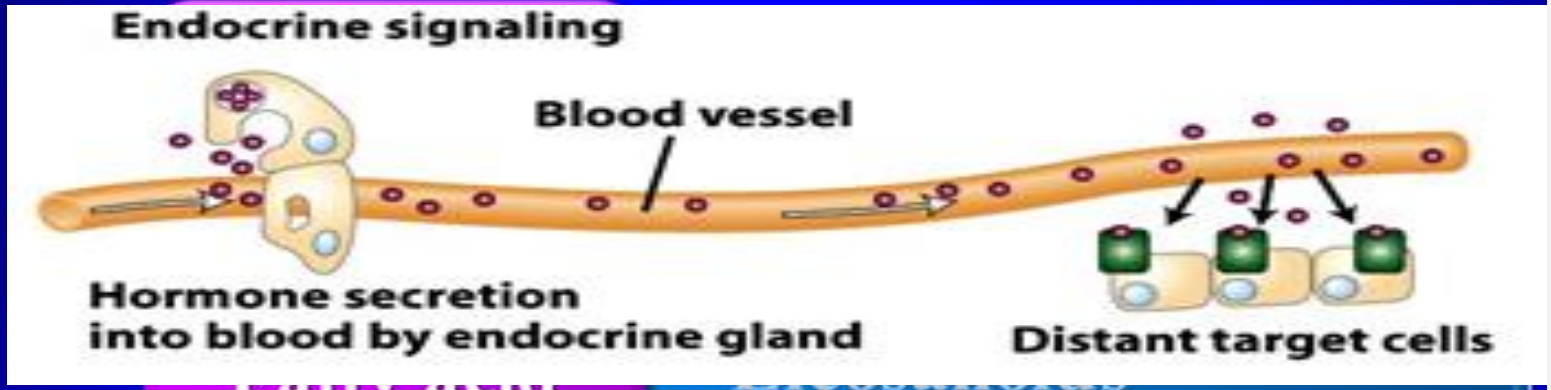
AUTACOIDS

They include:

Aminoacid derivatives	• Histamine • Serotonin
derivatives	
Gas	NO



AUTOCOIDS

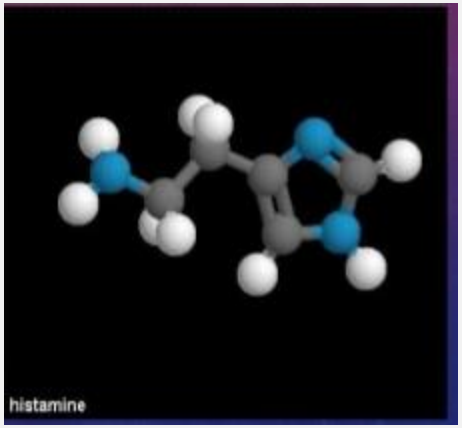
01

ILOS

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

To study the agents which enhance or block their effects

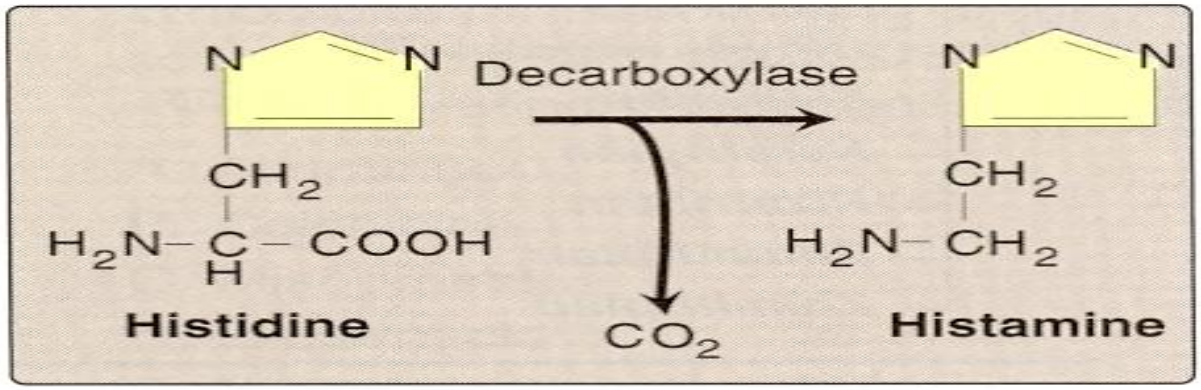
HISTAMINE



HISTAMINE

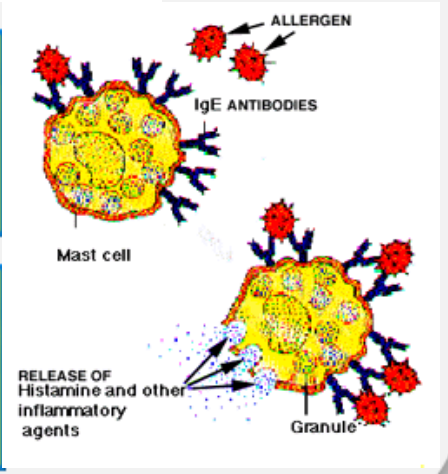
02

Synthesis:- from L- histidine



Stored in mast cells, basophils, lung, intestinal mucosa

Release:- during allergic reaction, inflammatory reaction



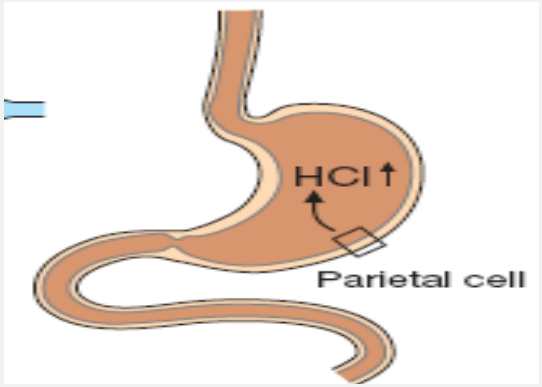
HISTAMINE RECEPTORS

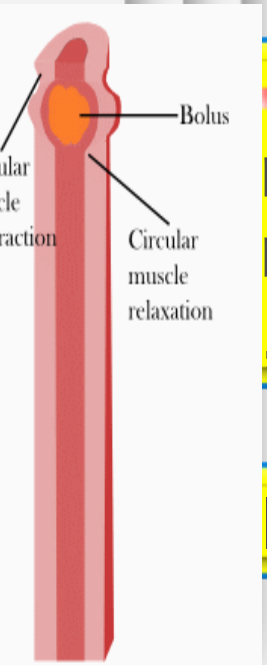
03

Receptor Type	Major Tissue Locations	Major Biologic Effects
H_1	smooth muscle, endothelial cells,	acute allergic responses
H_2	gastric parietal cells, Cardiac muscle,	secretion of gastric acid
H_3	central nervous system	neurotransmission
H_4	mast cells, eosinophils, T cells	regulating immune responses

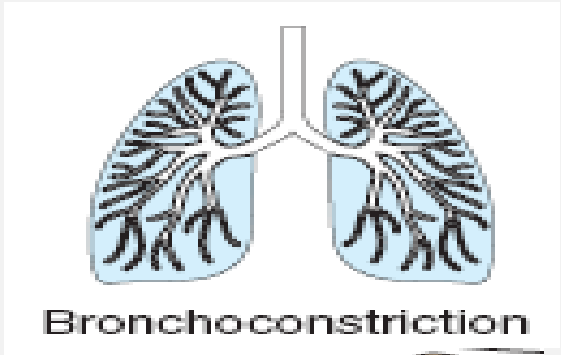
ACTIONS

Histamine stimulates gastric acid secretion , through H_2- receptors

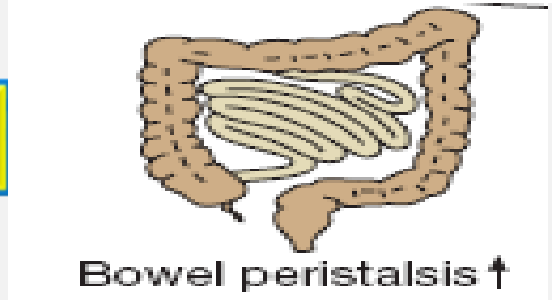




Stimulation of H_1- receptors contract smooth muscles, bronchioles ,uterus



Increases bowel peristalsis



ACTIONS

05

Slow IV or SC injection causes flushing of skin, raises temperature, increases blood flow to the periphery, increases heart rate & CO

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

06

HISTAMINE H_1 RECEPTOR BLOCKERS

First generation

Diphenhydramine, promethazine

Second generation

Citrizine, fexofenadine

HISTAMINE H_1 RECEPTOR BLOCKERS

07

- 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

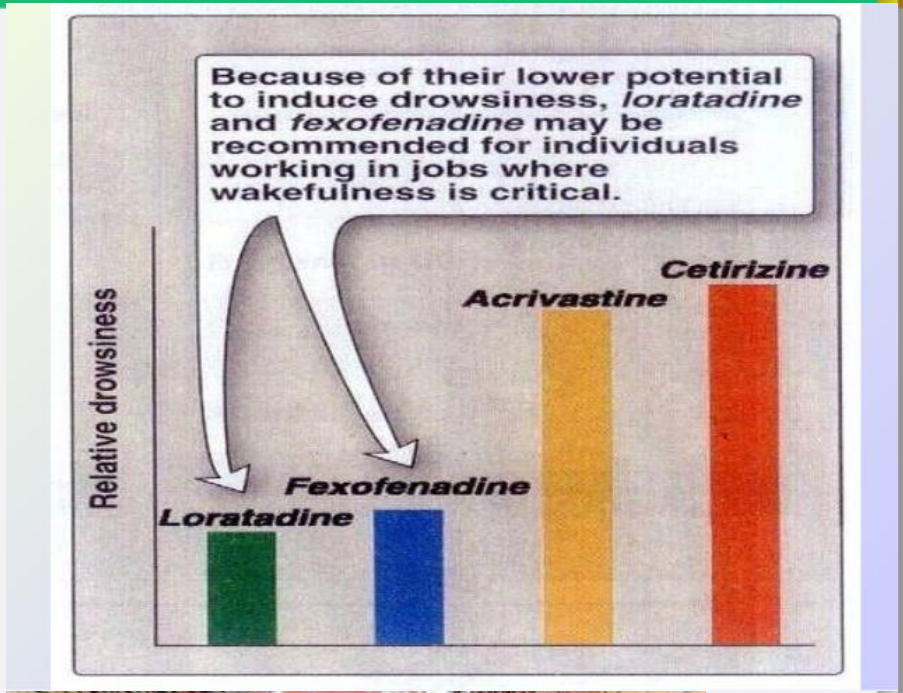
Clinical uses

Allergic conditions such as:-

Allergic rhinitis

Conjunctivitis

Urticaria



H_2- RECEPTOR BLOCKERS

Cimetidine

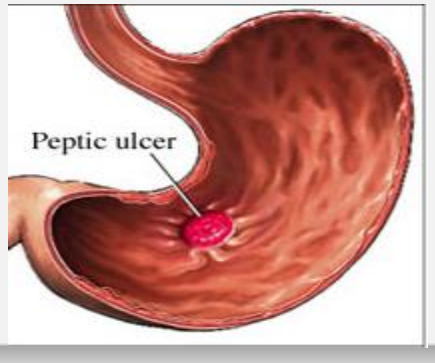
Histamine plays an important role in the formation and secretion of HCl by activation of H_2 receptors

