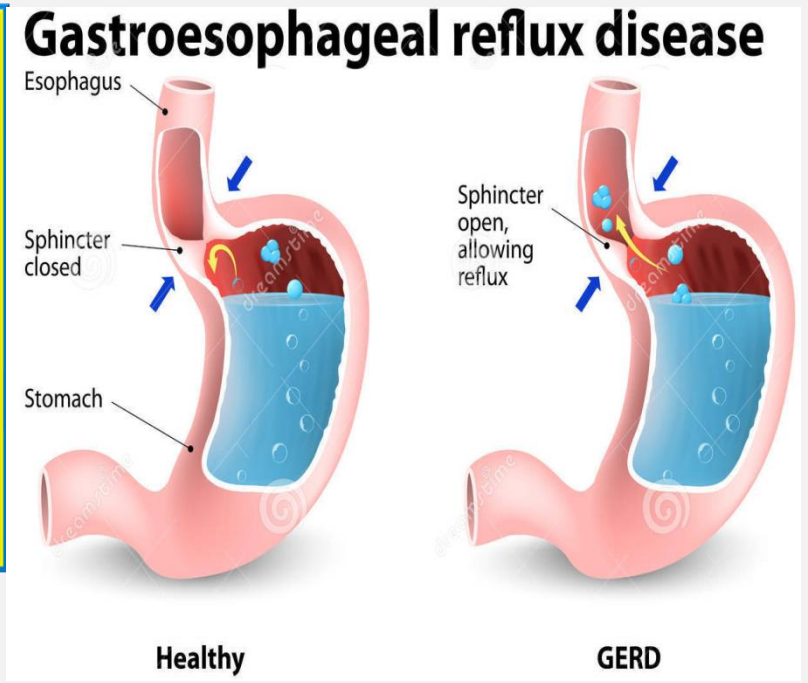
- **CNS;-**stimulates some neurons & inhibits others, inhibits release of other neurotransmitters.

