Lecture (8&9)

Autacoids

pharmacology
Team 438

MED438
KING SAUD UNIVERSITY

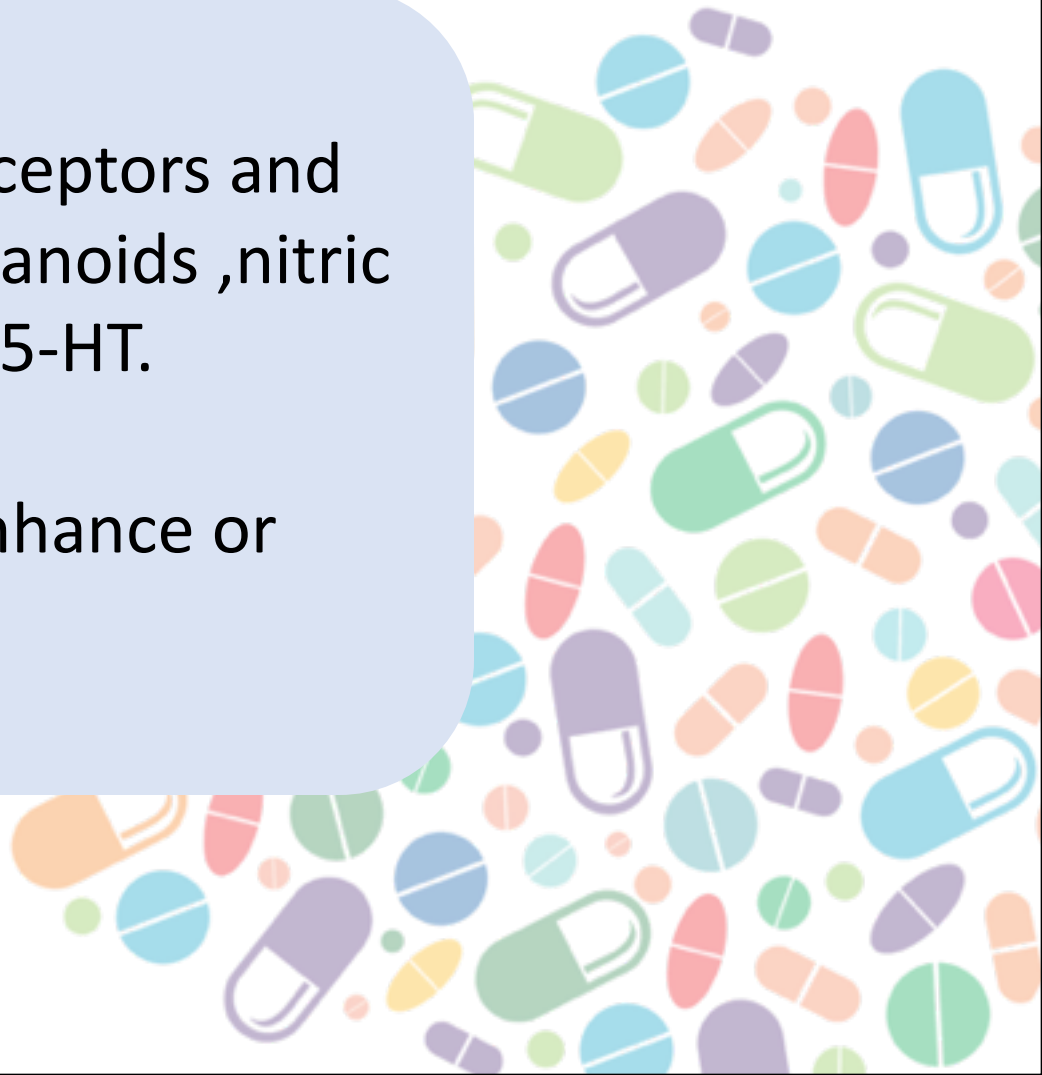
- Red : important
- Black : in male / female slides
- Pink : in girls slides only
- Blue : in male slides only
- Green : notes, Extra

Reviewed by Razan AlRabah & Khalid Alkhani

Editing link (very important)

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.



Definition of Autacoids

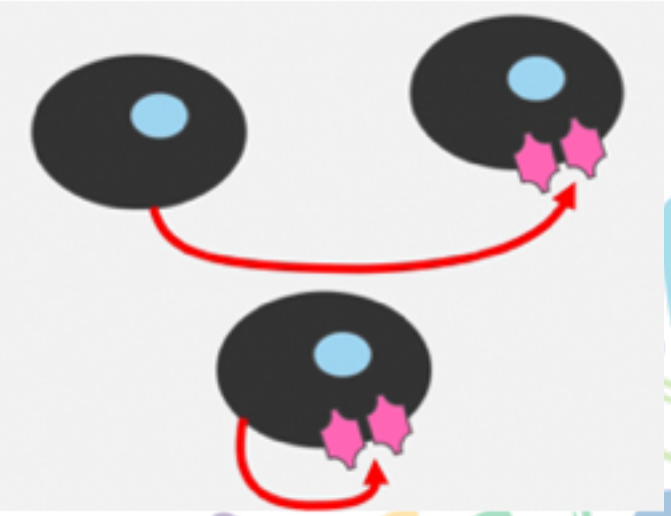
Autacoids are biomaterial substances that Are synthesized and metabolized locally they effect each of :

1. Glands
2. Nerves
3. Smooth muscles
4. Platelets and other tissues

They are either :

