

AUTACOIDS

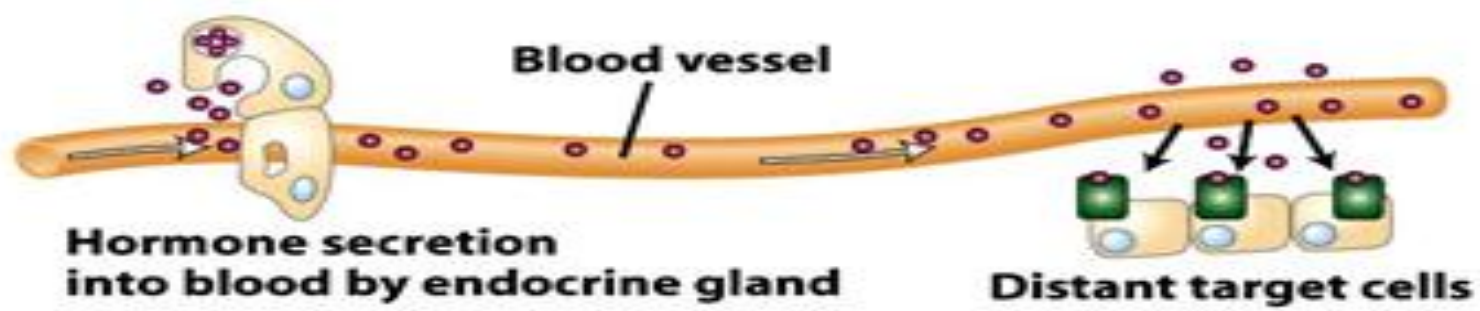
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They include:

Aminoacid derivatives

- Histamine
- Serotonin

Endocrine signaling



Hormone secretion into blood by endocrine gland

Distant target cells

Fatty acid derivatives

Gas

NO

NO

ILOS

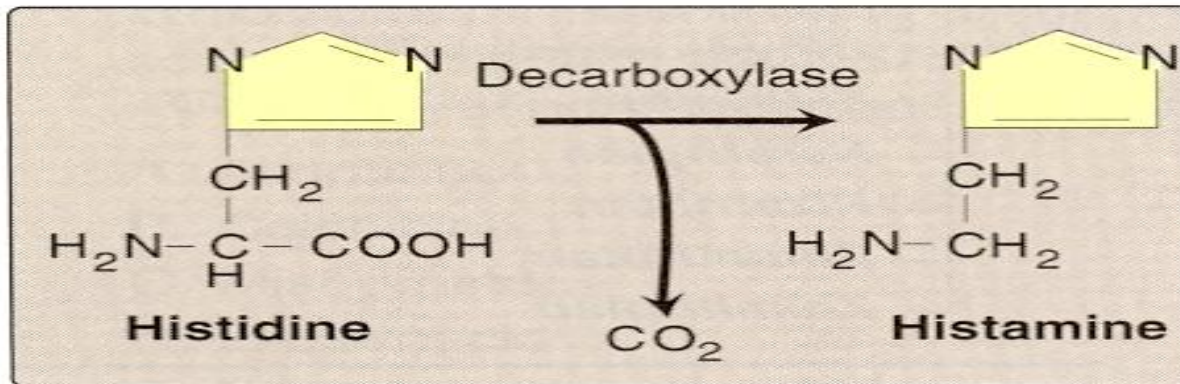
To describe the synthesis, receptors and functions of histamine, eicosanoids, nitric oxide, angiotensin, kinins & 5-HT

To study the agents which enhance or block their effects

HISTAMINE

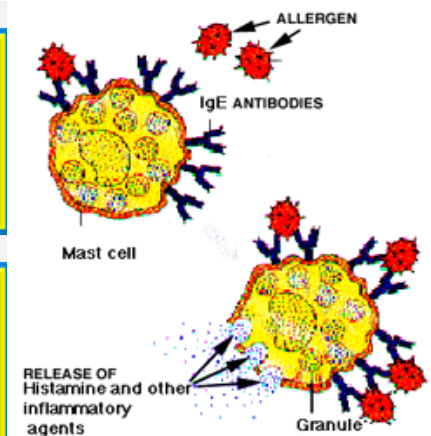
02

Synthesis:- from L- histidine



Stored in mast cells, basophils, lung, intestinal mucosa

Release:- during allergic reaction, inflammatory reaction

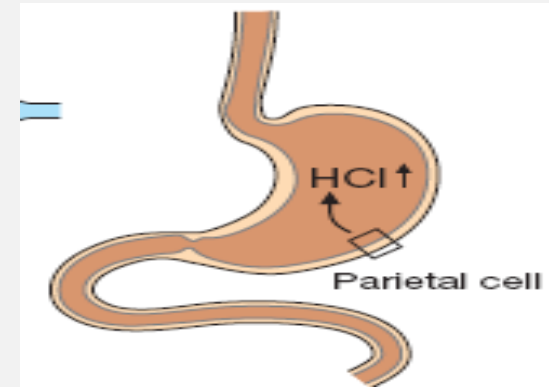


HISTAMINE RECEPTORS

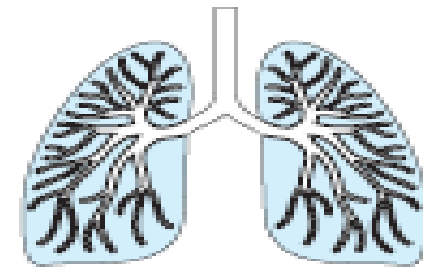
03

Receptor Type	Major Tissue Locations	Major Biologic Effects
H₁	smooth muscle, endothelial cells, brain	acute allergic responses
H₂	gastric parietal cells, Cardiac muscle, mast cells, brain	secretion of gastric acid
H₃	central nervous system	neurotransmission
H₄	mast cells, eosinophils, T cells	regulating immune responses

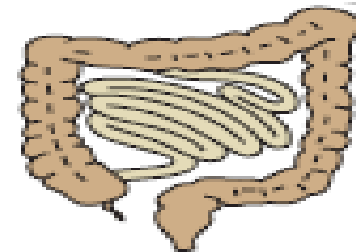
Histamine stimulates gastric acid secretion, through H₂- receptors



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



Bronchoconstriction



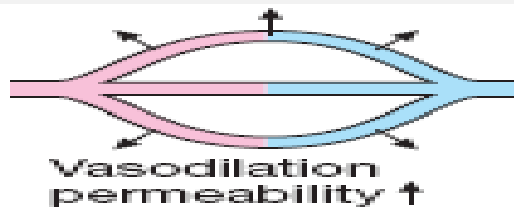
Bowel peristalsis ↑

Increases bowel peristalsis

Slow IV or SC injection causes flushing of skin, raise temperature, increase blood flow to the periphery, increase 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 H₁ RECEPTOR BLOCKERS

First generation

Diphenhydramine ,cyclizine ,promethazine

Second generation

Loratidine, Citrizine, fexofenadine

HISTAMINE H₁ RECEPTOR BLOCKERS

07

First generation

Has a Sedating effect

Clinical uses

⊕ Allergic rhinitis

⊕ Urticaria

⊕ Insomnia

⊕ Motion sickness



Urticaria



HISTAMINE H₁ RECEPTOR BLOCKERS

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Second generation

+ Non-sedating effect

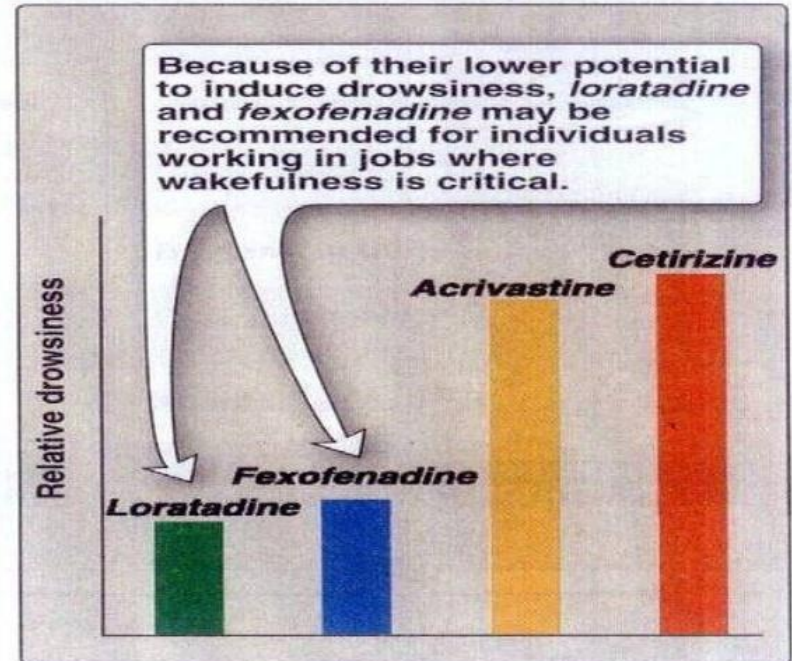
Clinical uses

Allergic conditions such as:-

Allergic rhinitis

Conjunctivitis

Urticaria



H₂- RECEPTOR BLOCKERS

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Cimetidine, ranitidine, famotidine

