Autocrine and Paracrine mediators and their antagonists

Dr.Abdul latif Mahesar
Pharmacology.

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Intended learning objectives.

- Cell to cell communication
- local hormones which play role in communication
- Histamine, Eicosanoids ,nitric oxide , Angiotensins, kinins.
- their synthesis and role in body functions
- Agents which increase or block their functions

• HISTAMINE

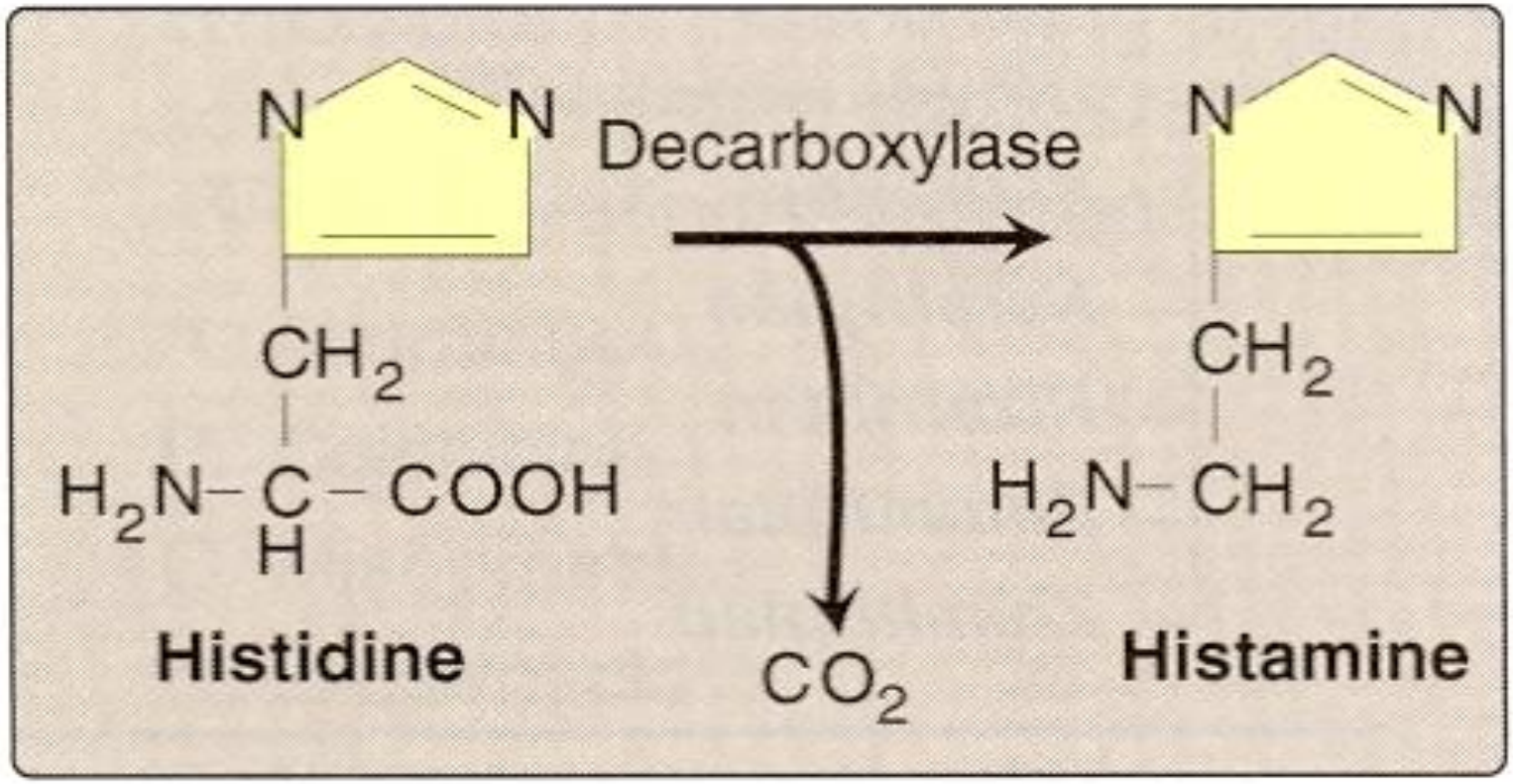
- It is an amine synthesized from an amino acid histidine
- Stored in vesicles

