Pharmacology
Team 437

تحت المراجعة
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Autocoids

Objectives:

- 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.

Titles Very important Terms Extra informations

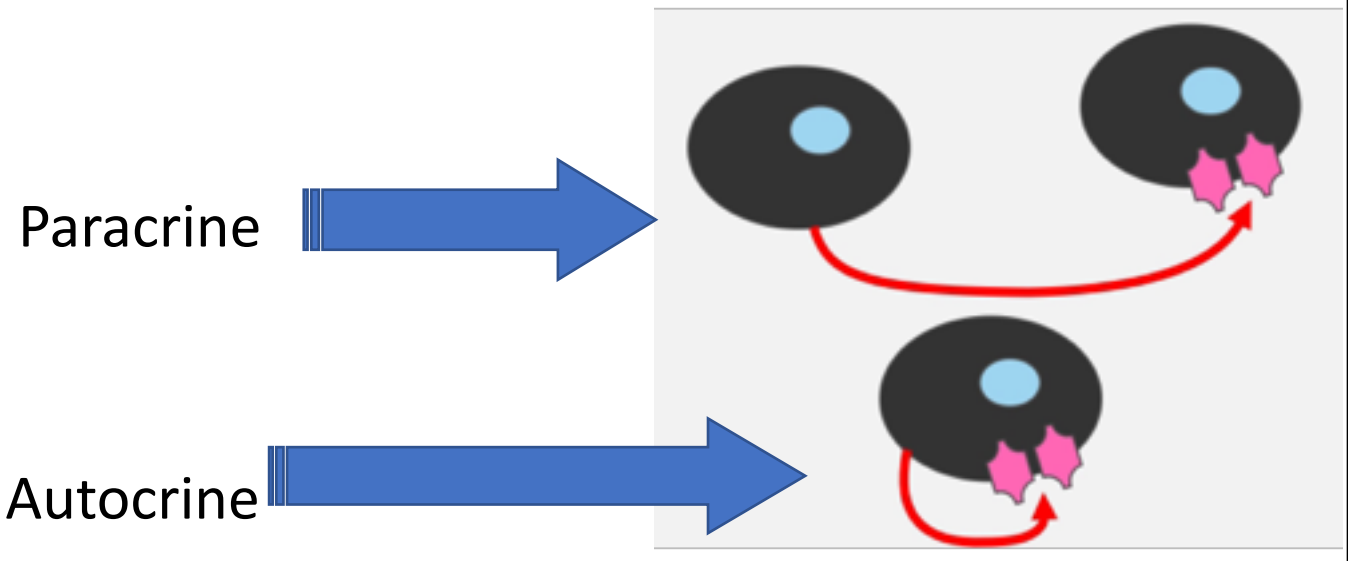
Success Doesn't Come To You, You Go To It!

Autocoids

Autacoids are biomaterial substances that Are synthesized and metabolized locally , they may effect each of :

1-glands
2-nerves
3-smooth muscles
4-platlets and other tissues

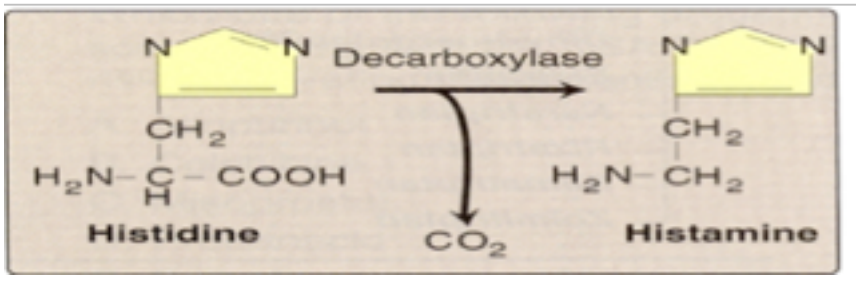
They either be autocrine or paracrine :



- the autacoids derivate from other substance :

Original	Derivatives
Amino acids	Histamine
	Serotonin
Endogenous peptide	Kinins
	Angiotensin
Fatty acids	Eicosanoid
Gas	nitrogen (NO)

-Histamine is synthesized from histidine



-histamine is stored in **mast cells & basophil** & **lungs**

There are 4 types of histamine receptors :

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

-Stimulation of H1 cause contraction of **smooth muscles** & **uterus** & **bronchioles &** increase **bowel peristalsis**

(انقباضات الأمعاء)

-stimulation of H2 cause secretion of **gastric acid** in stomach

Administration of histamine

Rapid IV	Slow IV & SC	Indermal injections
1- fall in blood pressure 2-increase CSF pressure 3-Headache	1-Increase temperature 2-Flushing skin Increase heart rate & blood flow	Itching

Types of H Blockers & examples & clinical uses

Type of H blocker	Examples	Clinical uses	
H1	1st G* 1-Diphenhydramine 2-promethazine	**1-Allergic rhinitis 2-urticarial** (joint effect of both of generations)	**1-insomnia 2-motion sickness**
	2ND G 1-citrizine 2-fexofenadine		Conjunctivitis
H2	Cimetidine	1-Gastritis 2-Peptic ulcer	
H3	Betahistine	Vertigo & balance disturbances	

* The major difference between 1st & 2nd generations is the first one cause sedating effect