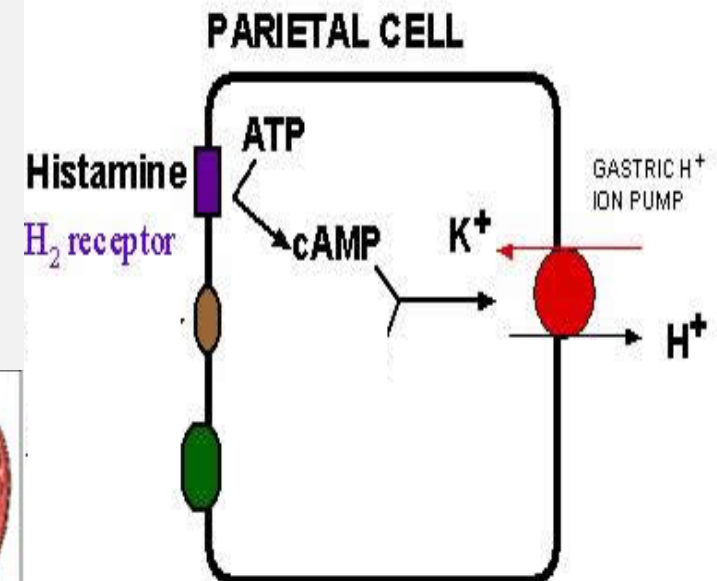
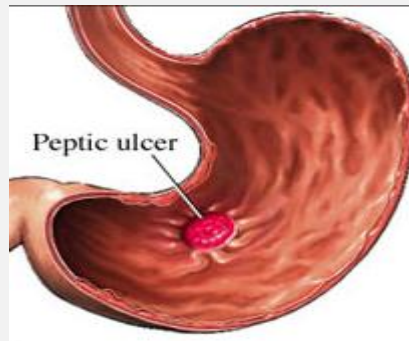
Histamine plays an important role in the formation and secretion of HCl by the activity of H₂ receptors

Blockers of H₂ receptors inhibit gastric acid secretion

Used for the treatment of:

Gastritis

Peptic ulcers



H₃- RECEPTOR BLOCKERS

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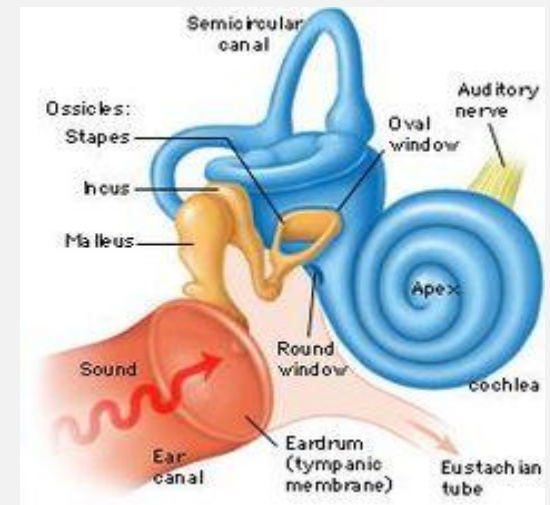
BETAHISTINE

