Autacoids

Lectures no. 8 & 9

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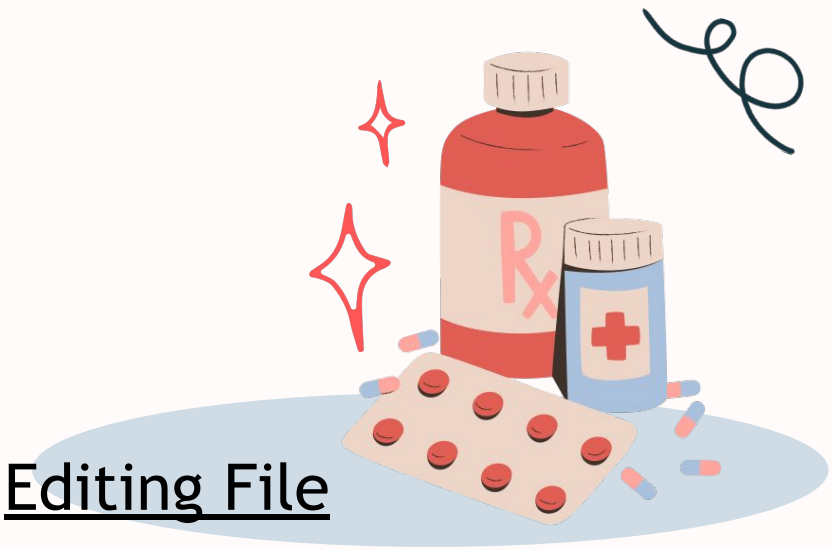

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Objectives

- 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.

Quizlet (Histamine drugs)

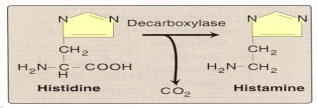
Quizlet (PG analogs)

Autacoids

What are Autacoids?	**They are hormone like substances that act :** **1- autocrine** (self remedy)**:** act locally **in** the site of synthesis. **2- paracrine:** produce action **near** their site of synthesis (in other site of the body). - The general effect of autocoids is local, though it can be moved into circulation (in abnormal situations). In other words, autacoids are produced , act , and are metabolized **locally.**
They include:	**1) amino acid derivatives:** • Histamine • Serotonin (5-HT) **2) Fatty acid derivatives:** • Eicosanoids **3) Gases:** • Nitric Oxide (NO) **4) Endogenous peptides:** • Angiotensin • Kinins

1- Histamine

Histamine

Synthesis	Histamine is synthesized from **L-Histidine** (**Decarboxylation by Decarboxylase enzyme**) 
Stored in	Lung , Basophils , Mast cells, Intestinal mucosa
Released	- During Allergic reactions - Inflammatory reaction
Physiological Antagonist	**Epinephrine** (Adrenaline) -emergency- not enough alone to stop Histamine so we use some medications in the next slide
Receptors type	H1(most common)-H2-H3-H4(Less common)

well be explained in the next slides

H_1-Receptors

EXOCRINE EXCRETION

Increased production of nasal and bronchial mucus, resulting in respiratory symptoms.

BRONCHIAL SMOOTH MUSCLE

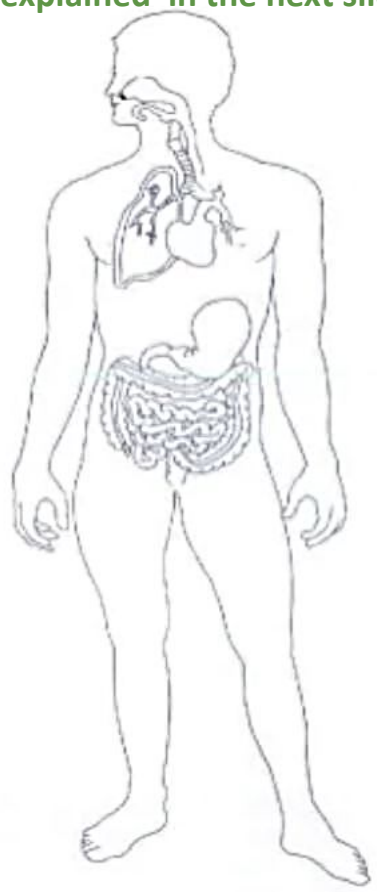
Constriction of bronchioles results in symptoms of asthma, decreased lung capacity.

INTESTINAL SMOOTH MUSCLE

Constriction results in intestinal cramps and diarrhea.

SENSORY NERVE ENDINGS

Cause itch and pain



H_1-and H_2-Receptors

CARDIOVASCULAR SYSTEM

Lowers systemic blood pressure by reducing peripheral resistance. Causes positive chronotropism (mediated by H_2 receptors) and a positive inotropism (mediated by both H_1 and H_2 receptors).

SKIN

Dilation and increased permeability of the capillaries results in leakage of proteins and fluid into the tissues. In the skin this results in the classical "triple response" - wheal formation, reddening due to local vasodilation, and flare ("halo").

H_2-Receptors

Stomach

Stimulation of gastric hydrochloric acid secretion.

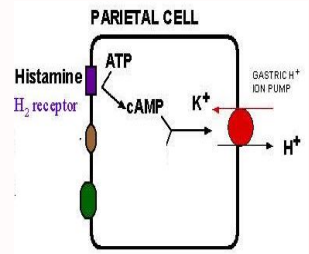
Histamine Receptors

Type	Major Tissue location	Biologic Effect/Actions	Blockers (antagonists)
H1	-Smooth muscles -Endothelial cells -Brain	1- **Acute allergic response** (Major Biologic Effect). 2- **Exocrine excretion** افراز خارجي**:** Increased production of nasal and bronchial mucus, resulting in respiratory symptoms. **3- Contraction of:** - Intestinal smooth muscle (result in increased bowel peristalsis, cramps and diarrhea). - Bronchioles (Bronchoconstriction) (result in asthma, decreased lung capacity). - Uterus. 4- **Sensory nerve endings:** -Cause itch حكة and pain.	**First generation** (has a sedating effect يسبب نعاس, lipophilic & cross BBB Blood brain barrier): e.g.: Diphenhydramine,Promethazine. **Clinical uses:** -Allergic Rhinitis -Urticaria تصبغات حمراء على الجلد -Motion sickness -Insomnia الأرق **Second generation** Non sedating effect: e.g.Fexofenadine (almost impossible to cross BBB), Cetirizine (#note444: Cetirizine can partially cross to BBB),Loratadine **Clinical uses:** Allergic conditions such as : - Allergic rhinitis - Conjunctivitis التهاب الطبقة الشفافة في العين -Urticaria تصبغات حمراء على الجلد (#note444: 2nd Gen is preferable in elderly and jobs requiring wakefulness).

#med444

sedating effect: Diphenhydramine & Promethazine > Cetirizine > Fexofenadine

Histamine Receptors cont.