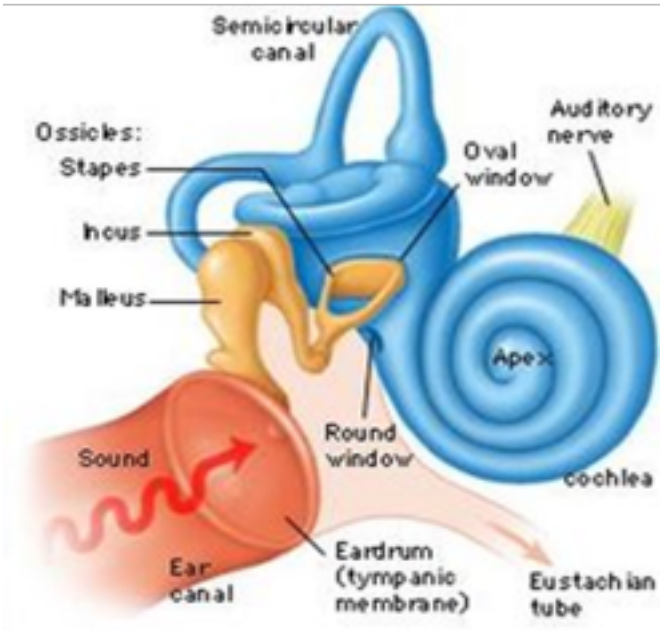
H3- receptor blockers

betahistine

It produces dilatation of blood vessels in inner ear

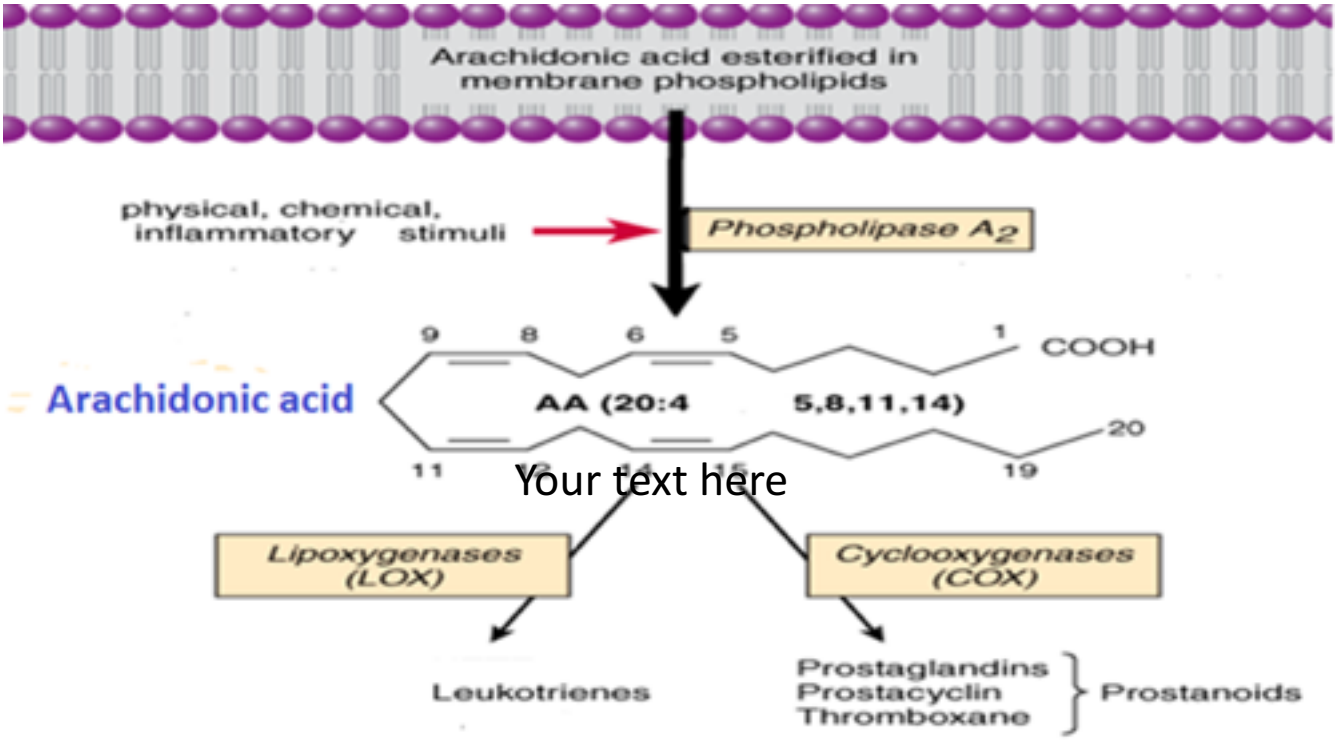
Used in treatment of:-

Vertigo and balance disturbances

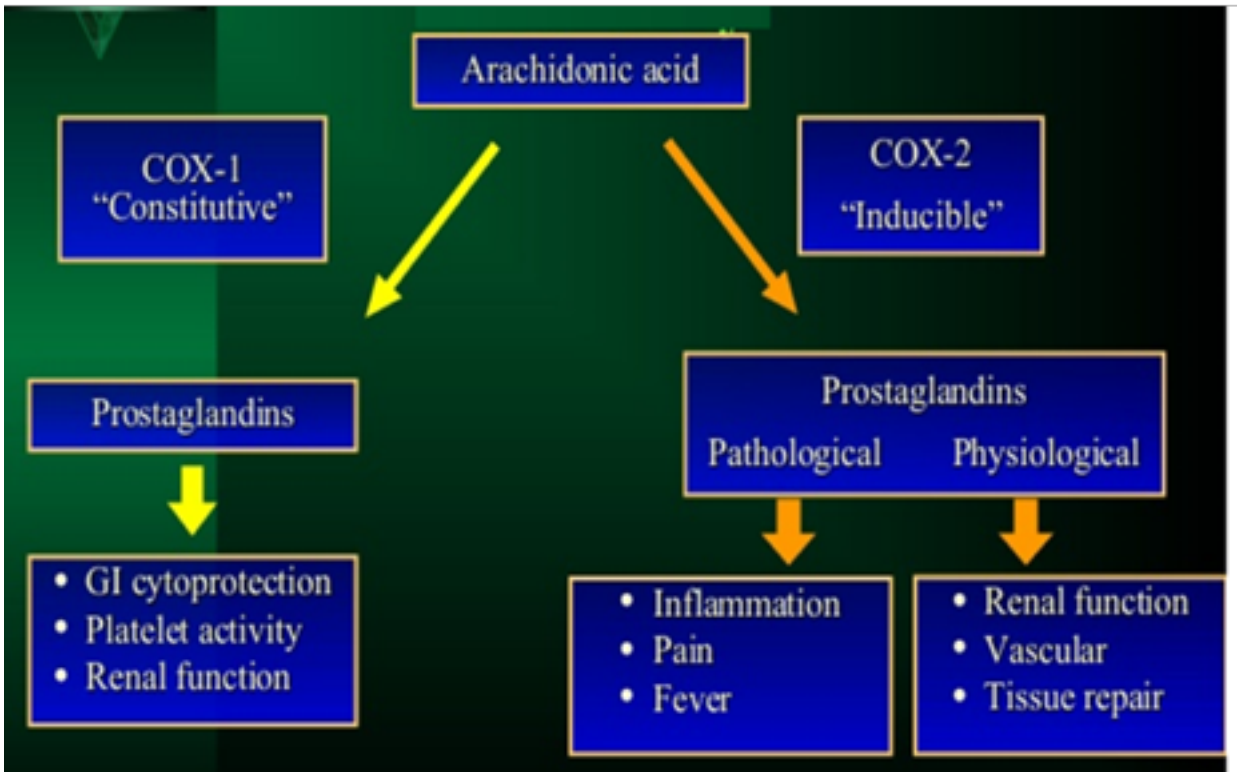


eicosanoids

synthesis



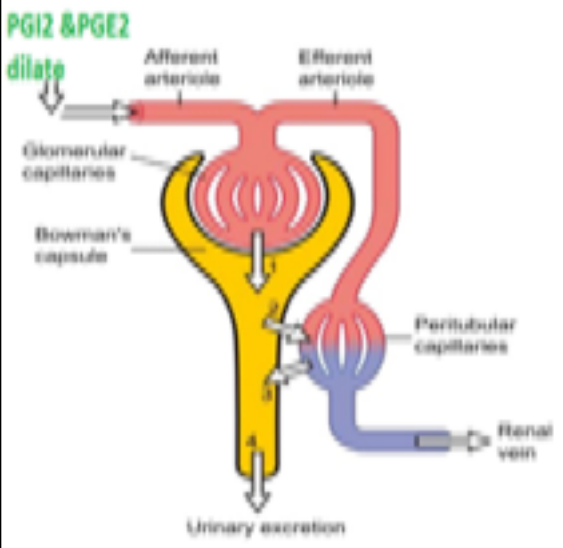
Cox Isozymes:-

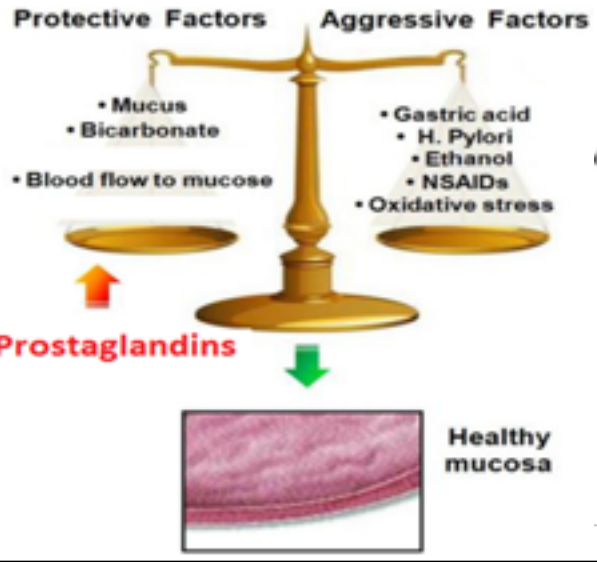


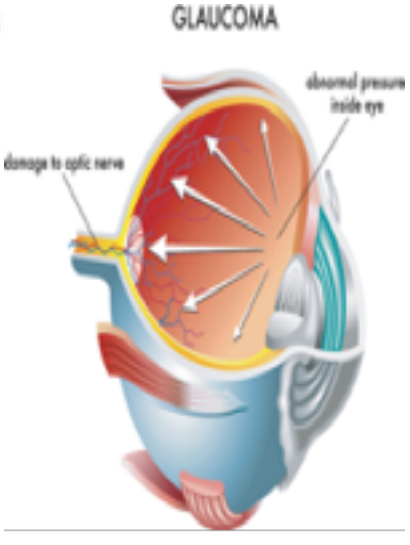
Actions of prostaglandins