It produces dilatation of blood vessels in inner ear

Used in treatment of:-

Vertigo and balance disturbances

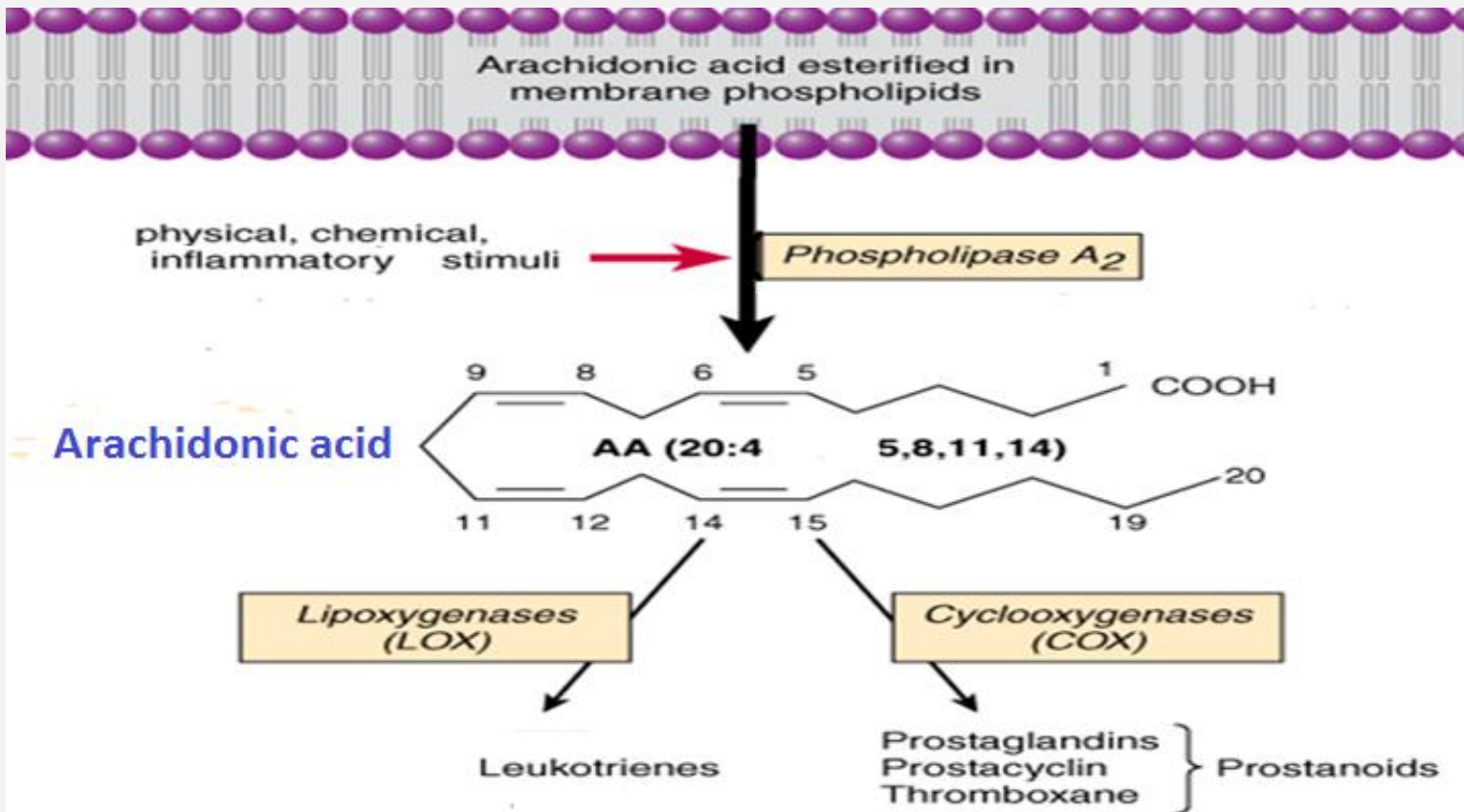
May produce headache and insomnia

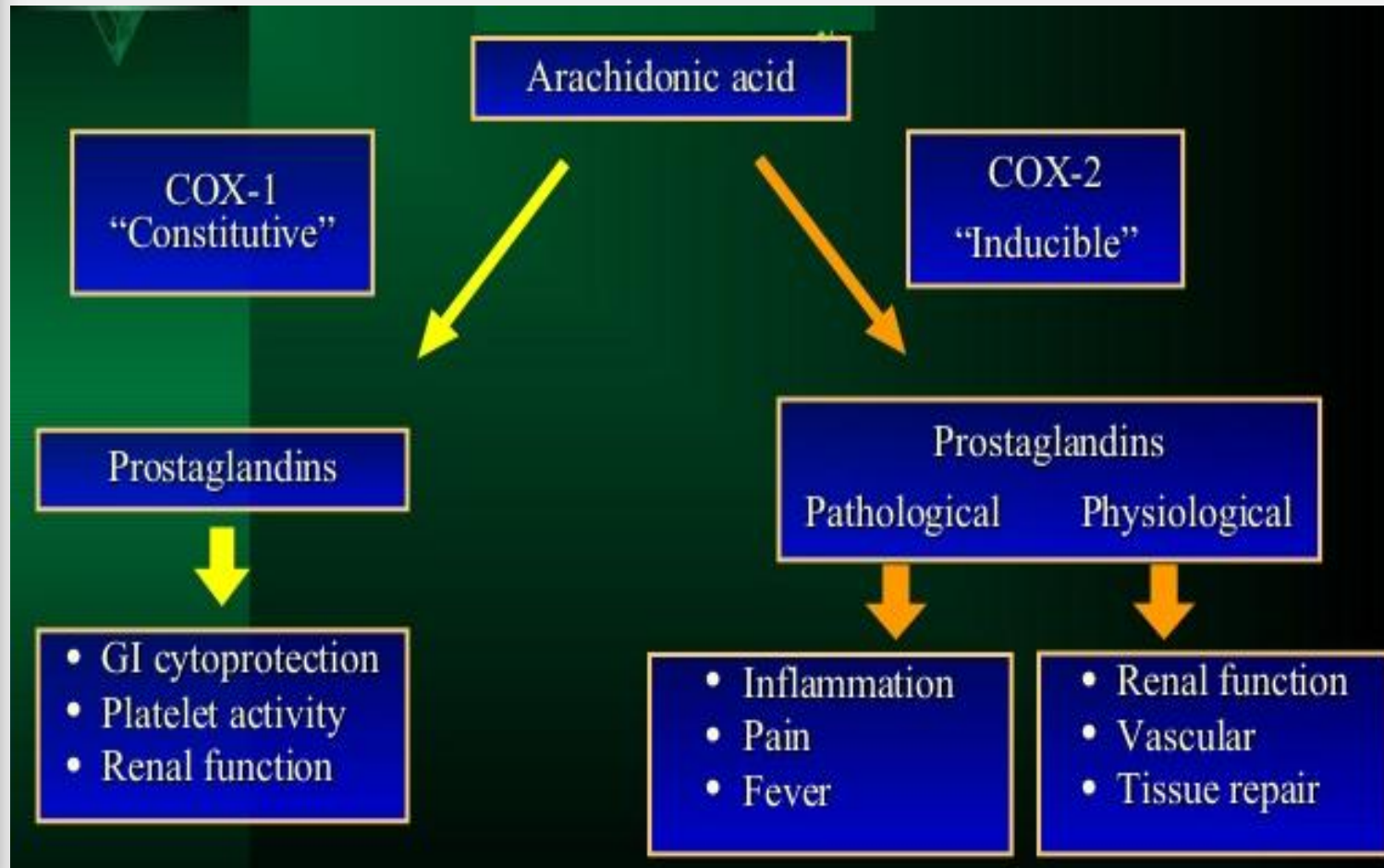


EICOSANOIDS

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SYNTHESIS





ACTIONS OF PROSTAGLANDINS

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They are proinflammatory

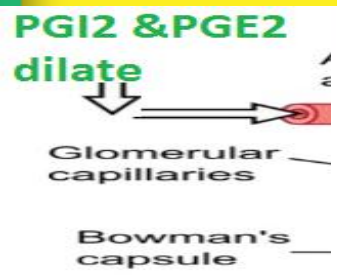
Cause vasodilatation of vascular smooth muscle

Inhibition of platelets aggregation/ increase platelet aggregation

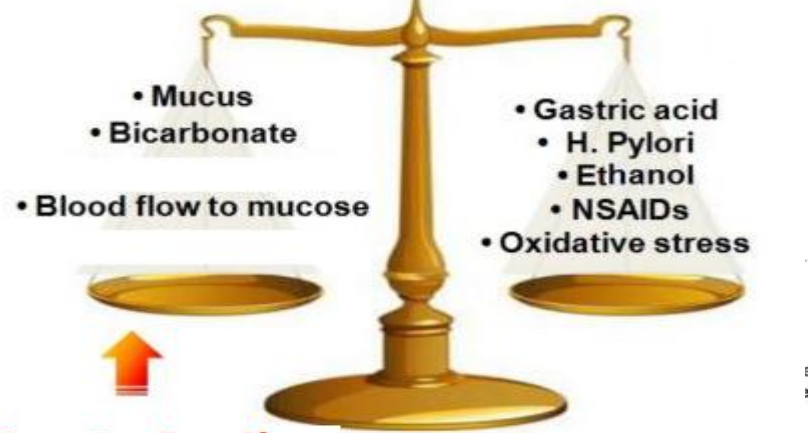
Sensitize neurons to cause pain

Induce labor

ACTIONS OF PROSTAGLANDIN



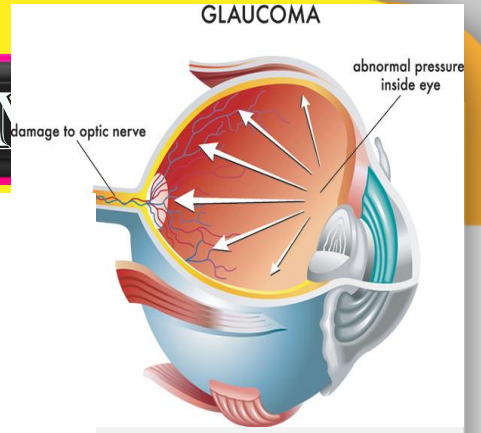
Protective Factors **Aggressive Factors**



