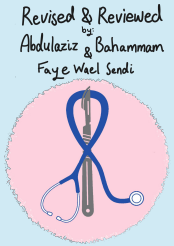


MED441
KING SAUD UNIVERSITY

Autocids Paracrine Mediators (Part I & II)

Important
Main Text
Male slides
female slides
Extra information
Doctors notes

For any future corrections Editing file

If you didn't understand any part from this lecture Click here

Objectives

1. To describe the synthesis, receptors & function of histamine, 5-HT , eicosanoid , nitric oxide , angiotensin,& kinins
2. To study the agents which enhance or block their effects

Autacoids

Definition :
Autacoids are biomaterial substances that are synthesized and metabolized locally

They are either :

They affect

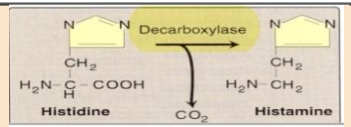
- Glands
- Nerve
- Smooth muscle
- Platelets & other tissues

They include :

- **Amino acids :**
  1- Histamine
  2- serotonin
- **Fatty acid:**
  3-Eicosanoids
- **Gases:**
  4-Nitric Oxide (NO)
- **Endogenous Peptides:**
  5- Angiotensin
  6-kinins

Histamine

Extra: the name of reaction is decarboxylation

Synthesis	Histamine is synthesized from L-Histidine. 
Stored	❑ Lung ❑ Basophils ❑ Mast cells ❑ Intestinal mucosa
Released During	❑ Allergic reactions ❑ Inflammatory reaction
Physiological Antagonist	Epinephrine (Adrenaline)

Administration of Histamine/ Action

Extra: الهستامين ما يعطى كدواء لانه جدًا ضار في الحاله الطبيعية فعشان كذا الادوية الي نستخدمها تكون ادوية توقف اخراج الهستامين

Rapid IV

- Fall in blood pressure
- Increase in CNF pressure
- Headache

Slow IV & SC

- Increase temperature
- Flushing skin (redness:Vasodilation)
- Increase heart rate & COP (through increasing Ca2+ influx)
- Edema
- Increase blood flow to the periphery

Intradermal

- Itching

Extra: the headache is caused because the dilated blood vessels apply pressure on the CNF fluid in the brain . From439

IV: Intravenous
SC: Subconscious

Histamine

Extra: When histamine bind to H1 receptor it increases Acetylcholine & Glutamate which have a role in your wakefulness , so when we block H1 that mean we will have sedating effect

Histamine Receptor (type)	Major Tissue location	Major Biologic Effect/Actions	These drugs that stop histamine effect **Bookers**	Clinical Use of Blocker
H1	Smooth muscle, Endothelial cells , Brain	Acute allergic response, contract smooth muscle (Except Blood vessels) (contract smooth muscles, bronchioles, uterus + Increases bowel peristalsis)	First generation ❏ Diphenhydramine ❏ Promethazine	Has sedating effect : use to treat : ❏ Allergic Rhinitis ❏ Urticaria ❏ Motion sickness ❏ Insomnia (الارق)
			Second generation ❏ Cetirizine ❏ Fexofenadine هذا النوعين من البلوكيرز النعاس الي تسببه بسيط مقارنة بالجيل الاول فعشان كذا يفضل استخدامه للأشخاص الي عندهم اعمال الصباح From436	Non-Sedating effect Use to treat Allergic condition such as : ❏ Allergic Rhinitis (nose) ❏ Conjunctivitis (eye) ❏ Urticaria
H2	Gastric parietal cells , Cardiac muscle , mast cell , Brain	H2 receptor of histamine play an important role in the formation & secretion of HCL (gastric acid) & increase in COP (cardiac output)	❏ Cimetidine	Inhibits gastric acid secretion Use to treat : ❏ Gastritis ❏ Peptic ulcer

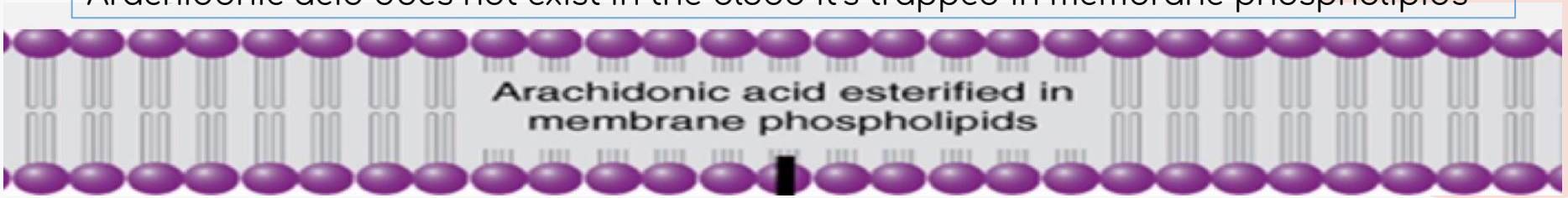
Histamine

Histamine Receptor (type)	Major Tissue location	Major Biologic Effect/Actions	These drugs that stop histamine effect **Bookers**	Clinical Use of Blocker
H3	Central Nervous system	Neurotransmitter	❑ Betahistine (It produces dilation of blood vessel in inner ear)	Use to treat : ❑ Vertigo of Ménière's disease & Other balance of vestibular origin Side effect: May produce headache & insomnia
H4	Mast cells, Eosinophils,T-cell	Regulating immune response	—	——

Dr Note :You should know if they didn't mention which receptor they mean H1

Eicosanoids

Arachidonic acid does not exist in the blood it's trapped in membrane phospholipids