Paracrine →

Autocrine →

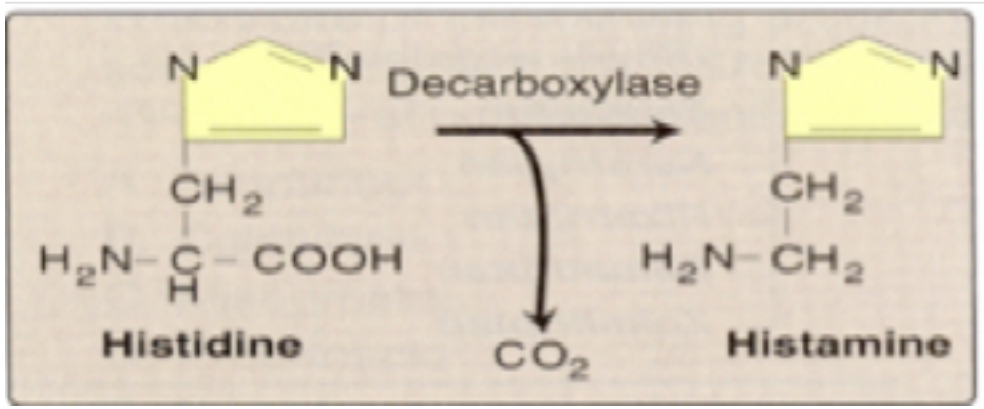


Derivatives of Autacoids

Original	Amino acids	Endogenous peptide	Fatty acids	Gas
Derivative	1.Histamine 2.Serotonin	1.Kinins 2.Angiotensin	Eicosanoid	Nitrogen (NO)

Histamine

- Histamine is synthesized from histidine
- Stored in mast cells & basophil & lungs



Types of 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 **CO** (cardiac output)
H_3	Central nervous system	**Neurotransmission**
H_4	Mast cells, Eosinophiles, T-cells	Regulating **immune** responses

H_2 stimulation causes **secretion** of **gastric acid** in stomach

H_1 stimulation causes smooth muscle, bronchiole, and uterus **contraction**

Administration of Histamine

Rapid IV

- fall in blood pressure
- increase CSF
- Headache

Slow IV & SC

- Increase temperature
- Flushing skin
- Increase heart rate & blood flow
- Edema

Intradermal

- Itching

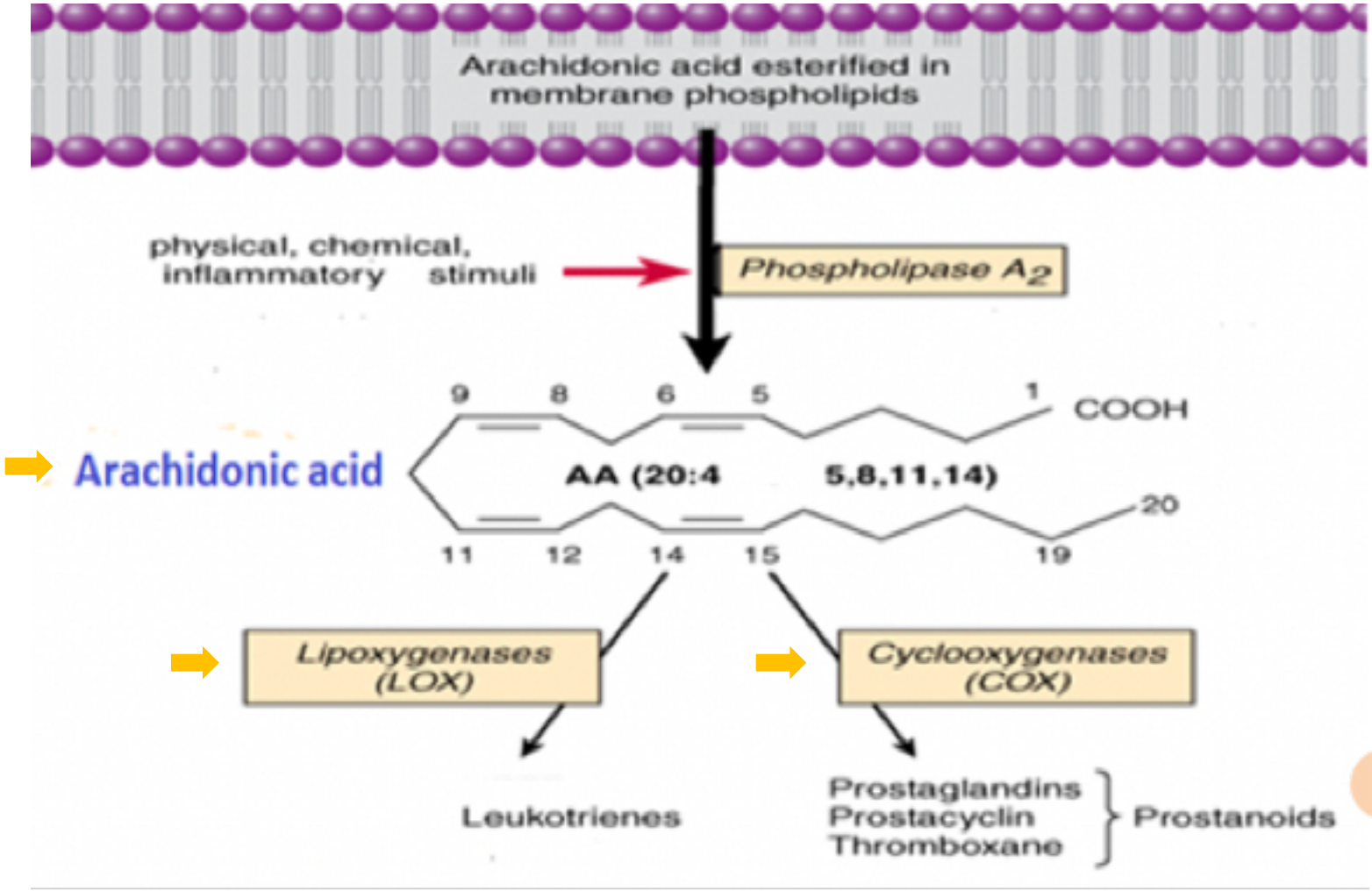
Types of H Blockers & examples & clinical uses

