

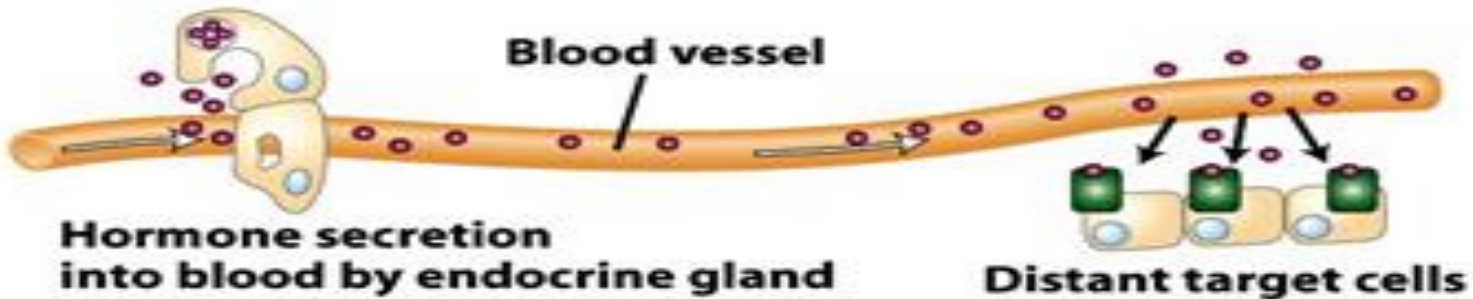
AUTACOIDS

They include:

Aminoacid derivatives

- Histamine
- Serotonin

Endocrine signaling



Fatty acid derivatives

Eicosanoids

Gas

NO

AUTACOIDS

ILOS

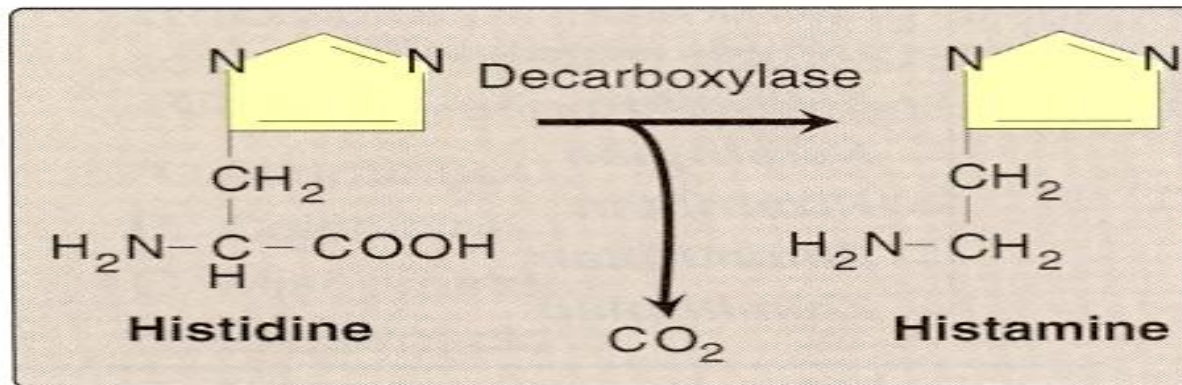
To describe the synthesis, receptors & functions of histamine, eicosanoids, nitric oxide, angiotensin, kinins & 5-HT

To study the agents which enhance or block their effects.

1 – Histamine

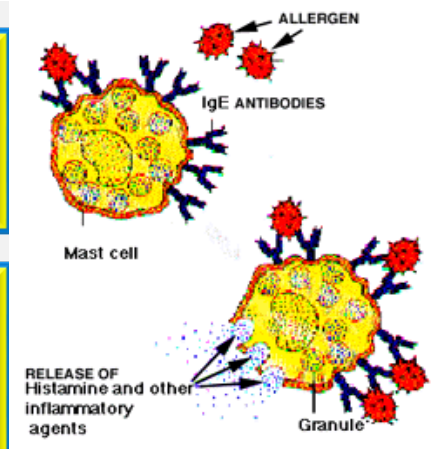
HISTAMINE

Synthesis:- from L- histidine



Stored in mast cells, basophils, lung, intestinal mucosa

Release:- during allergic reaction, inflammatory reaction



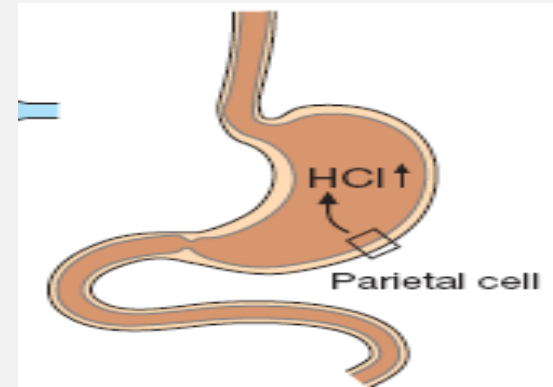
HISTAMINE RECEPTORS

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

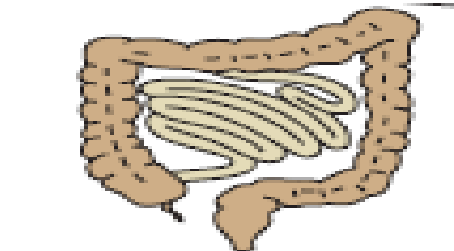
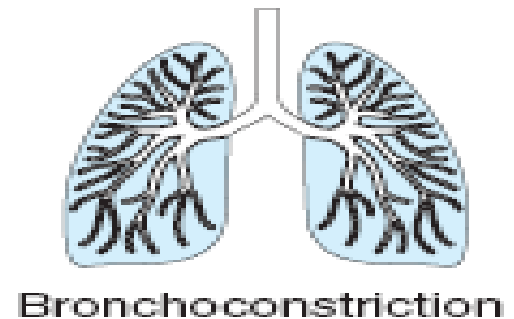
* COP: cardiac output

ACTIONS

Histamine stimulates gastric acid secretion, through H₂- receptors



• Stimulation of H₁-receptors contract smooth muscles, bronchioles, uterus



Increases bowel peristalsis

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 H₁ RECEPTOR ANTAGONISTS :

First generation

Diphenhydramine, Promethazine

Second generation

Cetirizine, Fexofenadine.

HISTAMINE H₁ RECEPTOR BLOCKERS

First generation

Has a sedating effect

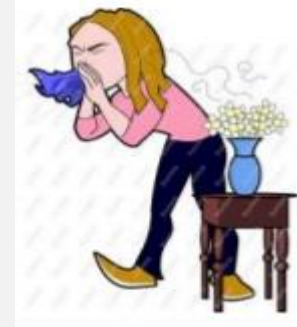
Clinical uses:

+ Allergic rhinitis

+ Urticaria

+ Insomnia

+ Motion sickness



Urticaria



HISTAMINE H₁ RECEPTOR BLOCKERS

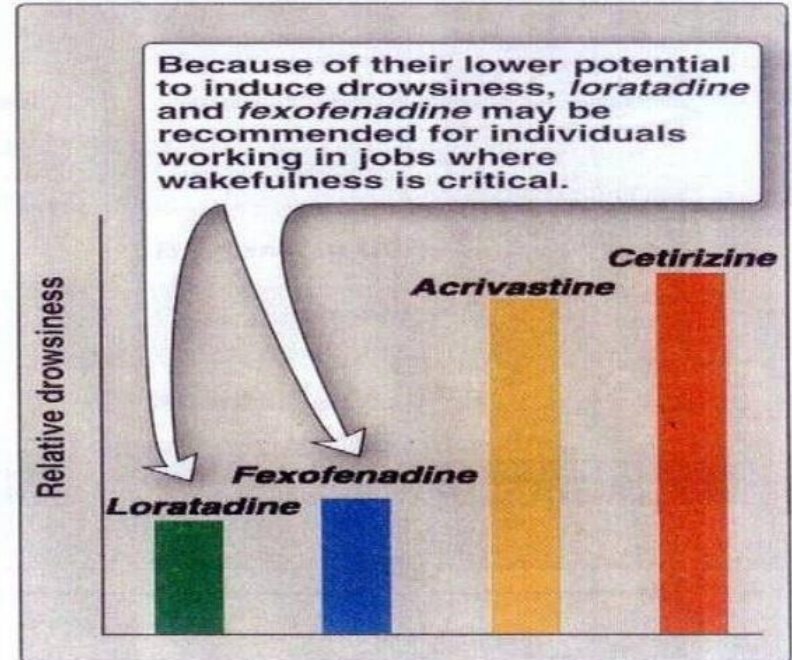
Second generation

+ Non-sedating effect

Clinical uses

Allergic conditions such as:-

- Allergic rhinitis
- Conjunctivitis
- Urticaria.