Type	Major Tissue location	Major Biologic Effect/Actions	Blockers (antagonists)	Clinical Use of Blocker
H2	-Gastric parietal cells(in stomach) -Cardiac muscle -mast cells -Brain	1-formation & secretion of HCL (gastric acid) 2-increase in COP (cardiac output)	-Cimetidine -Ranitidine	**Inhibits** gastric acid secretion **Used to treat:** -**Gastritis** التهاب المعدة -**Peptic ulcer** القرحة الهضمية 
H3 Don't forget The third number in numbers	Central Nervous system The third letter in English	Neurotransmitter	-Betahistine (It produces dilatation of blood vessel in inner ear) and increase permeability out the ear so it will reduce fluid —>balance	**Used to treat :** -**Vertigo** دوخة of Ménière's disease (caused due to accumulation of fluid in the inner ear) & Other balance disturbance of vestibular origin inner ear **Side effect:** May produce headache because of the vasodilation & insomnia
H4	Mast cells, Eosinophils,T-cells	Regulating immune response		

#med444
H1 Blocker 1st Gen, is used to treat insomnia (makes you sleepy)
H3 Blocker causes insomnia (doesn't make you sleepy)

-Omeprazole (proton pump inhibitor)
(#note444:Omeprazole reduces amount of hcl in stomach but it is not an h2 antagonist it is a proton pump inhibitor)

Q
Test yourself

Administration/Action of Histamine

SC = subcutaneous

Slow IV or SC injection

-increase temperature

-Flushing skin (redness Vasodilation)

-Increase heart rate & COP (through increasing Ca2+ influx)

-Edema (increased vasc perm)

-Increase blood flow to the periphery

Intradermal injection

Causes Itching.

Rapid IV bolus injection

-Fall in blood pressure

-Increase in CSF pressure (intracranial pressure ICP)

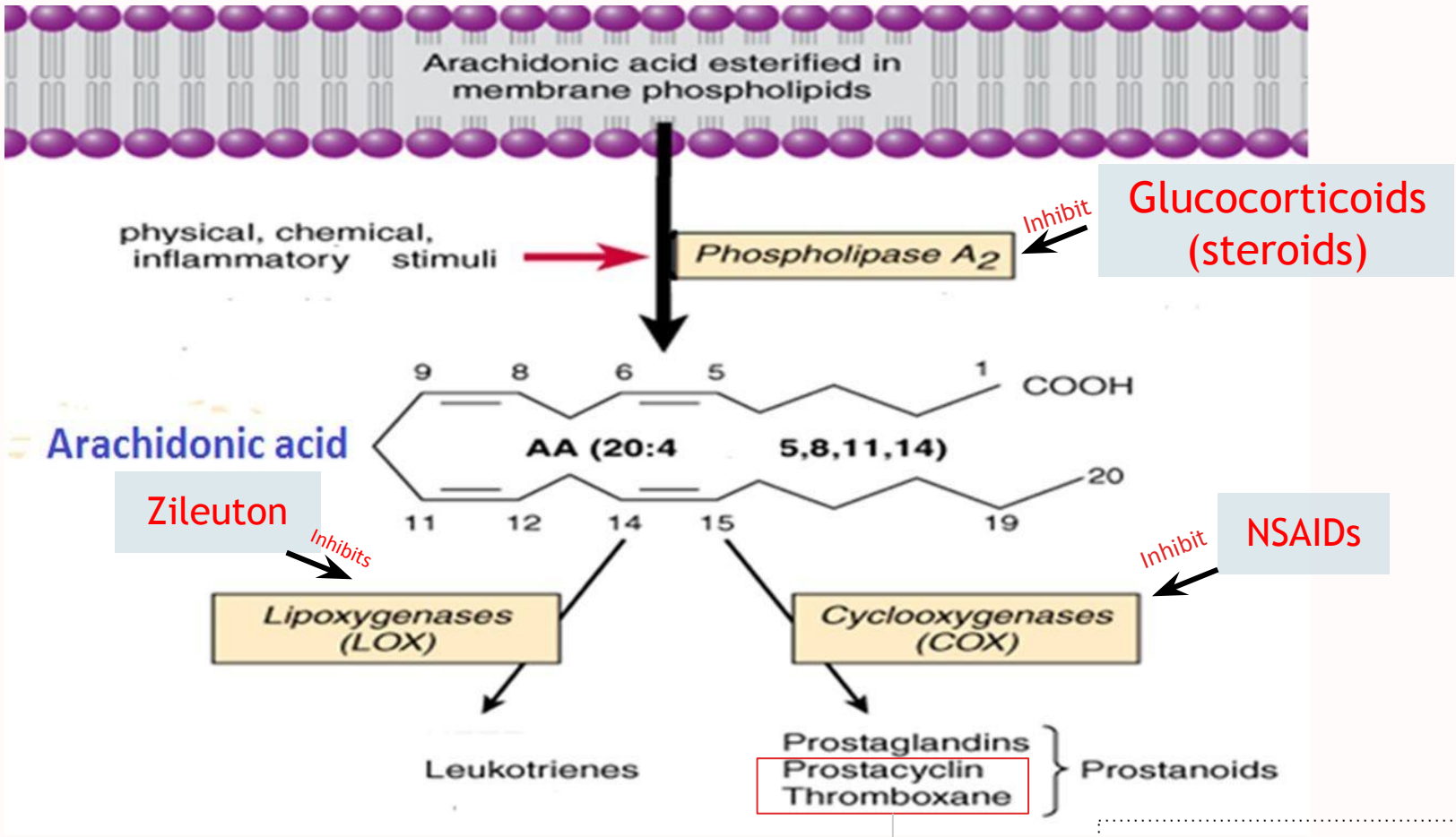
-Headache due to dilation of blood vessels

-which will apply pressure on the CSF in brain

2- Eicosanoids

Don't forget

Eicosanoids



these are the Cyclic endoperoxides (PGG2,PGH2) that are in the next slide

Drugs used in the previous reaction

- Glucocorticoids will inhibit Phospholipase A2 so it will keep the Arachidonic acid trapped in the phospholipids membrane.
- Zileuton will inhibit LOX (lipoxygenase) enzyme so it will prevent Leukotrienes formation.
- NSAIDS will inhibit COX (cyclooxygenase) enzyme so it will prevent Prostanoids formation.

cox isozyme

Arachidonic acid

normally /physiologically present without any stimuli(good type)

activated during injury/inflammation(bad type)

COX-1 "Constitutive" (protective)

Prostaglandins

- GI cytoprotection
- Platelet activity
- Renal function

COX-2 "Inducible" (pathological)

Prostaglandins

Pathological

- -Inflammation
- -Pain
- -Fever

Physiological

- -Renal function
- -Vascular
- -Tissue repair

Cyclic endoperoxides (PGG2,PGH2) (COX)

By Prostacyclin synthase

By Thromboxane synthase

Prostacyclin

-antiaggregation

- vasodilatation

opposite to each other

Thromboxane

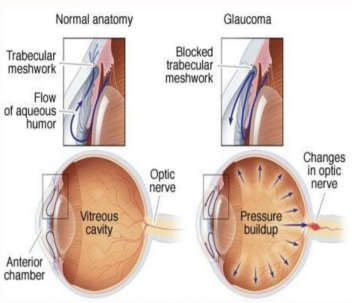
-aggregation

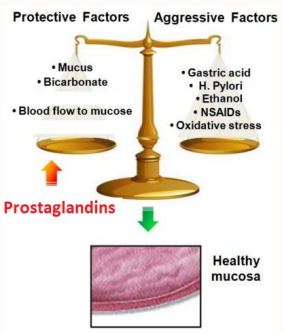
- vasoconstriction

Note from med439:
-constitutive COX produces prostaglandins that are useful because they help maintain homeostasis (found normally in the body), so inhibition of COX1 is undesirable.
-Inducible COX produces some prostaglandins that are not normally found in healthy individual; they are found in inflammation, so inhibition is desirable.