Actions of prostaglandins

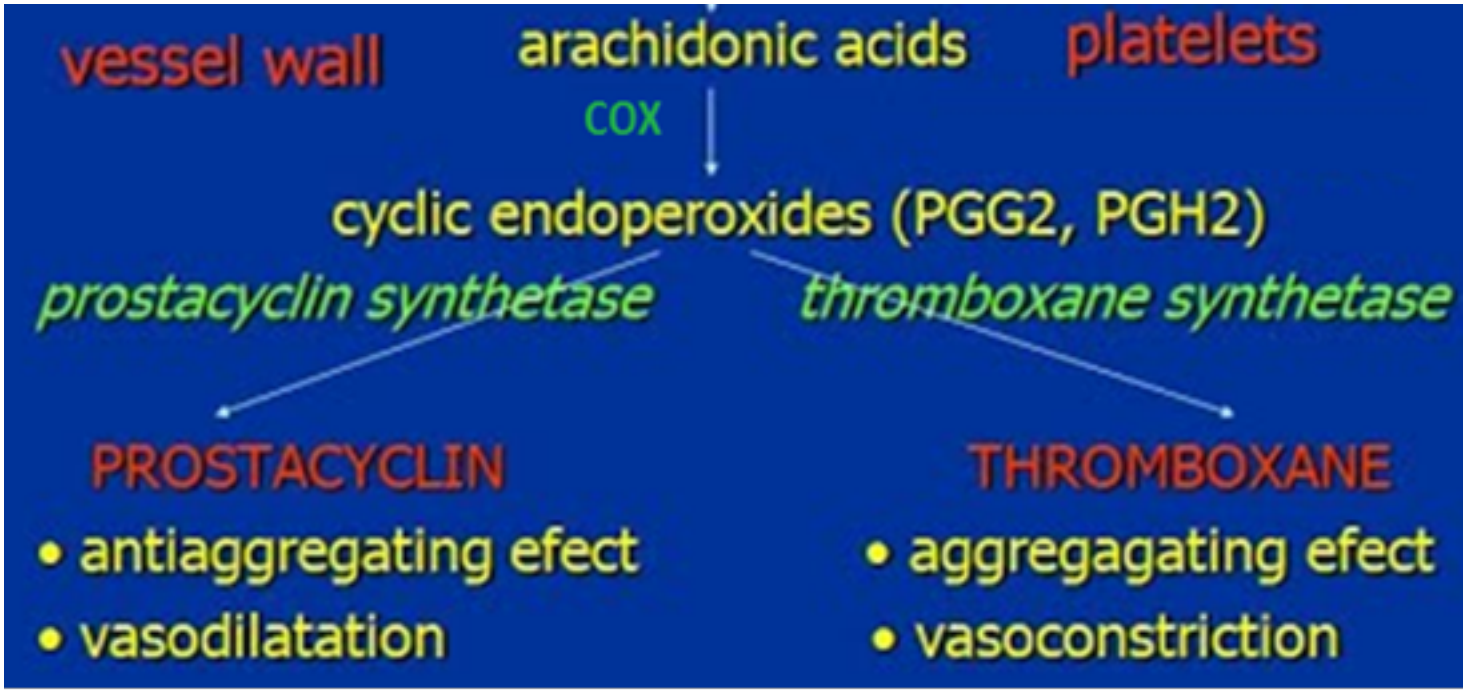
They are proinflammatory
Cause vasodilatation of vascular smooth muscle
Inhibition of platelets aggregation/ increase platelet aggregation
Sensitize neurons to cause pain
Induce labor
Decrease intraocular pressure
Acts on thermoregulatory center of Hypothalamus to ↑ body temperature
Acts on kidney to increase glomerular filtration
Acts on parietal cells of stomach to protect gastric mucosa