H₂- RECEPTOR BLOCKERS

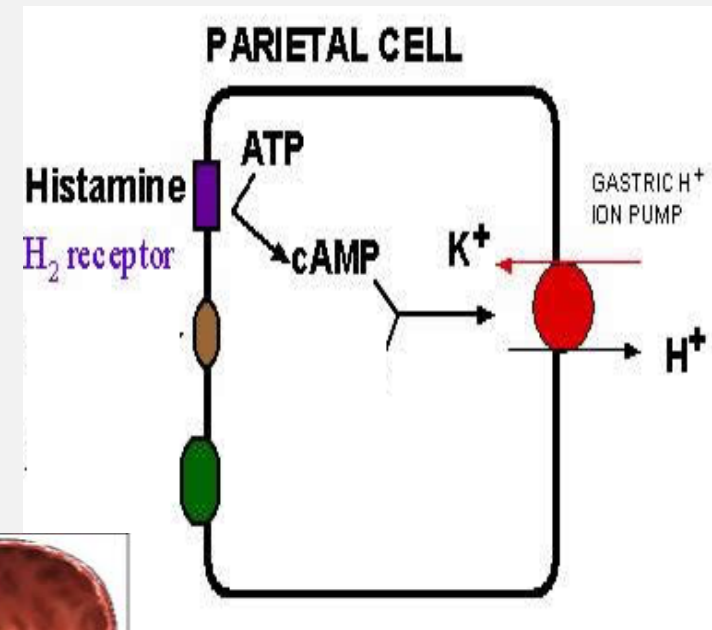
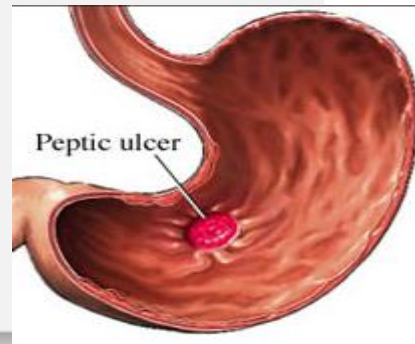
Histamine plays an important role in the formation & secretion of HCl by the activity of H₂ receptors

e.g. Cimetidine

Blockers of H₂ receptors inhibit gastric acid secretion

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:

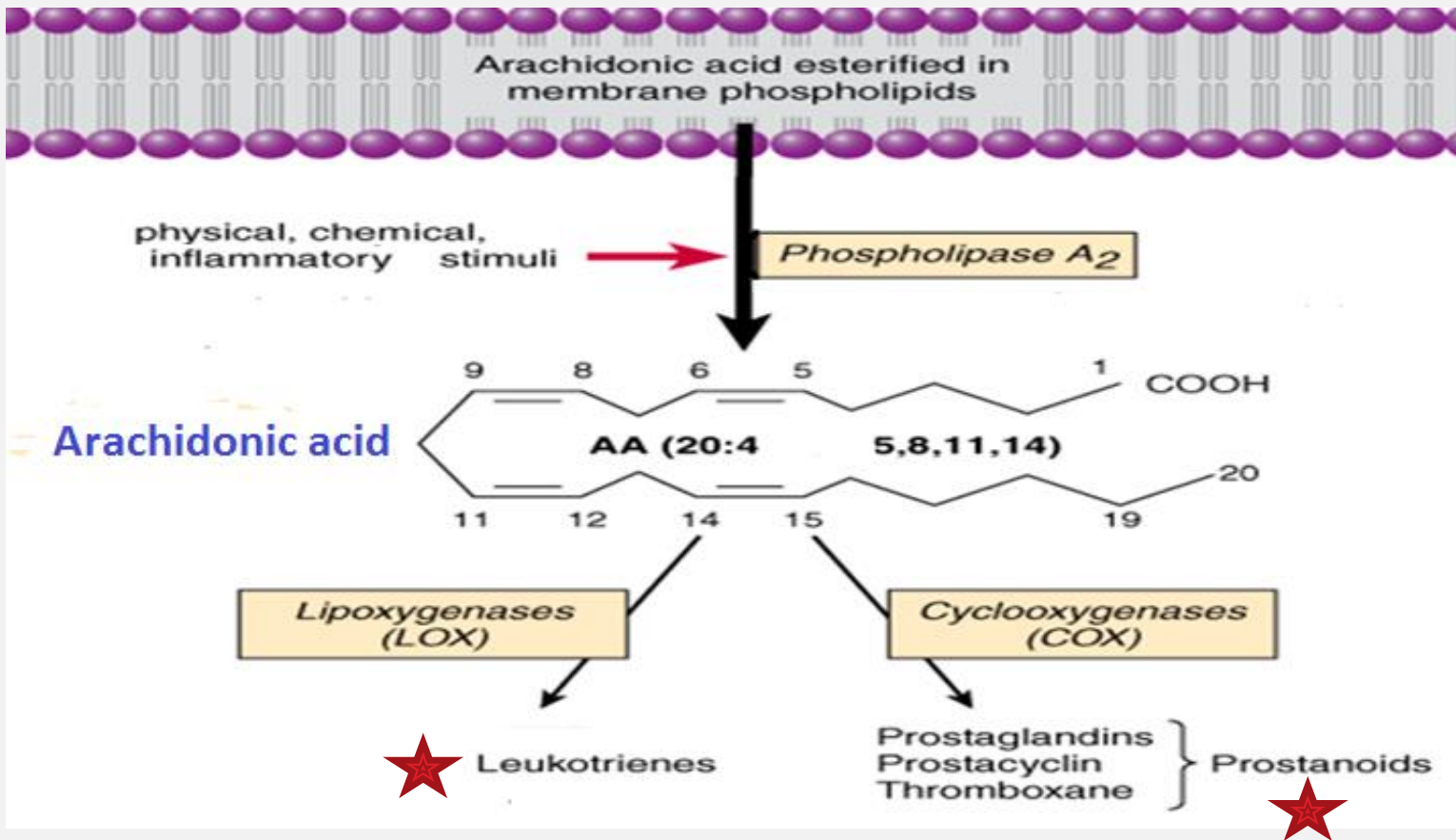
May produce headache & insomnia.