Prostaglandins



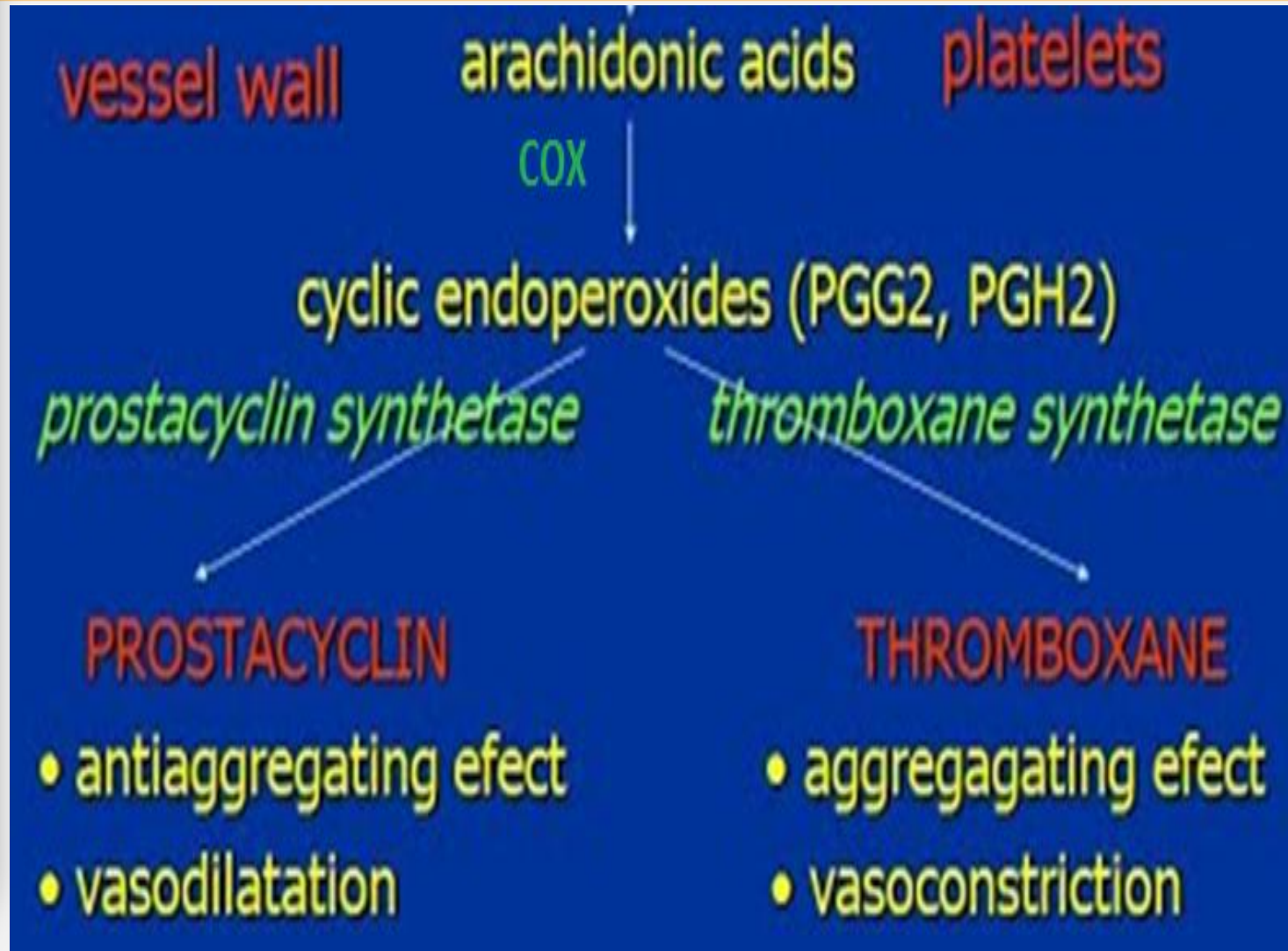
Healthy mucosa



Acts on kidney filtration

ular

Acts on parietal cells of stomach to protect gastric mucosa



CLINICAL USES OF PGS ANALOGS

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Carboprost

Induce abortion in first trimester

Latanoprost

Glaucoma

Misoprostol

Peptic ulcer

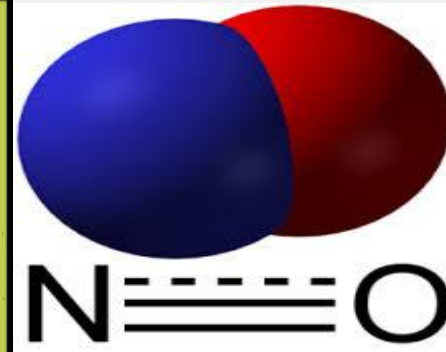
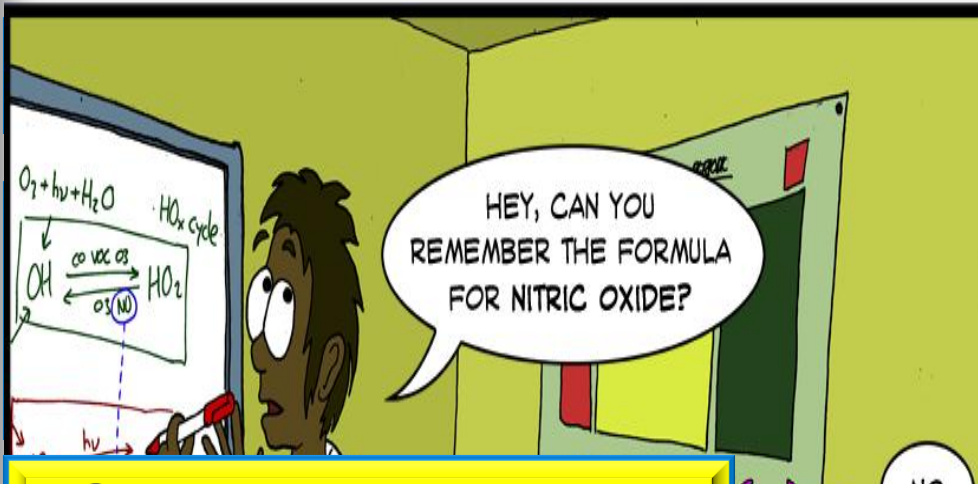
Alprostadil

Erectile dysfunction

Zileuton (lipoxygenase inhibitor)

Zafirlukast (leukotriene receptor blocker)

Bronchial asthma



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

NOS Stimulants & Inhibitors

Activators
acetylcholine
serotonin,
bradykinin
histamine

Inhibitor
hemoglobin

lukesurl.com

the enzyme nitric oxide synthase

ISOFORMS OF NOS

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**Neuronal NOS
(nNOS)**

- Neurons
- Skeletal muscle

**Endothelial NOS
(eNOS)**

- Endothelium
- Cardiac myocytes
- Osteoblasts
- Osteoclasts

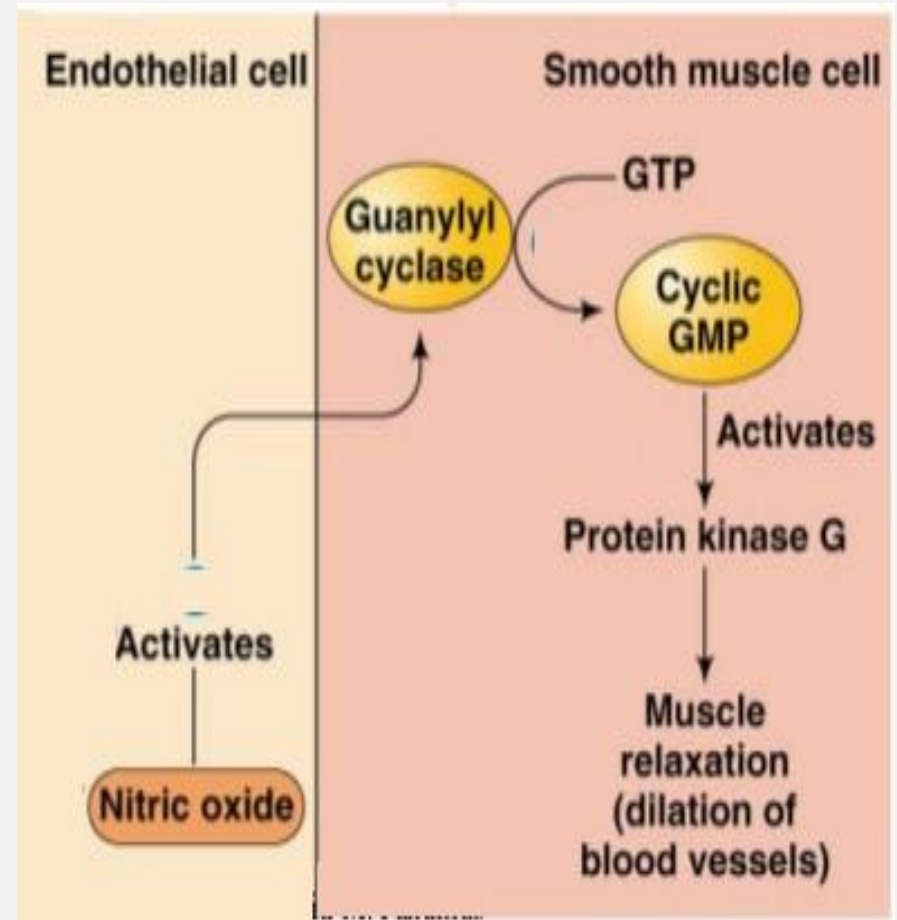
**Inducible NOS
(iNOS)**

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

**Constitutive Forms
(Physiological)**

Pathological

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



Inhibition of platelet and monocyte adhesion and aggregation

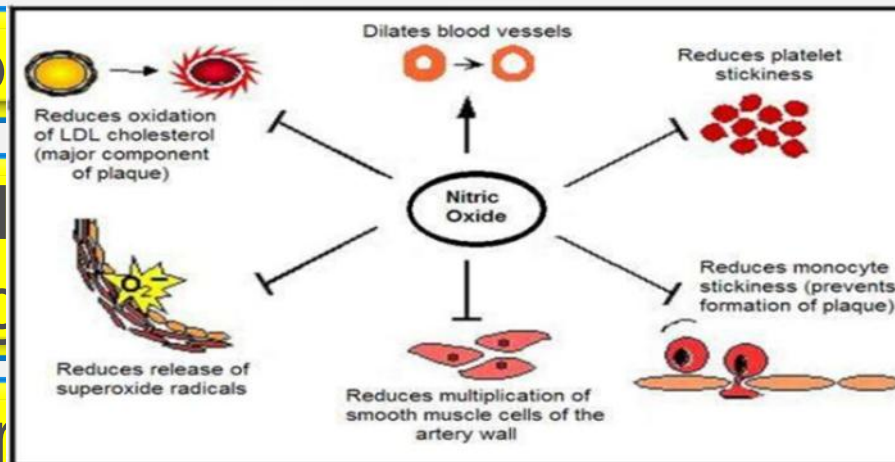
Inhibition of smooth muscle proliferation;