Prostacyclin VS. thromboxane



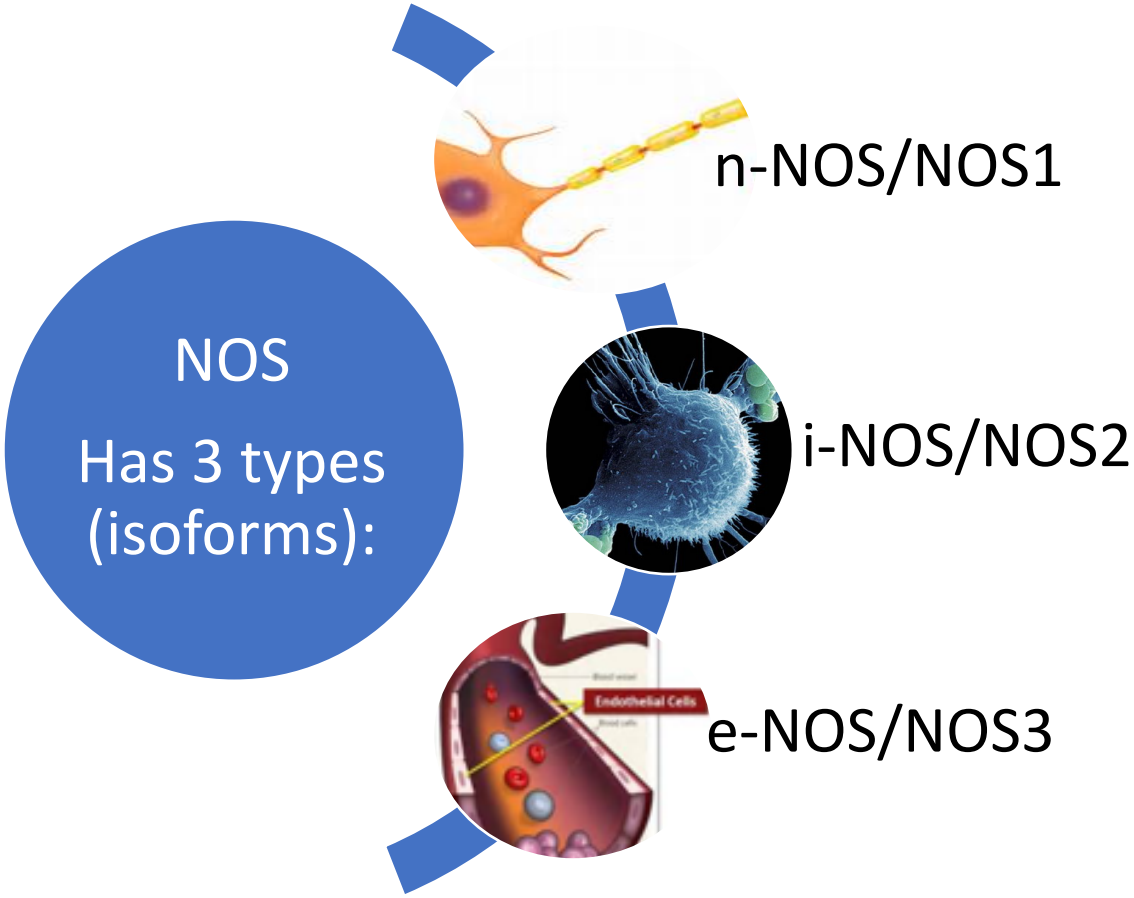
Clinical uses of PGs analogs

Drug	Use
Carboprost	Induce abortion in first trimester
Latanoprost	Glaucoma
Misoprostol	Peptic ulcer
Alprostadil	Erectile dysfunction
Zileuton	lipoxygenase inhibitor and Bronchial asthma
Zafirlukast (leukotreine receptor blocker)	Bronchial asthma

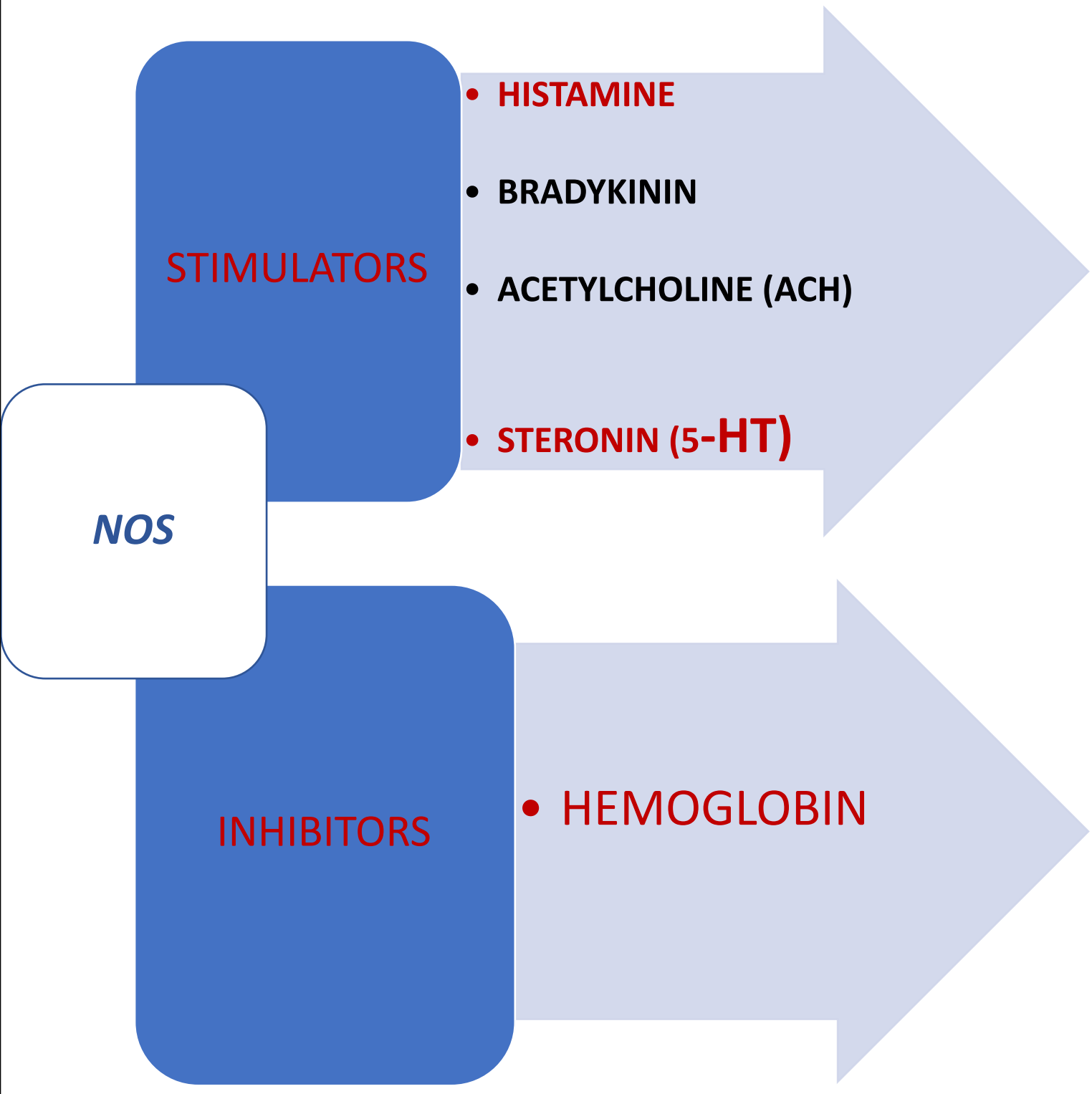
Nitric Oxide (NO)

Nitric oxide : is a highly diffusible stable gas .