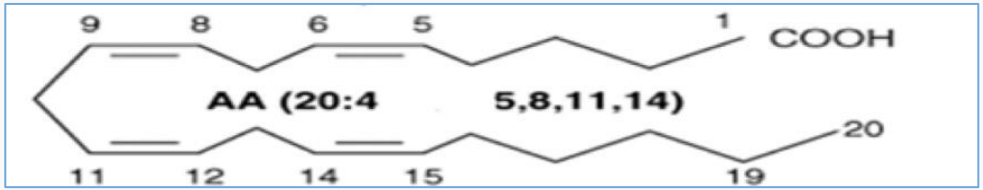


When there is physical - chemical inflammatory

This will activate

Phospholipase A2 enzyme

What does it do?
It will get the Arachidonic acid out in the blood



Arachidonic acid

Lipoxygenases
LOX

Cyclooxygenases
COX

Leukotrienes

Now it is in the blood
It Either become

Prostanoids

- Prostaglandins
- Prostacyclin
- Thromboxane

Important Drugs for the previous reaction

Glucocorticoids will inhibit Phospholipase A2 so it will keep the Arachidonic acid trapped in the phospholipids membrane (the most important drug)

Zileuton will inhibit LOX enzyme so it will prevent Leukotrienes formation

NSAIDS will inhibit COX enzyme so it will prevent Prostanoids formation

Cox Isozymes

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.
Prostaglandins

COX-1 Constitutive
normally produced in our body

- Prostaglandins
  - GI cytoprotection
  - Platelet Activity
  - Renal Function

COX-2 Inducible
Induced in injury-
Inflammation
-pain

- Prostaglandins
  - Pathologic
    - Inflammation
    - Pain
    - Fever
  - Physiologic
    - Renal function
    - Vascular
    - Tissue repair

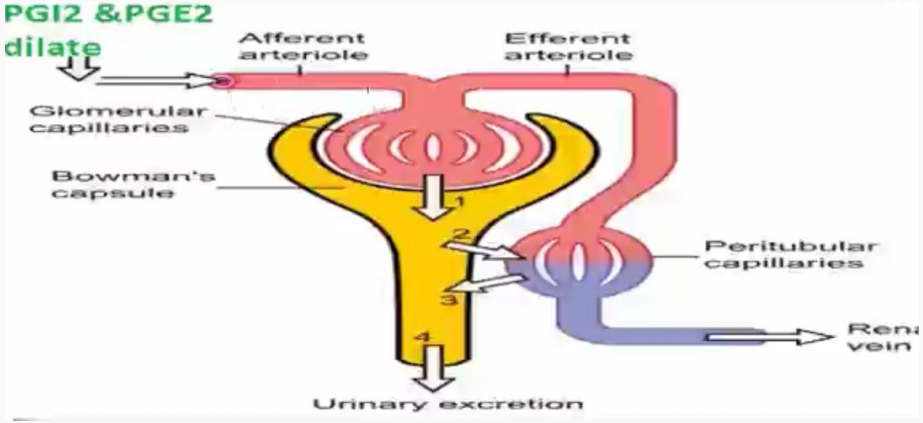
Cyclic endoperoxides (PGG2,PGH2)

- Prostacyclin
  - Anti Aggregating efect
  - Vasodilation
- Thromboxane
  - Aggregating effect
  - Vasoconstriction

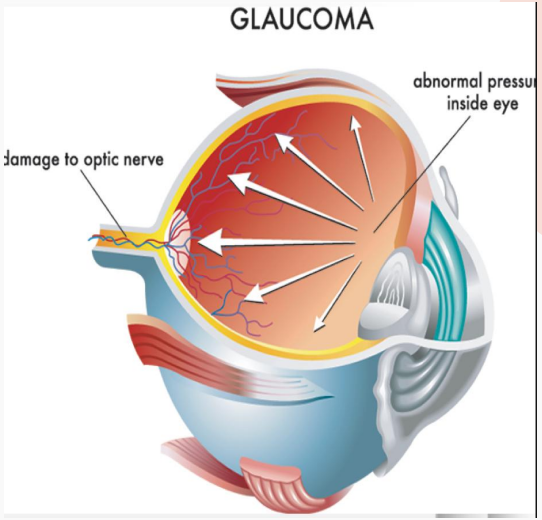
Opposite effects

Actions of prostaglandins

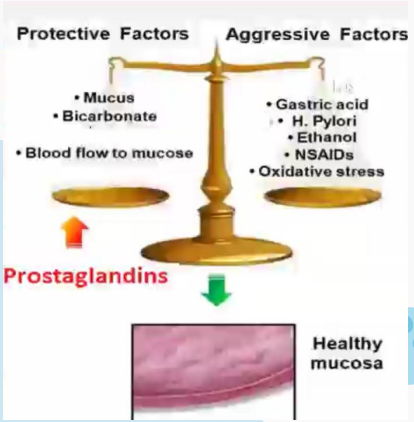
- They are pro-inflammatory
- Cause vasodilation (PGI2 & PGE2)
- High PG conc: inhibits of platelet aggregation
- Low PG conc: increases platelet aggregation
- Sensitize neurons to cause pain
- Induce labor (in last trimester to contract uterus)
- Decrease intraocular pressure
- Acts on thermoregulatory hypothalamus to increase body temperature
- Acts on kidney to increase glomelur filtration (Vasodilation increases permeability which means more filtration)
- Acts on stomach parietal cells to protect gastric mucosa (protects stomach)



Afferent arteriole is vasodilated by prostaglandins so the blood flow will increase and this leads to more Glomerular filtration

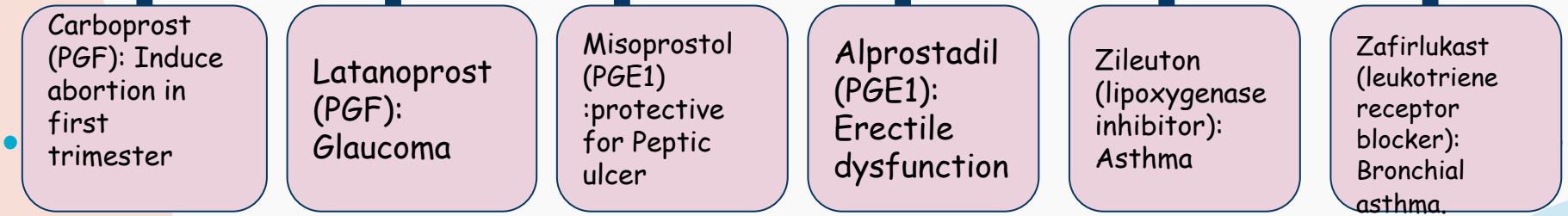


Prostaglandins will decrease the intraocular pressure by increasing the secretion of aqueous humor out of the eye and this will reduce the intraocular pressure