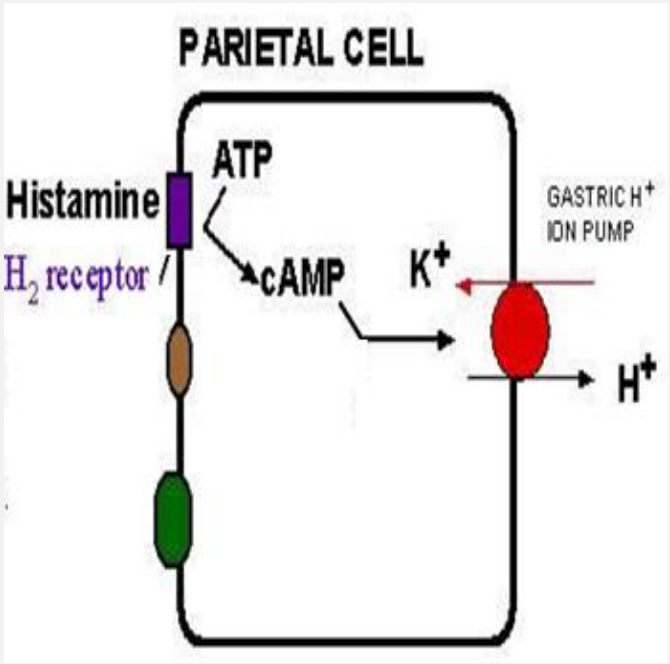
Blockers of H_2 receptors inhibit gastric acid secretion

Used for the treatment of:-

Gastritis

Peptic ulcers





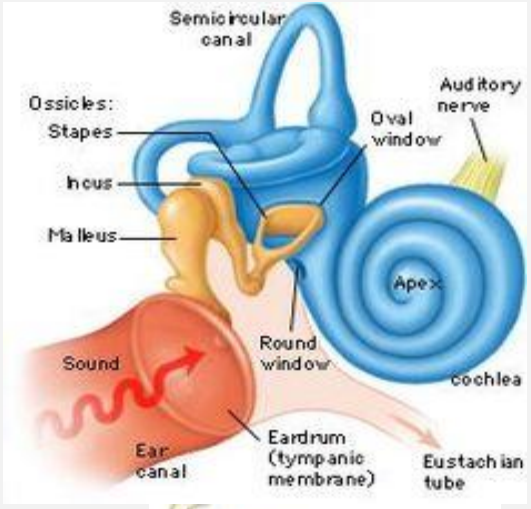
H3- RECEPTOR BLOCKERS

BETAHISTINE

It produces dilatation of blood vessels in inner ear

Used in treatment of:-

Vertigo and balance disturbances



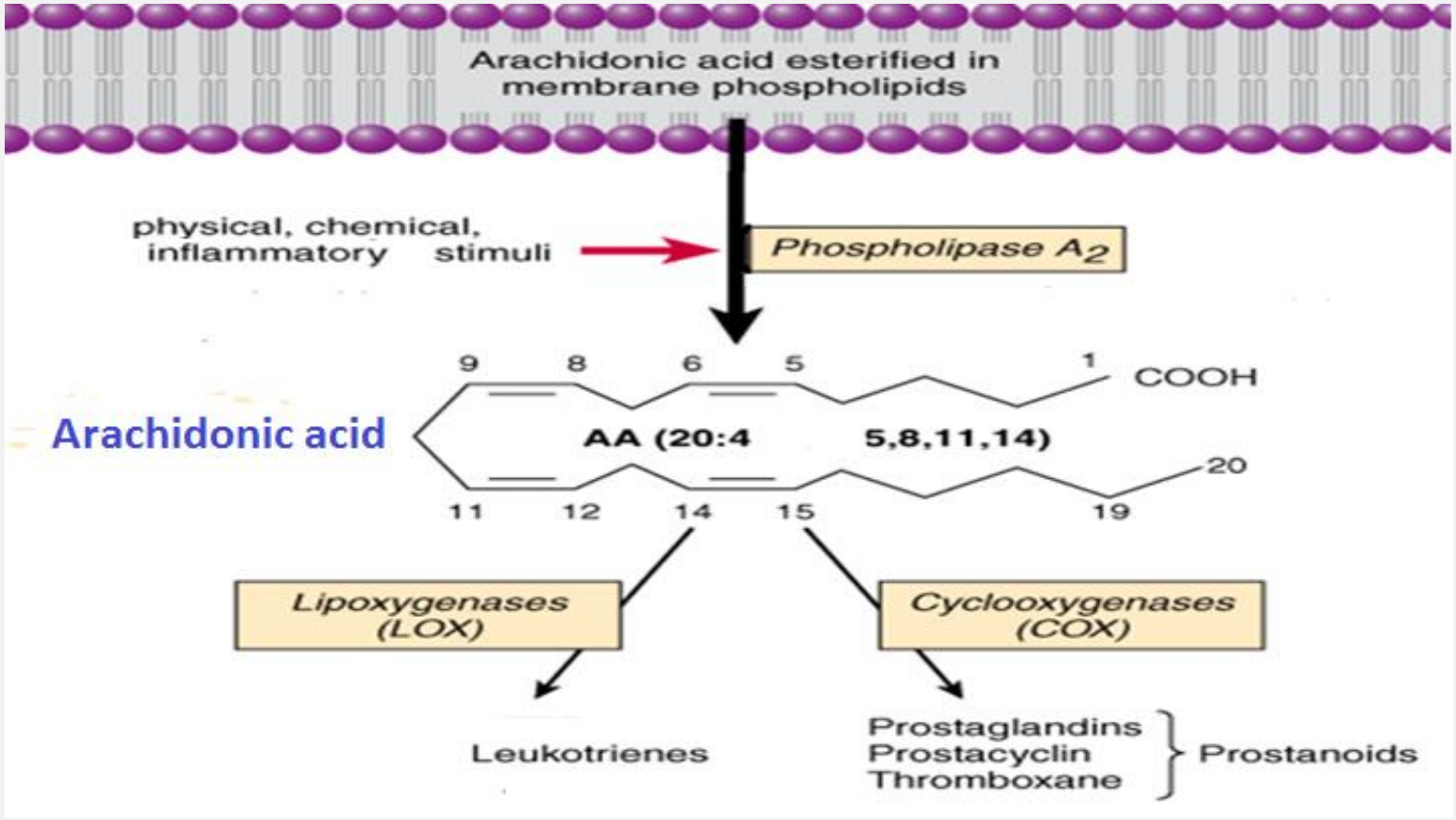
EICOSANOIDS

"An aspirin a day will help prevent a heart attack if you have it for lunch instead of a cheeseburger."

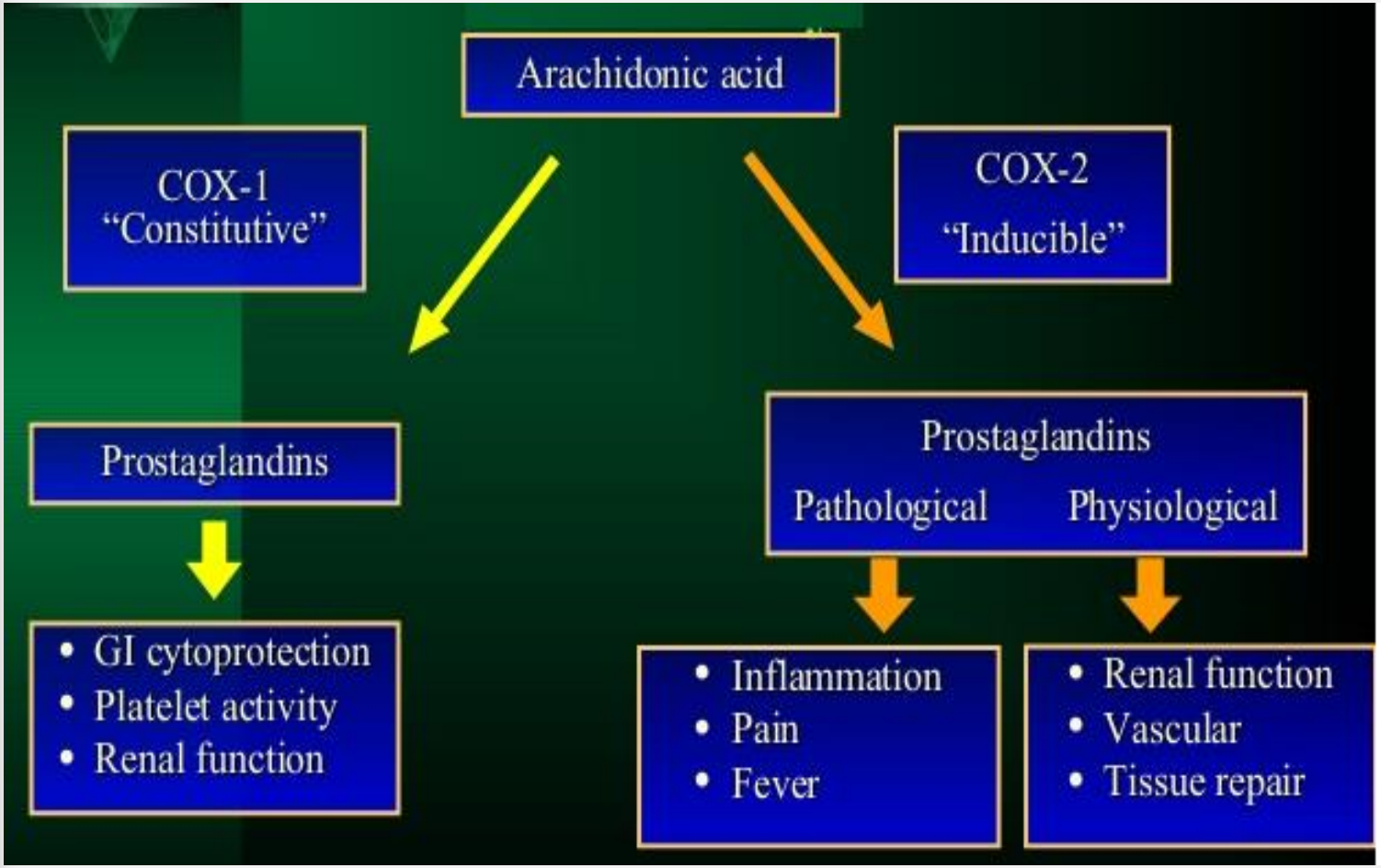
EICOSANOIDS

11

SYNTHESIS



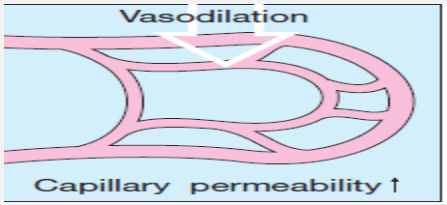
COX ISOZYMES



ACTIONS OF PROSTAGLANDINS

They are proinflammatory

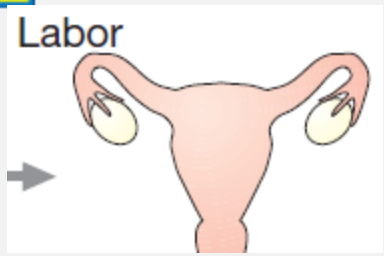
Cause vasodilatation of vascular smooth muscle