Storage Sites

- Highest amounts in ***mast cells***
- **Basophils**
- **Skin**
- **Lung**
- **Intestinal mucosa**
- **Stomach**
- **Brain**

Bio synthesis

it is synthesized by decrboxylation of amino acid histidine



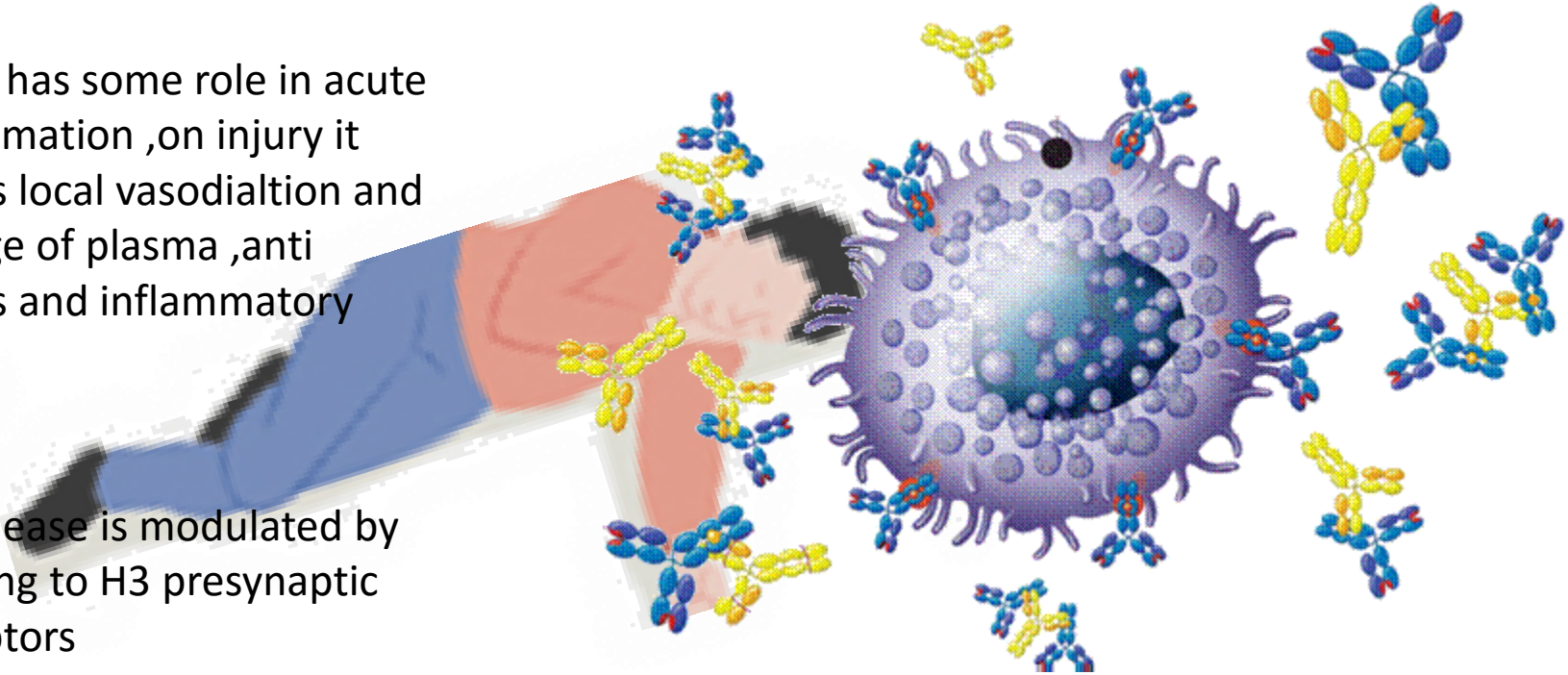
RELEASE

❖Primary mechanism, during allergic reactions on sensitizing [**IgE antibody** interacts with **antigen** on the surface of mast cells]

Mast cells get degranulated and release histamine and leads to allergic reactions.

It also has some role in acute inflammation ,on injury it causes local vasodialtion and leakage of plasma ,anti bodies and inflammatory cells.