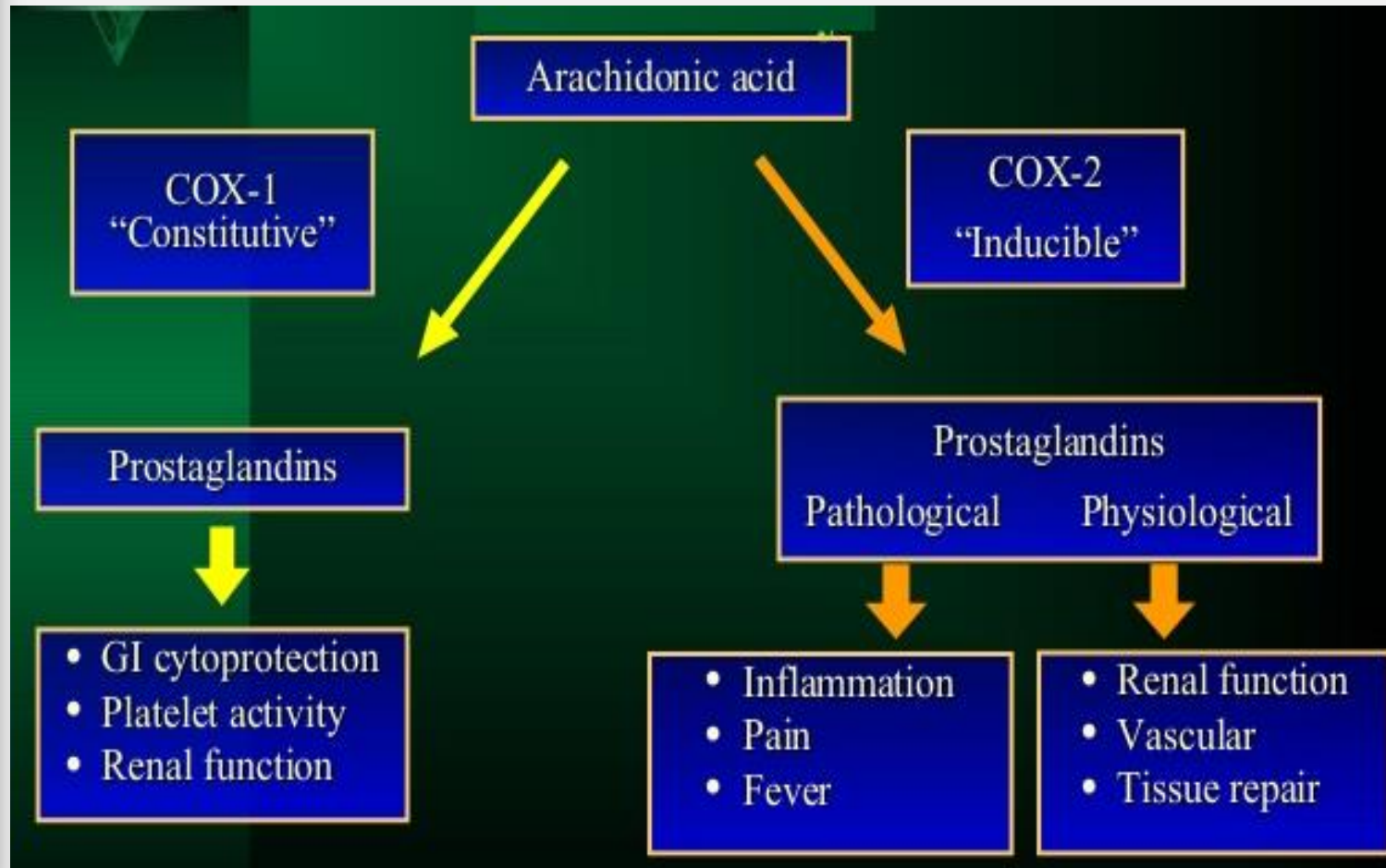
2– Eicosanoids

EICOSANOIDS

SYNTHESIS



COX ISOZYMES



ACTIONS OF PROSTAGLANDINS

They are pro-inflammatory

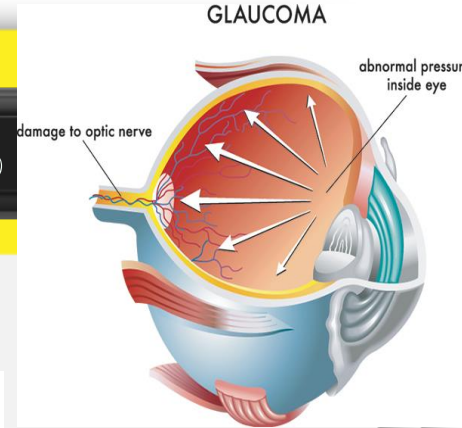
Cause vasodilatation of vascular smooth muscle

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

Sensitize neurons to cause pain

Induce labor.

ACTIONS OF PROSTAGLANDINS



PGI₂ & PGE₂
dilate

Glomerular capillaries

Bowman's capsule

Protective Factors

Aggressive Factors

- Mucus
- Bicarbonate
- Blood flow to mucose

- Gastric acid
- H. Pylori
- Ethanol
- NSAIDs
- Oxidative stress

Prostaglandins



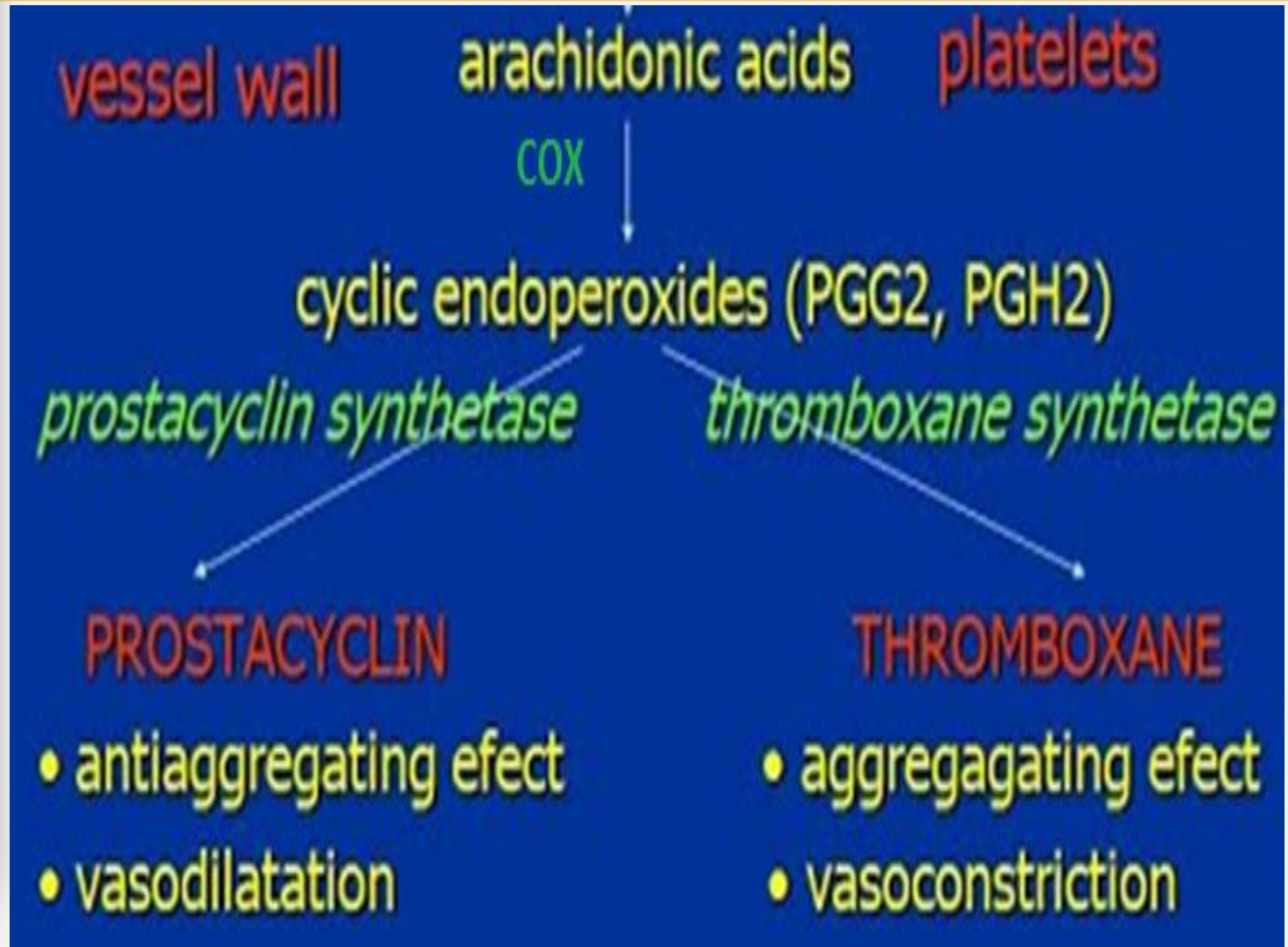
Healthy mucosa

Acts on kidney
filtration

ular

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

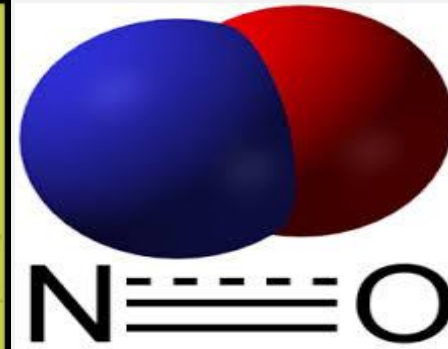
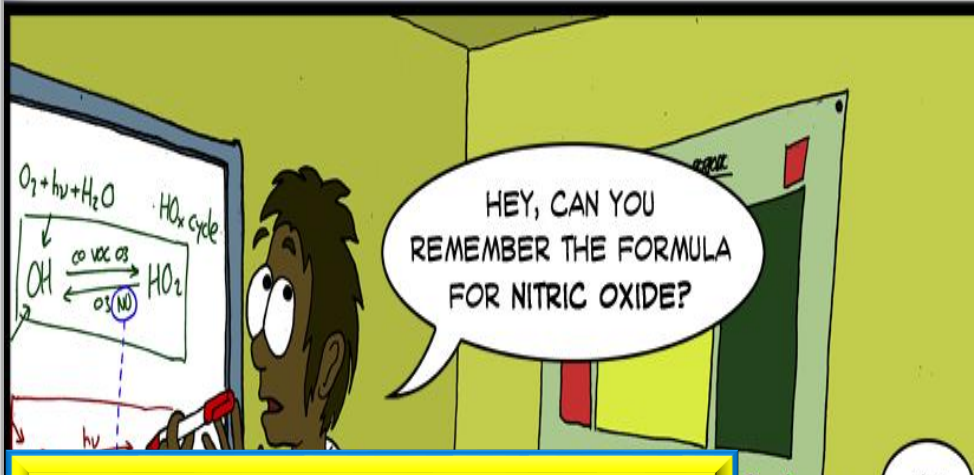
Alprostadil (PGE₁): Erectile dysfunction

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

NOS Stimulants & Inhibitors

Activators
acetylcholine
serotonin,
bradykinin
histamine

Inhibitor
hemoglobin

lukesurl.com

the enzyme NOS.