Protection against atherogenesis

Synap

Host of
pathog

Cytopr



and CNS

s on

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

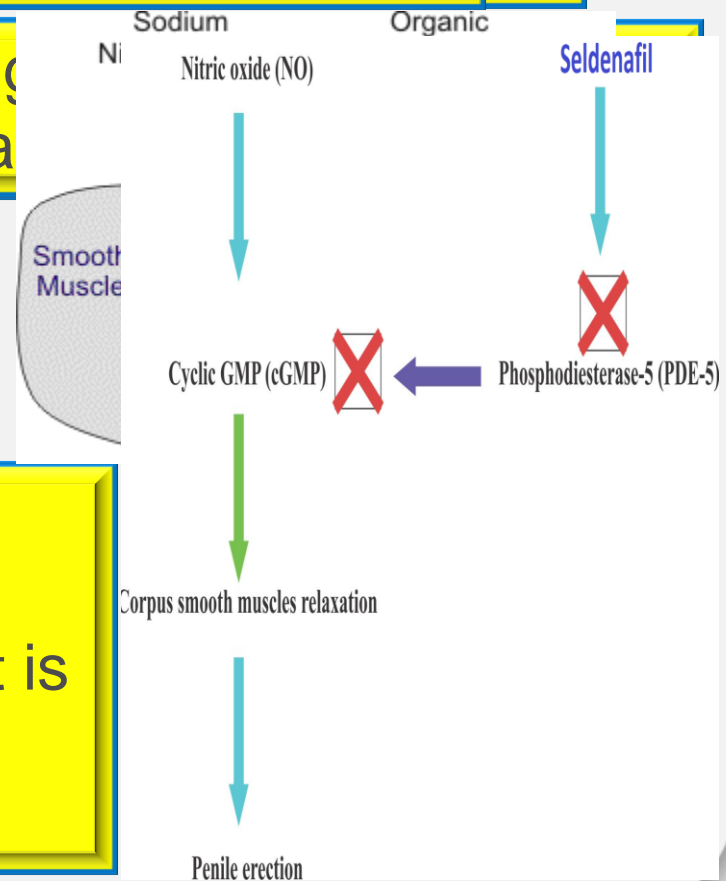
NO IN THERAPEUTICS

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

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

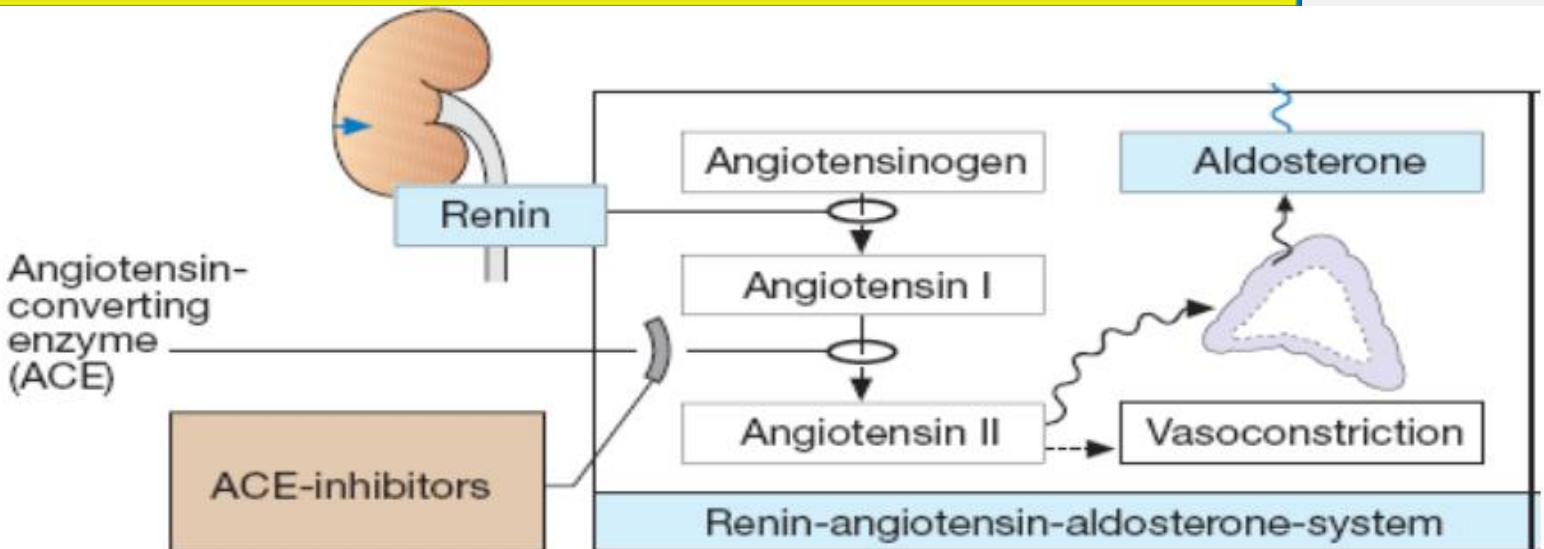
Sildenafil potentiates the action of NO on corpora cavernosa smooth muscle. It is used to treat erectile dysfunction



Biosynthesis

Renin released from the kidney converts angiotensinogen to Ag I

ACE converts Ag I to Ag II



ACTIONS OF ANGIOTENSIN II

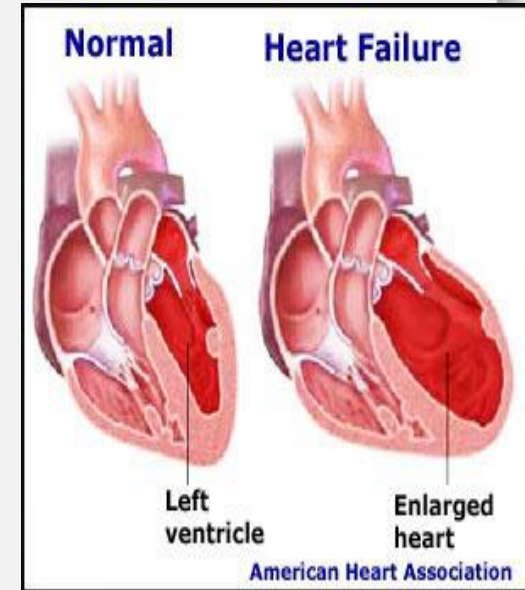
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Promotes vasoconstriction directly or indirectly by releasing NA & AD

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)



ACE inhibitors:
captopril, enalapril

Angiotensin
receptor blockers
(ARBs): losartan,
valsartan



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

ACE INHIBITORS

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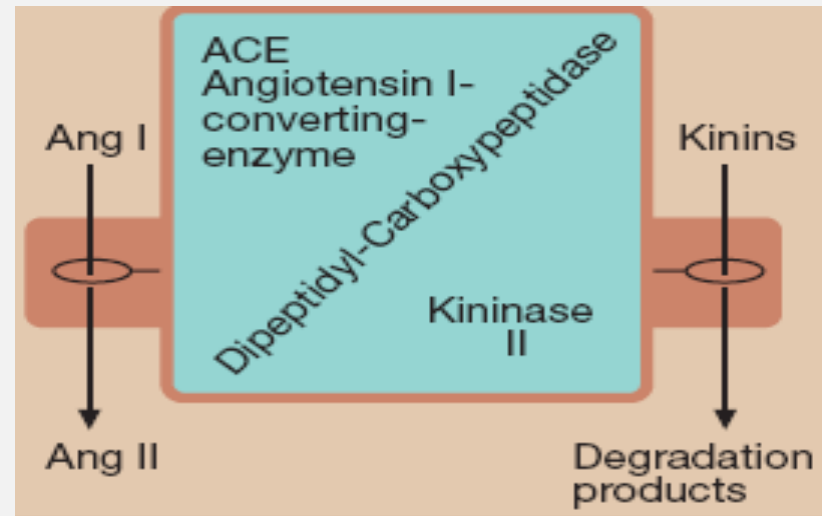
Cause a fall in blood pressure in hypertensive patients especially those with high rennin levels