Its release is modulated by binding to H3 presynaptic receptors



- Enzymes as trypsin or drugs such as morphine or other chemicals can also liberate histamine

- Tissue injury by trauma or burn

Histamine receptors

Receptor Type	Major Tissue Locations	Major Biologic Effects
H_1	smooth muscle, endothelial cells	acute allergic responses
H_2	gastric parietal cells	secretion of gastric acid
H_3	central nervous system	neurotransmission
H_4	mast cells, eosinophils, T cells	regulating immune responses

Effects Of Histamine

Pain ,itching,hives

Hypotension, tachycardia, flushing

- **Headache, visual disturbances, increase**
- **skin temperature**

- **Excessive secretion of gastric acids,diarrhea**
- **Bronchoconstriction, dyspnea,**

Histamine receptors antagonists

Physiologic antagonists: its effects can be reduced by physiologic antagonism such as epinephrine which acts on different receptors but produces effects opposite to histamine especially in anaphylaxis.

Specific receptor blockage:

Of Blocking of histamine receptors.

Specific histamine blockers are indicated in particular receptor stimulations.

First generation H1 receptor Blockers.

Diphenhydramine ,

cyclizine ,

promethazine

Second generation H1 receptor blockers

Loratidine

Citrizine

Diphenhydramin (First generation)

H_1 antagonists (Blockers)

- Has a Sedating effect
- Clinical uses :
  - Insomnia
  - Motion sickness

Loratadine (Second generation)

- **Non-sedating effect**

Clinical uses

- **Allergic conditions as :**
  - **allergic rhinitis**
    - **Conjunctivitis**
      - **Urticaria**

Cimetidine

H_2 antagonists

- Histamine plays an important role in the formation and secrtion of HCl by the activity of H2 receptors. Blocker of H2 receptors inhibit of gastric acid secretion
- Used for the treatment of
- peptic ulcers

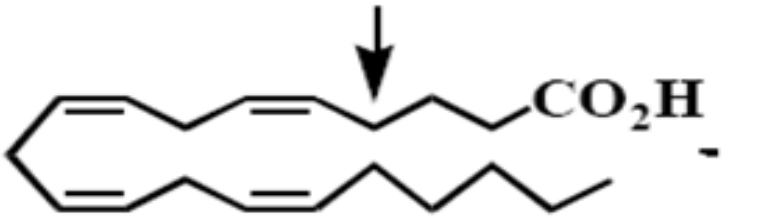
BETAHISTINE

H_3 antagonists

- Its effect produced is dilatation of blood vessels in inner ear.
- Used in treatment of
- vertigo and Balance disturbances.
- May produce headache and insomnia.