Actions of Prostaglandins

	action
1	They are pro-inflammatory
2	Cause vasodilation of vascular smooth muscle → (PGI2, PGE2)
3	↑ High PG conc → inhibition of platelets aggregation ↓ ↓ Low PG conc → increase platelet aggregation ↑
4	Sensitize neurons to cause pain
5	Induce labor (In last trimester to contract uterus) and Induce abortion
6	Decrease intraocular pressure (by increasing secretion of aqueous humor (fluid in the eye) through anterior chamber, thus decreasing pressure.)
7	Acts on thermoregulatory center of hypothalamus to **<u>increase</u>** body temperature
8	Acts on kidney to increase glomelur filtration #444: By vasodilation of afferent arterioles which increases filtration.
9	Acts on parietal cells of stomach to protect gastric mucosa Protects stomach





Clinical uses of PG analogs

Note: we use analogs because PGs have short duration of action

- Carboprost (PGF): Induce abortion in 2nd trimester
- Latanoprost (PGF): Glaucoma
- Misoprostol (PGE1): Peptic ulcer (not 1st line treatment)
- Alprostadil (PGE1): Erectile dysfunction
- Zileuton (lipoxygenase inhibitor): Asthma
- Zafirlukast (leukotriene receptor blocker): Bronchial asthma

#note444: know the drug and type of prostaglandin.
Ex: Latanoprost is PGF

#note444
Ex: Patient who is prescribed NSAIDs for a long duration also takes Misprostol to protect the stomach

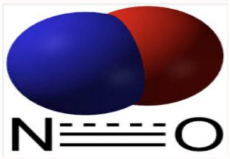
Q

Test yourself

- First four drugs are analogs meaning they produce similar effects of those PGs but have a more prolonged effect . Whereas Zileuton inhibits LOX & Zafirlukast targets the receptor to block its action.

3- Nitric Oxides

Nitric Oxide

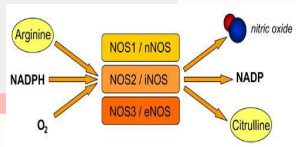


Biosynthesis
Synthesized from L-arganine by nitric oxide synthase (NOS)

There are 3 isoforms of the enzymeNOS.

NO release is stimulated by:
-Acetylcholine
-Serotonin (5-HT)
-Bradykinin and Histamine

NO release is inhibited by:
-Hemoglobin



Isoforms of NOS

composed of 3 types

Neuronal nNOS	Endothelial eNOS	Inducible iNOS
- Neurons - Skeletal muscles	- Endothelium - Cardiac myocytes - Osteoblasts - Osteoclasts	- Macrophages - Kupffer cells - Neutrophils - Fibroblasts - Vascular smooth muscle
Constitutive forms (physiological)		Inducible forms (pathological)

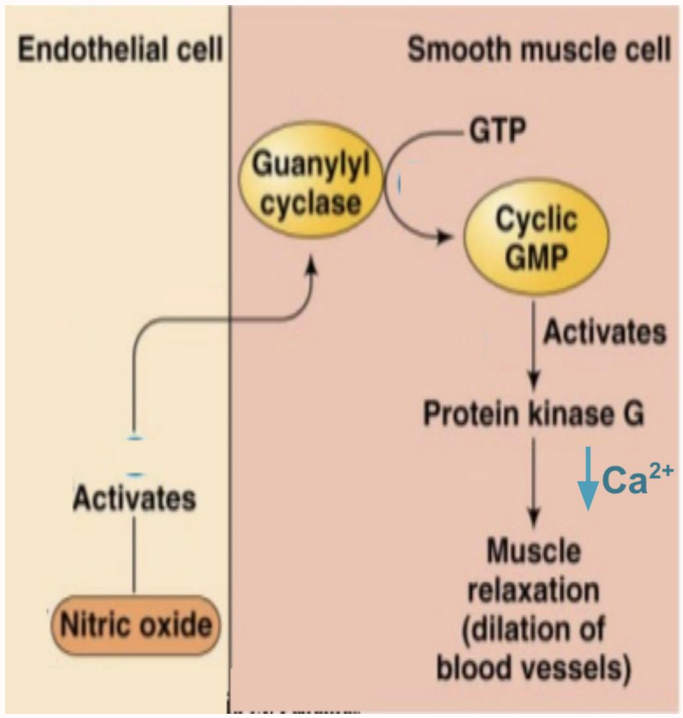
Note: Kupffer cells are macrophages in the liver

NO Mechanism of action

Step 1 Combining with haem in guanylate cyclase .

Step 2 Activating the enzyme increasing cGMP

Step 3 Thereby lowering [Ca2+]



Explanation

Step 1: Nitric oxide activates the enzyme guanylyl cyclase enzyme.

Step 2: Guanylyl cyclase converts GTP to cyclic GMP.

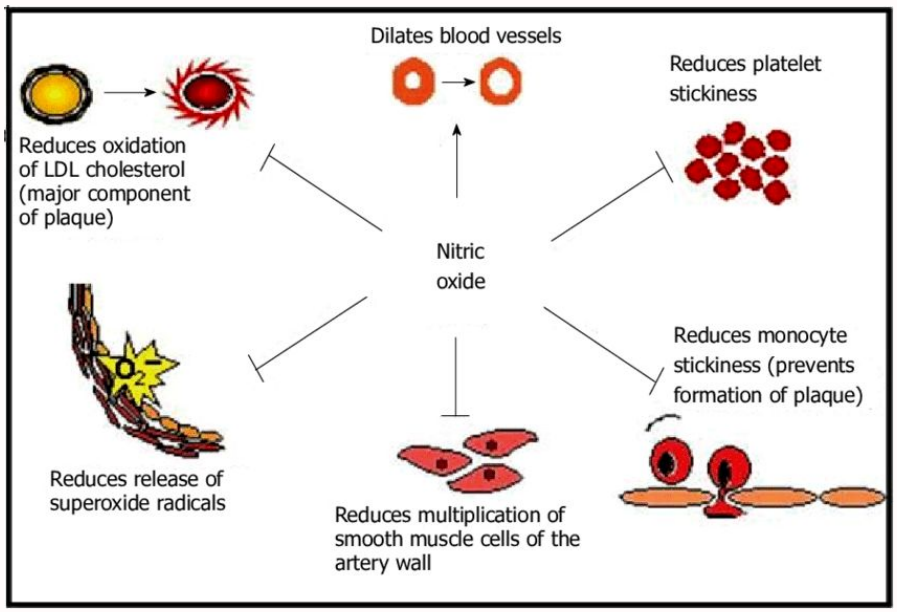
Step 3: cGMP activates protein kinase G.