CLINICAL USES

Hypertension

Cardiac failure

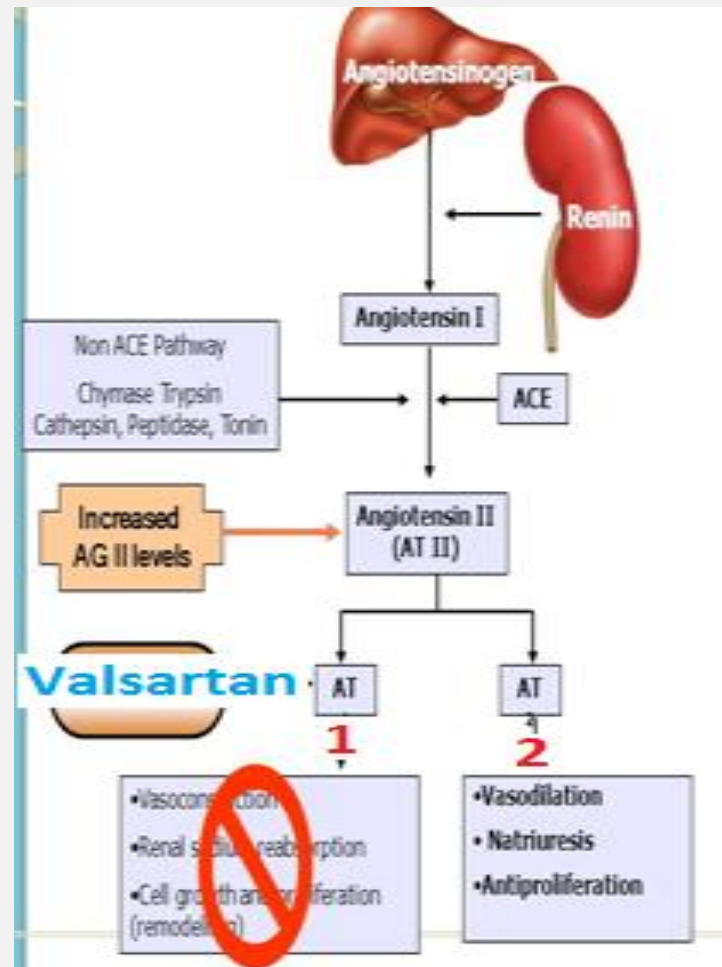
Following myocardial infarction



Angiotensin receptors
AT I & AT II

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

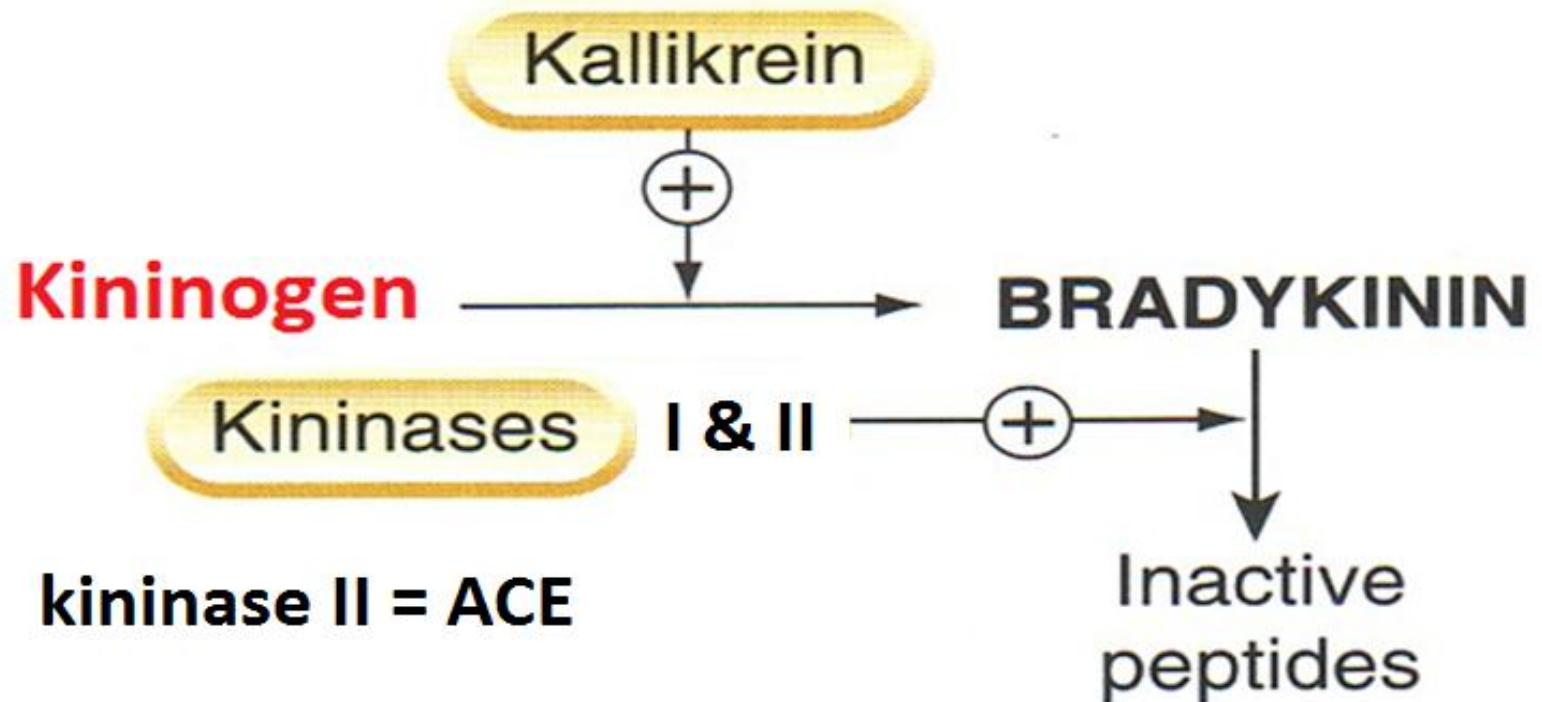


KININS

28

Are Bradykinin & kallidin

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



ACTIONS OF BRADYKININ

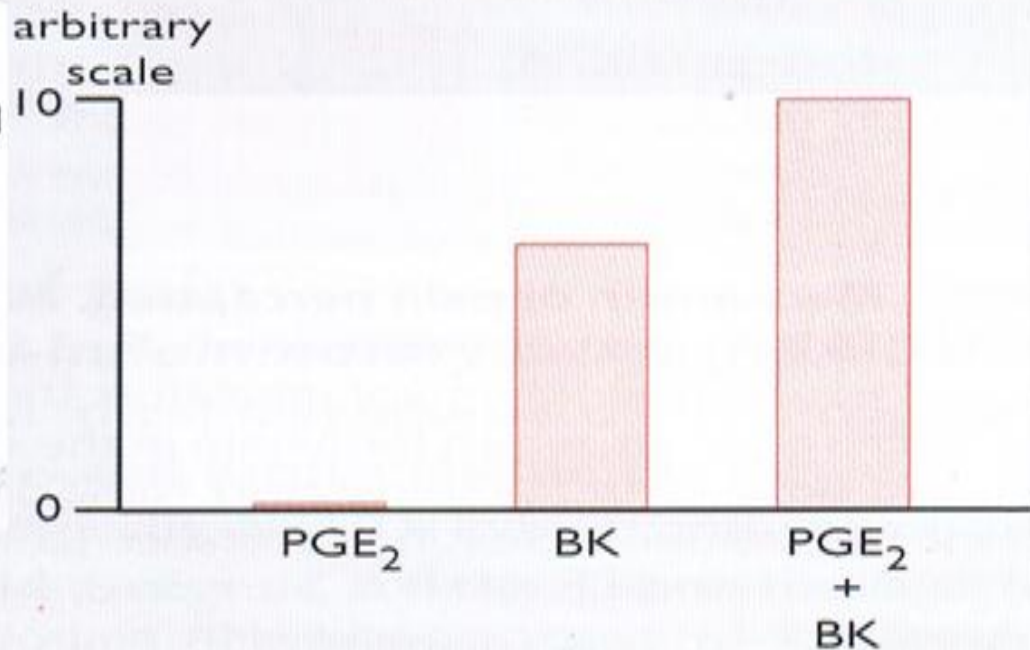
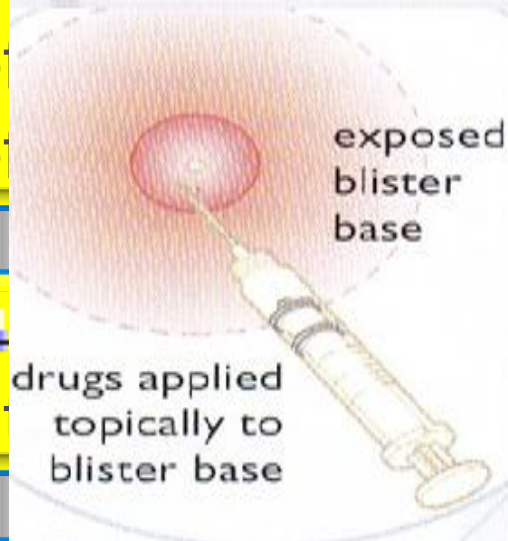
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Causes pain, this effect is potentiated by PG. Has a role in inflammation