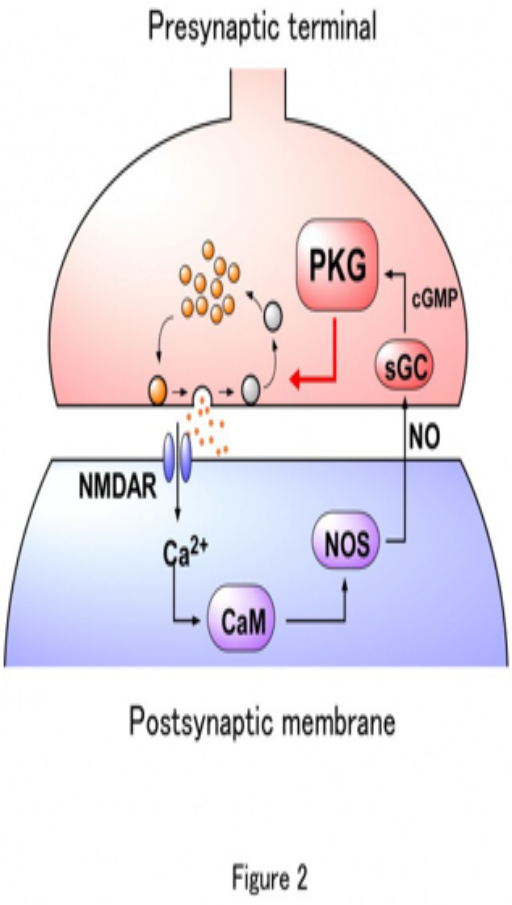
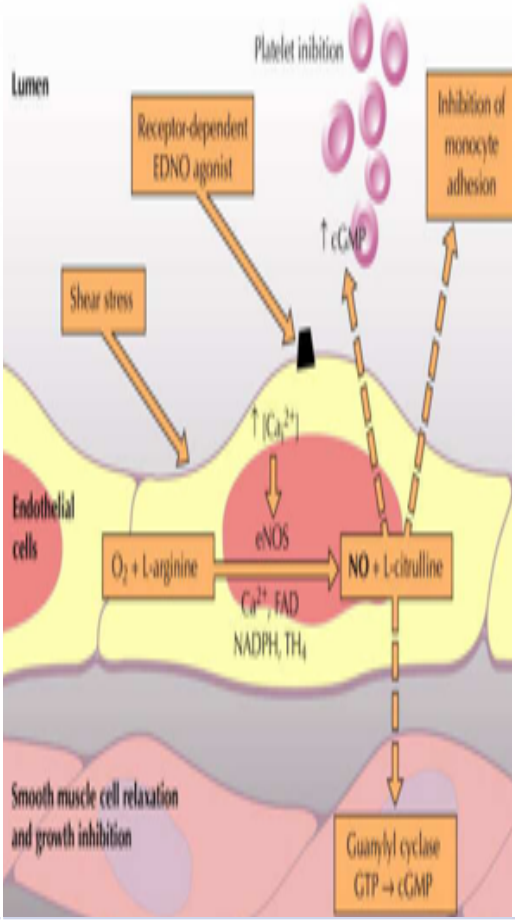
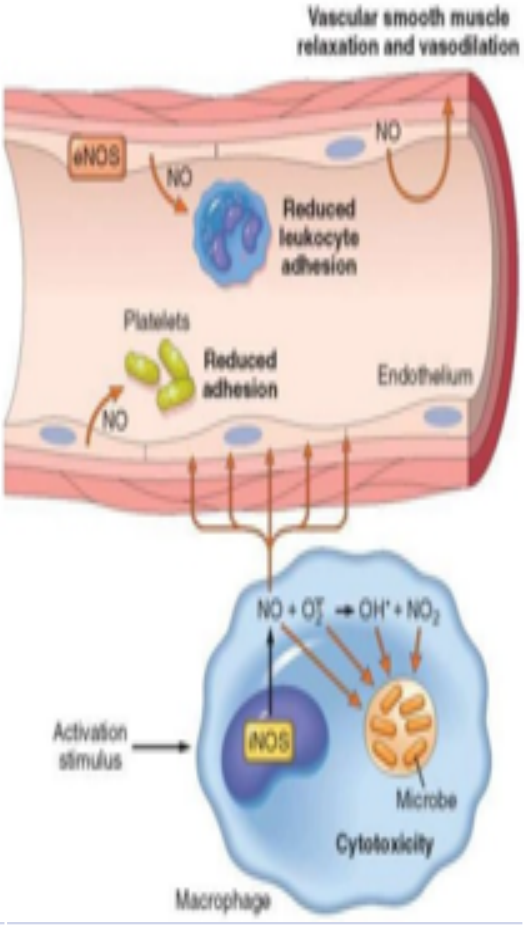
(NOS): Nitric oxide synthase



NOS STIMULATORS AND INHIBITORS



LOCATION OF NOS ISOFORMS

NOS Neuronal (nNOS)	Endothelial NOS (eNOS)	NOS Inducible (iNOS)
• Neurons • Skeletal muscle	• Endothelium • Cardiac myocytes • Osteoblasts • Osteoclasts	• Macrophages • Kupffer cells • Neutrophils • Fibroblasts • Vascular smooth
 Figure 2		
Physiological (constrict and dilate)		Pathological immune response

Action Of NO :