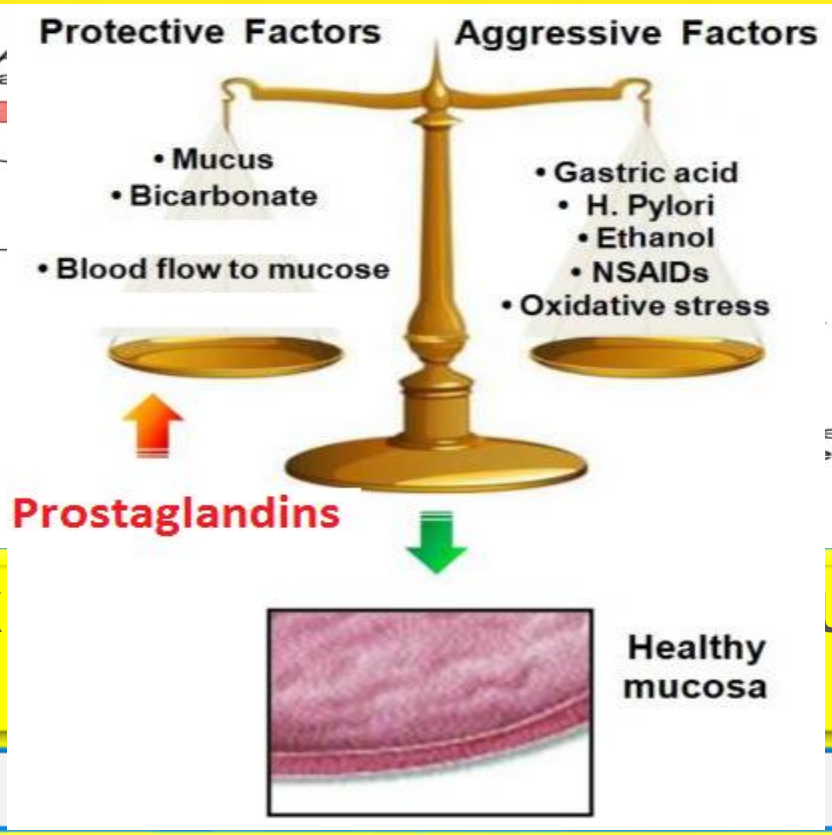
Inhibition of platelets aggregation/ increase platelet aggregation

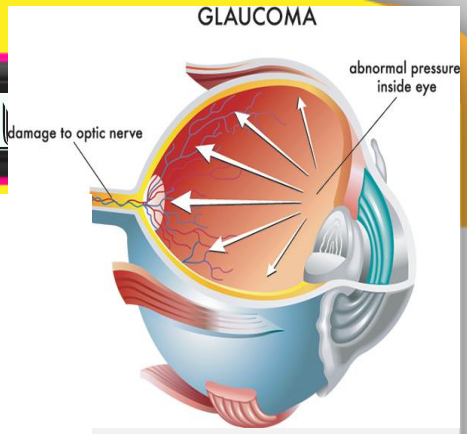
Sensitize neurons to cause pain

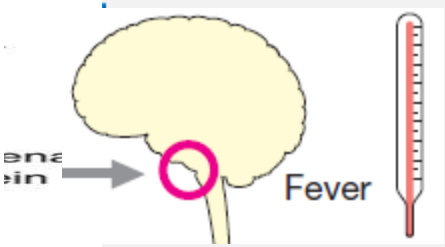
Induce labor



ACTIONS OF PROSTAGLANDI



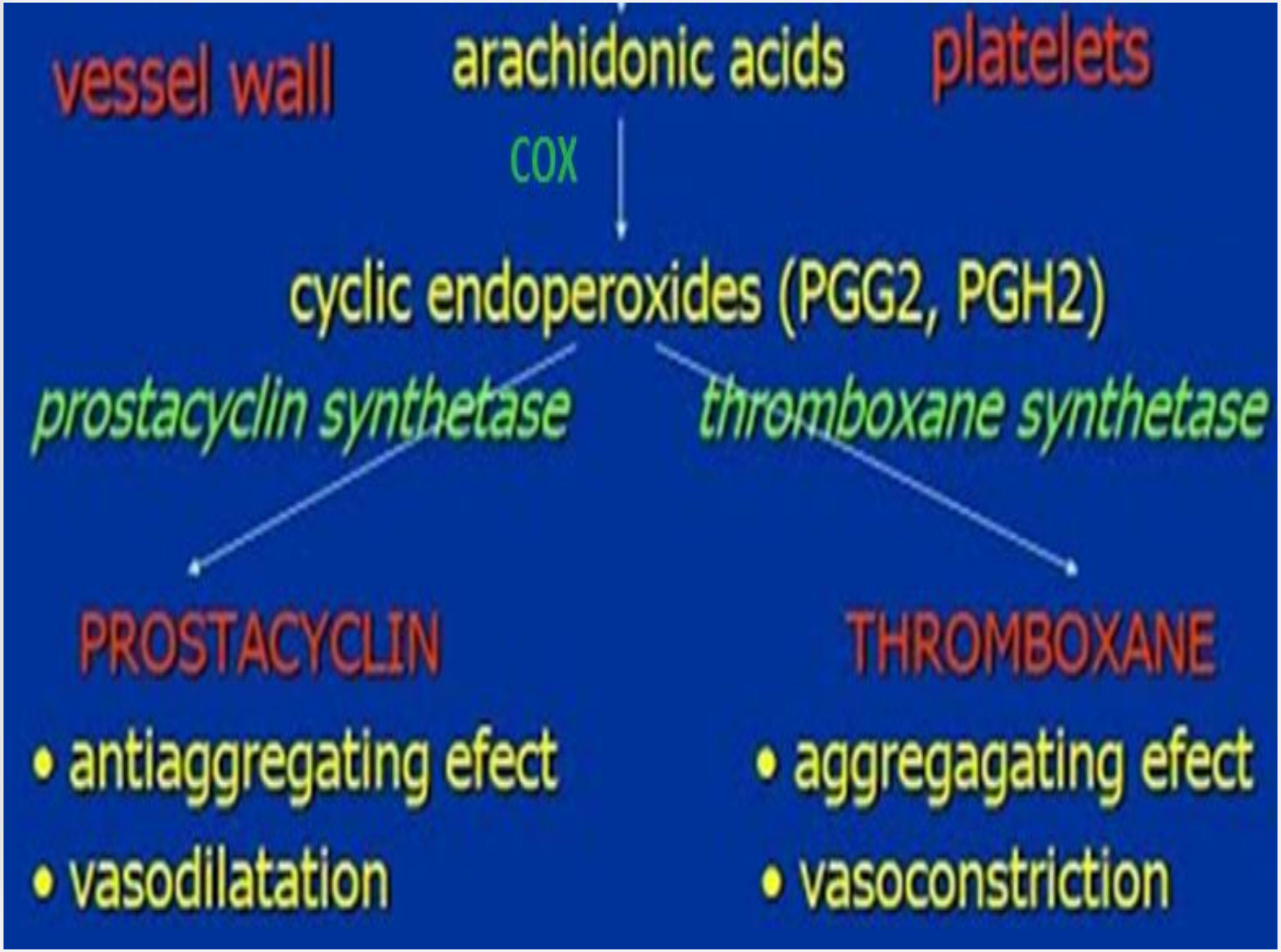




Acts on k ular filtration

Acts on parietal cells of stomach to protect gastric mucosa

PROSTACYCLIN VERSUS THROMBOXANE



CLINICAL USES OF PGS ANALOGS

Carboprost	PGF2α	Induce abortion in first trimester
Latanoprost	PGF2α	Glaucoma
Misoprostol	PGE1	Peptic ulcer
Alprostadil	PGE1	Erectile dysfunction

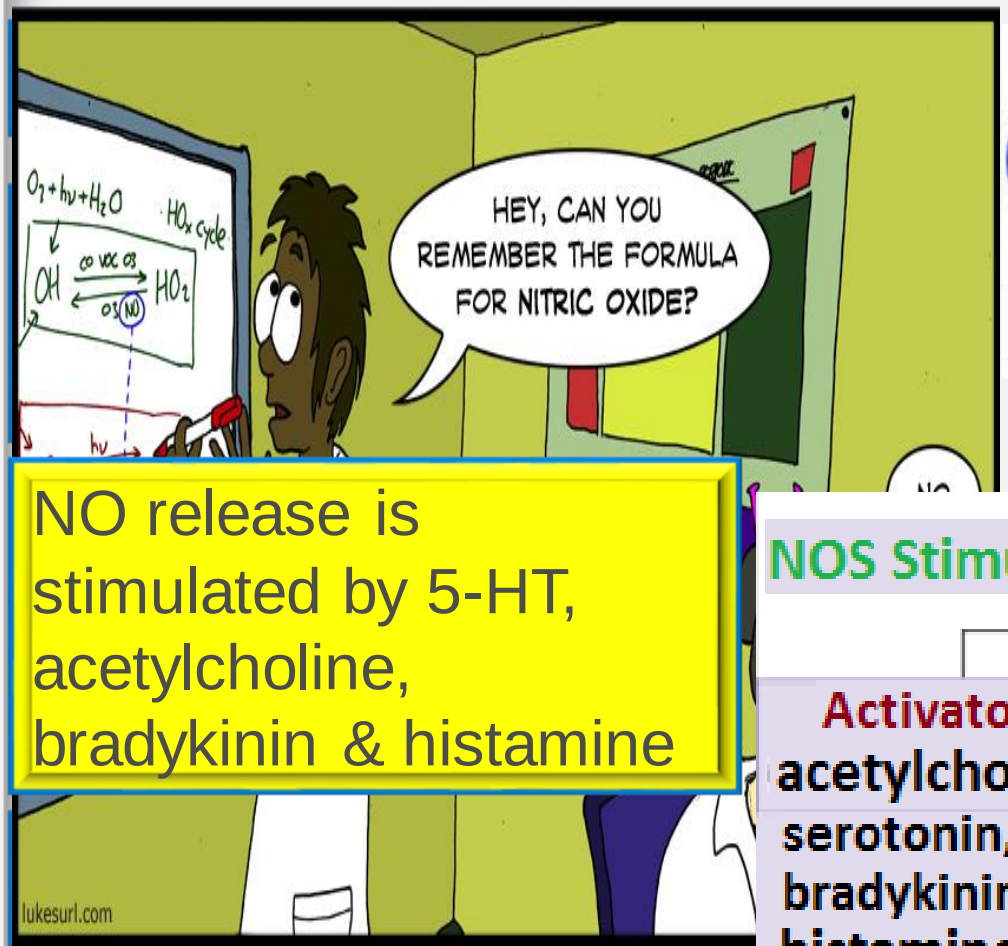
Zileuton (lipoxygenase inhibitor)