If injected locally, it dilates arterioles & increases permeability

increases vascular permeability

drugs applied topically to blister base



Secretion in airways & GI

RECEPTORS & CLINICAL USES

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↓ Receptors B₁ & B₂

↓ B₁ inducible under condition of inflammation

↓ Low affinity to bradykinin

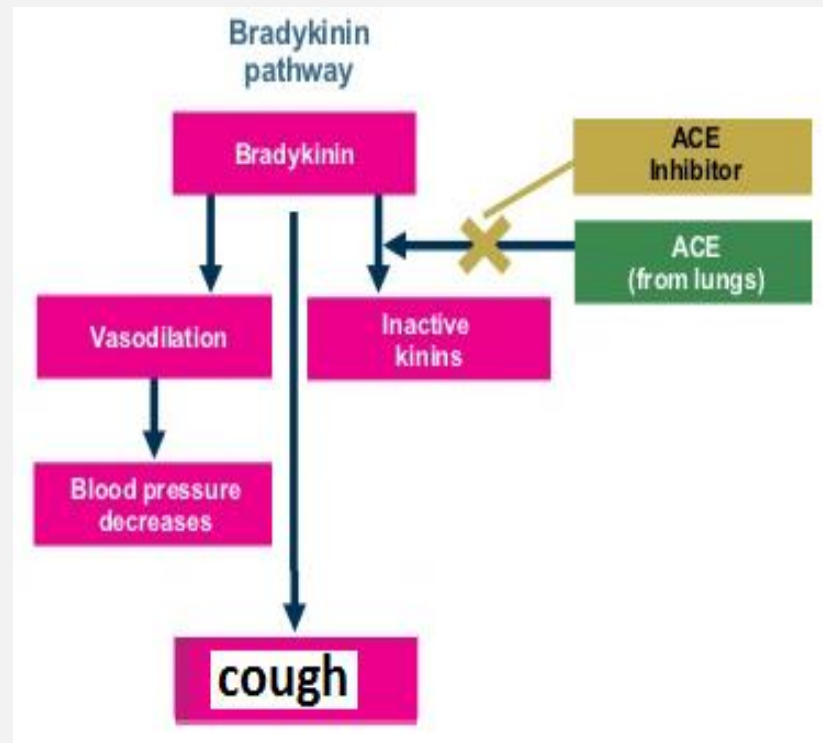
↓ B₁ receptor plays a significant role in inflammation & hyperalgesia

↓ B₂ constitutive

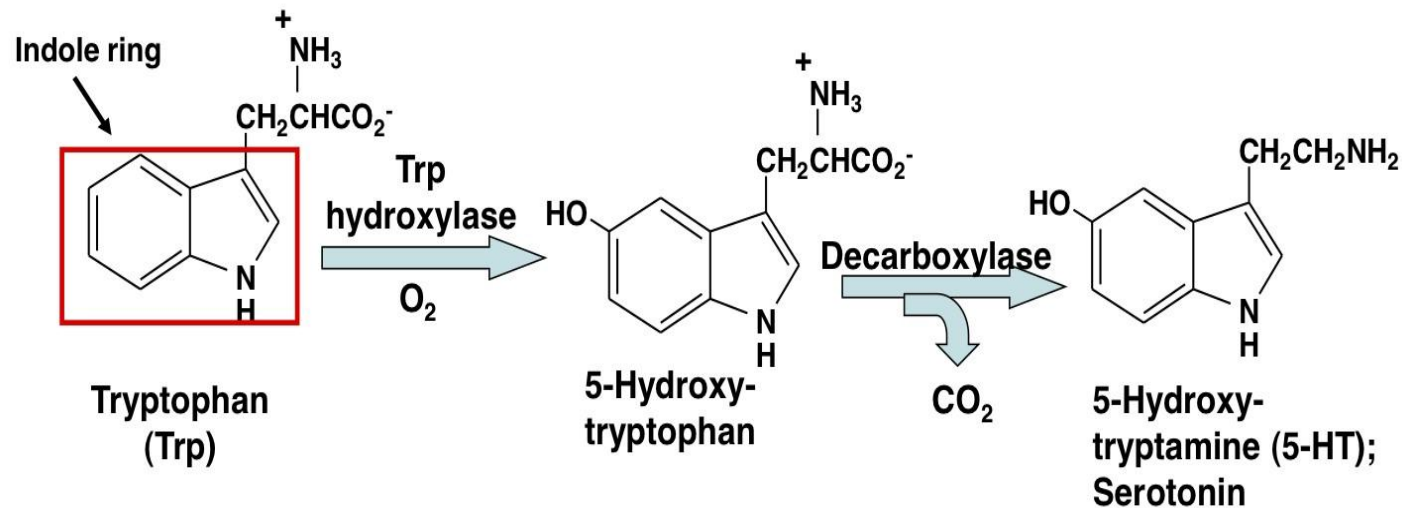
↓ High affinity to bradykinin & mediates the majority of its effects

⊕ No current use of bradykinin

⊕ Increased bradykinin is implicated in the therapeutic efficacy and cough produced by ACEIs