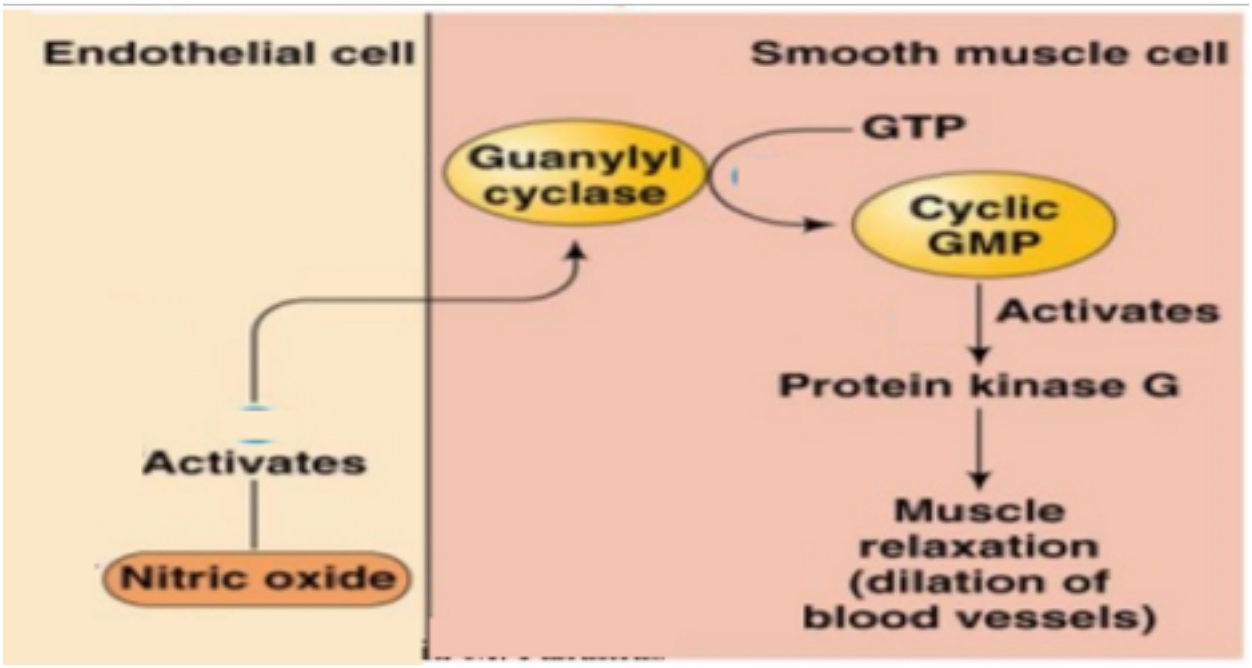
- Inhibition of platelet and monocyte adhesion and aggregation.(in blood coagulation cascade)
- Inhibition of smooth muscle proliferation.
- Inhibition of angiogenesis
- Protection against atherogenesis.
- Atherogenesis: formation of fatty plaques in the arteries.
- Synaptic effect in the peripheral and central nervous system.Potentiation of long-term memory.
- Host defense and cytotoxic effect on pathogens. Quantity of (NO) act as free radical.
- Cytoprotection
- Vasodilation: (paracrine)

Summary of NOS action :

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 mechanism of action :

- Activates guanylate cyclase
- increasing cGMP
- and thereby lowering [Ca2+]



(No) therapeutic uses :

- diabetes, hypertension & atherosclerosis causes reduction of Endothelial (NO) production.
- NO is used in critical care to treat pulmonary hypertension in neonates*1 .
- NO is used in patients with right ventricular failure secondary to pulmonary embolism
- NO donors*2 used e.g. in hypertension & angina pectoris.
- Sildenafil potentiates the action of NO on corpora cavernosa smooth muscle. used to treat erectile dysfunction

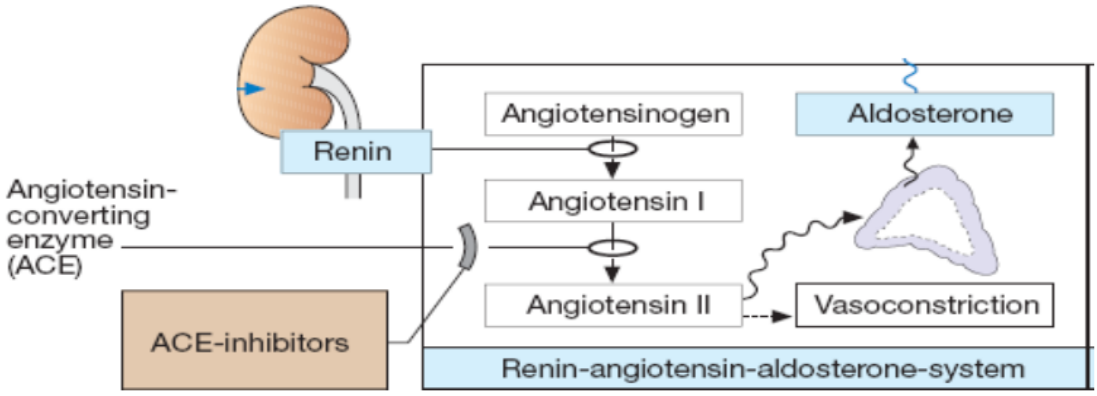
1=جنين غير مكتمل النمو*

2=Drugs that Produce NO*

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

is a peptide hormone that causes vasoconstriction and a subsequent increase in blood pressure. It is part of the reninangiotensin system, which is a major target for drugs that lower blood pressure. Angiotensin also stimulates the release of aldosterone, another hormone, from the adrenal cortex.

Angiotensin inhibitors "ACE"	**Angiotensin receptor blockers "ARBs"**
Those are captopril and enalapril.	Those are Isoartan and valsartan.

USEFUL VIDEO:Renin Angiotensin Aldosterone System(Click here)

Video:Renin-Angiotensin-Aldosterone System

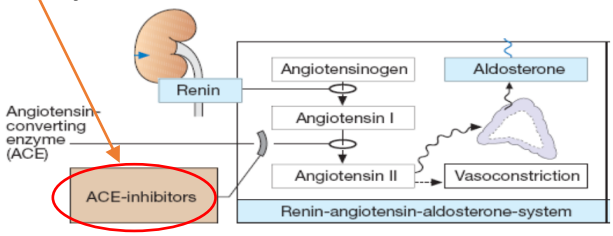
Angiotensin inhibitors "ACE"

Those inhibitors cause a fall in the blood pressure in hypertensive patients especially those with high rennin levels.

Rennin is a hormone. Renin's primary function is therefore to eventually cause an increase in blood pressure, leading to restoration of perfusion pressure in the kidneys. Renin is secreted from juxtaglomerular kidney cells, which sense changes in renal perfusion pressure, via stretch receptors in the vascular walls.