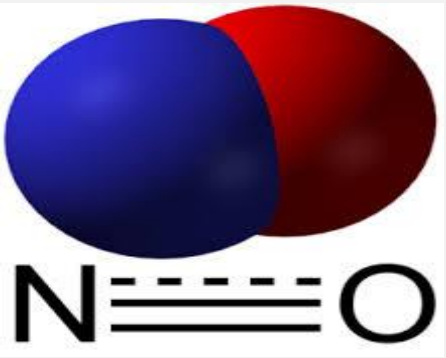
Zafirlukast (leukotreine receptor blocker)

Bronchial asthma

NITRIC OXIDE

NITRIC OXIDE





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

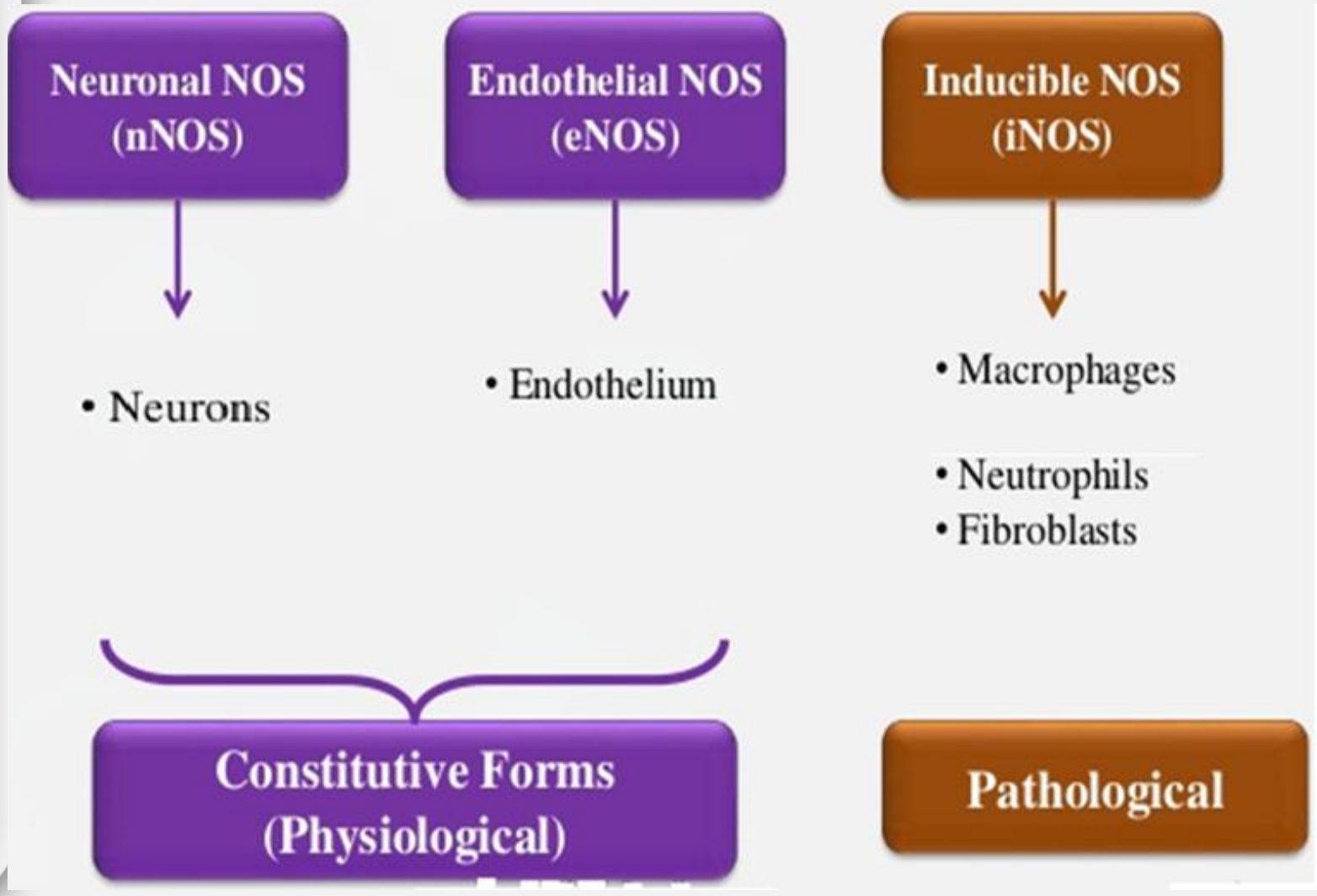
the enzyme nitric oxide synthase

NOS Stimulants & Inhibitors

Activators
- acetylcholine
- serotonin,
- bradykinin
- histamine

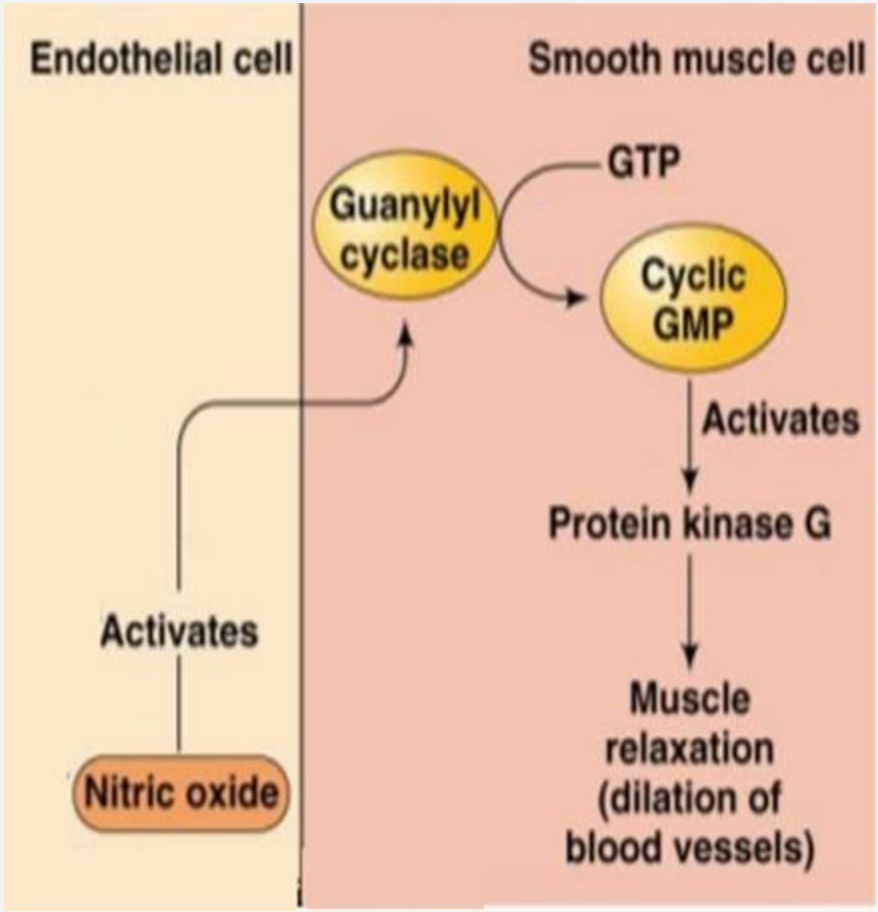
Inhibitor
- hemoglobin

ISOFORMS OF NOS



NO MECHANISM OF ACTION

Activates guanylate cyclase, increasing cGMP and thereby lowering $[Ca^{2+}]_i$



ACTIONS OF NO

Inhibition of platelet and monocyte adhesion and aggregation

Inhibition of smooth muscle proliferation

Protection against atherogenesis

Host defense and **cytotoxic** effects on pathogens

Cytoprotection

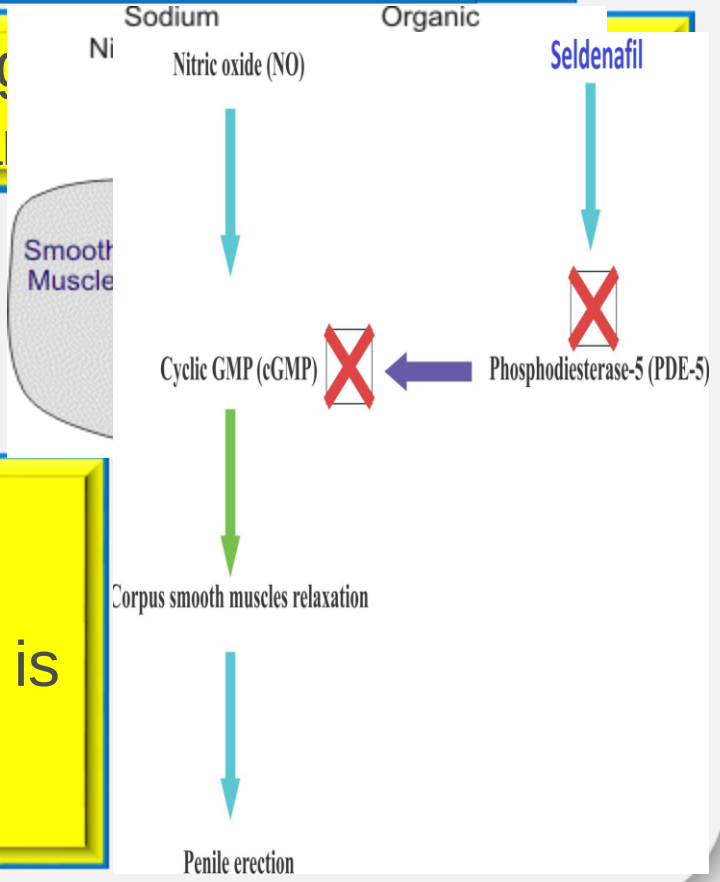
ACTIONS OF NOS

nNOS	eNOS	iNOS
• Cardiac function, Peristalsis, Sexual arousal	• Vascular tone,	• In response to attack by parasites, bacterial infection and tumor growth • Causes septic shock, autoimmune conditions