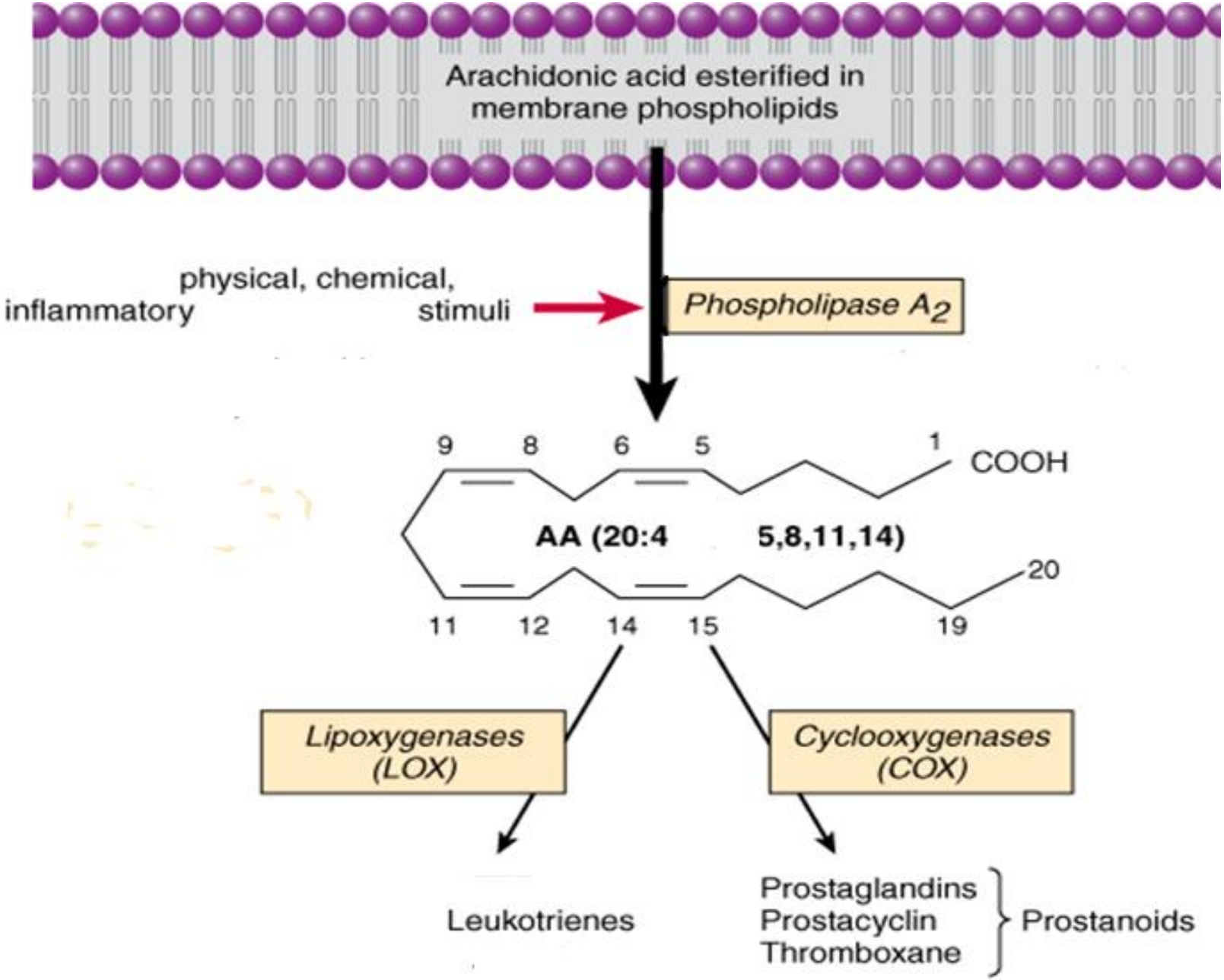
Eicosanoids

These are 20 carbon atom fatty acids.