Physiological antagonist: epinephrine

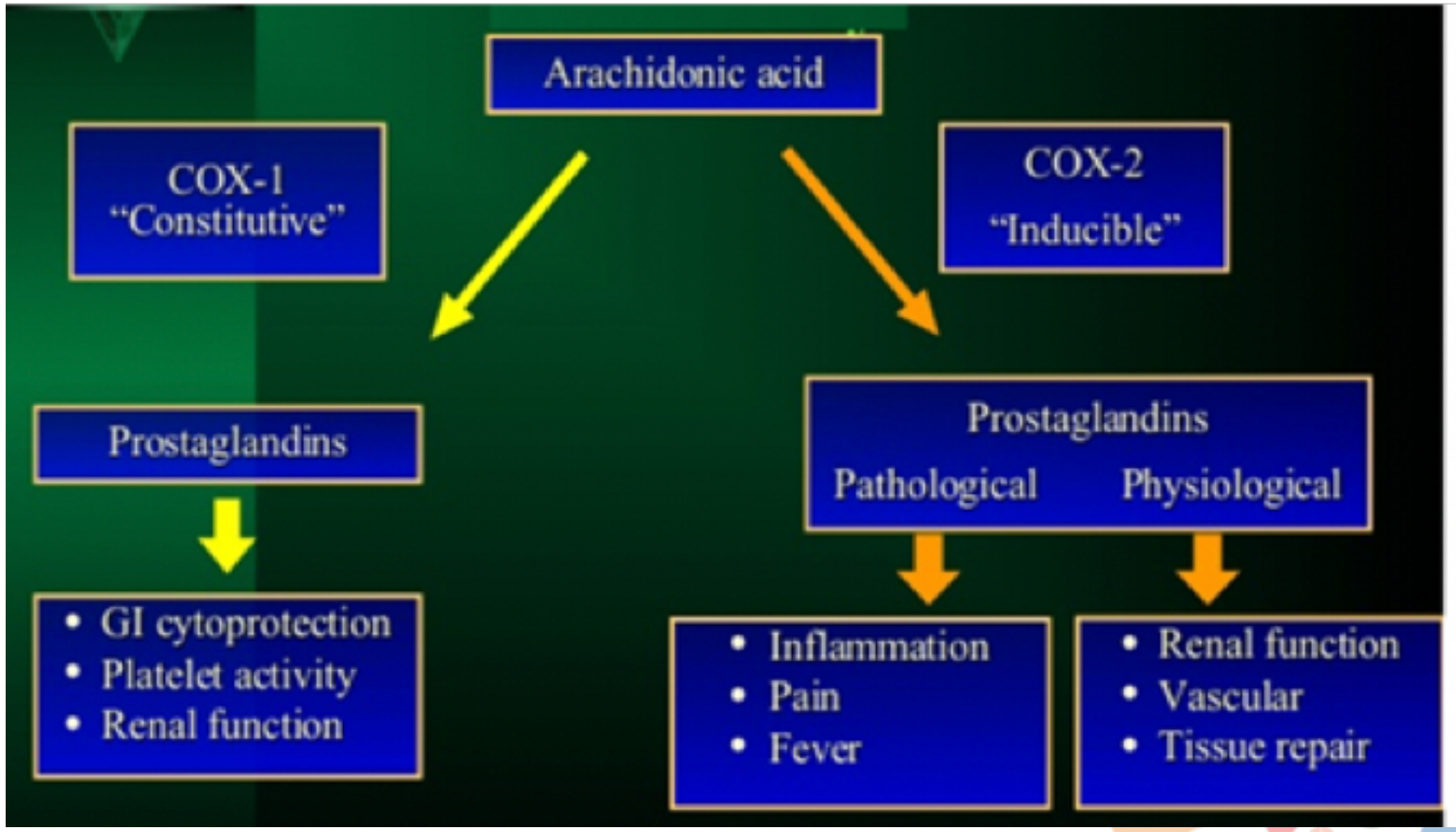
Type of blocker	examples	Clinical uses
H1	First Gen: Diphenhydramine Promethazine Second Gen: Cetirizine Fexofenadine	First generation: Has a sedating effect • Allergic rhinitis • urticarial • insomnia • Motion sickness ---------- Second generation: NO Sedating effect • Allergic rhinitis • Conjunctivitis • Urticaria
H2 (inhibits gastric acid secretion)	Cimetidine	Used in treatment of: 1-Gastritis (inhibits gastric acid secretion) 2-Peptic ulcer
H3 (causes dilatation of vessels in inner ear)	Betahistine	Used in treatment of: Vertigo and balance disturbances