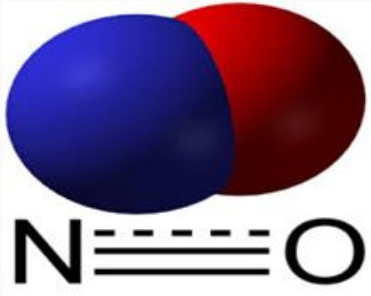
Prostaglandins help in stomach protection

Clinical uses of PGs analogs Carboprost (PGF): Induce abortion in first trimester



Extra information
Why we use analogs with PGF ?
Because usually PGF has short duration of action so we use analogs to provide similar action

Nitric Oxide



Nitric acid

Biosynthesis of nitric oxide:	Synthesized from L- arginine by nitric oxide synthase (NOS)
Nitric oxide stimulators	acetylcholine, 5-HT bradykinin & histamine , serotonin
Nitric oxide inhibitor	Hemoglobin

There are 3 isoforms of the enzyme nitric oxide synthase

Constitutive forms (physiological)

Neurons nitric oxide

- Neurons
- Skeletal muscle

Endothelial nitric oxide

- Endothelium
- Cardiac myocytes
- Osteoblasts
- Osteoclasts

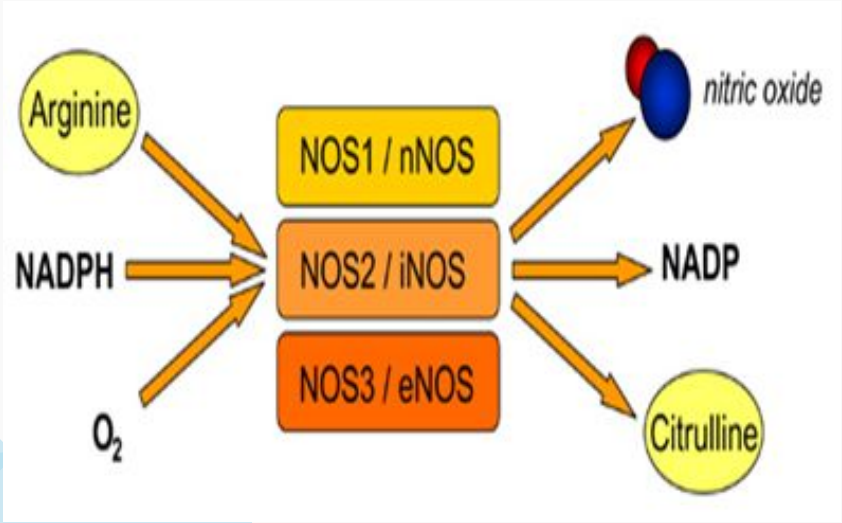
Inducible forms

(pathological)

-macrophages
-kupffer cells
-neutrophils
-fibroblasts
-vascular smooth muscle

Female dr note: Kupffer cells is macrophages liver

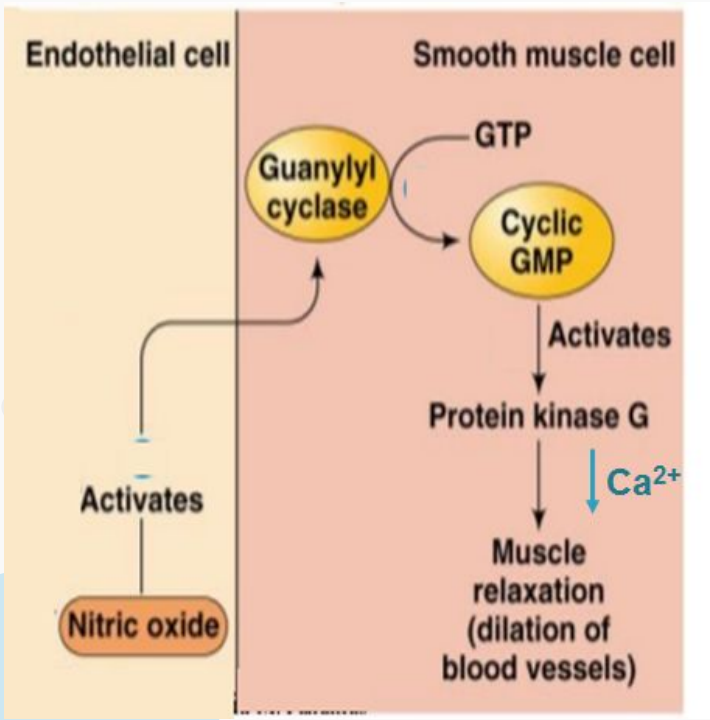
Female slides only:



Substrate → Product

Arginine	Citrulline
NADPH	NADP
O2	Nitric oxide

NO Mechanism of Action



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

explanation:

Step 1: nitric oxide activates the enzyme guanylyl cyclase enzyme

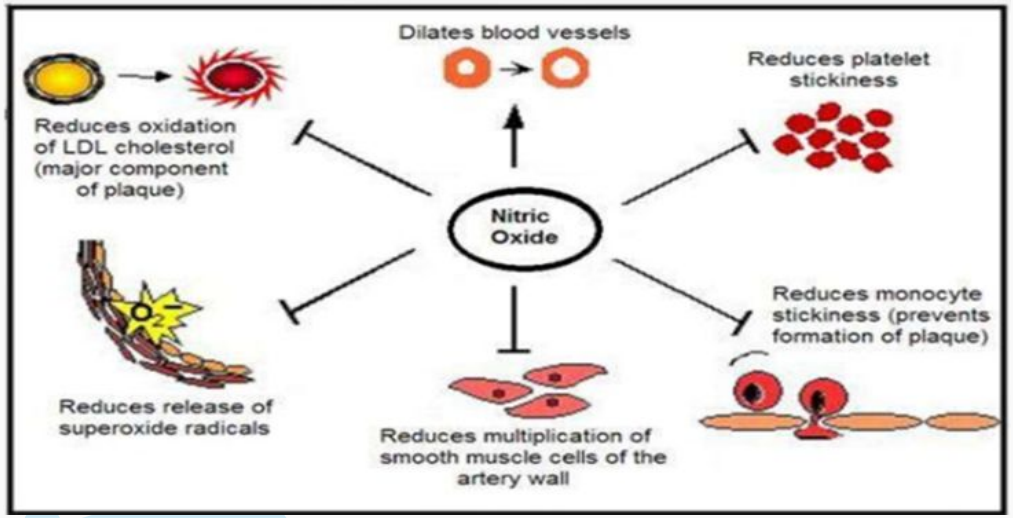
Step 2: guanylyl cyclase converts GTP to cyclic GMP

Step 3: cGMP activates protein kinase G

Step 4: protein kinase G reduces calcium level which leads to muscle dilation

Female Dr note:
Calcium acts on both heart and blood vessels

Actions of NO



Female dr notes: Unlike histamine which is stored in mast cells, nitric acid is produced on demand (only when the body needs it)

1. inhibition of platelets and monocytes adhesion and aggregation
2. Protection against atherogenesis
3. Inhibition of smooth muscle proliferation
4. Host defense cytotoxic effects pathogens
5. Cytoprotection

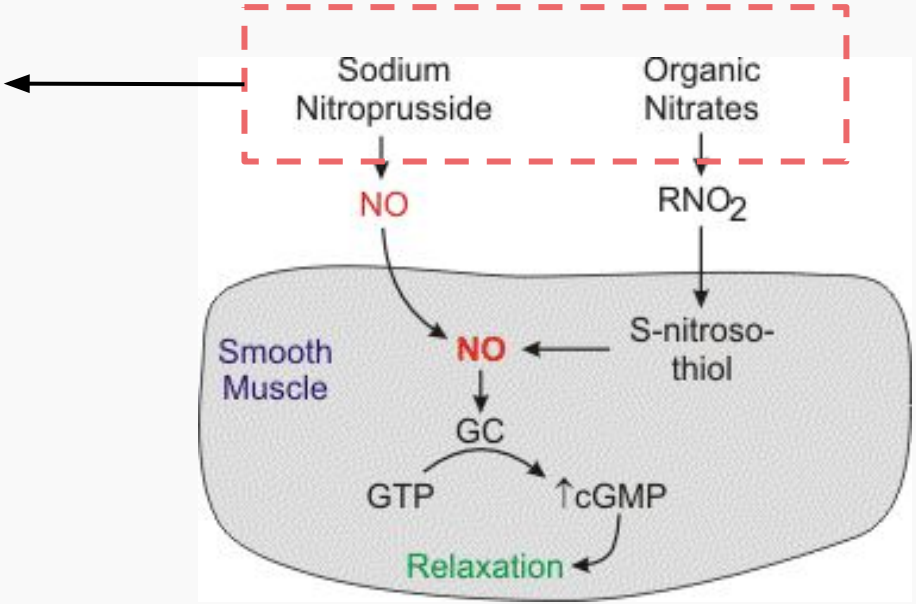
Actions of NO

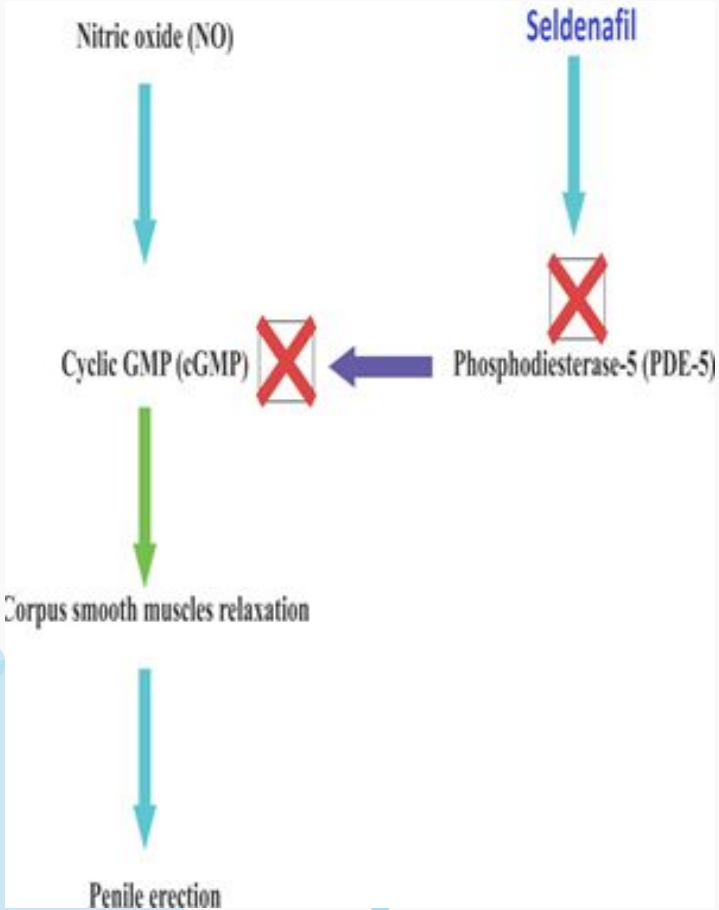
Neuronal Nitric acids	Endothelial Nitric acids	Inducible nitric acid
• long term potentiation (on nerves and nerves endings) • Cardiac function, peristalsis, sexual arousal	• Vascular tone, insulin secretion, airway tone, regulation of cardiac function and angiogenesis • Embryonic heart development	• In response to attack by parasites bacterial infection and tumor growth • Cause septic shock , autoimmune condition

Nitric oxide 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 is used in critical care to treat pulmonary hypertension in neonates (inhaled by the patients in emergencies)
4	NO is used in patients with right ventricular failure secondary to pulmonary embolism.
5	**Sildenafil** potentiates the action of NO on corpora cavernosa smooth muscle. (It is used to treat erectile dysfunction.)