ISOFORMS OF NOS

Neuronal NOS (nNOS)

- Neurons
- Skeletal muscle

Endothelial NOS (eNOS)

- Endothelium
- Cardiac myocytes
- Osteoblasts
- Osteoclasts

Inducible NOS (iNOS)

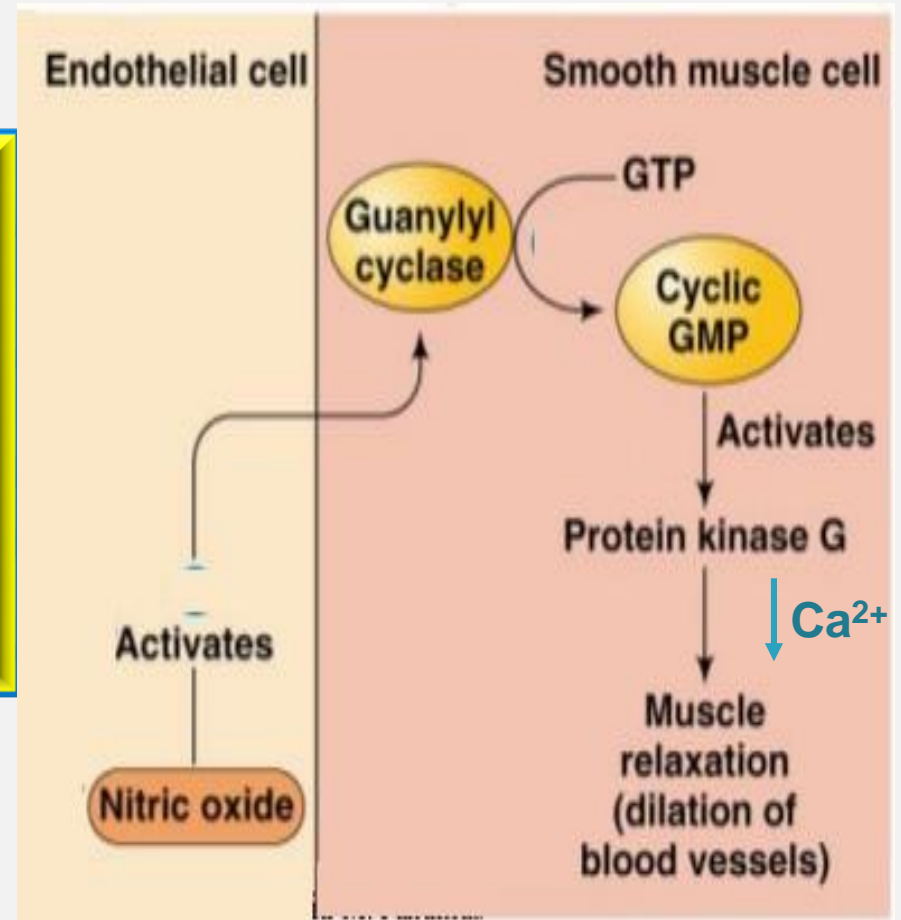
- Macrophages
- Kupffer cells
- Neutrophils
- Fibroblasts
- Vascular smooth muscle

Constitutive Forms
(Physiological)

Pathological

NO MECHANISM OF ACTION

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

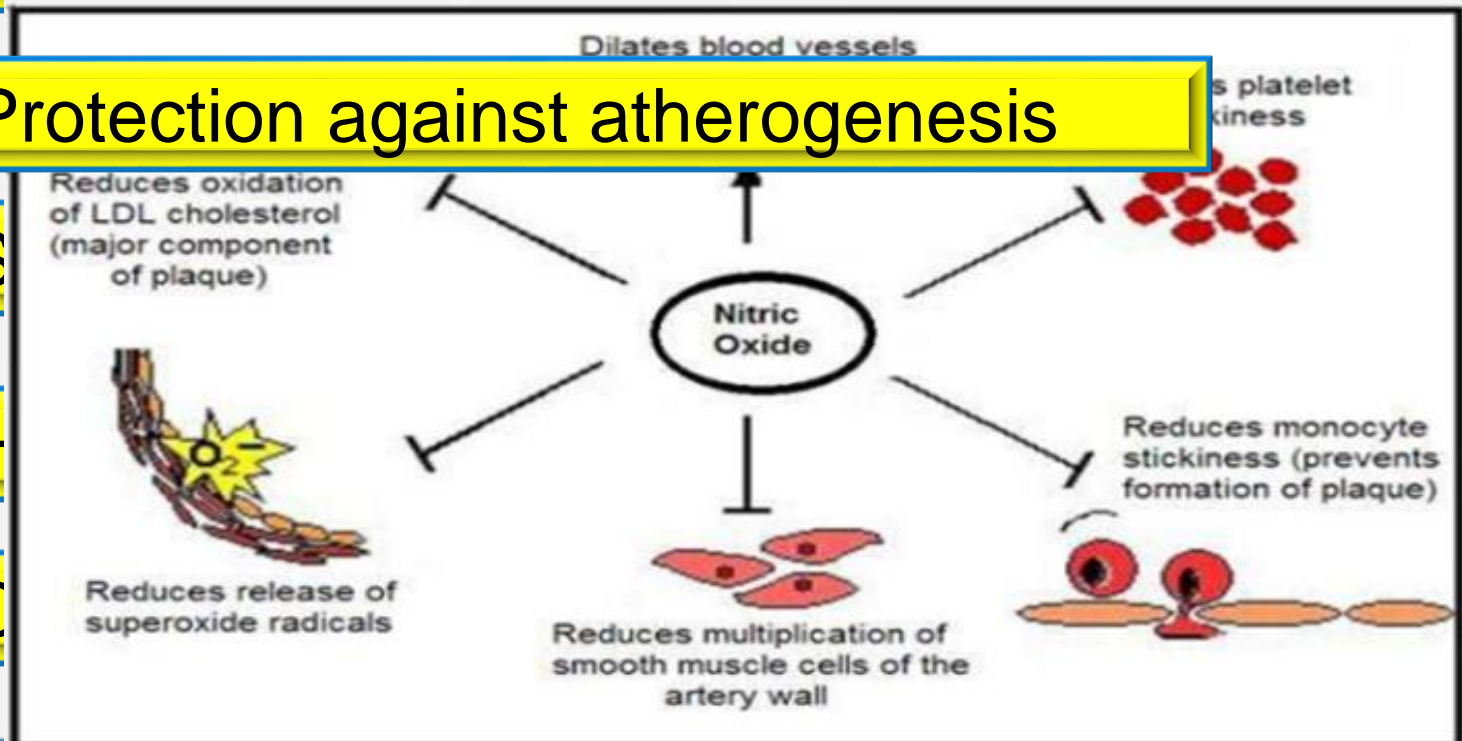


ACTIONS OF NO

Inhibition of platelet & monocyte adhesion & aggregation

Inhibition of smooth muscle proliferation

Protection against atherogenesis



ACTIONS OF NOS

nNOS

- Long Term Potentiation
- Cardiac function, Peristalsis, Sexual arousal

eNOS

- Vascular tone, Insulin secretion, Airway tone, Regulation of cardiac function and angiogenesis
- Embryonic heart development

iNOS

- In response to attack by parasites, bacterial infection and tumor growth
- Causes septic shock, autoimmune conditions

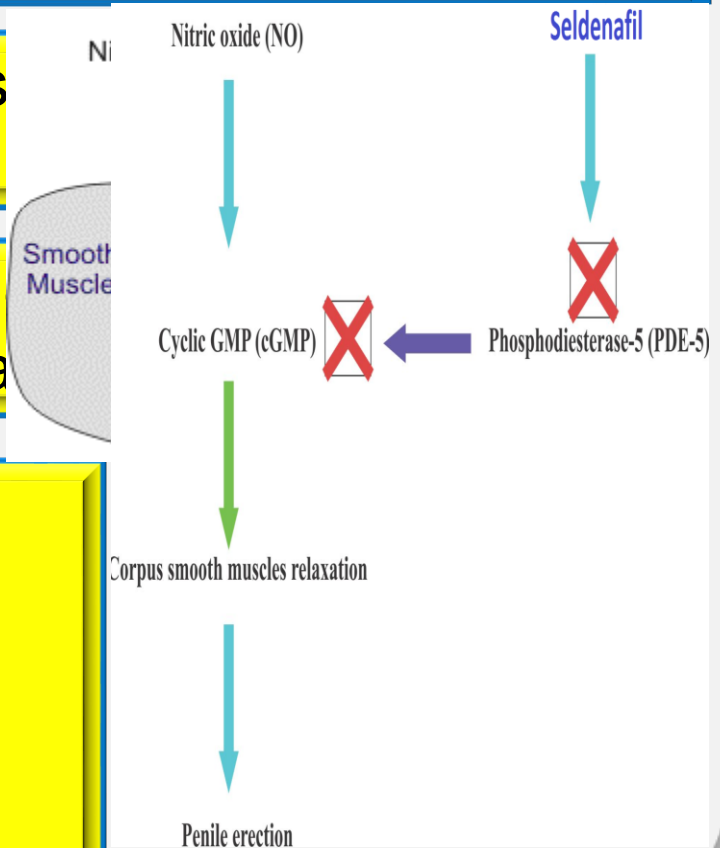
NO IN THERAPEUTICS

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

Overproduction of NO occurs in diseases (e.g. Parkinsonism)