Clinical uses of Angiotensin inhibitors "ACE"

- hypertension
- cardiac failure
- myocardial infarction



Angiotensin receptor blockers

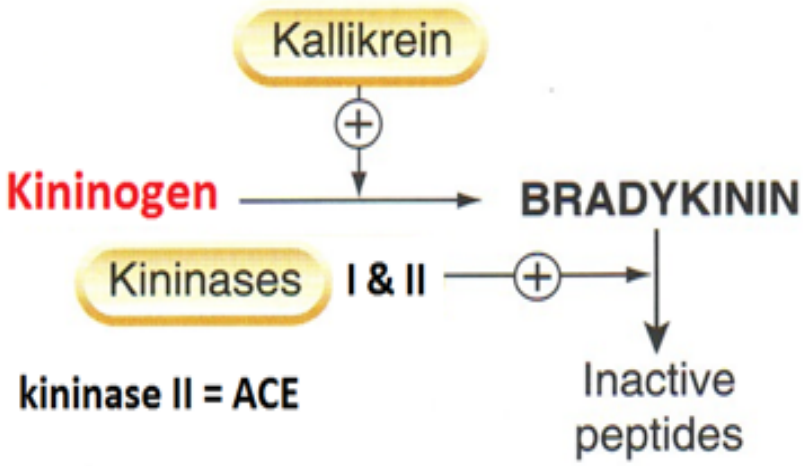
- Angiotensin receptors AT I & AT II
- AT 1 receptors predominate in vascular smooth muscle, mediate most of the known actions of Ang, coupled to G proteins & DAG
- Similar uses to ACEI

RAAS =Renin angiotensin-aldosterone System(للفهم)
How is RAAS activated? By binding of the active form Ag2 with AT1 receptor that leads to Aldosterone secretion So Angiotensin is a hormone that stimulates Aldosterone secretion in the kidney As a result, the Sympathetic Nervous System is stimulated and following actions will take place

Kinins

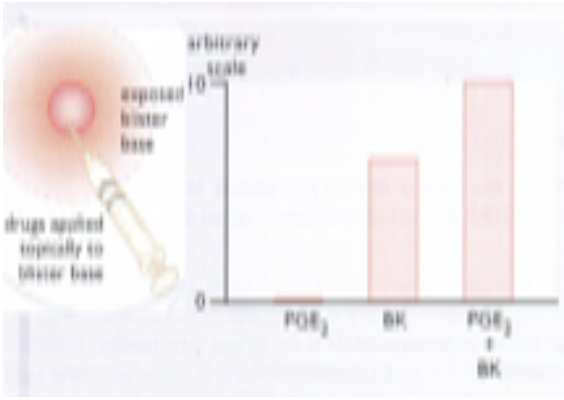
Are Bradykinin & kallidin Bradykinin is formed by proteolytic cleavage of circulating proteins (kininogens)

Bradykinin is a vasodilator



Actions of bradykinin:

- Potent vasodilator , reduces blood pressure
- Causes pain, this effect is potentiated by prostaglandins. Has a role in inflammation
- If injected locally it dilates arterioles [→generation of PGI release of NO] and increases permeability of post capillary venules
- Constricts most smooth muscles , intestine , uterus, bronchiole, contraction is slow and last long
- Stimulation of epithelial ion transport & fluid secretion in airways & GIT

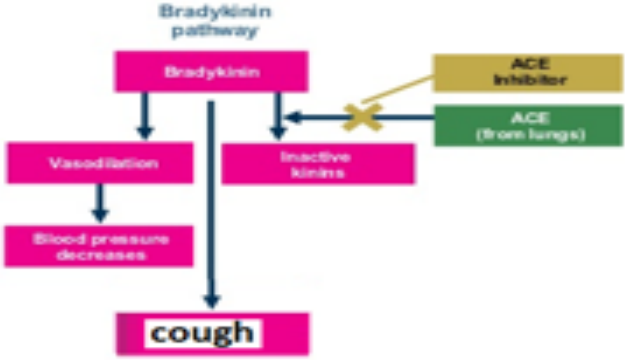


Receptors & clinical uses

B_1	B_2
inducible under condition of inflammation	constitutive
Low affinity to bradykinin & mediates the majority of its effects	High affinity to bradykinin & mediates the majority of its effects
significant role in inflammation & hyperalgesia(increase sense of pain	mediates the majority of its effects

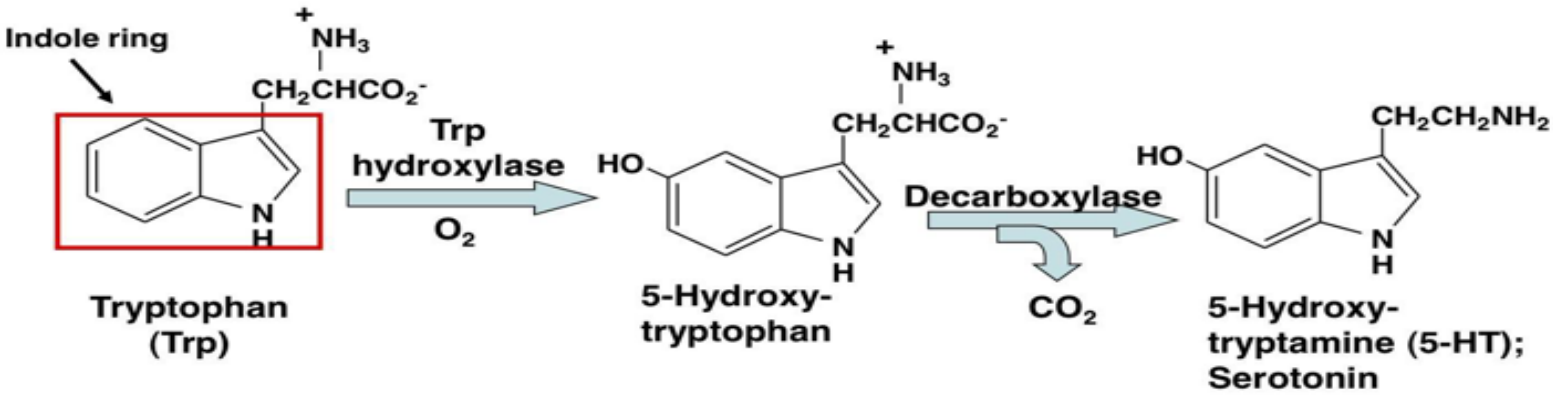
Therapeutic uses:

- No current therapeutic use of bradykinin
- Increased bradykinin is implicated in the therapeutic efficacy and cough produced by ACEIs