Nitric acids donors

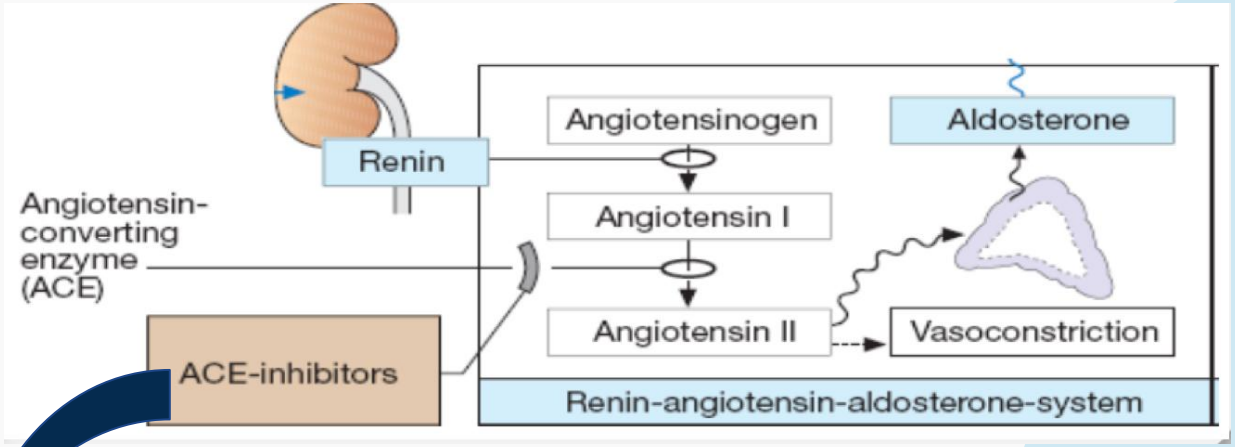




mechanism of Sildenafil:

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

Angointensin



Angiotensinogen : circulating protein in the blood that comes from the liver

Renin : circulating protein that comes from the kidney

Renin will convert Angiotensinogen to Angiotensin I (inactive)

ACE will convert Angiotensin I to Angiotensin II (Active)

Angiotensin II affection

1. Vasoconstriction will increase blood pressure
2. Increases aldosterone secretion and this will support blood pressure

when this whole system is activated ?
When there is a change in blood pressure

ال ACE هو الي يحول Angiotensin I الى Angiotensin II الي يرفع ضغط الدم
ف المرضى مع ضغط الدم العالي نعطيهم ACE inhibitors الي يثبط ال ACE ف يمنع تكوين angiotensin II الي يرفع ضغط الدم

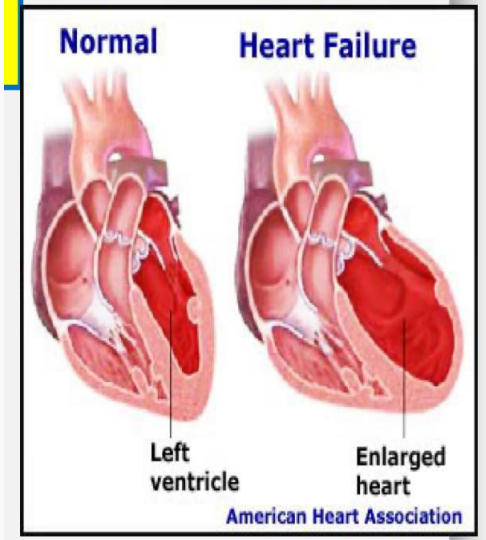
Actions of angiotensin II

1-Promotes vasoconstriction directly or indirectly by releasing NA & AD

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).

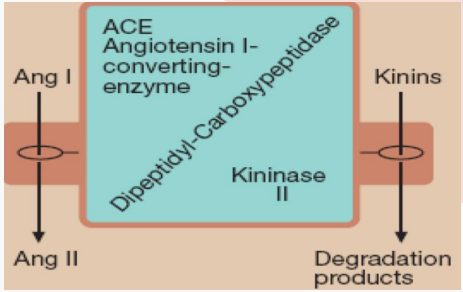


ANGIOTENSIN INHIBITORS

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

CLINICAL USES: Hypertension - Cardiac failure - myocardial infarction

Eg. Captopril , enalapril



ANGIOTENSIN RECEPTOR BLOCKERS

AT 1 receptor act has opposite effect to AT2 receptor

AT 1 receptors predominate in vascular smooth muscle, mediate most of the known actions of Ang, coupled to G proteins & DAG