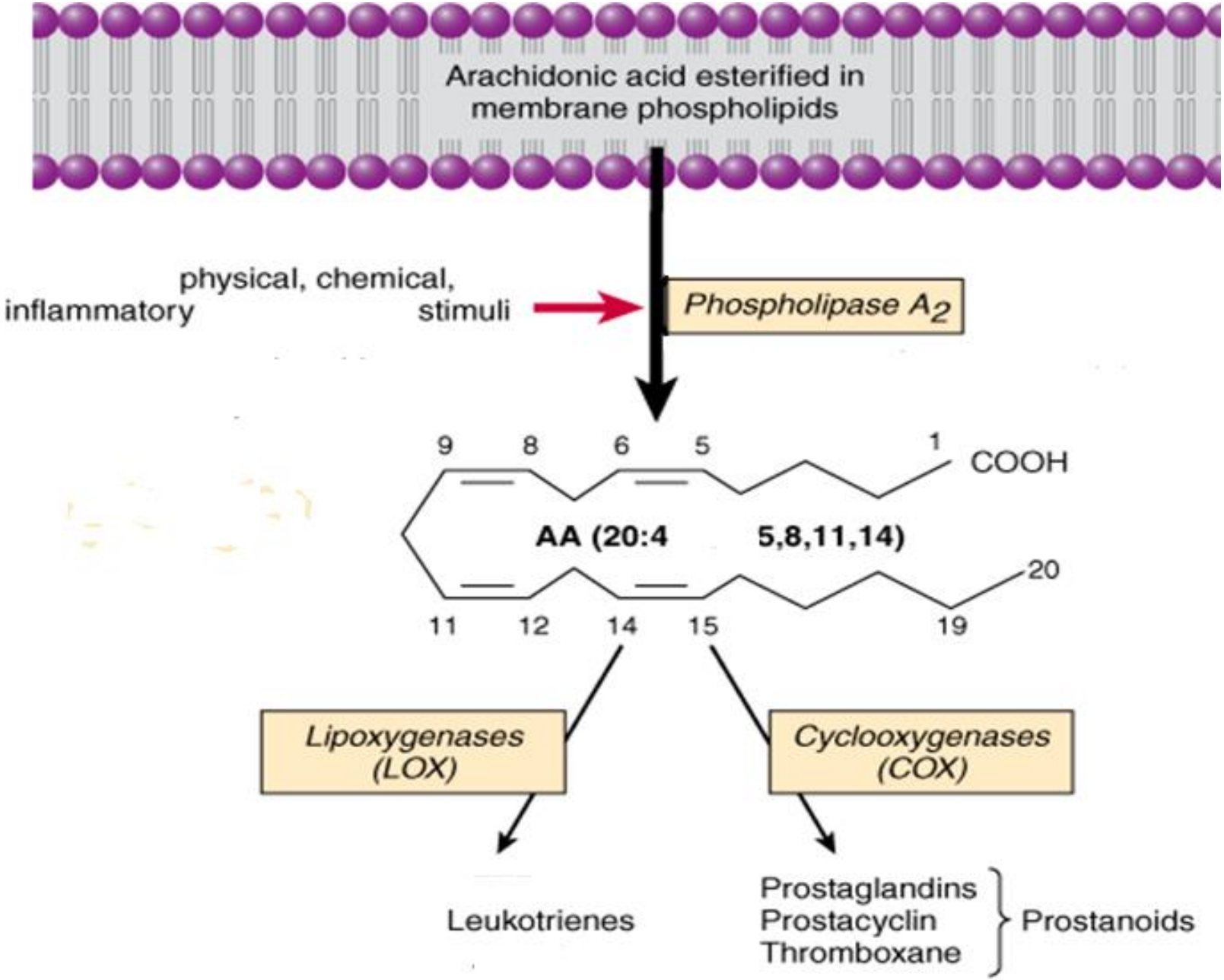


Arachidonic Acid or $20:4^{\Delta 5,8,11,14}$

PG2 Series


Arachidonic acid esterified in membrane phospholipids
physical, chemical, inflammatory stimuli
Phospholipase A2
9 8 6 5 1
COOH
AA (20:4 5,8,11,14)
20
11 12 14 15 19
Lipoxygenases (LOX)
Cyclooxygenases (COX)
Leukotrienes
Prostaglandins
Prostacyclin
Thromboxane
Prostanoids