NO is used in patients with right heart failure secondary to pulmonary hypertension

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



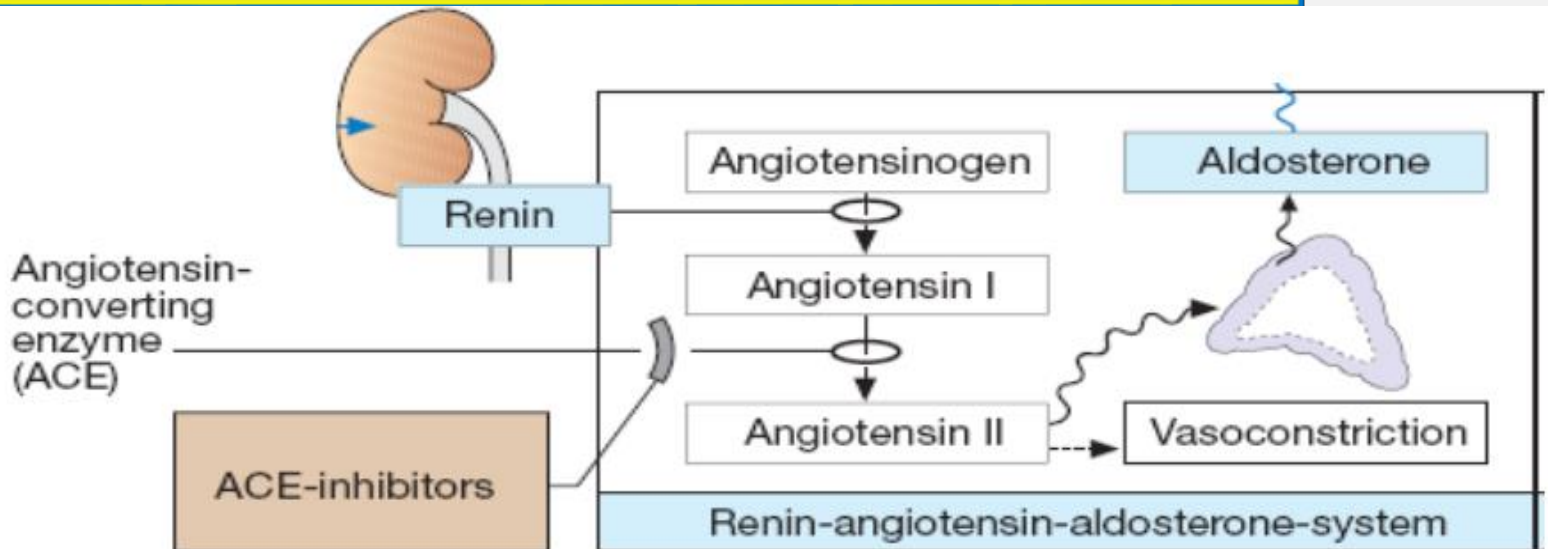
4- Angiotensin

ANGIOTENSIN

Biosynthesis

Renin released from the kidney converts angiotensinogen to Ag I

ACE converts Ag I to Ag II



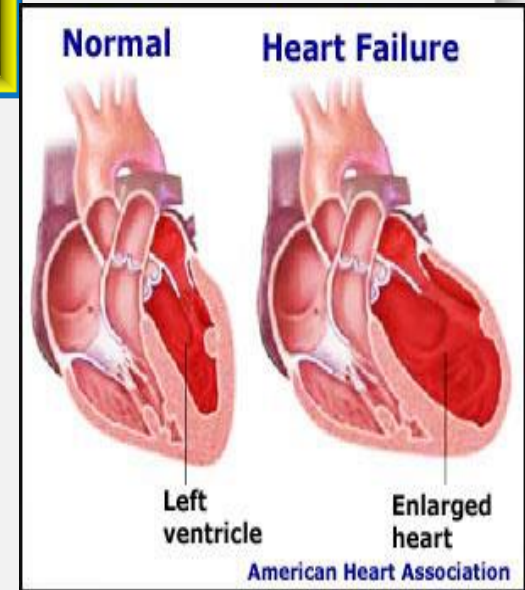
ACTIONS OF ANGIOTENSIN II

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.



Search ID: IJan1094
"No, taking an ACE inhibitor won't hurt your poker game."

ACE INHIBITORS

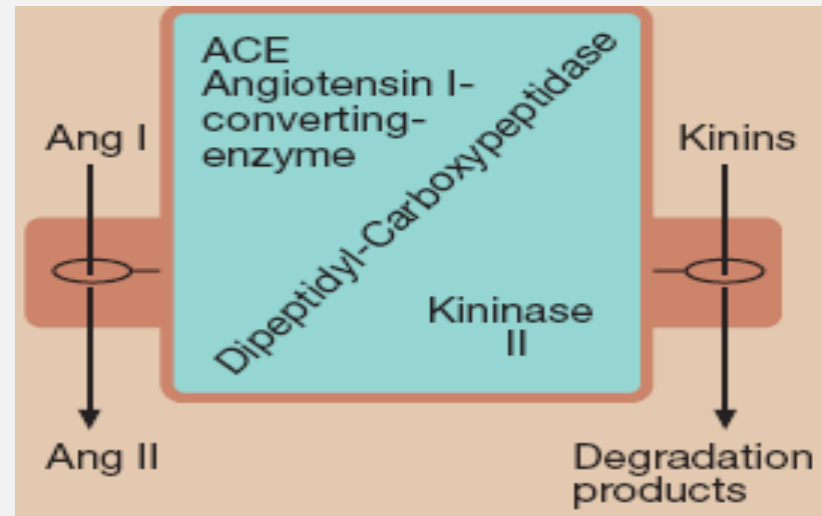
Cause a fall in blood pressure in hypertensive patients especially those with high rennin levels

CLINICAL USES:

Hypertension

Cardiac failure

Following myocardial infarction.