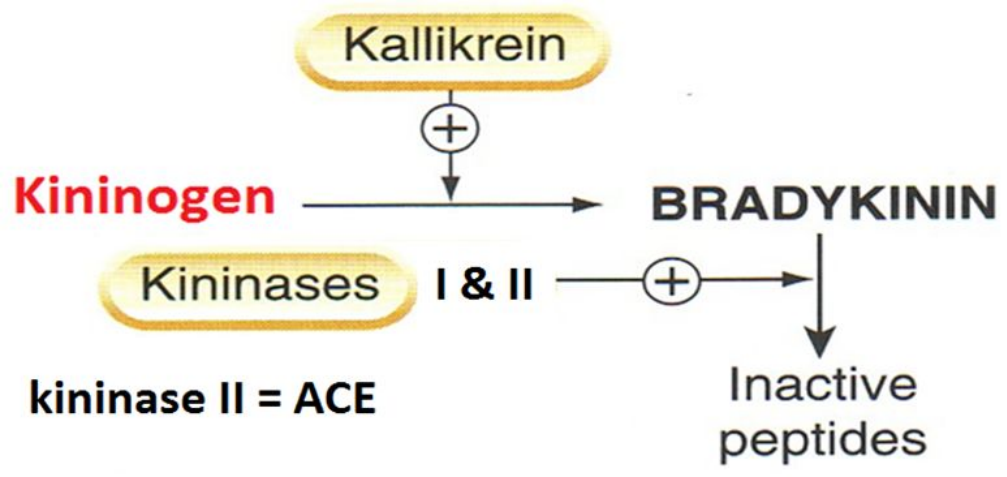
E.g. losartan,valsartan

The therapeutic uses of the ACE inhibitors and receptors are similar

Kinins

kinins

- Bradykinin
- kallidin



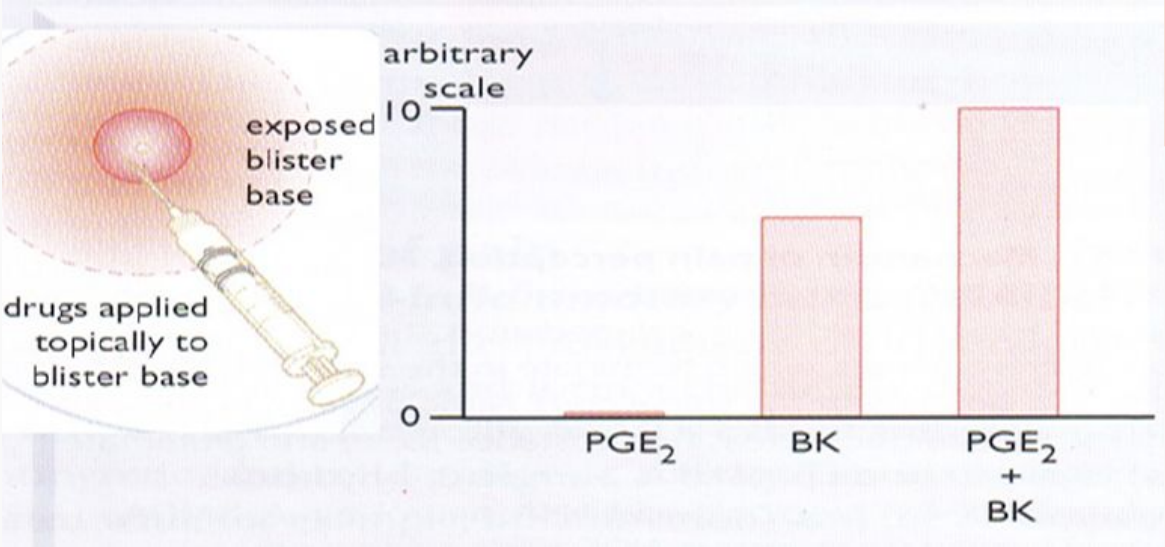
Bradykinin is formed by proteolytic cleavage of circulating proteins (kininogens)

Drs note:In this slide you must know:

1. kinogen with kallikrein will produce Bradykinin
2. Bradykinin is inactivated by kininase 1&2 or ACE

Actions of bradykinin

1. Potent Vasodilator, reduces blood pressure (10 times stronger than histamine)
2. If injected locally it dilates arterioles [generation of PGI release of NO] and increases permeability of post capillary venules (it's a vasodilator that produces other vasodilators)
3. Causes pain, this effect is potentiated by prostaglandins. 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



Dr note: if we inject PGE2 it causes inflammation
if we inject BK it causes a wider area of inflammation
If we inject PGE2+ BK they potentiate each other
(يعني يزودون مفعول بعض)

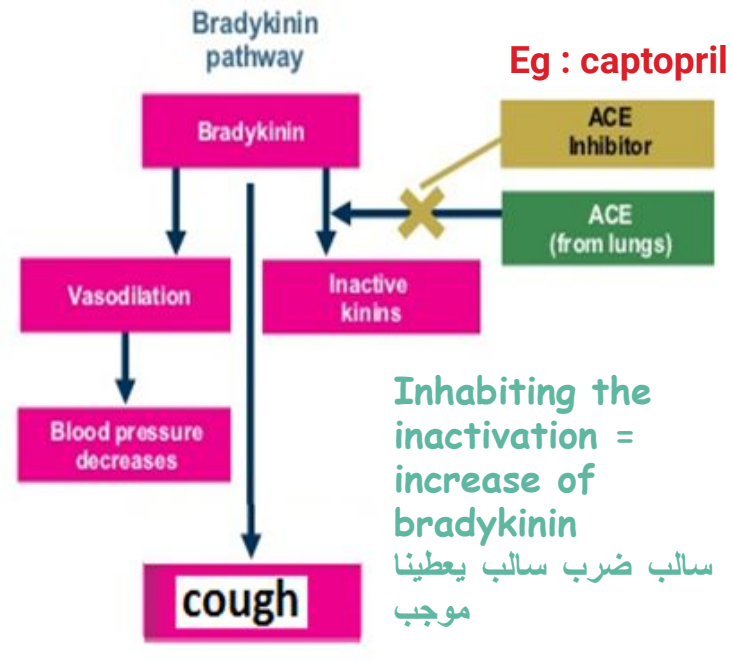
Receptors & clinical uses

1	Receptors B1 & B2 (both are G protein-coupled receptors)
2	B1 inducible under condition of inflammation
3	B1 receptor has low affinity to bradykinin plays a significant role in inflammation & hyperalgesia (hyperalgesia = pain sensation)
4	B2 constitutive High affinity to bradykinin & mediates the majority of its effects.