5-HT RECEPTOR AGONISTS

- **Buspirone:-** 5-HT1A agonist, effective anxiolytic

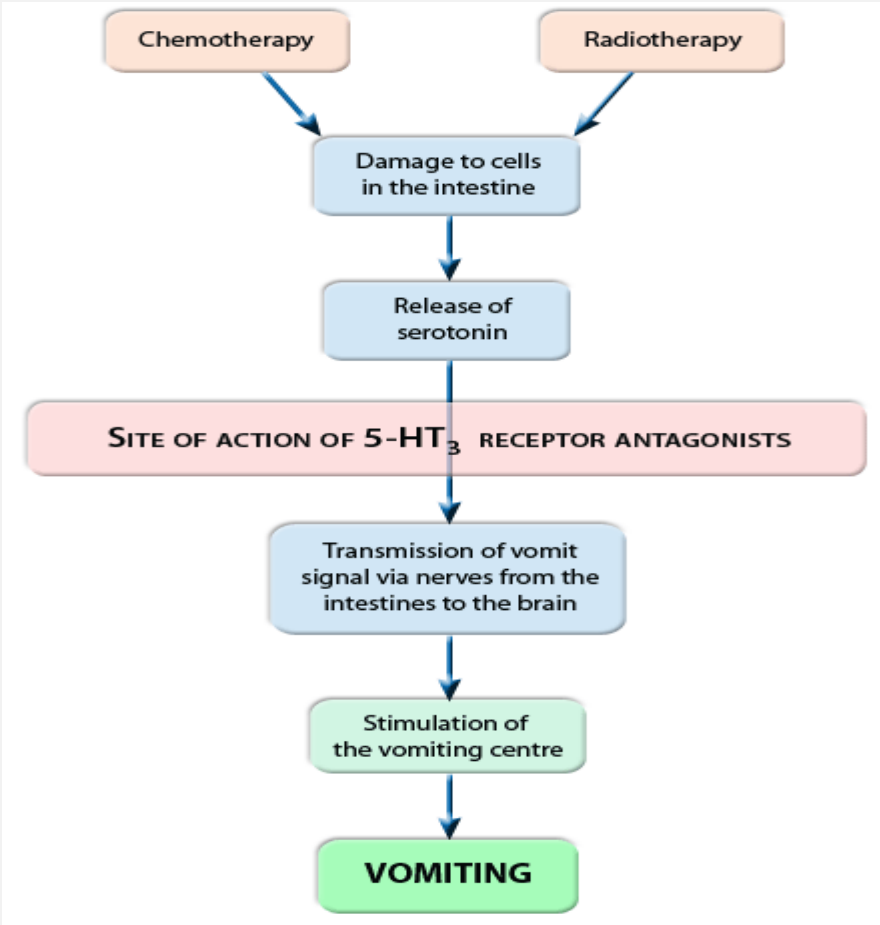
- **Cisapride:-**

5-HT4 -receptor agonist, used in gastroesophageal reflux & motility disorders.



5-HT RECEPTOR ANTAGONISTS

- **Selective 5-HT_3 antagonist**, **Ondansetron**, antiemetic action, for cancer chemotherapy



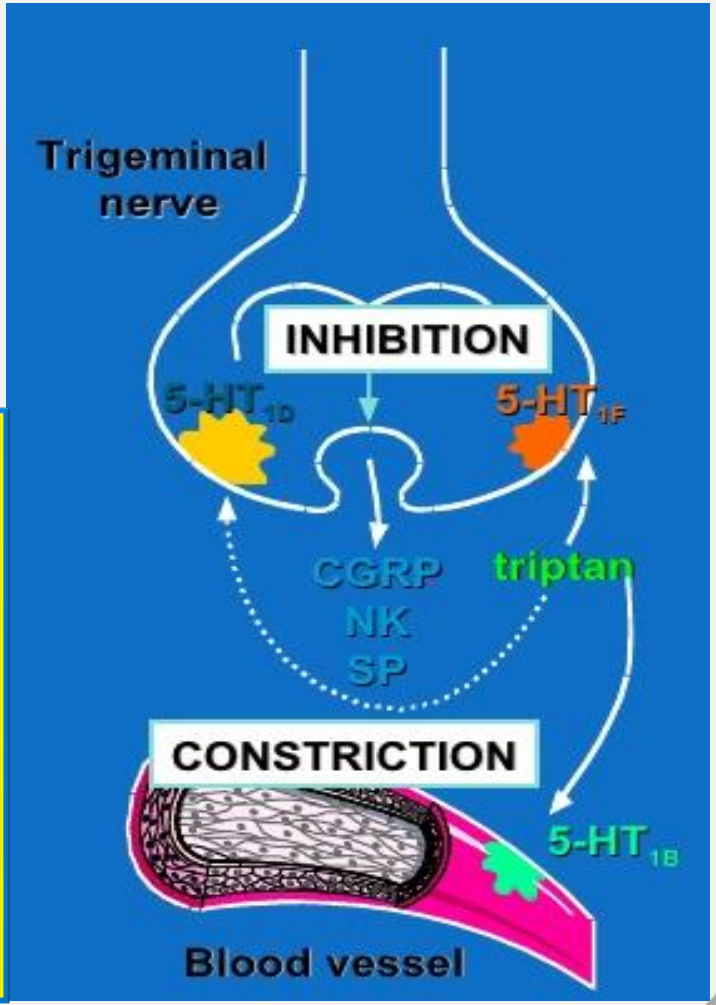
Clinical conditions in which 5-HT is implicated

1-Migraine

SUMATRIPTAN

5-HT 1B, 1D & 1F-receptor **agonists**, effective in acute migraine attack

It binds to 5HT1B, in cranial blood vessels causing **vasoconstriction** & 1D & 1F in presynaptic trigeminal nerve causing **inhibition** of pro- inflammatory neuropeptide release.



2- CARCINOID SYNDROME

- A malignant tumor of intestinal chromaffin cells
- The tumor releases 5-HT, SP, PGs, kinins & histamine causing flushing, diarrhea, bronchoconstriction & hypotension
- Serotonin antagonists (**cyproheptadine**, $5HT_2$ antagonist) could be administered to control diarrhea, flushing & malabsorption.