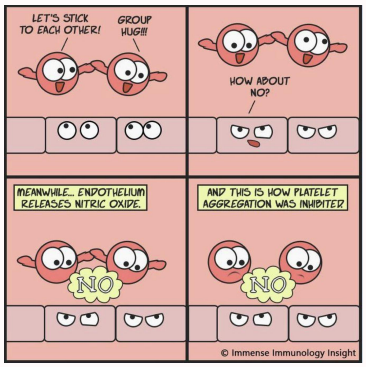
Step 4: protein kinase G reduces calcium level which leads to muscle relaxation (dilation of blood vessels).

Actions of NO

1. Inhibition of platelet and monocyte adhesion & aggregation.
2. Inhibition of smooth muscle proliferation
3. Protection against atherogenesis
4. Synaptic effects in the peripheral & CNS.
5. Host defense & cytotoxic effects on pathogens
6. Cytoprotection

Dr notes: Unlike Histamine which is stored in the body, nitric oxide is produced when in demand (only when the body needs it).





Actions of NOS

Neuronal Nitric Oxide (nNOS)

- Long term potentiation (on nerves and nerve endings)
- Cardiac function
- Peristalsis
- Sexual arousal

Endothelial Nitric Oxide (eNOS)

- Vascular tone (vasodilation)
- Insulin secretion
- Airway tone
- Regulation of cardiac function and angiogenesis
- Embryonic heart development

Inducible Nitric Oxide (iNOS)

- In response to attack by parasites
- Bacterial infection
- Tumor growth
- Septic shock
- Autoimmune condition

NO in therapeutics

1. Underproduction: Endothelial NO production is reduced in patients with diabetes, hypertension & atherosclerosis.

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

3. NO donors (Drugs) have well established therapeutic uses e.g. in hypertension & angina pectoris.

4. NO donors is used in critical care to treat pulmonary hypertension in neonates (inhaled by the patients in emergencies)

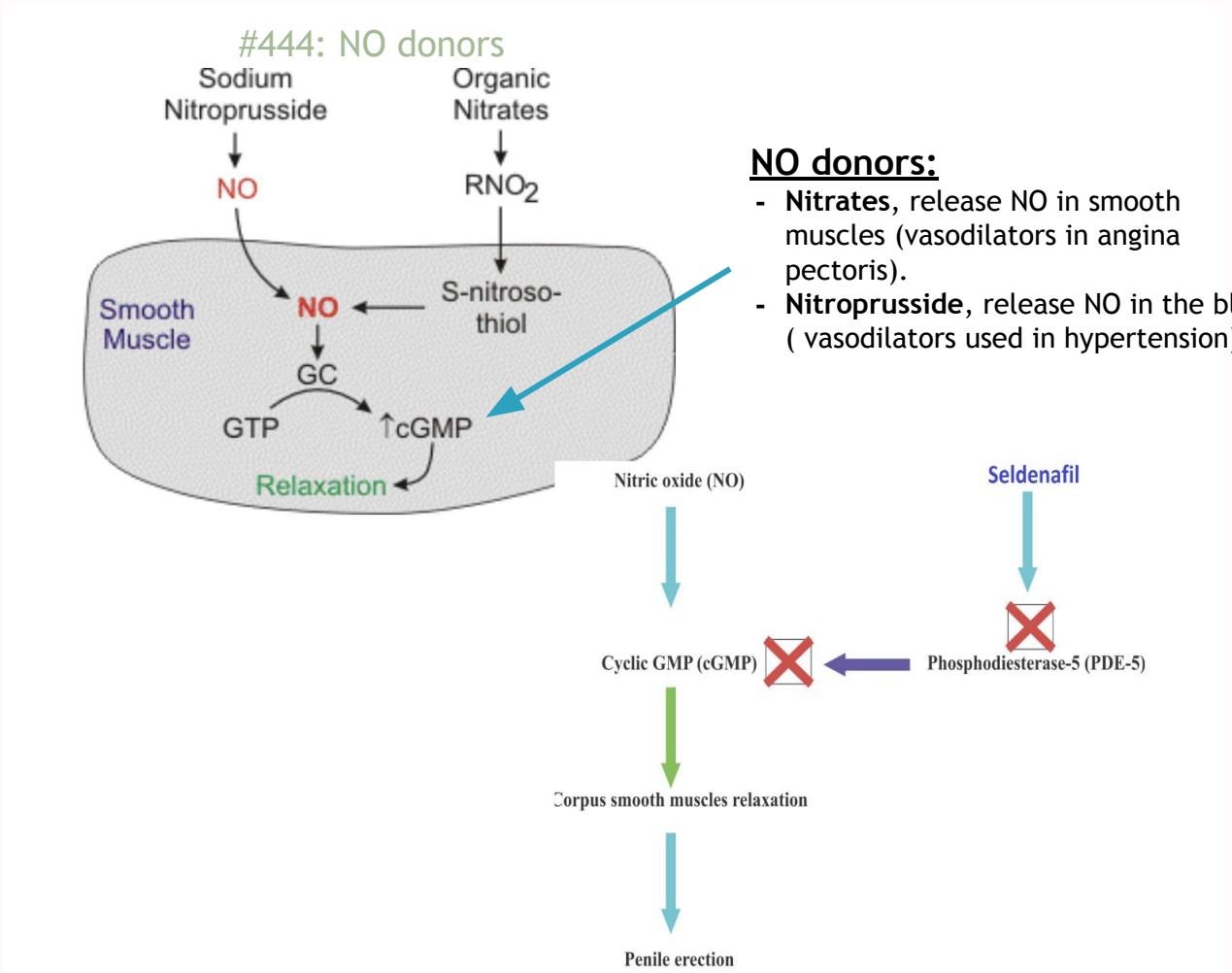
5. NO is used in patients with right ventricular failure secondary to pulmonary embolism.

6. **sildenafil** (viagra) حفظ: potentiates the action of NO on corpora cavernosa smooth muscle. (It is used to treat erectile dysfunction)

#note444: know when we use NO donors

Mechanism of Sildenfil

We know that Nitric Oxide works as an activator of cGMP right?
However, in this case there is an enzyme called PDE-5 which destroys the cGMP preventing the Nitric Acid from activating it and performing its function.
Sildenfil inhibits the PDE-5 enzyme so the cGMP is ready to be activated by the Nitric Oxide.



NO donors:

- **Nitrates**, release NO in smooth muscles (vasodilators in angina pectoris).
- **Nitroprusside**, release NO in the blood (vasodilators used in hypertension).