Drs note: which receptor has a higher efficacy? B2 receptor
B1 is only used in cases of inflammation and foreign objects

Therapeutic uses

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



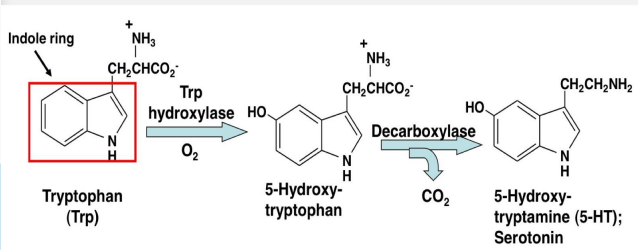
Increased bradykinin is implicated in the therapeutic efficacy & cough produced by ACEIs.

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

Serotonin (5-HT)

Serotonin (5-HT)

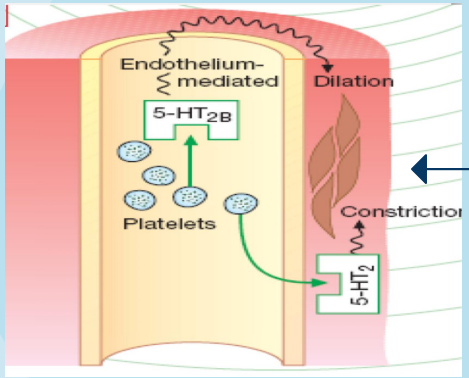
Definition : Serotonin is synthesized from the amino acid L-tryptophan



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

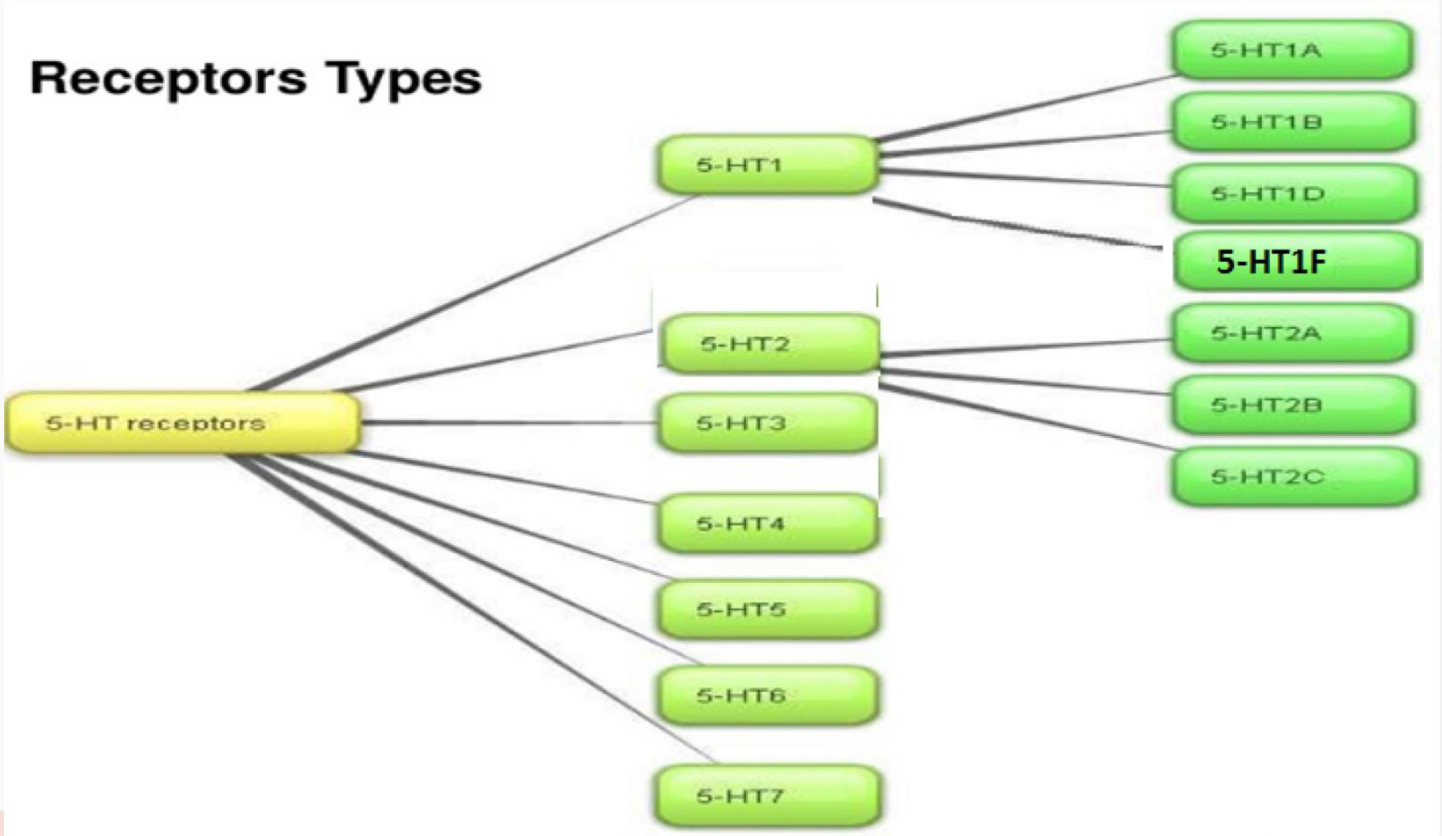
3] CNS: a neurotransmitter, in midbrain



Action :

- 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.
- 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.