Serotonin is synthesized from the amino acid L-tryptophan

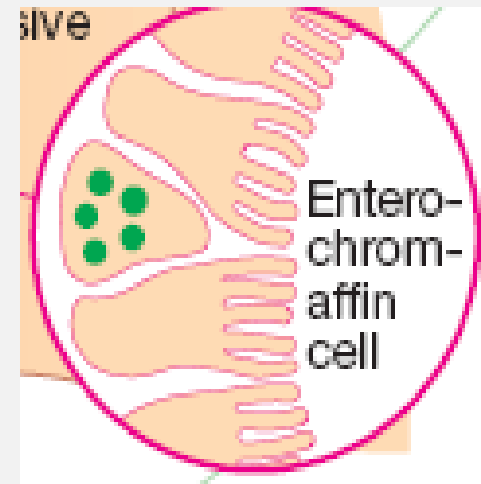


DISTRIBUTION

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

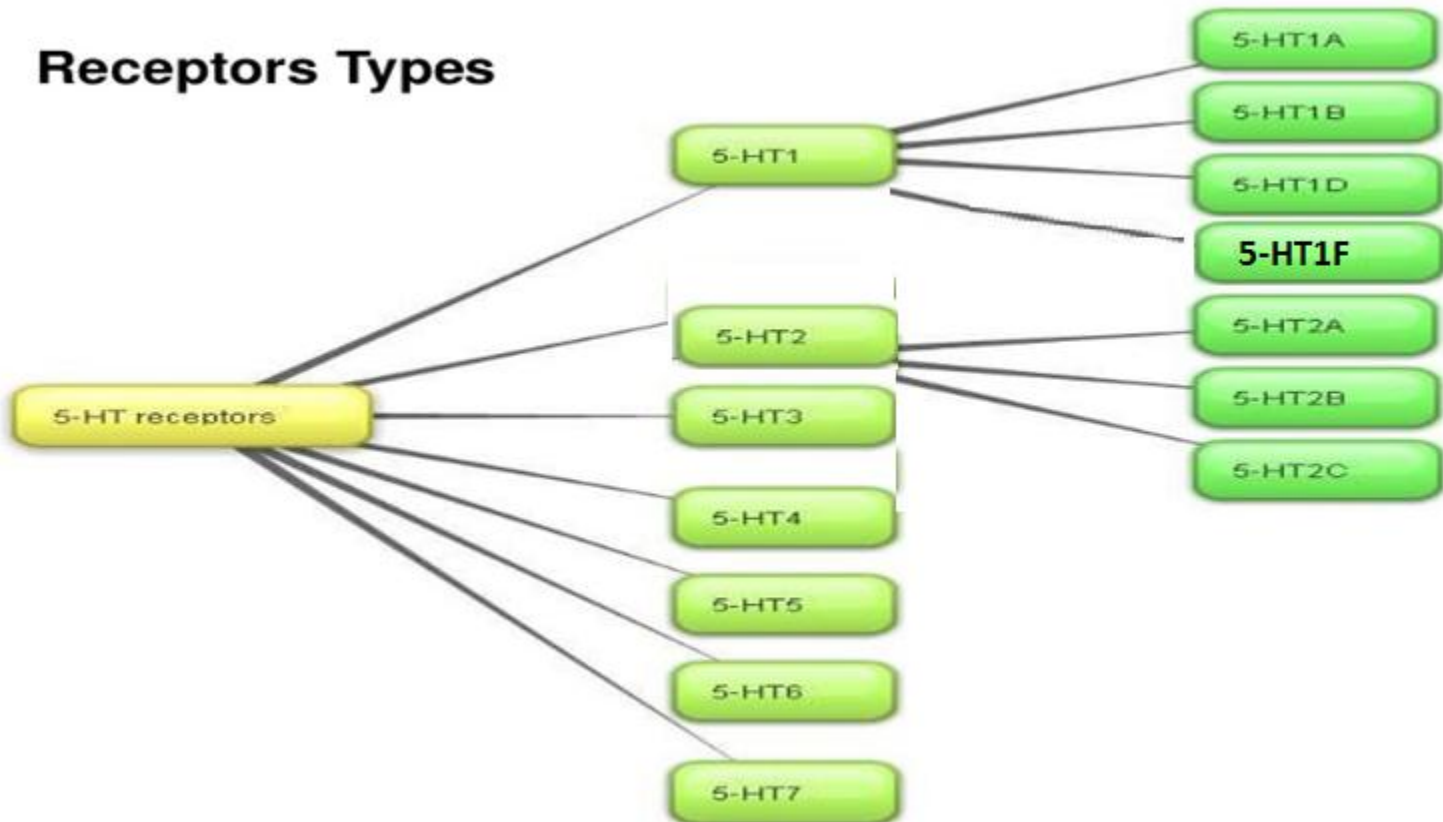
+2] Blood ,in platelets , released when aggregated , in sites of tissue damage

+3] CNS:-a neurotransmitter ,in midbrain



RECEPTORS

Receptors Types



ACTIONS OF 5-HT

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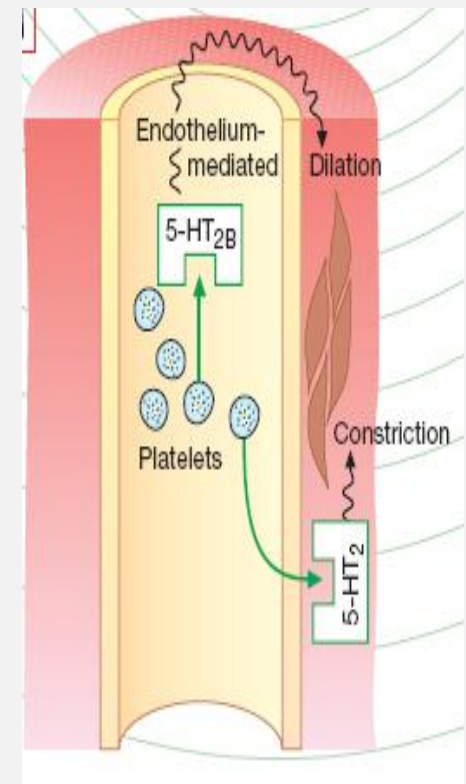
GIT:-5-HT increases motility

✚ 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



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

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

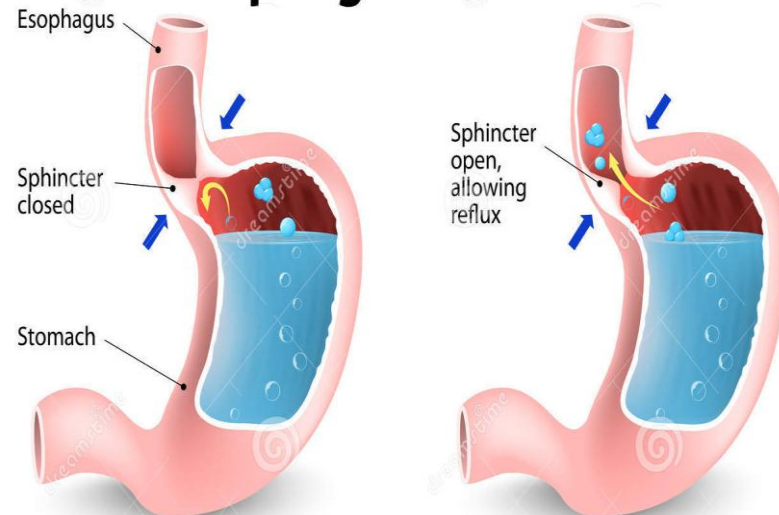
↓ **CNS;-** stimulates some neurons & inhibits others , inhibits release of other neurotransmitters

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



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

Gastroesophageal reflux disease



Healthy

GERD

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



CLINICAL CONDITIONS IN WHICH 5-HT IS IMPLICATED

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1-MIGRAINE



MIGRAINE HEADACHE

SCINTILLATING

PAIN IS OFTEN UNILATERAL AND THROBBLING IN QUALITY



PHOTOPHOBIA



MAY OCCUR WITH OR WITHOUT AURA



PHONOPHOBIA

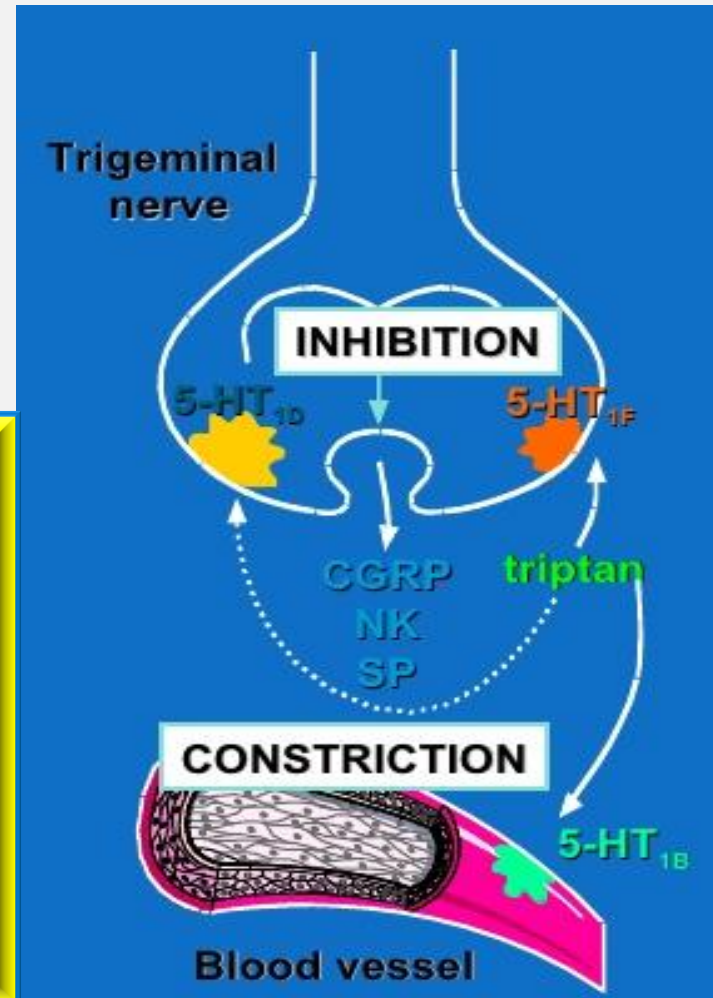
NAUSEA/VOMITING

SUMATRIPTAN

40

5-HT_{1D}, 1B & 1F-
receptor agonist ,
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

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↓ 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.