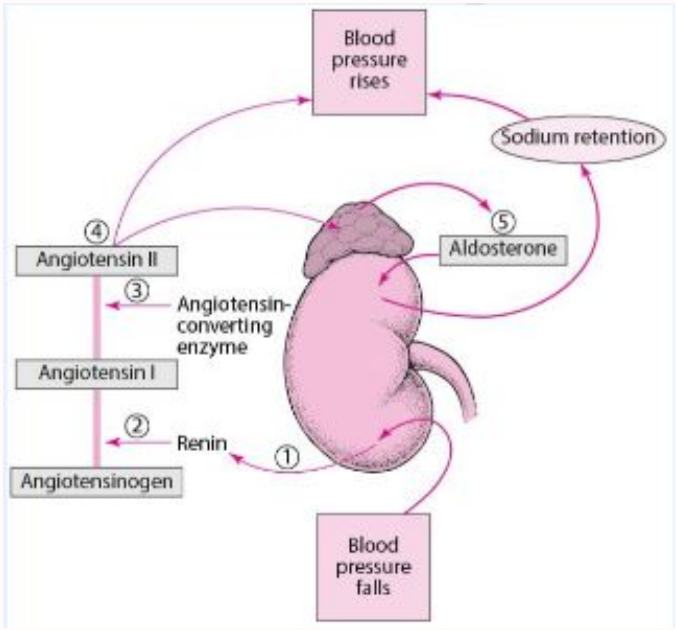
4- Angiotensin

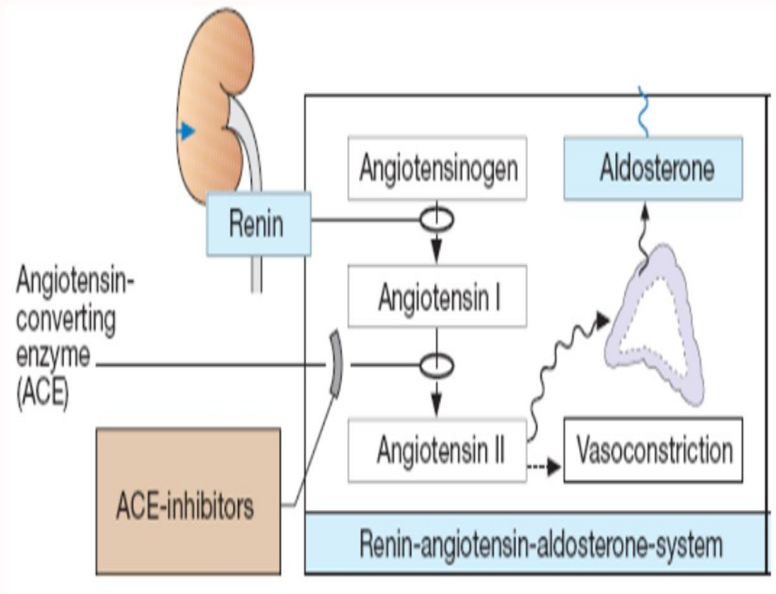
Angiotensin

For angiotensin

Biosynthesis :

- Renin released from the kidney converts angiotensinogen to Ag I (Inactive)
- Angiotensin converting enzyme (ACE) converts Ag I to Ag II (Active)
- Angiotensin**ogen**: circulating protein in the blood that comes from the liver (inactive form).
- Renin: circulating protein released from the kidney.





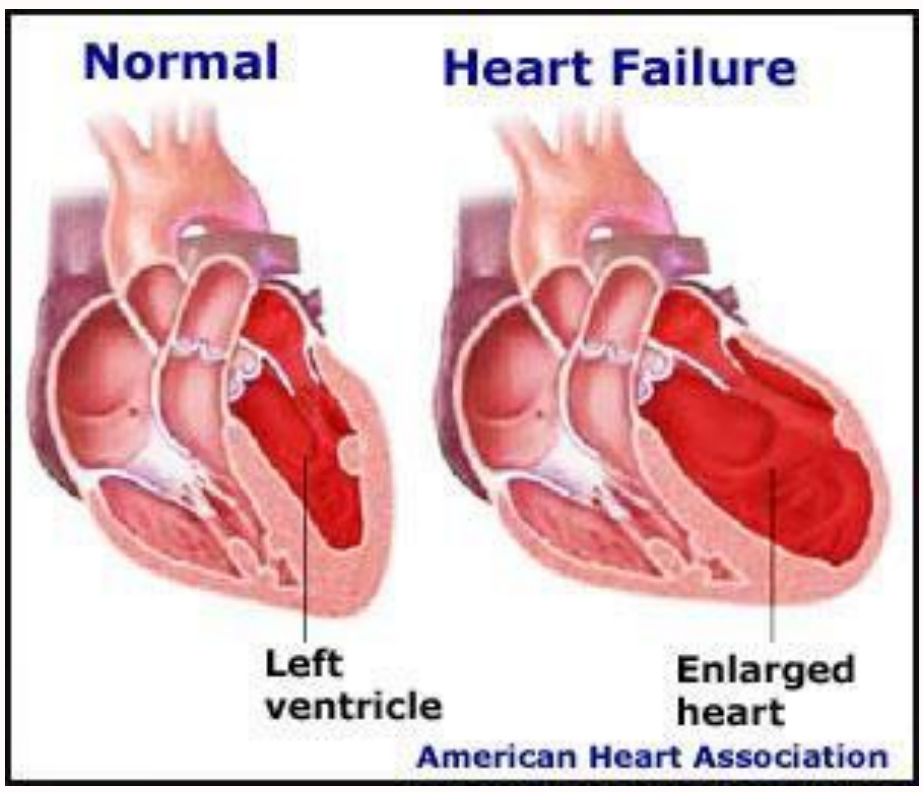
Renin يزداد لما يكون ضغط الدم
نازل ويحول Ag الى Ag I ثم يذهب
Ag I الى ال Lung ويصبح
Ag II بواسطة ACE

➔ Renin released from kidney converts angiotensinogen into AgI which is also converted into AgII by ACE . This results in vasoconstriction .It also promotes aldosterone secretion from adrenal cortex of adrenal gland which causes Na/H2O retention. ACE-inhibitors prevent conversion of AgI(inactive) to AgII(active).

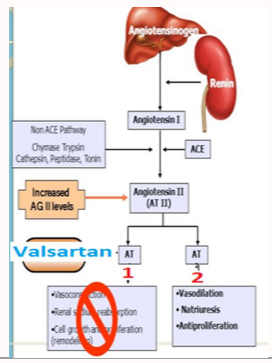
Actions of Angiotensin II

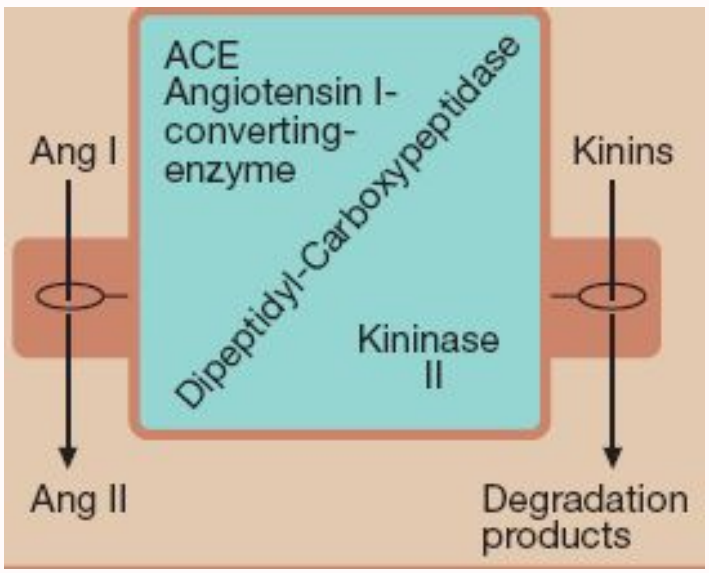
1. Promotes vasoconstriction directly or indirectly by releasing NA & AD. (Noradrenaline & Adrenaline)
2. Increases force of contraction of the heart by promoting Ca2+ influx.
3. Increases aldosterone release → sodium & water retention.
4. Causes hypertrophy of vascular & cardiac cells & increases synthesis & deposition of collagen by cardiac fibroblasts (remodeling).