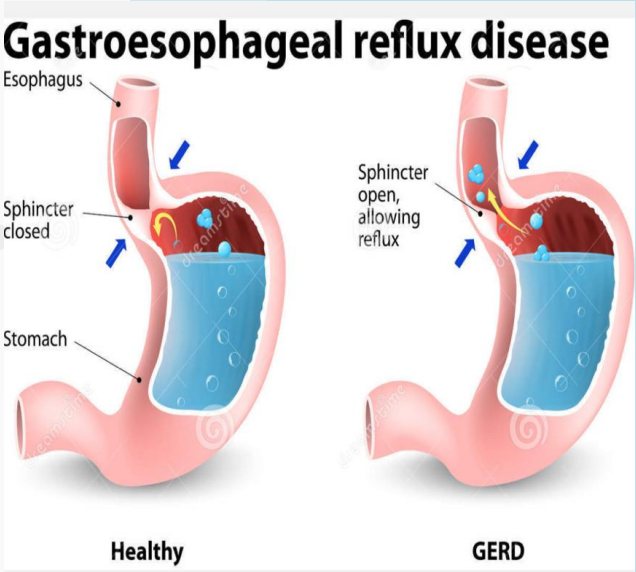
RECEPTORS


Receptors Types
5-HT receptors
5-HT1
5-HT1A
5-HT1B
5-HT1D
5-HT1F
5-HT2
5-HT2A
5-HT2B
5-HT2C
5-HT3
5-HT4
5-HT5
5-HT6
5-HT7

5 -HT RECEPTOR AGONISTS

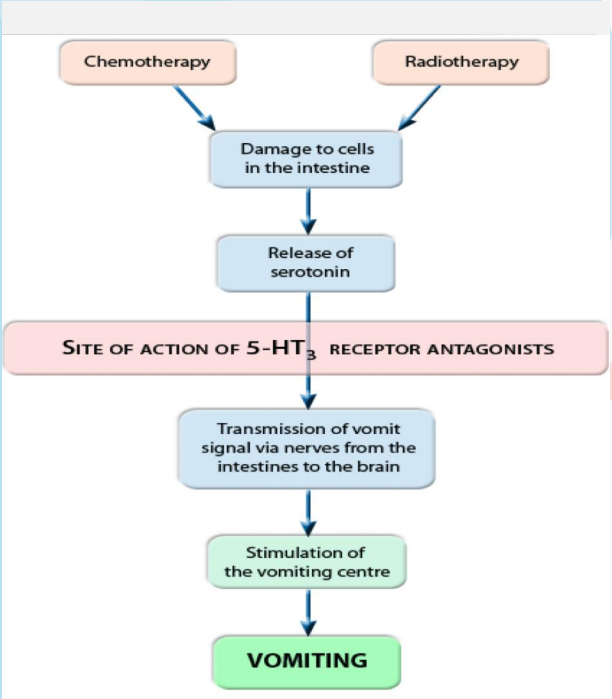
Buspirone:- 5-HT1A agonist, effective anxiolytic

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



5 -HT RECEPTOR ANTAGONISTS

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

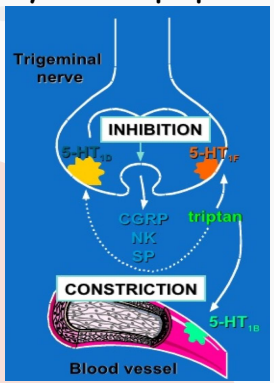


CLINICAL CONDITIONS IN WHICH 5-HT IS IMPLICATED

SUMATRIPTAN

5-HT 1B, 1D & 1F-receptor agonists, 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.

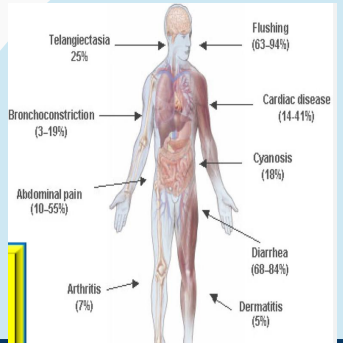


2 - CARCINOID SYNDROME

A malignant tumor of intestinal chromaffin cells

The tumor releases 5-HT, SP, PGs, kinins & histamine causing flushing, diarrhea, bronchoconstriction & hypotension

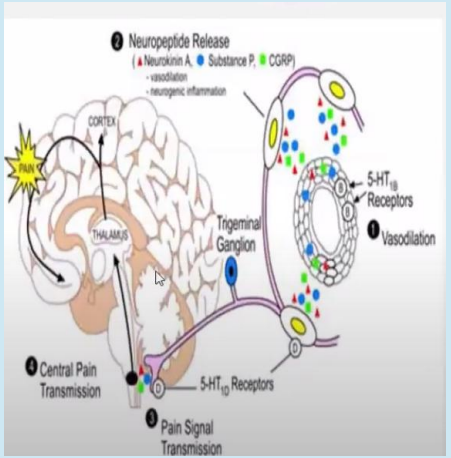
Serotonin antagonists (cyproheptadine, 5HT2 antagonist) could be administered to control diarrhea, flushing & malabsorption.



Migraine

Activation of trigeminal system leads to vasodilator peptide release promoting an inflammatory reaction

This increase flow of sensory traffic through the brain stem, the thalamus, the cortex



Quiz

1.H2 receptor blockers used to treat
A. Gastritis B. insomnia C. headache D. conjuntivitis

2. Histamine stored in :
A. Mast cells B. basophils C. lung D. All of them

3. which of the following increases bowel peristalsis
A)H1. B)H4. C)H5. D)H7

4. Which of the following causes a hypertrophy in the cardiac cells:
A)NO B) bradykinin C) angiotensin

5.Captopril is an example of
A) ACE inhibitor B) ACE activator C) Angiotensin receptor D) Renin inhibitor blocker

6.Which of the following receptors have High affinity to bradykinin
A)B1 B)B2 C)AT I D)AT II

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

Thank you

Team leaders

Lujain Alkhalaf - Salman Alotaibi

Female team members:

- Alanoud Albawardi
- Shaimaa Alqaoud
- Nada Alsaif
- Raneem Alanazi
- Ftoon Alenazi
- Areej Altamimi
- Sarah Alotaibi
- Rand Alshaya
- Rand aldajani

Male team members:

- Anas Alharbi
- Abdulrahman Alghamdi
- Abdullah Alotaibi
- Abdulaziz Aqusaiyer
- Bader Alshahrani
- Saad Alghadir
- Abdullah Alghamdi
- Mohammed Alsaqabi
- Abdulrahman Badghaish

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Special thanks to med439 team 🙏🏻