Eicosanoids

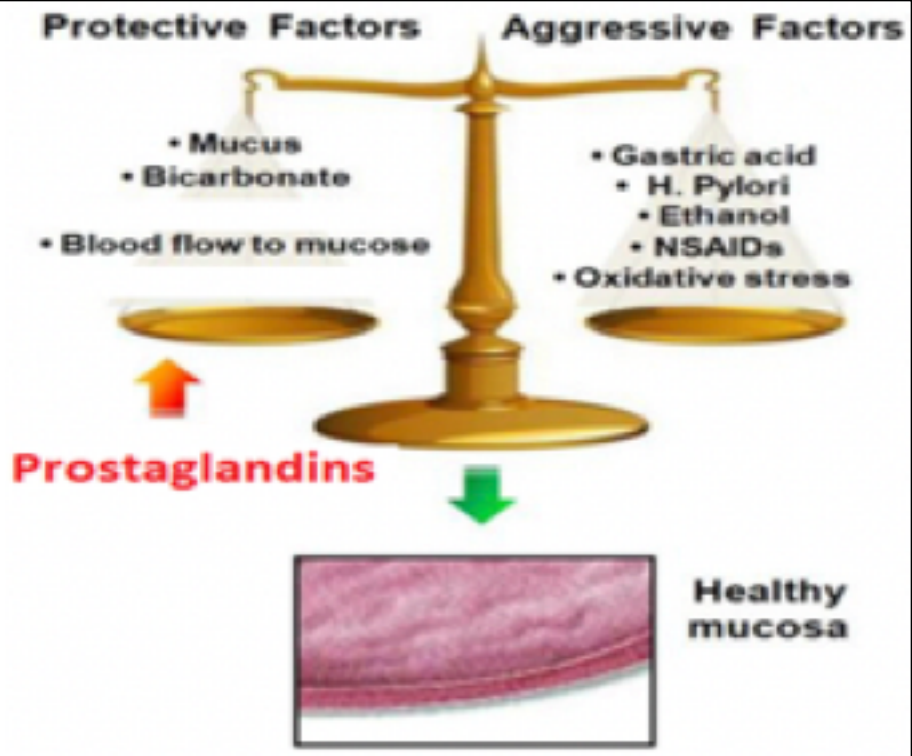
synthesis



Cox Isozymes:



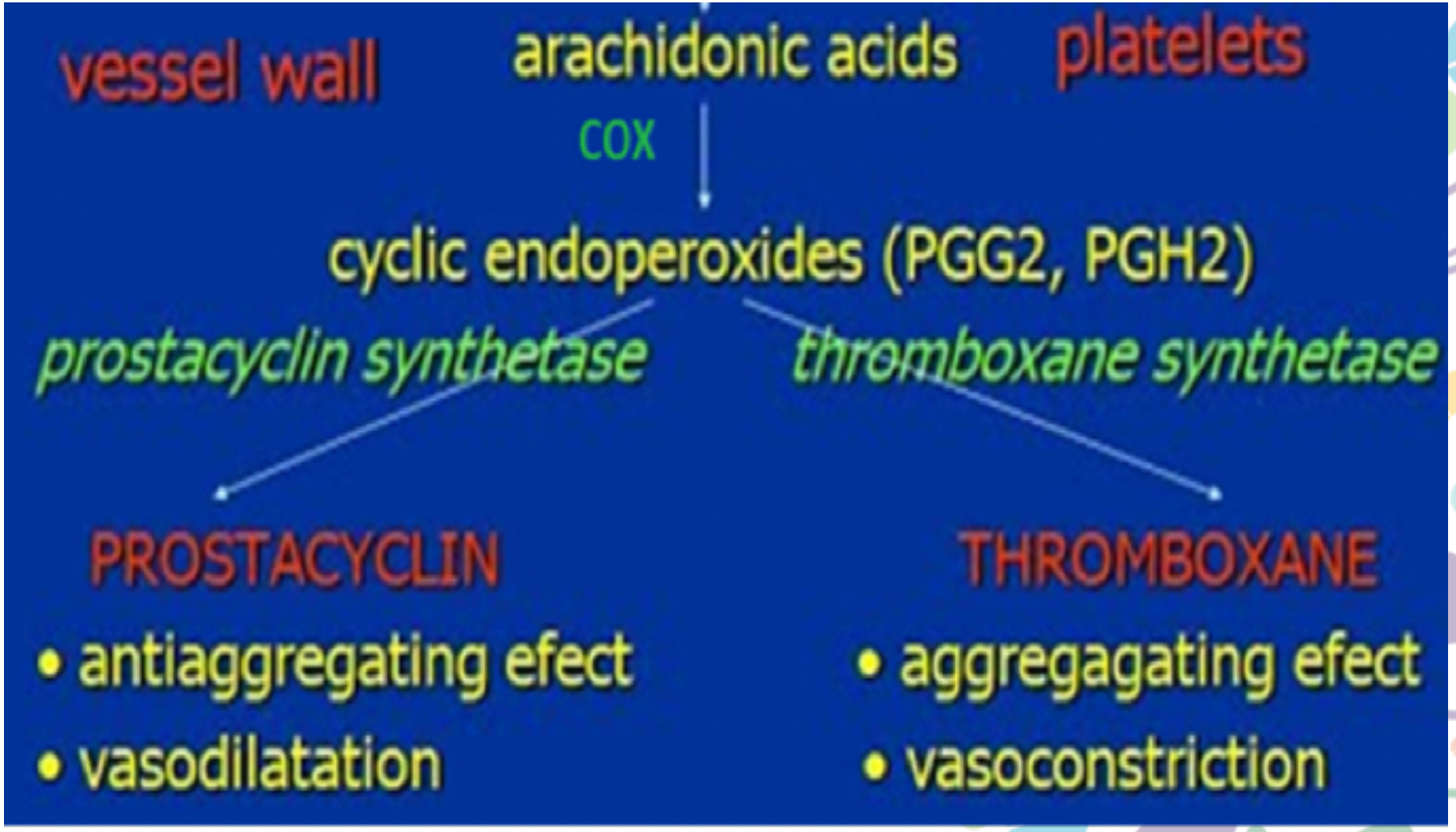
Prostaglandins



Actions of prostaglandins:

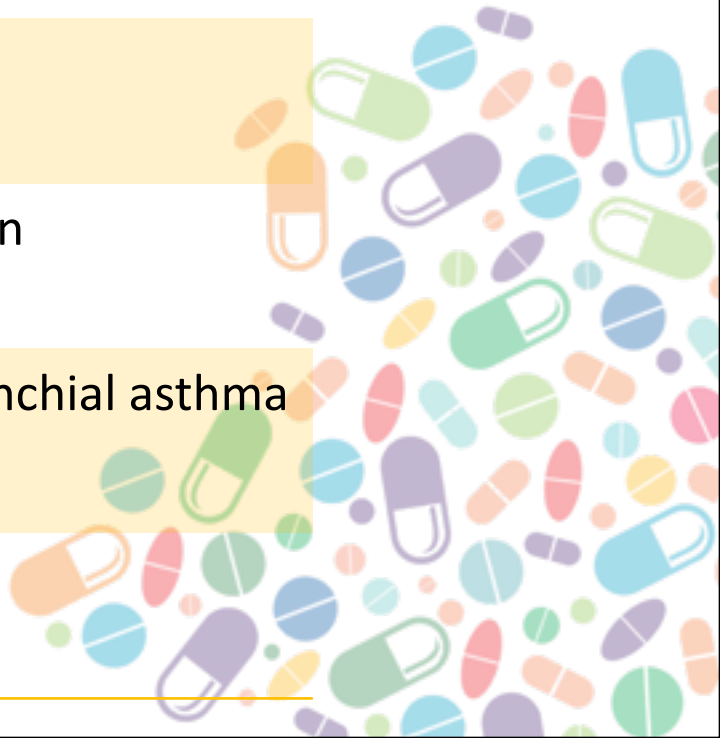
1. Proinflammatory
2. Vasodilatation
3. Inhibition & activation platelets aggregation
4. Pain
5. Induce labor
6. Decrease intraocular pressure
7. Acts on thermoregulatory center of hypothalamus to ↑ body temperature
8. Acts on kidney to increase glomerular filtration
9. Acts on cells of stomach to protect gastric mucosa

Difference between Prostacyclin and Thromboxane



Clinical uses of Prostaglandins analogs

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



Nitric Oxide (NO)

- Synthesized from L-arginine by nitric oxide synthase (NOS)
- NO release is

  Stimulated by

  5-HT (serotonin), acetylcholine, bradykinin, & histamine

  Inhibited By

  Hemoglobin

NOS isoform	Location	Action
NOS1/nNOS (physiological)	Neurons	Cardiac function, peristalsis, & sexual arousal
NOS2/iNOS (pathological)	Macrophages, neutrophils, & fibroblasts	In response to attack by parasites, bacterial infection, & tumor growth Causes septic shock & auto-immune conditions
NOS3/eNOS (physiological)	Endothelium	Vascular tone

Action of Nitric Oxide(NO)
1-inhibition of platelet and monocyte adhesion and aggregation
2-Inhibition of smooth muscle proliferation
3-Inhibition of angiogenesis
4-Protection against atherogenesis (formation of fatty plaques in the arteries)
5-Synaptic effect in the peripheral and central nervous system. Potentiation of long-term memory
6-Host defense and cytotoxic effect on pathogens. Quantity of (NO) act as free radical
7-Cytoprotection

Summary of NO Actions

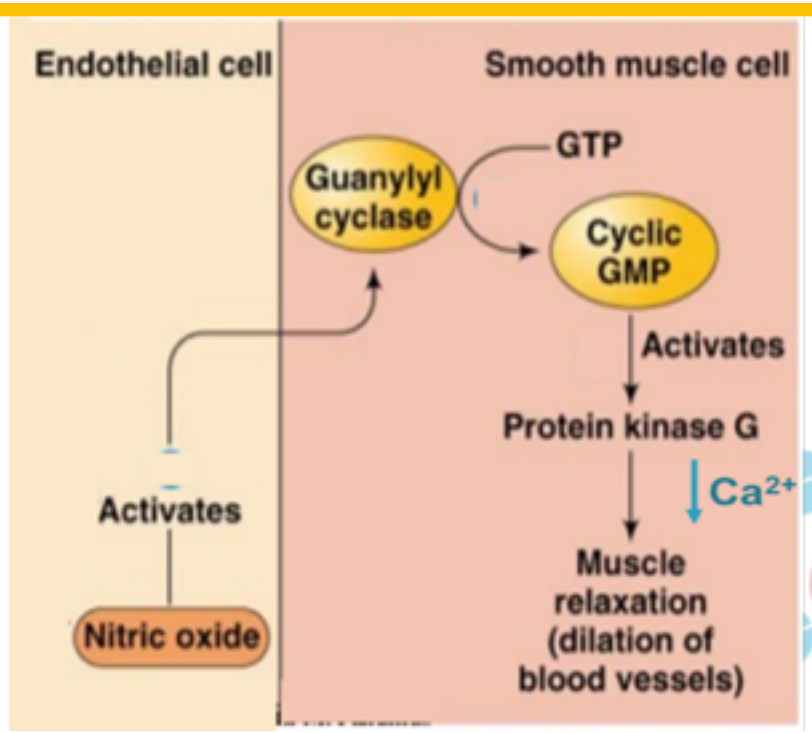
nNOS	eNOS	iNOS
• Cardiac function, Peristalsis, Sexual arousal	• Vascular tone,	• In response to attack by parasites, bacterial infection and tumor growth • Causes septic shock, autoimmune conditions