*Aldosterone is secreted from the adrenal gland

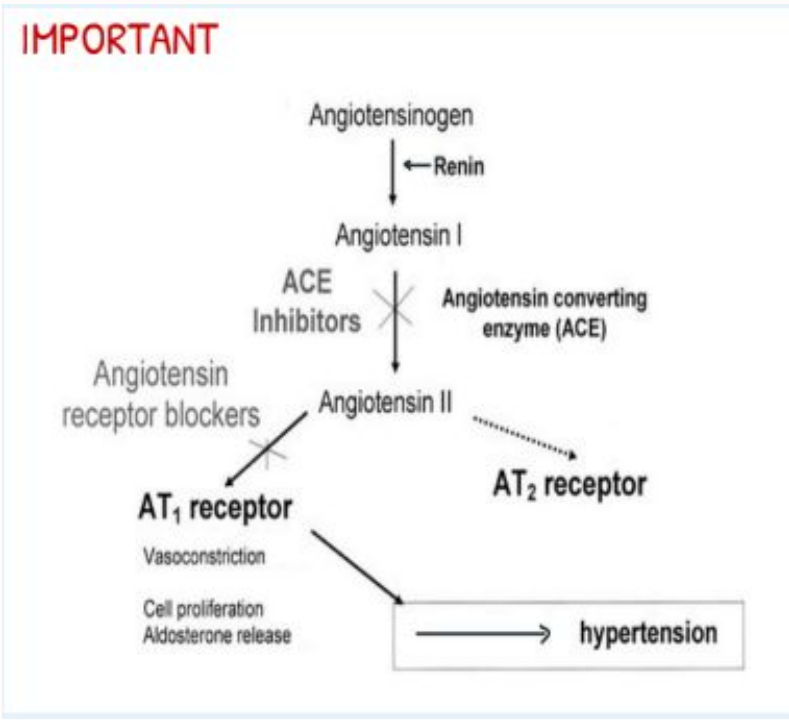


Angiotensin inhibitors

	Definition	Clinical uses	Inhibitors
ACE inhibitors	Cause a fall in blood pressure in hypertensive patients especially those with high **renin** levels	- Hypertension - Cardiac failure following myocardial infarction	Captopril
Ag receptors Blockers(ARBs)	-Angiotensin receptors AT1 & AT2 -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 (ACE Inhibitors)	- Hypertension - Cardiac failure following myocardial infarction	Losartan Also "Valsartan" 



Ag inhibitors Mechanisms



ACE= Kininase II

5- Kinins

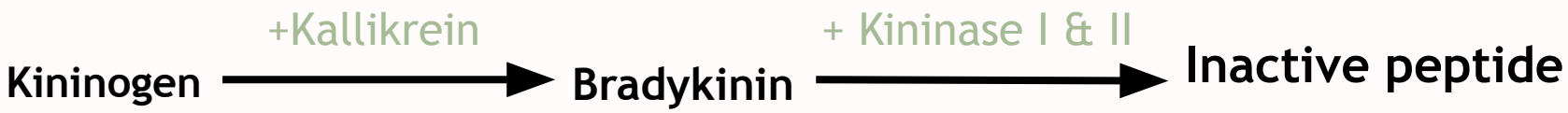
KININS

For Kinin & Serotonin

1.Bradykinin

2.Kallidin

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



441 notes: kininogen with kallikrein will produce Bradykinin kinins

Bradykinin is inactivated by kininase 1&2 (kininase II is another name for ACE)

Actions of Bradykinin

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

Receptors and clinical uses

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

B1 inducible under condition of inflammation

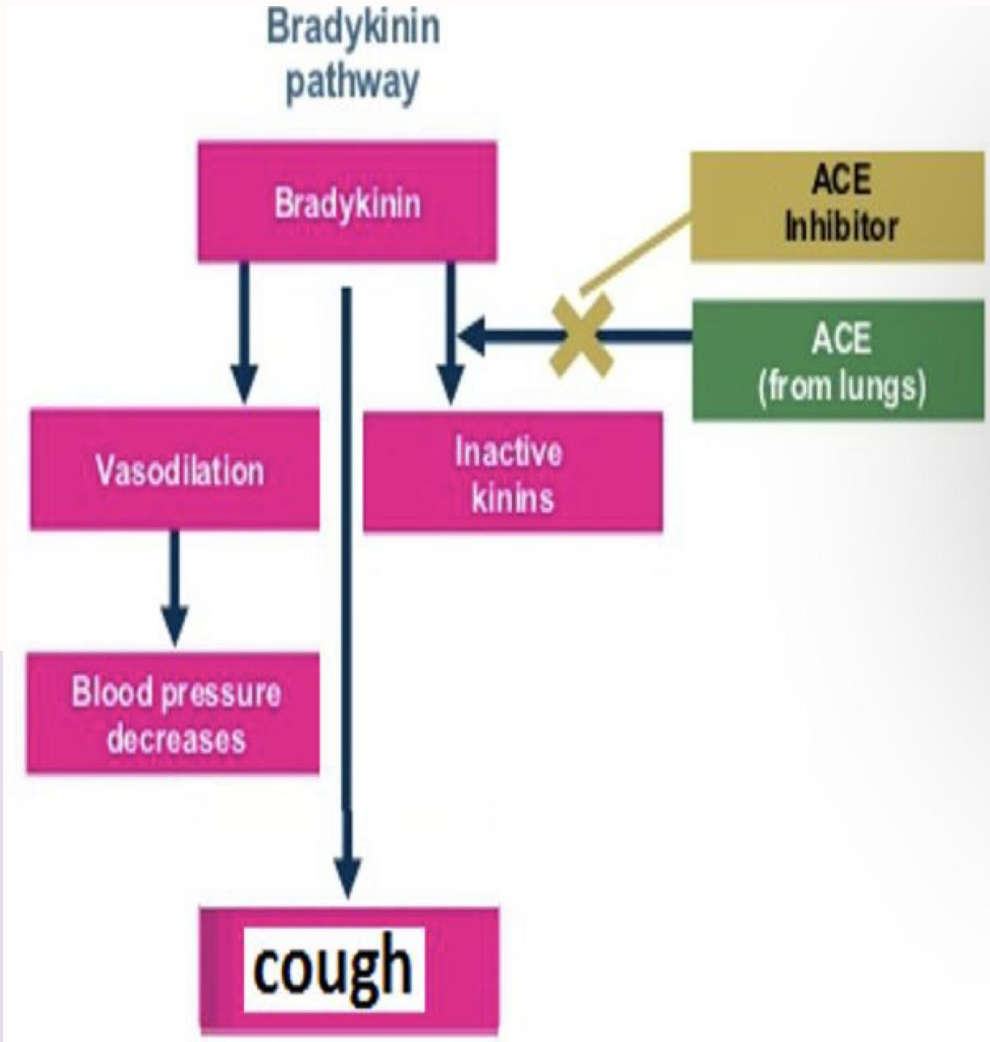
B1 receptor (pathologic)
-has low affinity to bradykinin
-plays a significant role in inflammation & hyperalgesia
(hyperalgesia = high pain sensation)

B2 constitutive (protective)
-has high affinity to bradykinin & mediates the majority of its effects.