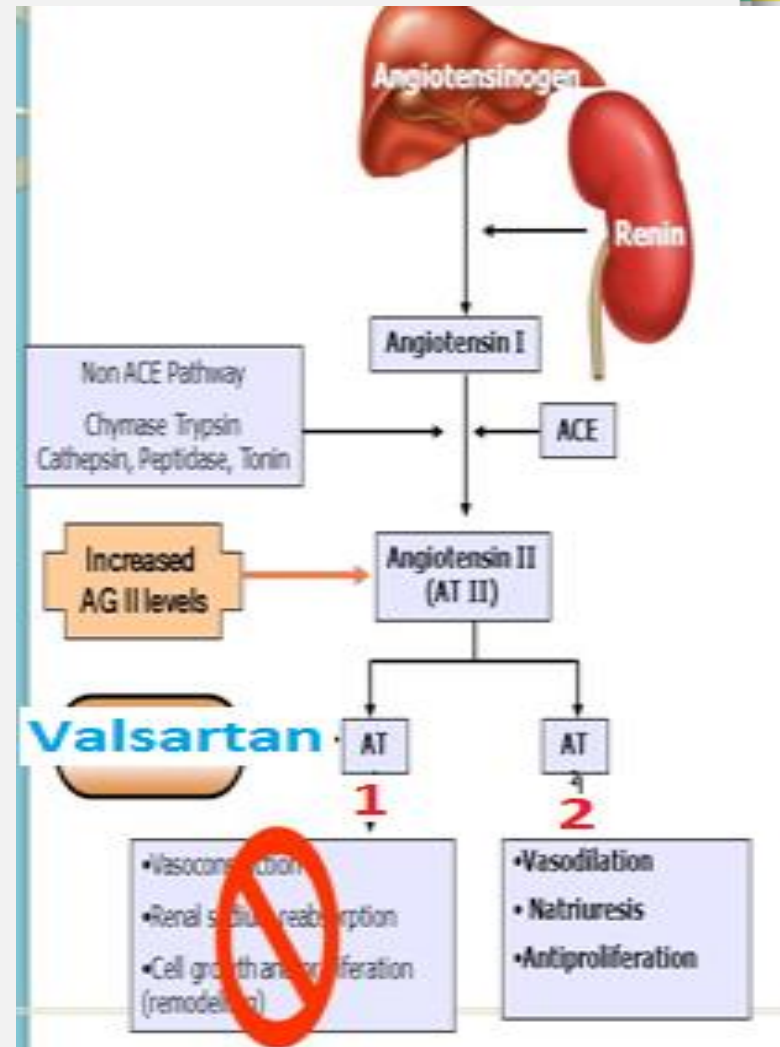


ANGIOTENSIN RECEPTOR BLOCKERS

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

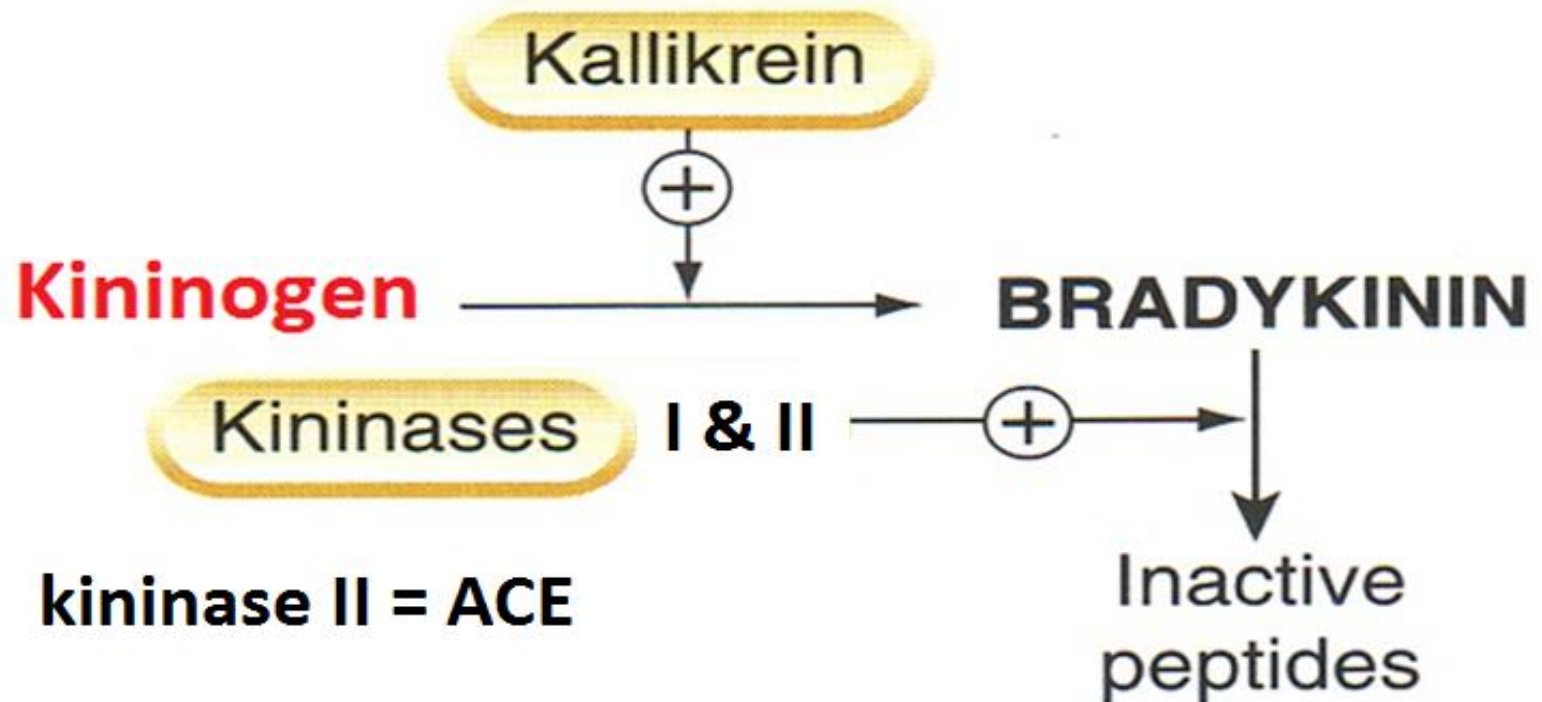


5– Kinins

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

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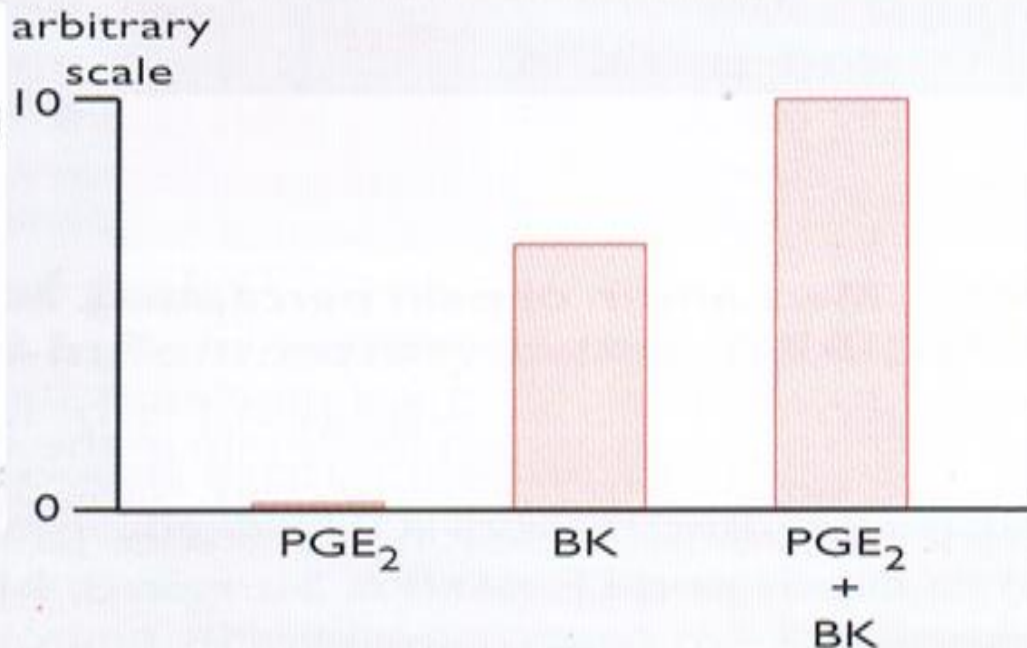
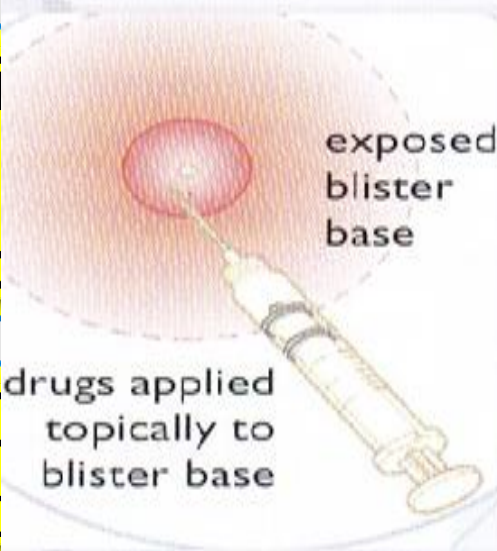
St

secretion in airways & GIT.

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RECEPTORS & CLINICAL USES

- ‡ Receptors B₁ & B₂ (both are G protein-coupled receptors)

- ‡ B₁ inducible under condition of inflammation

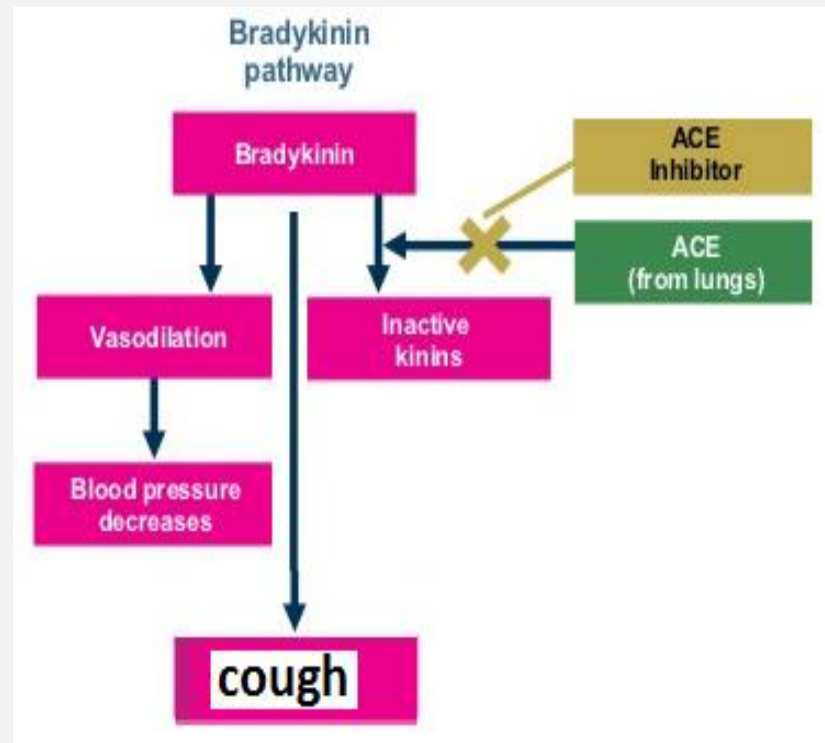
- ‡ B₁ receptor has low affinity to bradykinin
- ‡ plays a significant role in inflammation & hyperalgesia

- ‡ B₂ constitutive
- ‡ High affinity to bradykinin & mediates the majority of its effects.