NO Mechanism of Action

Activating Guanylate Cyclase

↑ **cGMP**

↓ **Ca^{2+}**

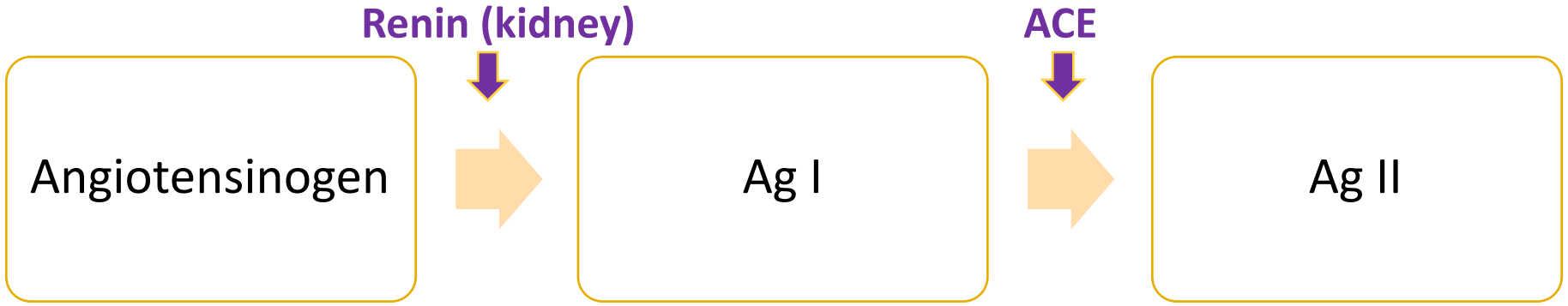


(No) Therapeutic uses:

1. NO is used in patients with right ventricular failure secondary to pulmonary embolism
2. Overproduction of NO occurs in neurodegenerative diseases (e.g. Parkinsonism)
3. NO is used in critical care to treat pulmonary hypertension in neonates (immature babies)
4. Endothelial NO production is reduced in patients with diabetes, hypertension & atherosclerosis
5. NO donors have uses e.g. in hypertension & angina pectoris (chest pain)

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

Angiotensin



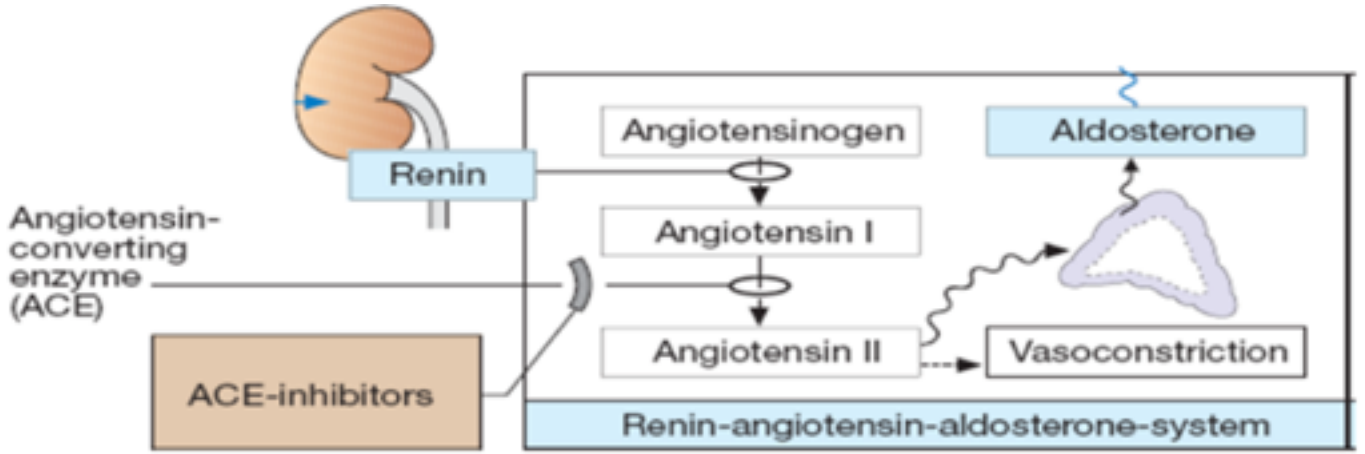
Actions of angiotensin II:

- Promotes vasoconstriction directly or indirectly by releasing NA & AD
- Increases force of contraction of the heart by promoting calcium influx
- Increase aldosterone release for sodium & water retention
- Causes hypertrophy of vascular and cardiac cells and increases synthesis and deposition of collagen by cardiac fibroblasts (remodeling)

ACE inhibitors	Angiotensin receptor blockers (ARB)
captopril	losartan
enalapril	valsartan