Therapeutic uses

-No current therapeutic use of bradykinin because it has severe hypotensive action but it helps the ACE inhibitors.

-Increased bradykinin is implicated in the therapeutic efficacy and cough produced by ACE inhibitors.



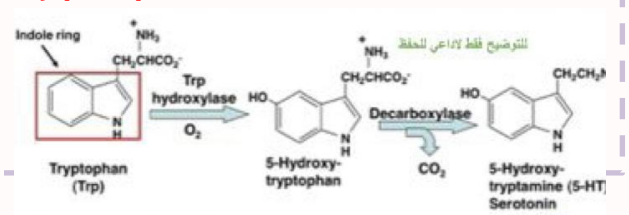
442 NOTE: The ACE inhibitor used for treatment of hypertension (such as captopril) works by inhibiting the inactivation of Bradykinin so Inhibiting the bradykinin increases which is good for hypertension treatment, however it causes of bradykinin cough because the bradykinin causes smooth muscle constriction in bronchioles

442 NOTE: Inhibiting the inactive kinins = increase bradykinin

6- Serotonin

Serotonin (5-HT)

-Serotonin is synthesized from the amino acid L-tryptophan and is also called 5-HT (5-hydroxytryptamine).



Actions

➔ **GIT:** increases motility

➔ Contracts uterus, bronchiole, other smooth muscles

➔ **Blood vessels:**
1-Contracts large vessels by a direct action & relaxes other vessels by releasing **NO**.
2-Increases capillary pressure & permeability.

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

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

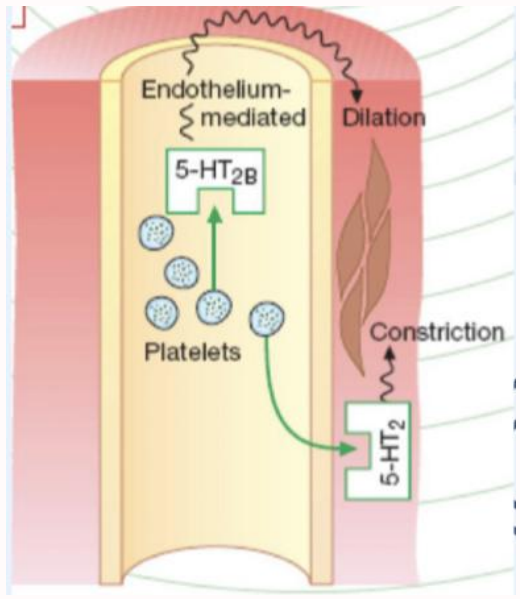
➔ **CNS:** stimulates some neurons & inhibits others,inhibits release of other neurotransmitters.

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



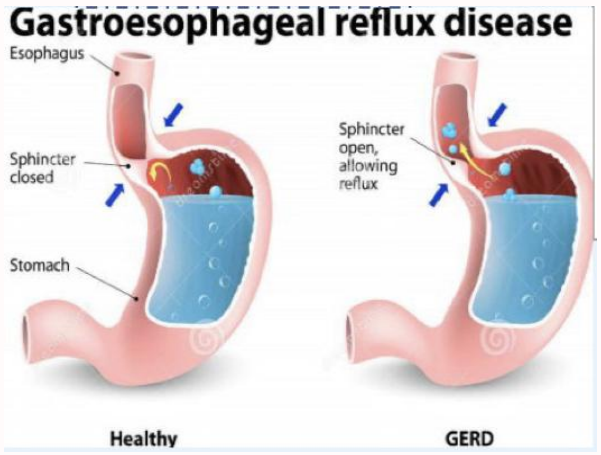
Serotonin (5-HT) Receptors

Receptor Subtypes	Signaling Mechanism	Distribution	Effects
5-HT_{1A} **Buspirone**	Gi, ↓ cAMP	Raphe nuclei, hippocampus	Regulates sleep, feeding and anxiety
5-HT_{1B}	Gi, ↓ cAMP	Substantia nigra, globus pallidus, basal ganglia	Neuronal inhibition, behavioral changes
5-HT_{1D} **sumatriptan**	Gi, ↓ cAMP	Brain	Vasoconstriction
5-HT_{1E}	Gi, ↓ cAMP	Cortex, hippocampus	Memory
5-HT_{1F}	Gi, ↓ cAMP	Globus pallidus, putamen	Anxiety, vasoconstriction
5-HT_{2A}	Gq, ↑ IP_3	Platelets, cerebral cortex	Cellular excitaton, muscle contraction
5-HT_{2B}	Gq, ↑ IP_3	Stomach	Appetite
5-HT_{2C}	Gq, ↑ IP_3	Hippocampus, substantia nigra	Anxiety
5-HT_{3} **ondansetron**	Na^+-K^+ ion channel	Area postrema, enteric nerves	Vomiting
5-HT_{4} **Cisapride**	Gs, ↑ cAMP	Cortex, smooth muscle	Gut motility
$5\text{-HT}_{5A,B}$	Gi, ↓ cAMP	Brain	Locomotion, sleep
5-HT_{6}	Gs, ↑ cAMP	Brain	Cognition, learning

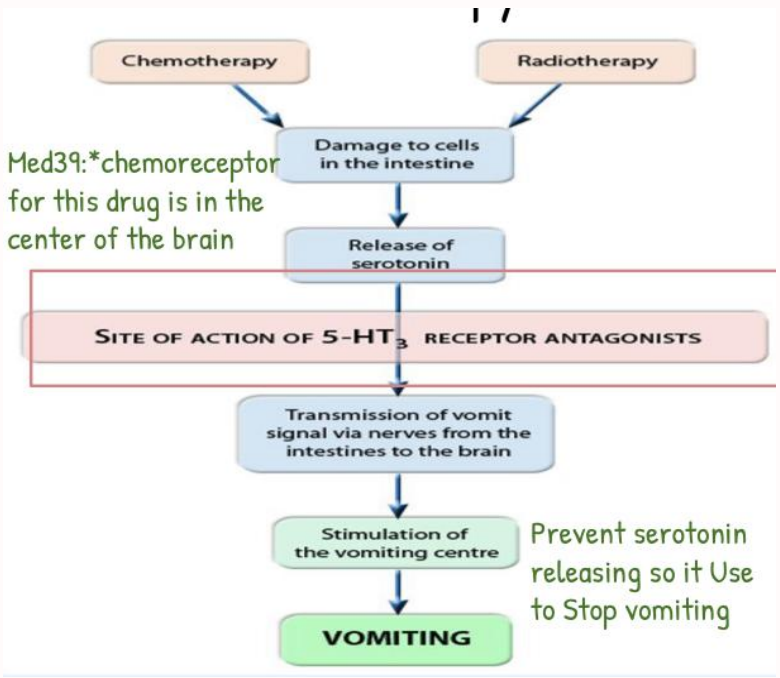
*Written are the drugs that target those receptors