NO IN THERAPEUTICS

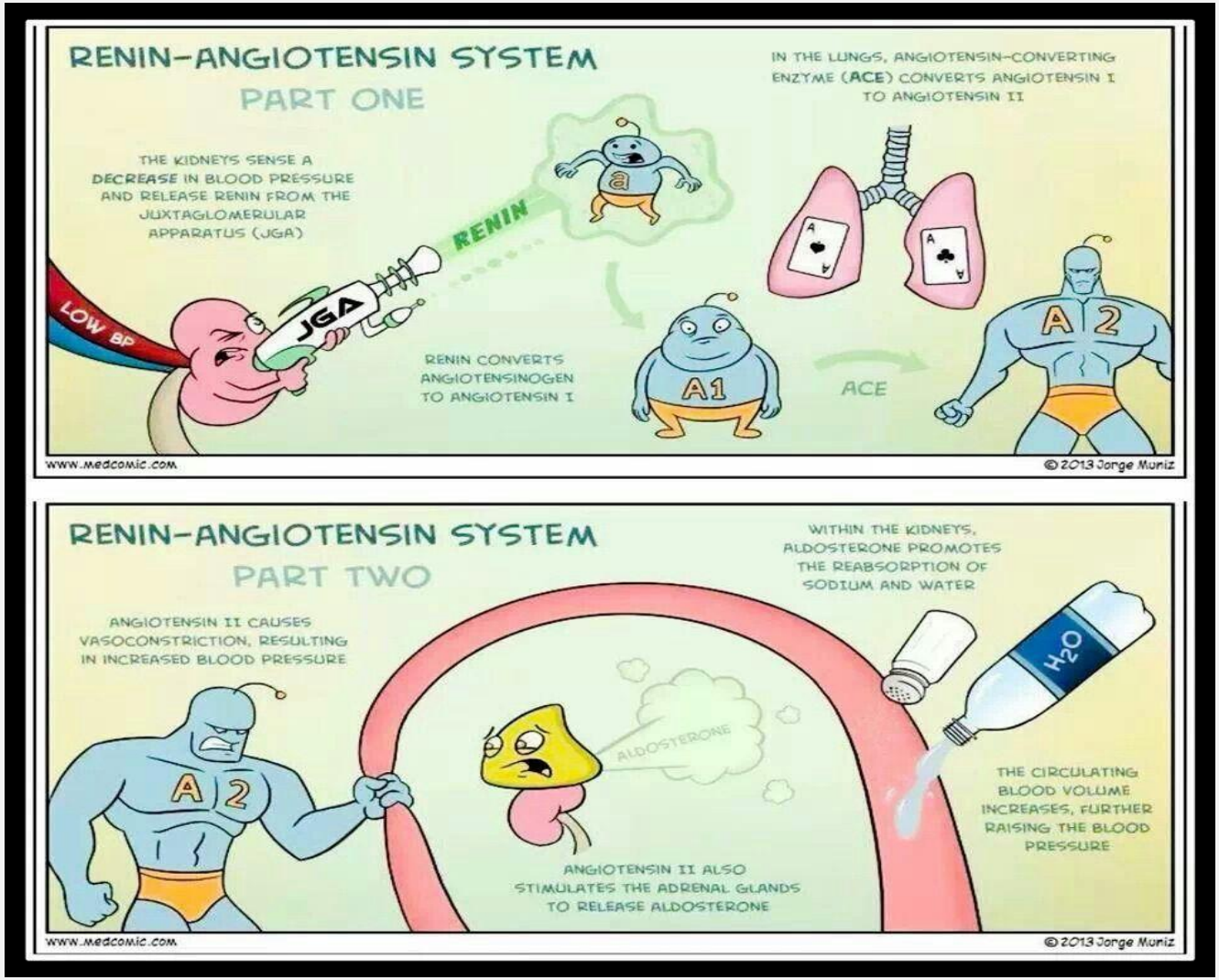
NO donors have well established therapeutic hts uses e.g. in hypertension & angina pectoris