THERAPEUTIC USES

✚ No current therapeutic use of bradykinin

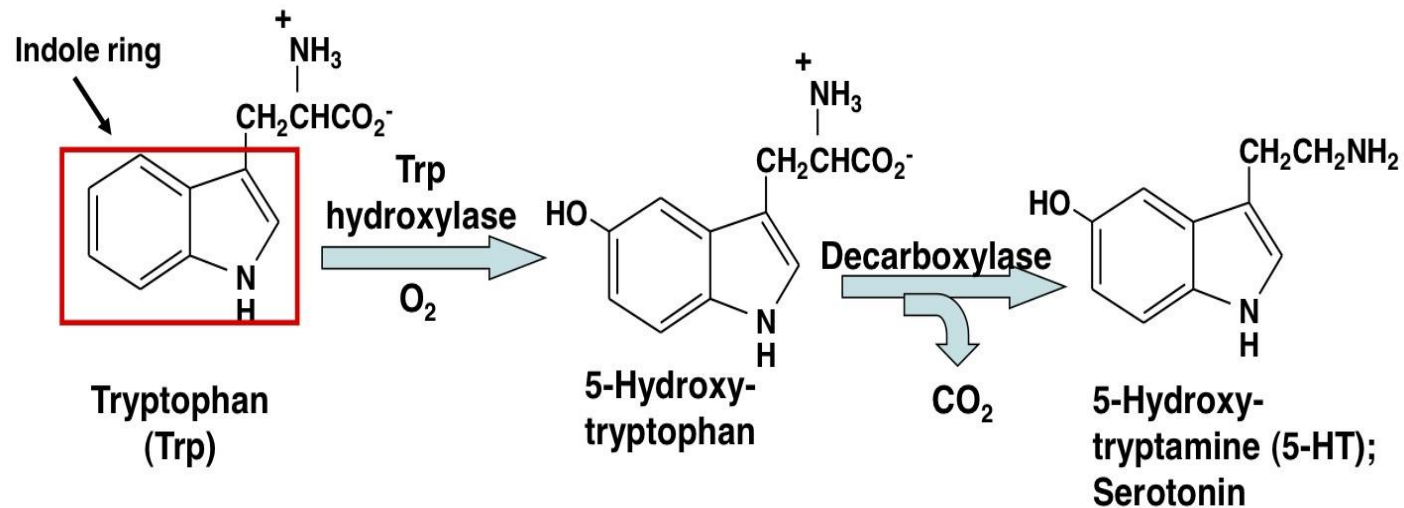
✚ **Increased** bradykinin is implicated in the therapeutic efficacy & cough produced by ACEIs.



6– Serotonin

SEROTONIN [5HT]

Serotonin is synthesized from the amino acid L-tryptophan



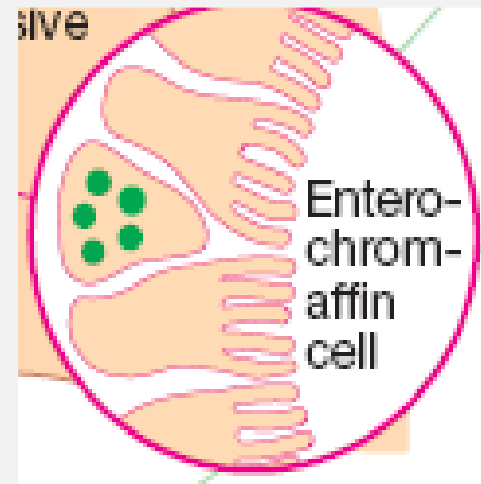
SEROTONIN [5-HT]

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

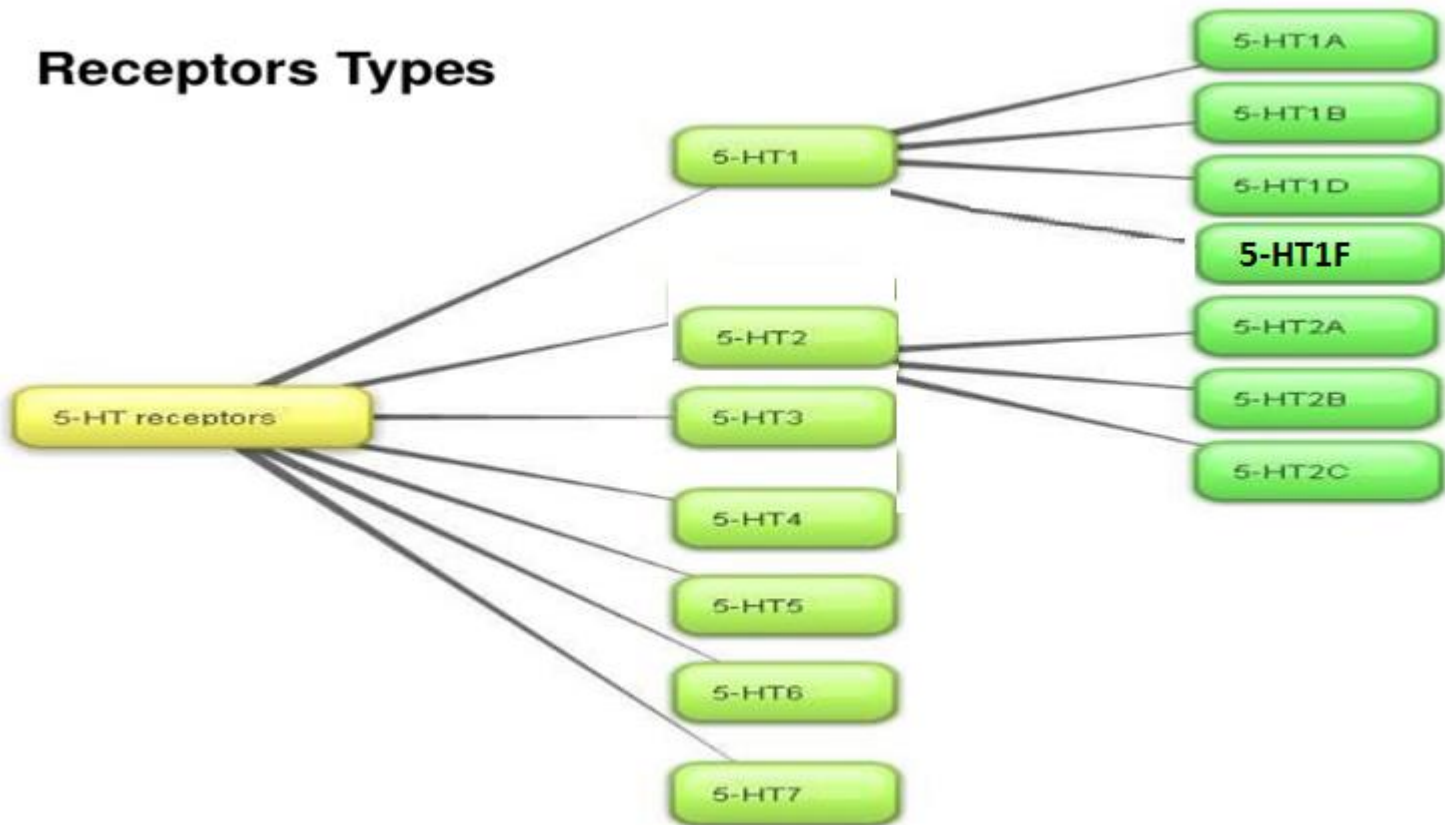
3] CNS: a neurotransmitter, in midbrain



5-HT

RECEPTORS

Receptors Types



ACTIONS OF 5-HT

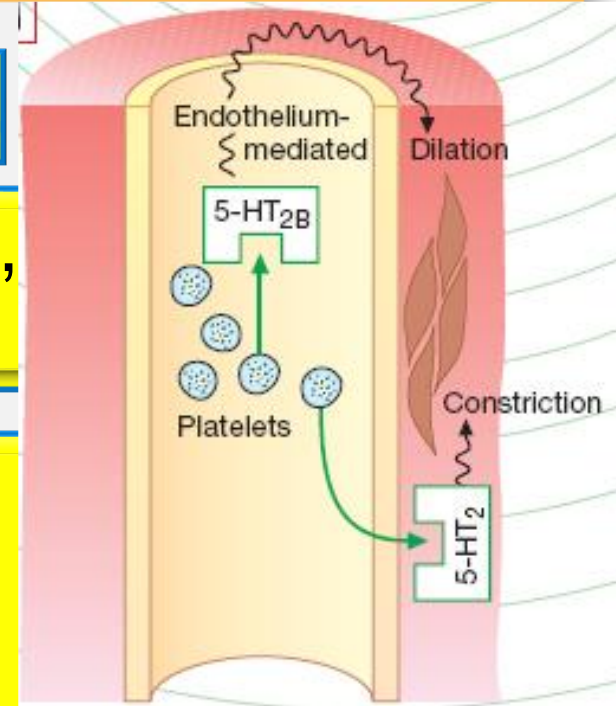
GIT: 5-HT increases motility

✦ 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.