Serotonin (5-HT) Receptor

5-HT RECEPTOR AGONISTS	5-HT RECEPTOR ANTAGONISTS
1)**Buspirone**: ➔ **5-HT1A agonist**,effective anxiolytic (helps decrease anxiety)	**Ondansetron** ➔ **Selective 5-HT3 antagonist.** has antiemetic action,(emesis=vomiting), for cancer chemotherapy
2)**Cisapride**: ➔ **5-HT4-receptor agonist**, used in gastroesophageal reflux and motility disorders (تسرع في عملية إفراغ المعدة)	



Med39:In gastroesophageal reflux, the gastric acid enters the esophagus through an open sphincter causing burning sensation -> patients are given antacids or prokinetic drugs (increases motility, decreasing ! the amount of contents in the stomach)



CLINICAL CONDITIONS IN WHICH 5-HT IS IMPLICATED

1-Migraine

• Activation of trigeminal system leads to vasodilator peptides release promoting an inflammatory reaction.

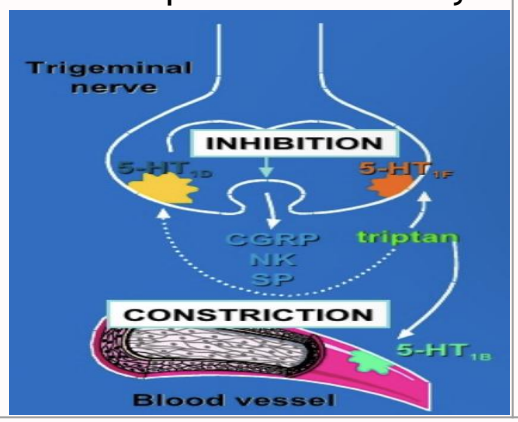
• This increases the flow of sensory traffic through the brainstem, the thalamus, the cortex.

Med39:Neuropeptides release causinq vasodilation and neurogenic inflammation⟶ causing inhibition of Migraine, causing vasodilation only-> pain pro- inflammatory neuropeptide

E.g. SUMATRIPTAN

5-HT 1B, 1D & 1F-receptor agonists, effective in acute migraine attack (binds with 3 types of 5-HT) inflammatory reaction.

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

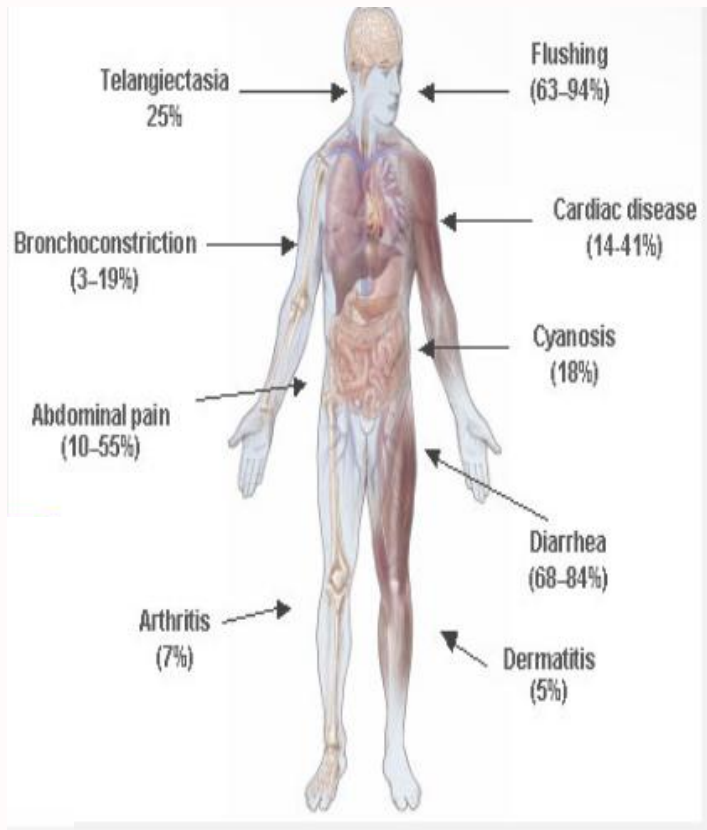


2-Carcinoid Syndrome

• 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. Med39:They don't treat malignancy just control the symptoms



MCQs

Q1. formation & secretion of HCL (gastric acid) is the **Major Biologic Effect of?**			
a) Glucocorticoids	b) PGF	c) H2	d) H1

Q2. What kind of receptor blockers has non-sedating effect?			
a) H1 first generation	b) H4	c) H2	d) H1 second generation

Q3. NO release is inhibited by?			
a) Ach	b) Histamine	c) Hemoglobin	d) Cytokines

Q4. Sildenafil inhibits which of the following?			
a) PDE-5	b) H1	c) PG1	d) H3

Q5. What is the clinical use of Zileuton for?			
a) Asthma	b) Heart failure	c) Gluacoma	d) Peptic ulcer

Answers:

1) c
2) d
3) c
4) a
5) a

MCQs

Q6.Actions of bradykinin ?			
a) constricts vascular smooth muscles	b) increases blood pressure	c) constrict non-vascular smooth muscles	d) relieves pain

Q7.Which of the following is an antiemetic drug ?			
a)Cyproheptadine	b) Cisapride	c) Buspirone	d) Ondansetron

Q8.Serotonin is synthesised from the amino acid ?			
a) L-tryptophan	b) B-tryptophan	c) Arginine	d) Glutamic acid

Q9.Kininogen is converted into Bradykinin by addition of ?			
a) Kallikrein	b) Kininase I	c) Kininase II	d) a & b

Q10.What converts angiotensinogen to angiotensin I ?			
a) ACE	b) Renin	c) ACEI	d) aldosterone

Answers:
6)c
7)d
8)a
9)a
10)b

SAQS

Q1 .What does H3 blocker do?

Q1: It dilates blood vessels in the inner ear

Q2. List the 3 isoforms of NOS?

Q2: neuronal NOS, epithelial NOS, inducible NOS.

Q3. Which components stimulates the release of NO?

Q3: Acetylcholine, 5-H, Bradykinin & Histamine.

Q4.What is the mechanism of action of cimetidine?

Q4: Blocks H2 receptor → reduced production of HCL

Q5.What are the clinical uses of ACE inhibitors ?

-hypertension
-cardiac failure
-myocardial infarction

Q6. Give an example of Ag receptors blockers ?

-Losartan
-Valsartan

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