NO is used in patients with ri failure secondary to pulmona



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

ANGIOTENSIN

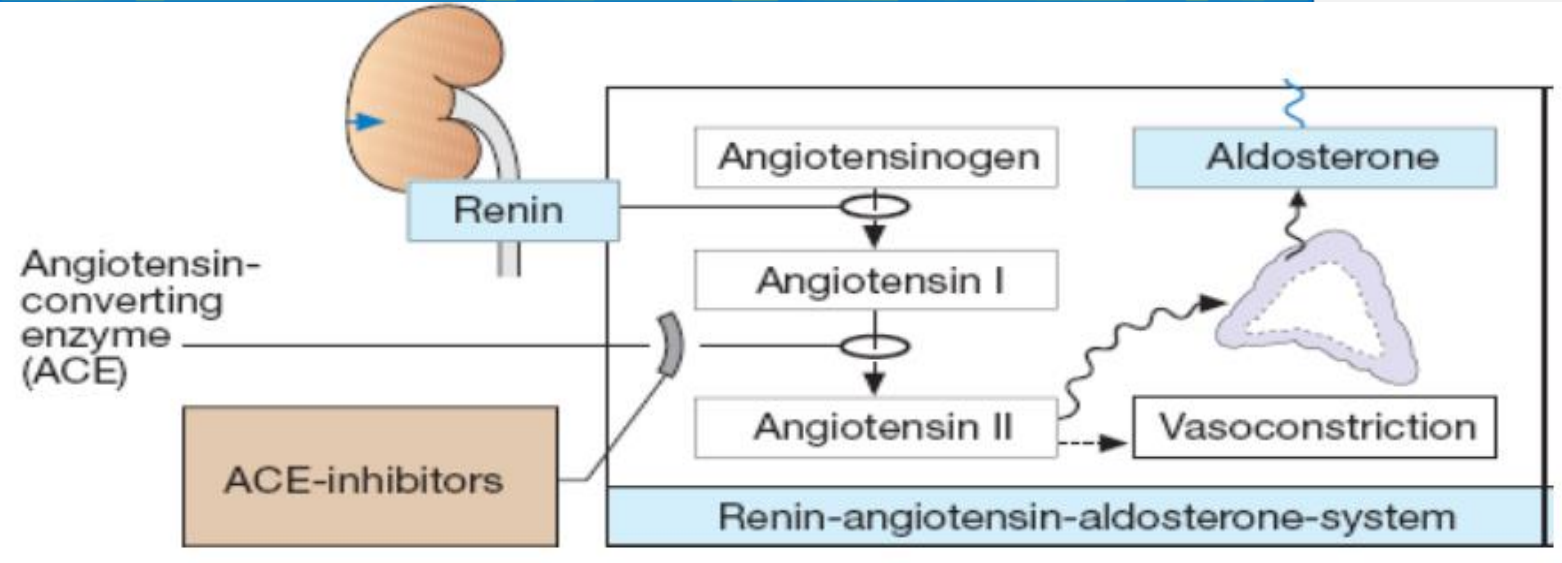


ANGIOTENSIN

Biosynthesis

Renin released from the kidney converts angiotensinogen to Ag I

ACE converts Ag I to Ag II



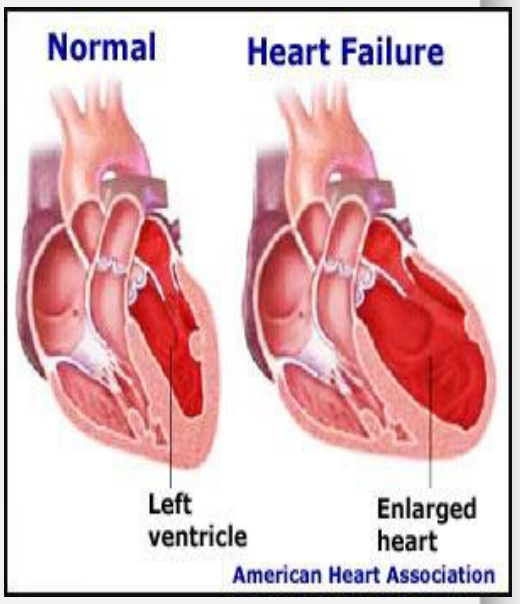
ACTIONS OF ANGIOTENSIN II

Promotes vasoconstriction directly or indirectly by releasing NA & AD

Increases force of contraction of the heart by promoting calcium influx

- Increases aldosterone release → sodium & water retention

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



ANGIOTENSIN INHIBITORS

ACE inhibitors: captopril, enalapril

Angiotensin receptor blockers (ARBs): losartan, valsartan

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

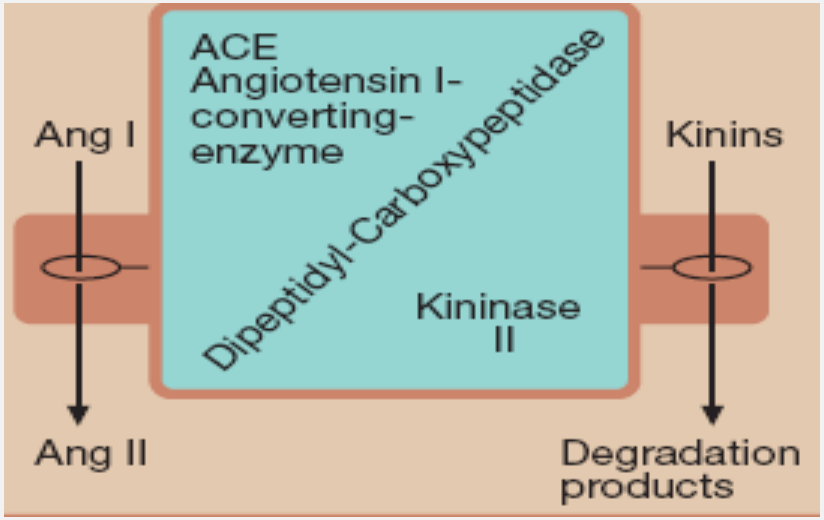
ACE INHIBITORS

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

CLINICAL USES

Hypertension

Cardiac failure



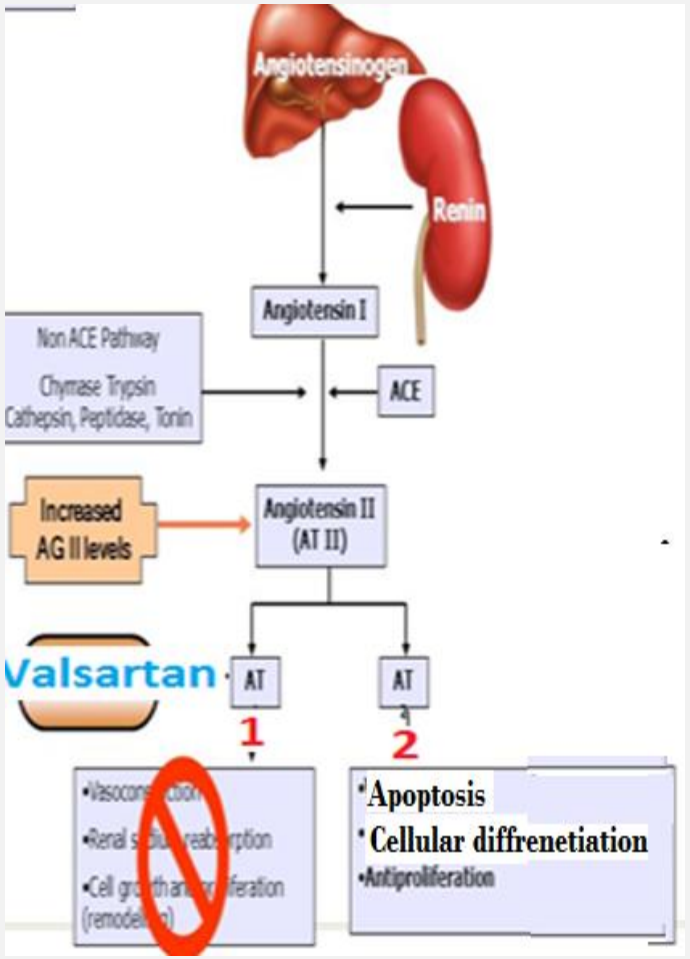
Following myocardial infarction

ANGIOTENSIN RECEPTOR BLOCKERS

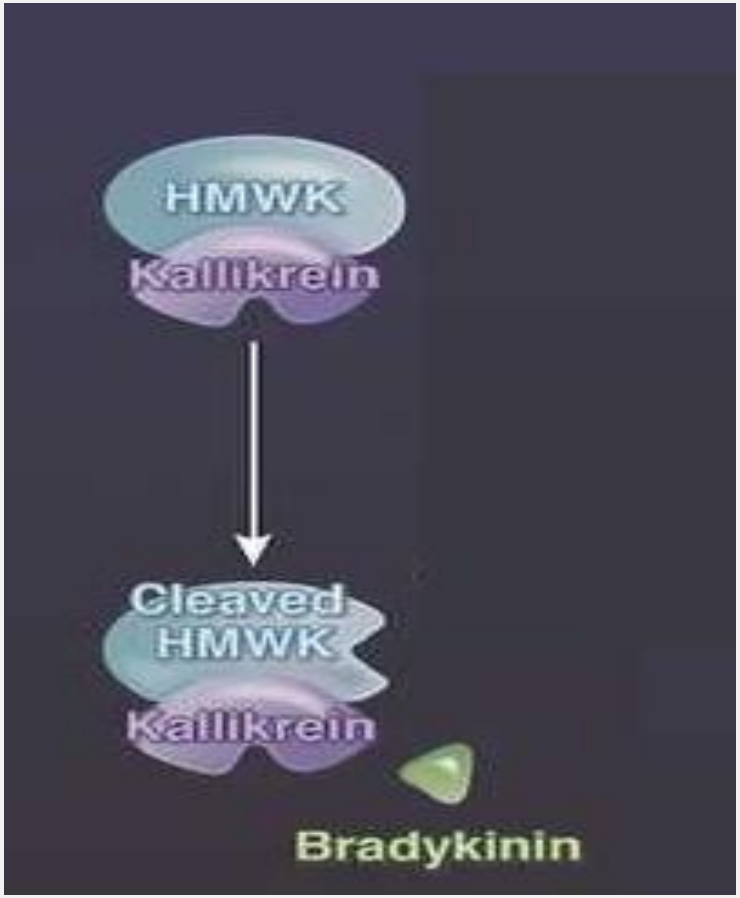