SEROTONIN 5-HT

Serotonin is synthesized from the amino acid L-tryptophan



Distribution of Serotinin 5-HT

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

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

CNS:- a neurotransmitter, in midbrain

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

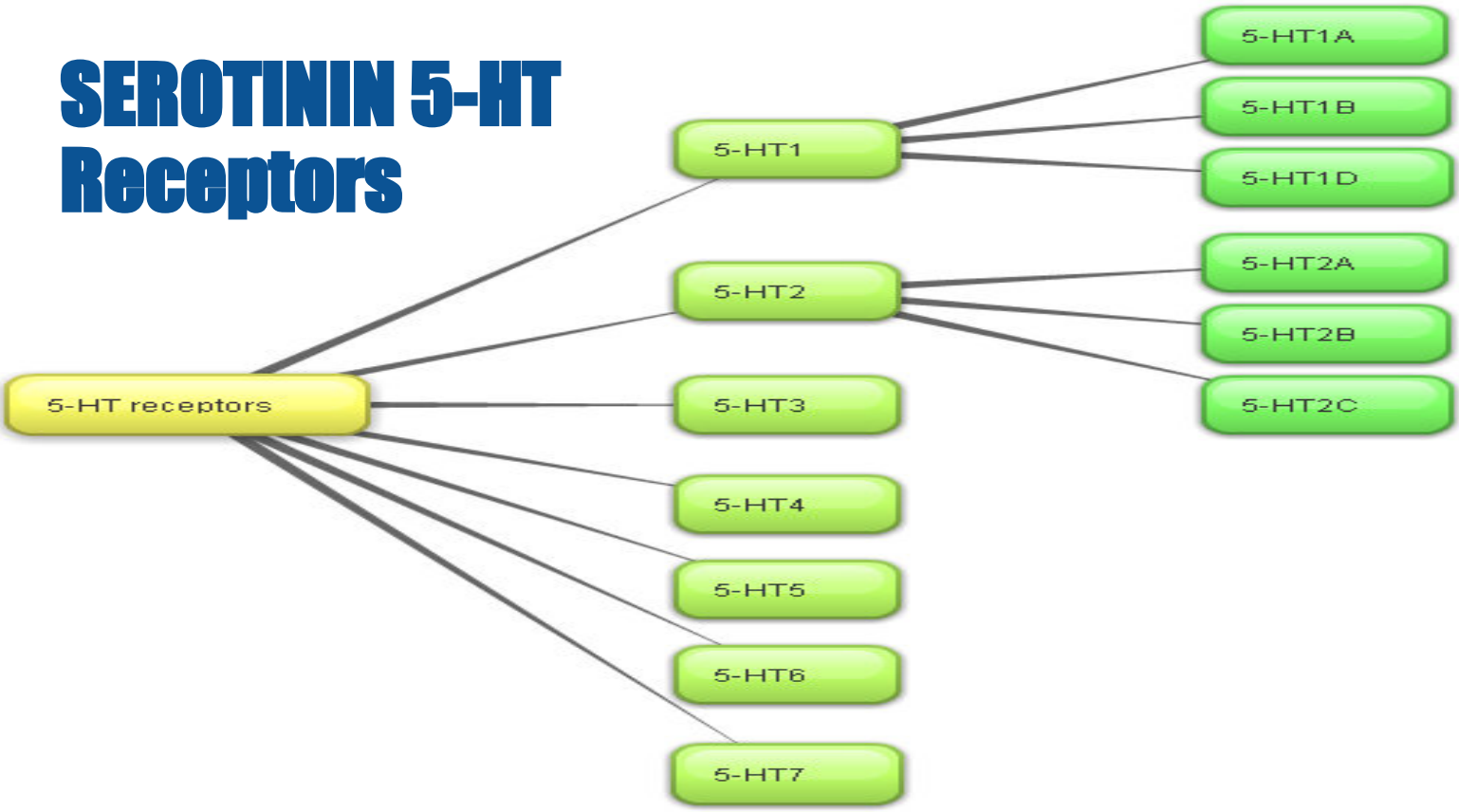
Increases capillary pressure & permeability

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

SEROTININ 5-HT Receptors

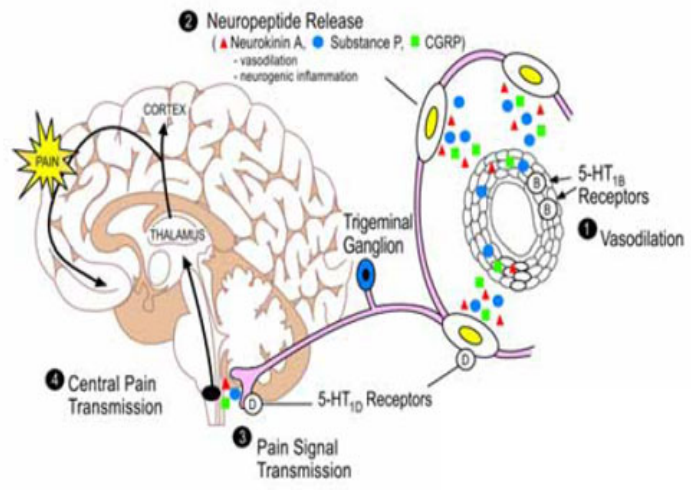


5-ht receptor agonists	5-ht receptor antagonists
Buspirone :-5-HT1A agonist , effective anxiolytic	Selective 5-HT3 antagonist, Ondansetron, antiemetic action , for cancer chemotherapy
Cisapride :-5-HT4 -receptor agonist, used in gastroesophageal reflux & motility disorders.	

Clinical conditions in which 5-ht is implicated:

1-migraine:

Activation of trigeminal system leads to peptides release promoting an inflammatory reaction. This increases flow of sensory traffic through the brain stem, the thalamus & the cortex



Sumatriptan

- 5-HT1D, 1B &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,** 5HT2 antagonist) could be administered to control diarrhea ,flushing & malabsorption

MCQs

1.what is the type of nos that is responsible for immune response?

A. e-nos B.i-nos C- n-nos d- a and c

2.which one of the following is considered a nos inhibitor ?

A-bradykinin B-histamine c-hemoglobin d-Ach

3. NITRIC OXIDE activates ?

A- cAMP b-GMP C-guanylate cyclase D-CA++

4.which one of the following is used for Glaucoma :

A.Zafirlukast B.Latanoprost

C.Alprostadil D. Ketoconazol

which one of the following is 5.lipooxygenase inhibitor

A.Corboprost B. Misoprostol C.Zileuton D.Betahistine

6- one is not an action of Serotinin 5-ht

A. increases motility

B. Contract of smooth muscles

C. Increase of Urine

D. Increases capillary pressure & permeability

7- which one of the following the 5-HT distribute to

A. a neurotransmitter, in midbrain

B. a smooth muscles

C. Pancreas

D. Thyroid glands

Answers

1.C 2.C 3.C 4.B 5.C 6.C 7.A

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Useful videos:

Antihistamine

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