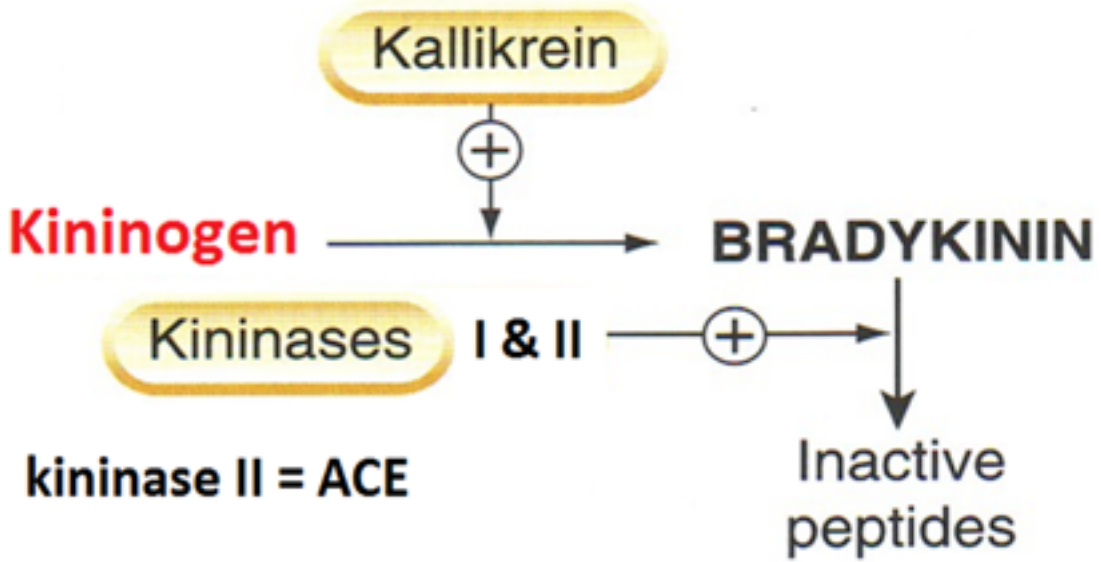
- Clinical uses:
  - Hypertension
  - Cardiac failure
  - Following myocardial infarction

- AT 1 receptors predominate in vascular smooth muscle, coupled to G proteins
- Similar uses to ACEI



Kinins

- Bradykinin & Kallidin



Actions of bradykinin:

- Causes pain, this effect is potentiated by prostaglandins. Has a role in inflammation
- Potent vasodilator reduces blood pressure
- 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:

- 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

Therapeutic uses:

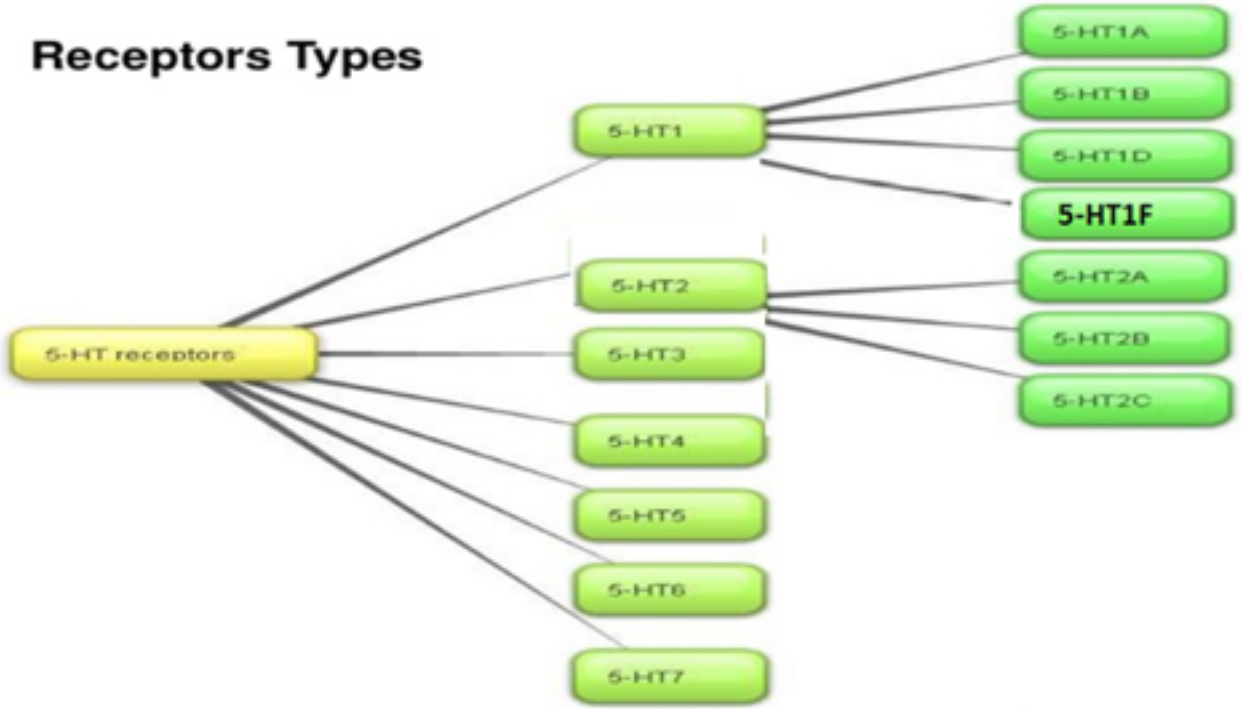
- No current therapeutic use of bradykinin
- Increased bradykinin is implicated in the therapeutic efficacy and cough produced by ACEIs

Serotonin (5-HT) – synthesized from L-tryptophan

Distribution:

- 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

5-HT receptor agonists	Buspirone, 5HT1A	effective anxiolytic
	Cisapride, 5HT4	used in gastroesophageal reflux & motility disorders
5-HT receptor antagonists	Ondansetron, 5HT3	antiemetic action, for cancer chemotherapy



Actions of 5-HT:

- GIT: 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: stimulates nociceptive neuron endings → pain
- CNS: stimulates some neurons & inhibits others, inhibits release of other neurotransmitters

Clinical conditions in which 5-HT is implicated:

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:

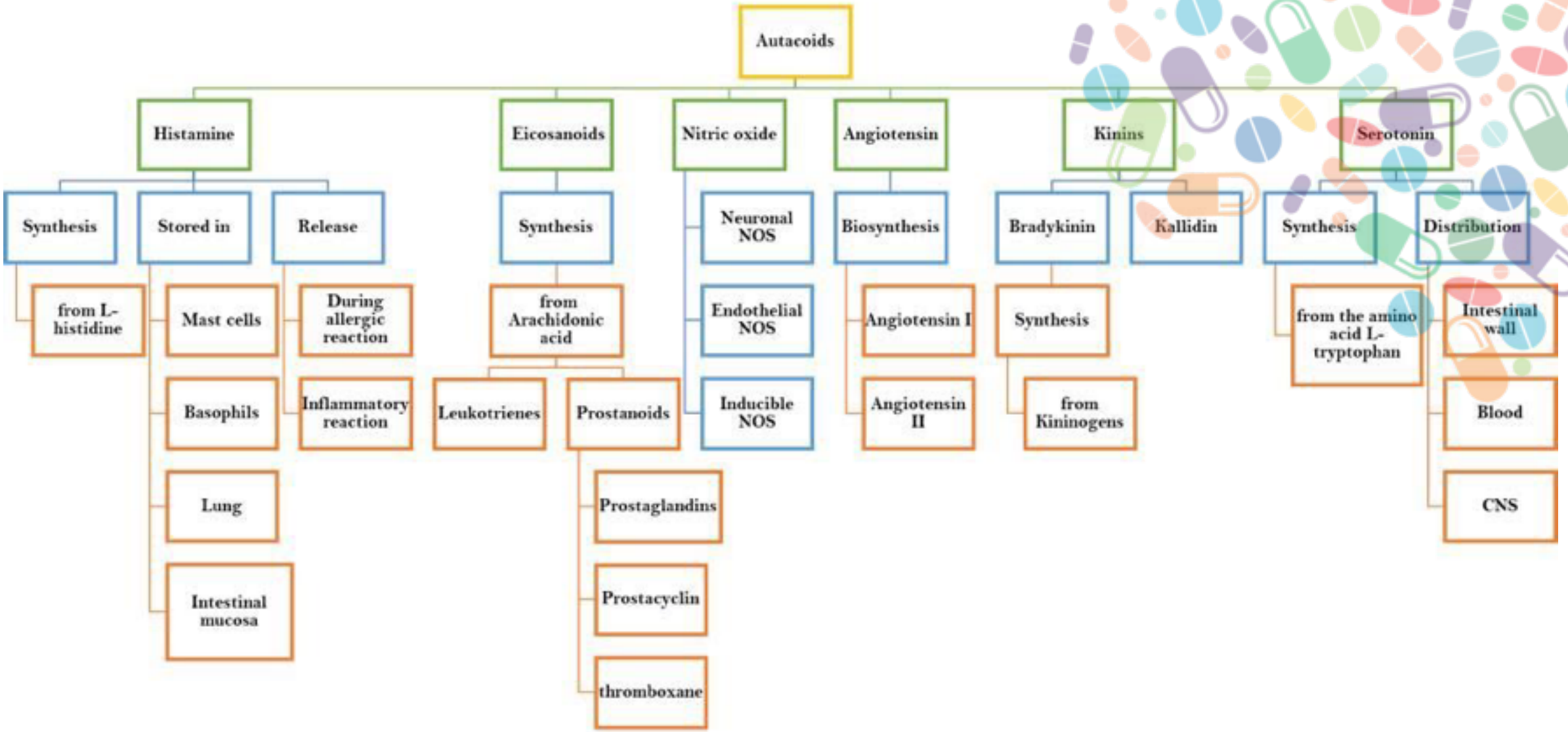
- Drug to treat migraines
- 5-HT1B, 1D &1F-receptor agonist, effective in acute migraine attack
- It binds to 5HT1B in cranial blood vessels causing vasoconstriction & 1D & 1F in presynaptic trigeminal nerve causing inhibition of pro inflammatory neuropeptide release

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


Autacoids
Histamine
Synthesis
from L-histidine
Stored in
Mast cells
Basophils
Lung
Intestinal mucosa
Release
During allergic reaction
Inflammatory reaction
Eicosanoids
Synthesis
from Arachidonic acid
Leukotrienes
Prostanoids
Prostaglandins
Prostacyclin
thromboxane
Nitric oxide
Neuronal NOS
Endothelial NOS
Inducible NOS
Angiotensin
Biosynthesis
Angiotensin I
Angiotensin II
Kinins
Bradykinin
Synthesis
from Kininogens
Kallidin
Serotonin
Synthesis
from the amino acid L-tryptophan
Distribution
Intestinal wall
Blood
CNS

MCQs

Rapid administration of Histamine causes?			
Flushing skin	Itching	Headache	AAAAAAAAAAAA
What inhibits Cox (cyclooxygenase)?			
Aspirin	Zileuton	Hemoglobin	Something
An action of 5HT…			
Decreasing motility	Inhibits aggregation	Decreasing capillary pressure	Secretion of gastric acid
Where is renin formed?			
Hepatocyte	CNS	Chromaffin cells	Kidney
The amino acid precursor for NO is…			
Tryptophan	Arginine	Histidine	Alanine

C, A, D, D, B

Good luck

Huge thanks to Abdullah Aldawood

Girls team leader

Nouf Alshammari

Boys team leader

Omar alghadeer

Girls team members

Reema Almutawa
Njoud Almutairi
Najla Alkilani
Shahad Althaqeb
Shahad Alsahil
Deana Awartani
Joud Alkhalifah
Reema Alserhani
Noura Almazrou

Boys team members

Abdulaziz Alghamdi
Alwaleed Alzunaidi
Abdulrahman Bedaiwi
Mohsen Almutairi
Bader Aldhafeeri
Abdullah Alassaf
Bassem Alkhuwaitir
Nasser Almutawa
Ziyad Alshareef
Mohammed Alshehri