Angiotensin receptors AT I & AT II

AT I receptors predominate in vascular smooth muscle, coupled to G proteins

Similar uses to ACEI



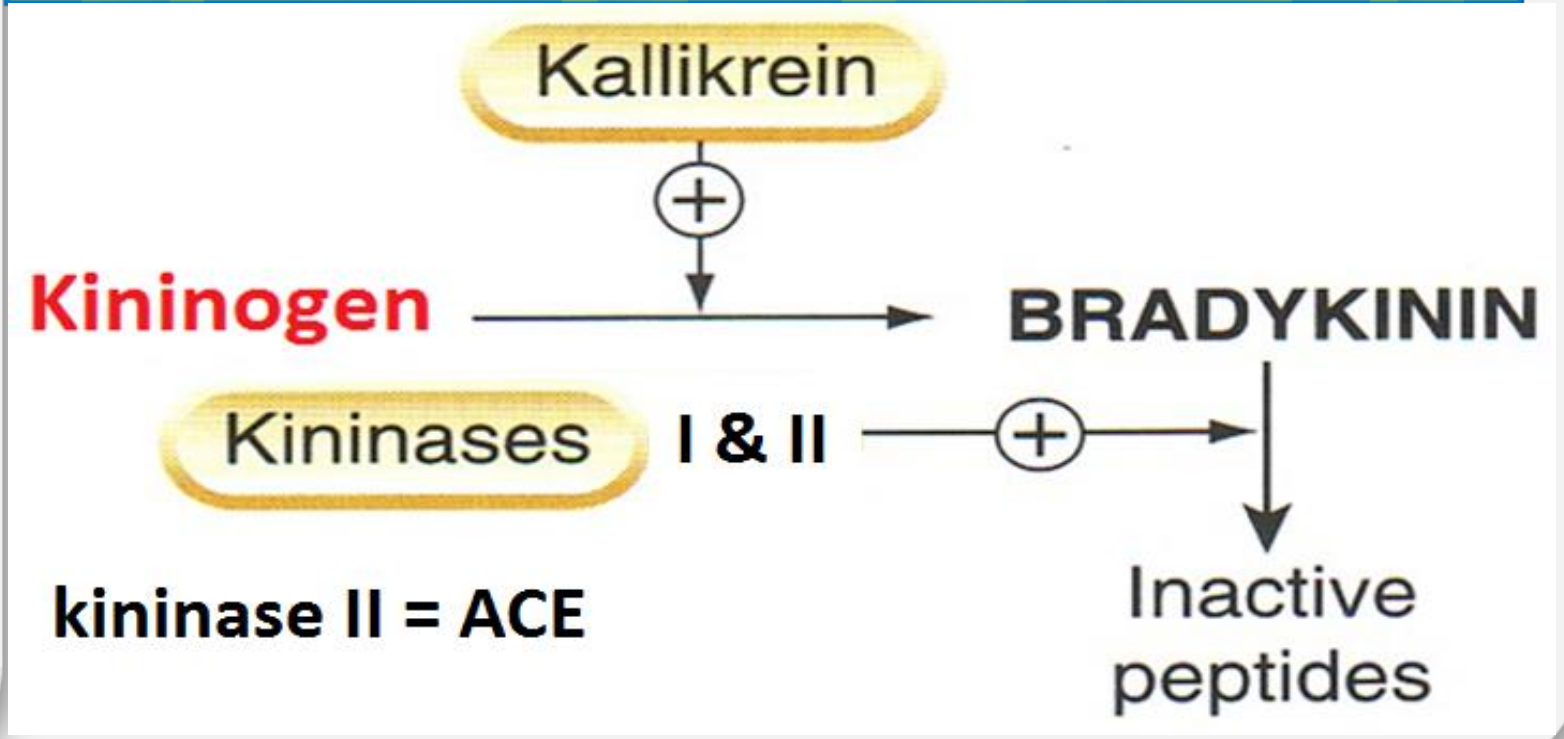
KININS



KININS

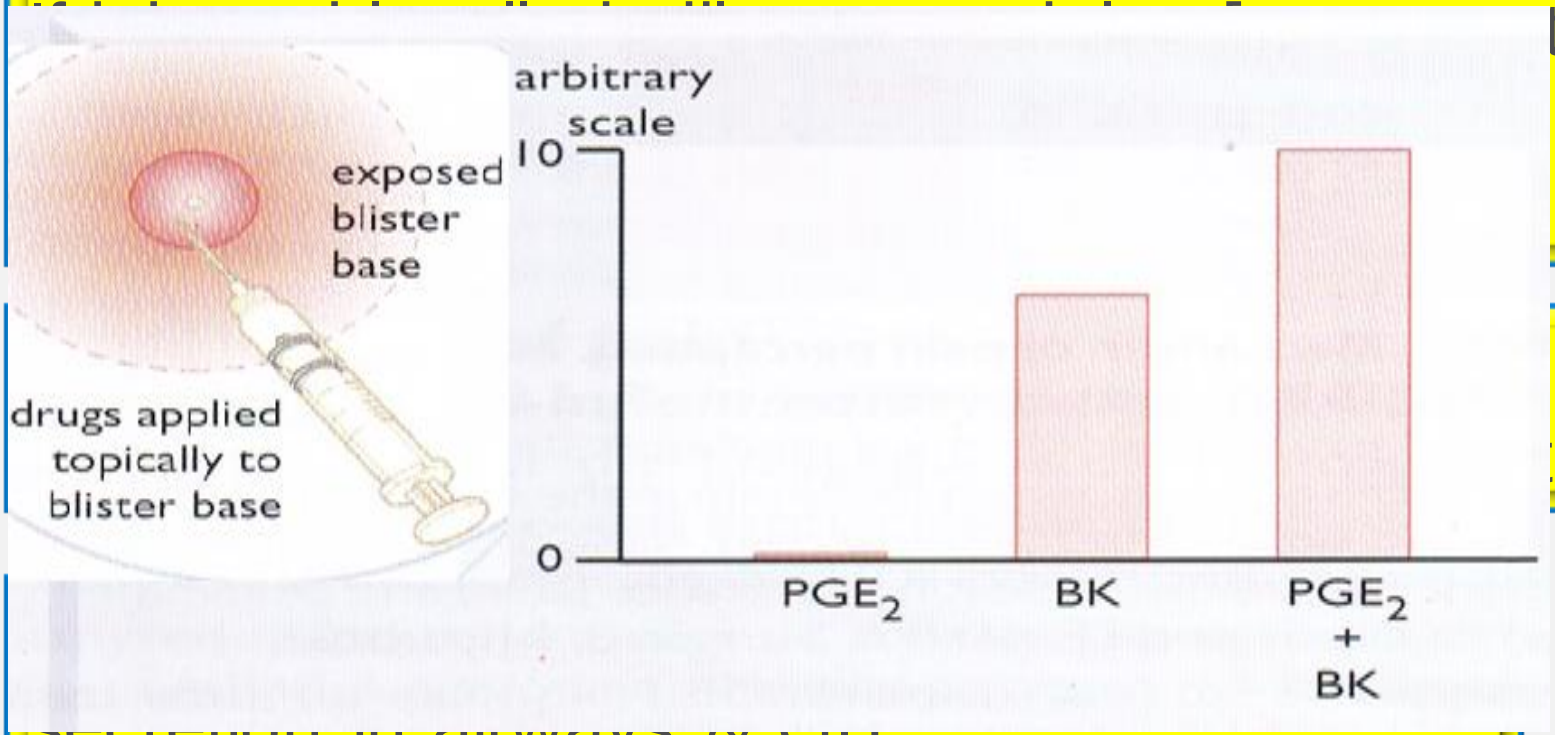
Are Bradykinin & kallidin

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



ACTIONS OF BRADYKININ

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



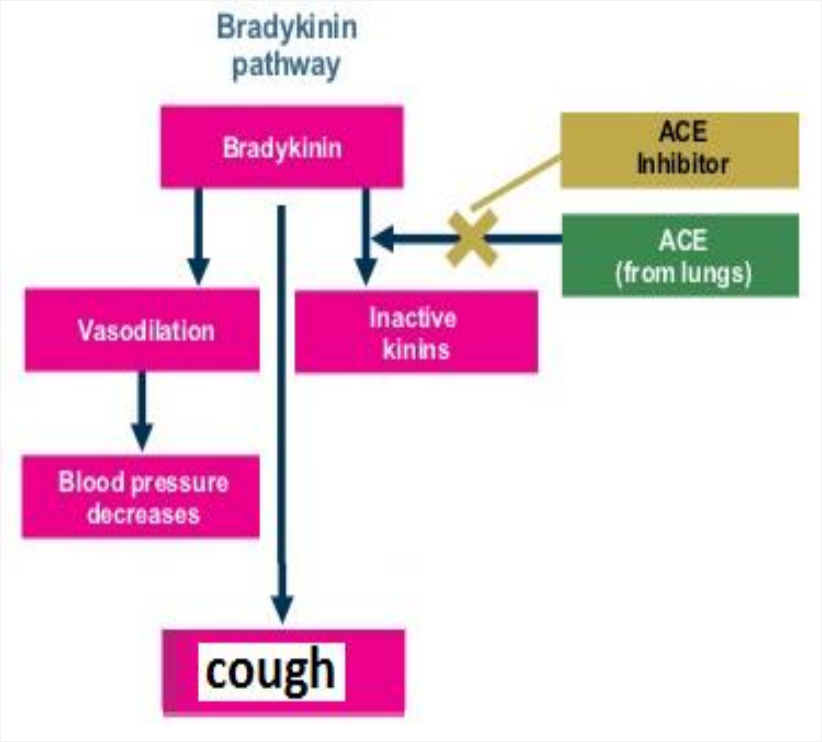
RECEPTORS & CLINICAL USES

- Receptors B_1 & B_2
- B_1 inducible under condition of inflammation
- Low affinity to bradykinin
- B_1 receptor 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 and cough produced by ACEIs

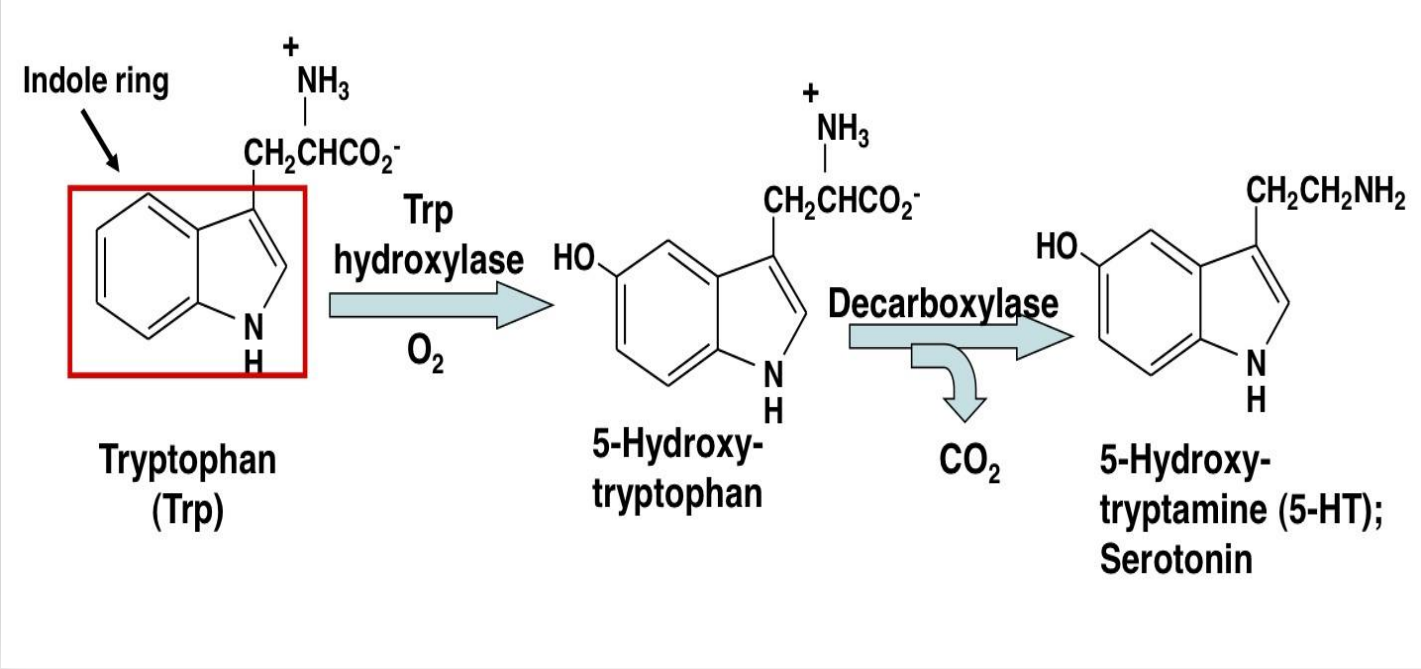


5-HT ACTIONS

SEROTONIN

SEROTONIN [5HT]

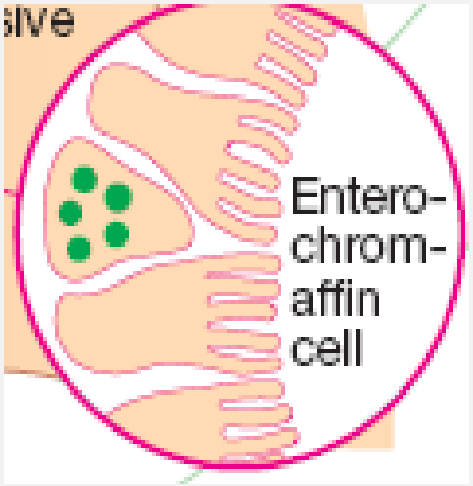
Serotonin is synthesized from the amino acid L-tryptophan



SEROTONIN [5-HT]

DISTRIBUTION

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

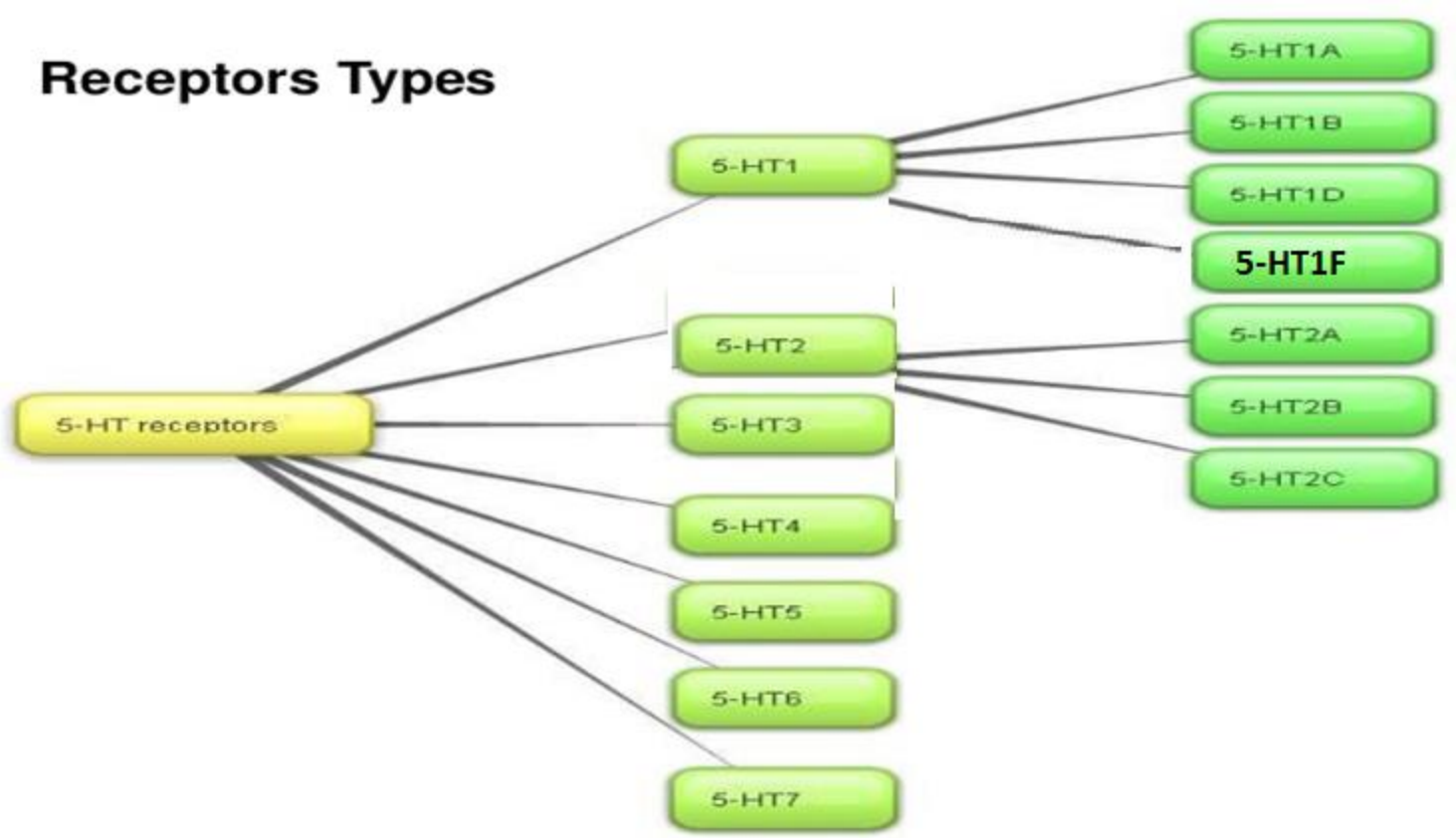


2]Blood ,in platelets , released when aggregated, in sites of tissue damage

3]CNS:-a neurotransmitter, in midbrain

SEROTONIN [5-HT]