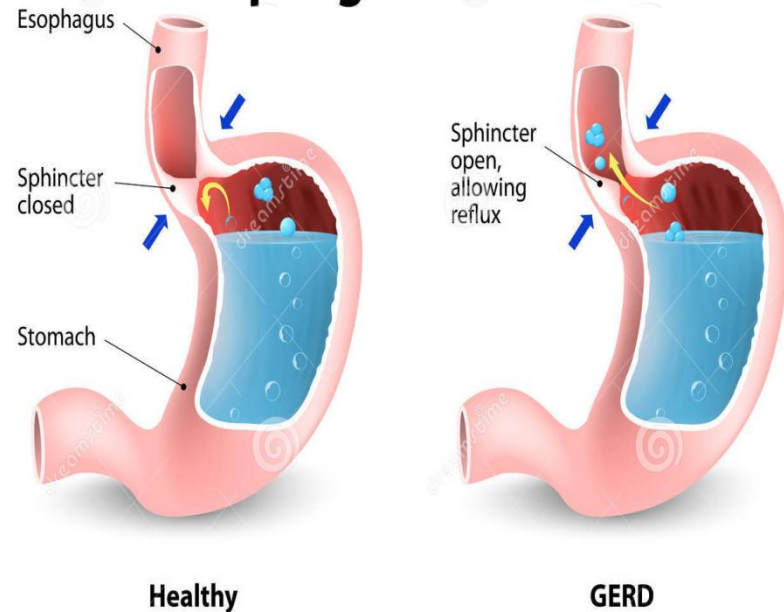
5-HT RECEPTOR AGONISTS

‡ **Buspirone**:- 5-HT_{1A} agonist, effective anxiolytic



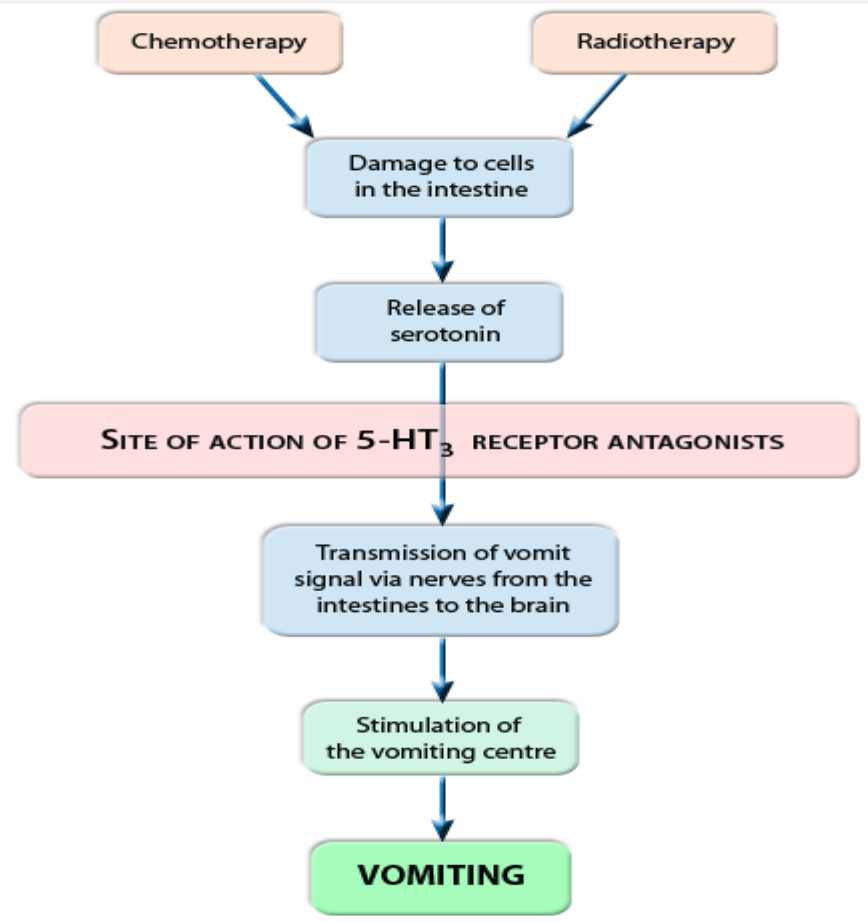
‡ **Cisapride**:- 5-HT₄ -receptor agonist, used in gastroesophageal reflux & motility disorders.

Gastroesophageal reflux disease



5-HT RECEPTOR ANTAGONISTS

↓ **Selective 5-HT₃ antagonist,**
Ondansetron,
antiemetic action,
for cancer
chemotherapy



CLINICAL CONDITIONS IN WHICH 5-HT IS IMPLICATED

1-MIGRAINE



MIGRAINE HEADACHE

PAIN IS OFTEN UNILATERAL AND THROBBING IN QUALITY



PHOTOPHOBIA

SCINTILLATING SCOTOMATA



MAY OCCUR WITH OR WITHOUT AURA



PHONOPHOBIA

LASTS 4 TO 72 HOURS

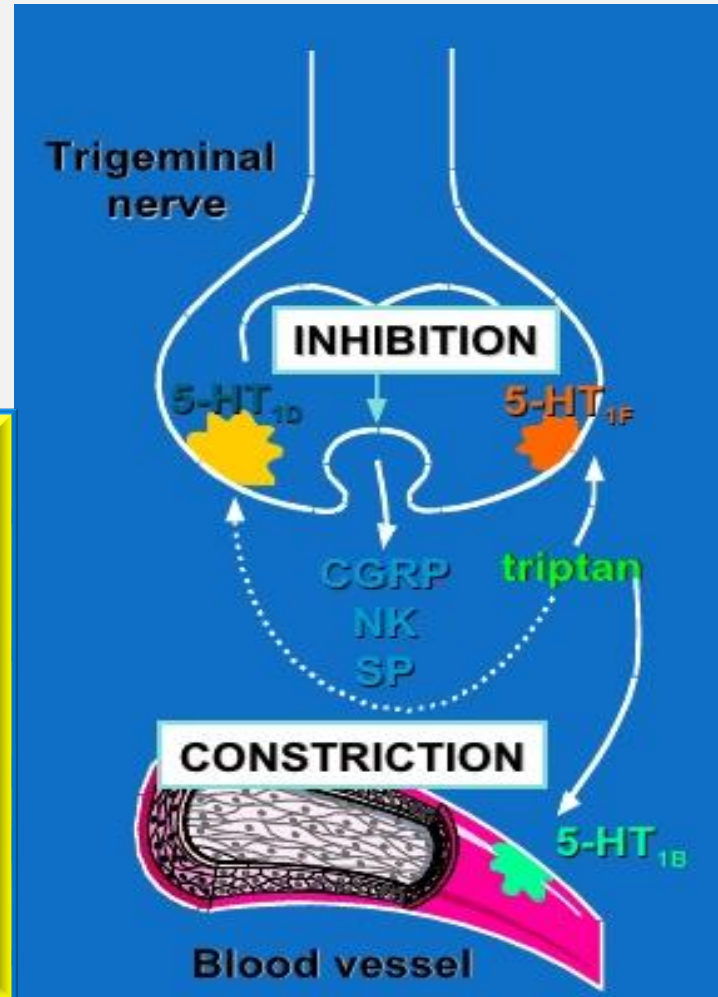


NAUSEA/VOMITING

SUMATRIPTAN

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

It binds to 5HT_{1B}, 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 (**cypheptadine**, 5HT₂ antagonist) could be administered to control diarrhea, flushing & malabsorption.