RECEPTORS



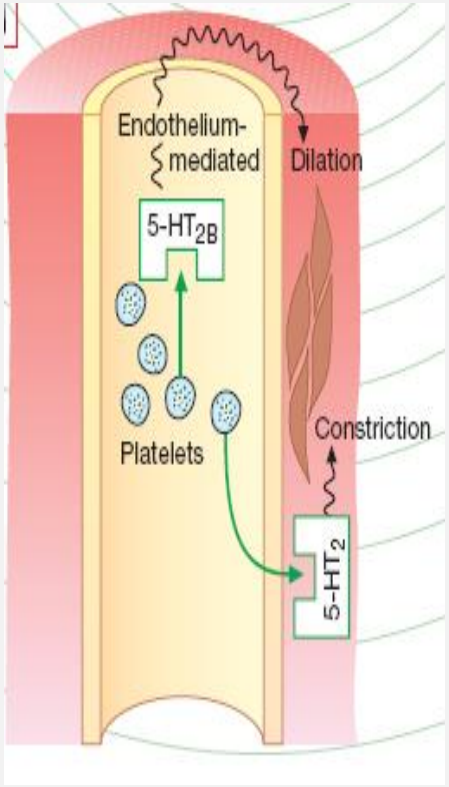
ACTIONS OF 5-HT

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

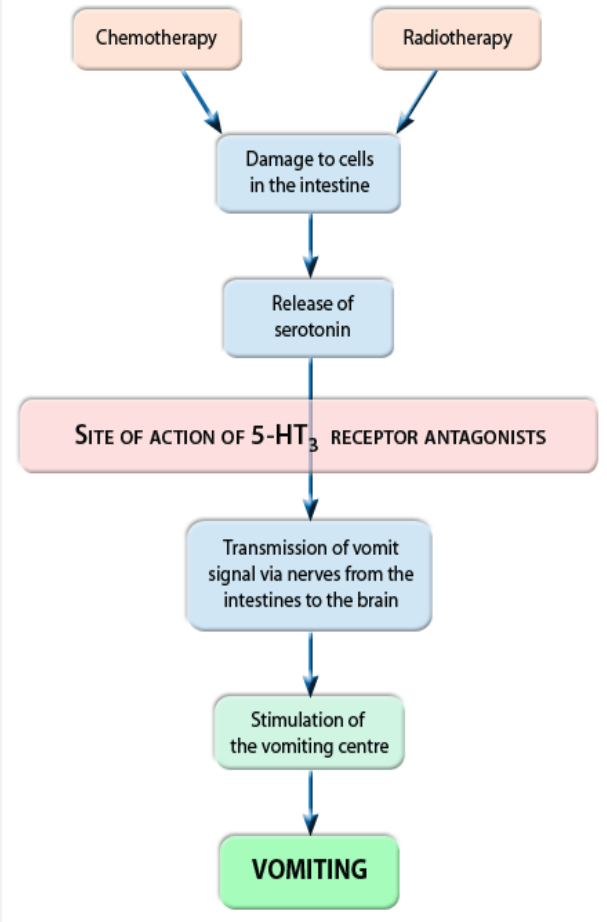
5-HT RECEPTOR AGONISTS

- **Buspirone :-** 5-HT$_{1A}$ agonist , effective anxiolytic

- **Cisapride:-** 5-HT$_4$ -receptor agonist, used in gastroesophageal reflux & motility disorders.

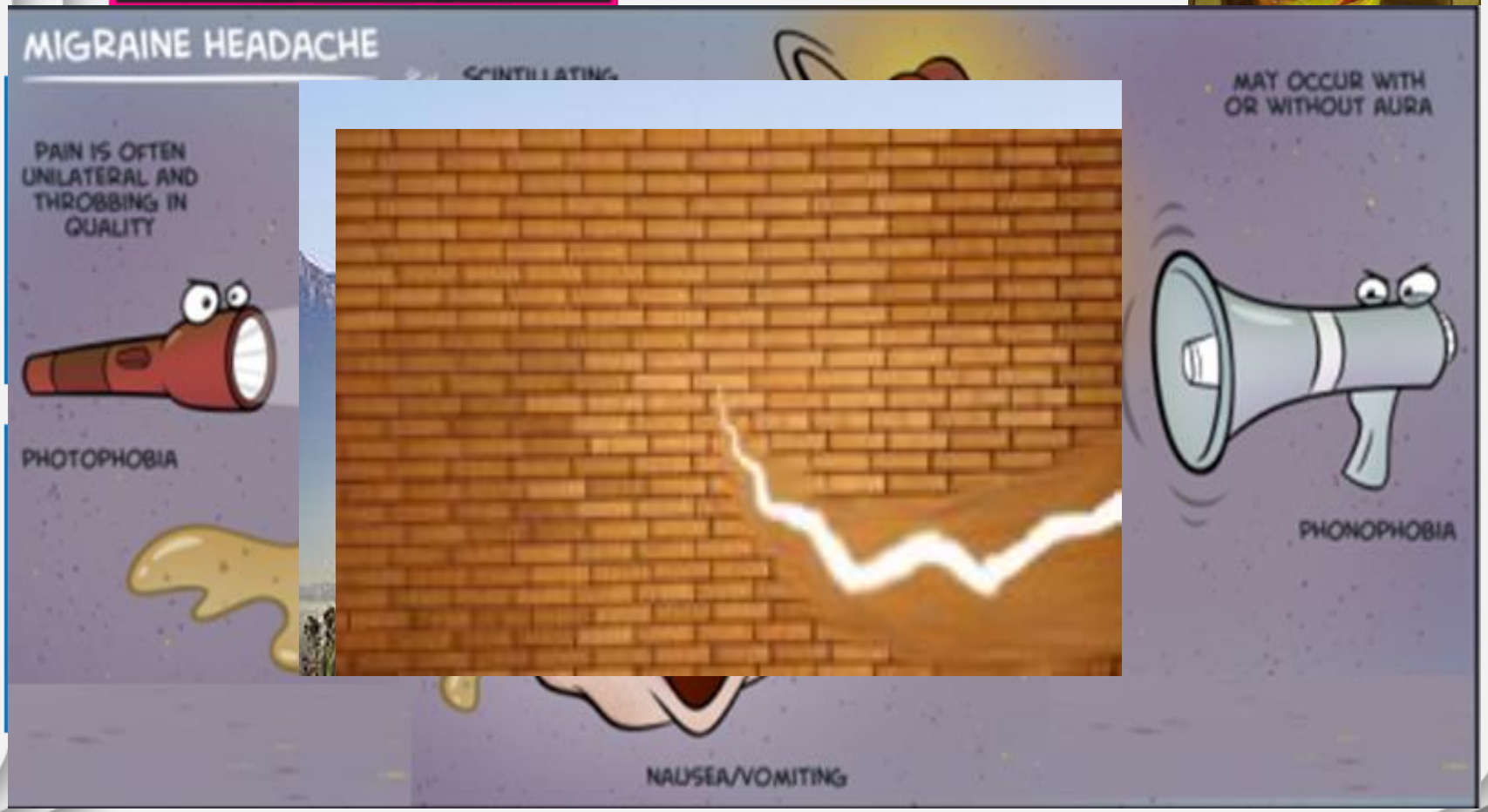
5-HT RECEPTOR ANTAGONISTS

- **Selective 5-HT$_3$ antagonist, Ondansetron**, antiemetic action for cancer chemotherapy



CLINICAL CONDITIONS IN WHICH 5-HT IS IMPLICATED

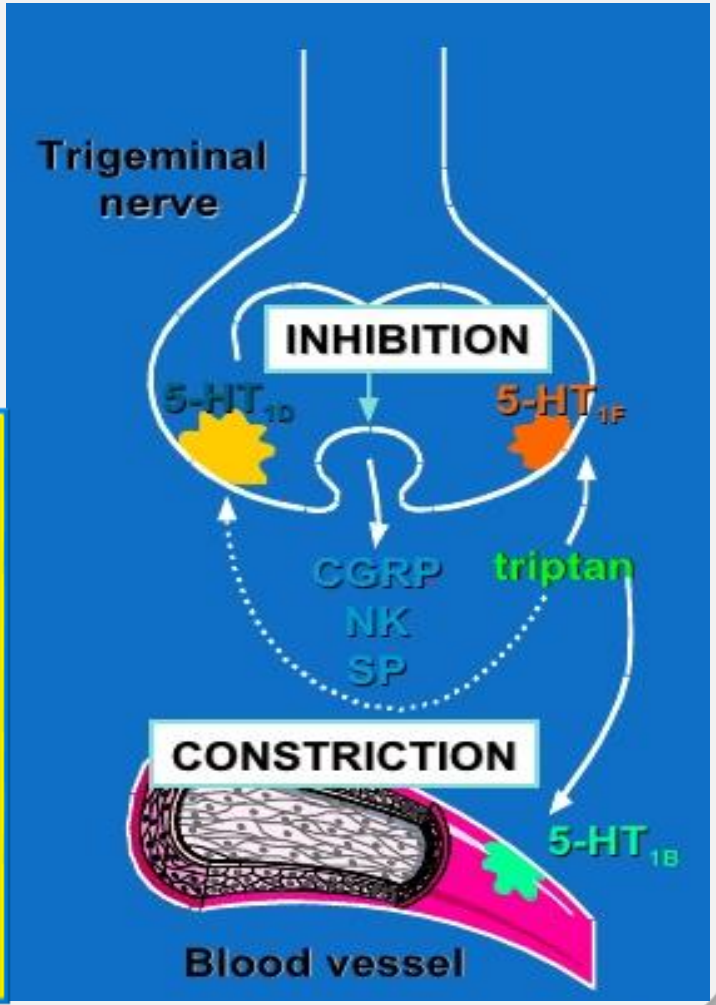
1-MIGRAINE



SUMATRIPTAN

5-HT1B,1D &1F-receptor agonist , 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.