INHIBITORS OF EICOSANOIDS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INHIBITORS OF EICOSANOIDS

Actions of prostaglandins

Causes vasodilatation of vascular smooth muscle cells

Causes inhibition of platelets aggregation

Sensitize neurons to cause pain

Induce labor

Decrease intraocular pressure

Acts on thermoregulatory center of hypothalamus

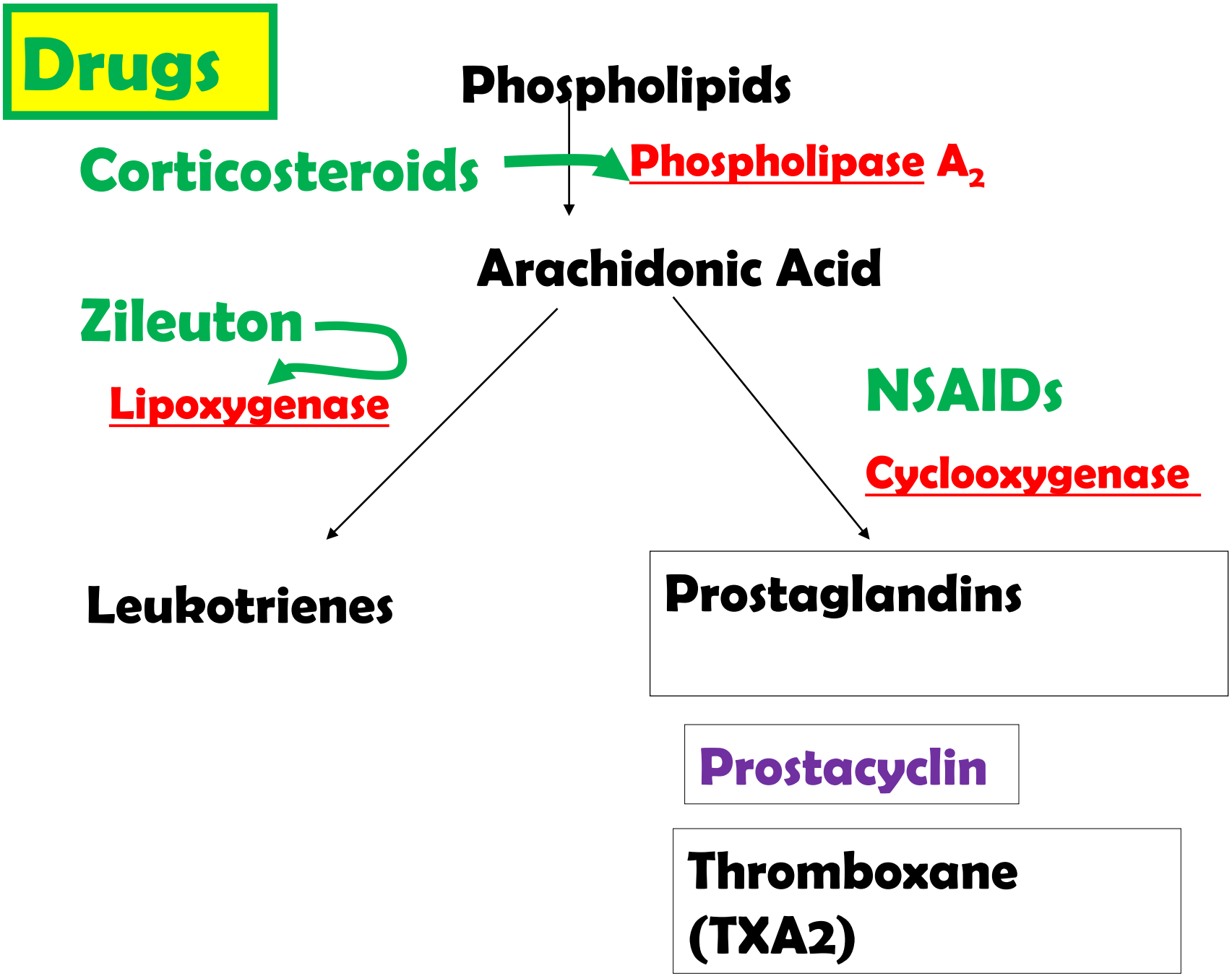
Acts on kidney to increase glomerular filtration

Acts on parietal cells of stomach to prevent gastric mucosa

Prostaglandin actions.

that stimulate contractility of the uterine
and other smooth muscle and have the ability to lower blood pressure, regulate acid secretion of the stomach, regulate body
temperature and platelet aggregation, and control inflammation and vascular perme ability.
They also affect the action of certain hormones.
First found in semen, they have since been found in cells throughout the body and in menstrual fluid.

Prostaglandins are used clinically to control postpartum hemorrhage, to temporarily manage patent ductus arteriosus, and to treat impotence in men
prostaglandin injections into the amniotic sac, an in-
hospital procedure, have been used as an **ABORTION TECHNIQUE** in pregnancies after the 16th week. About 30 minutes after an injection of prostaglandin $F_{2\alpha}$, contractions begin, and
abortion takes place within 19 to 20 hours.
These are also used in induction of labour.

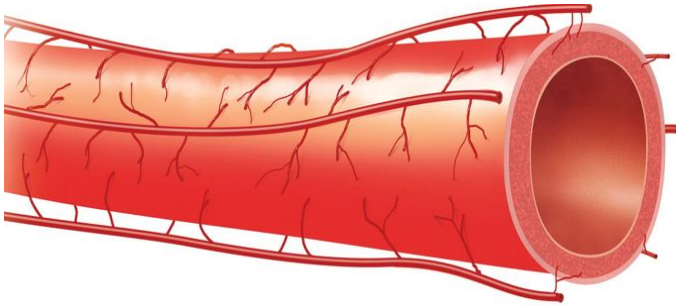

Drugs
Phospholipids
Corticosteroids
Phospholipase A_2
Arachidonic Acid
Zileuton
Lipoxygenase
NSAIDs
Cyclooxygenase
Leukotrienes
Prostaglandins
Prostacyclin
Thromboxane
(TXA2)

Comparison in actions between

- **Prostaglandins**
  - **Thromboxane A2**

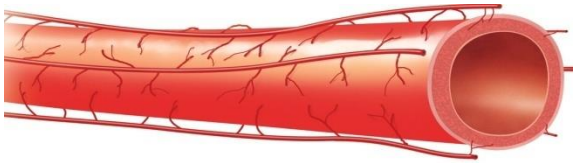
Vascular smooth muscles:

Prostaglandins



Potent vasodilators .

Thromboxane A_2

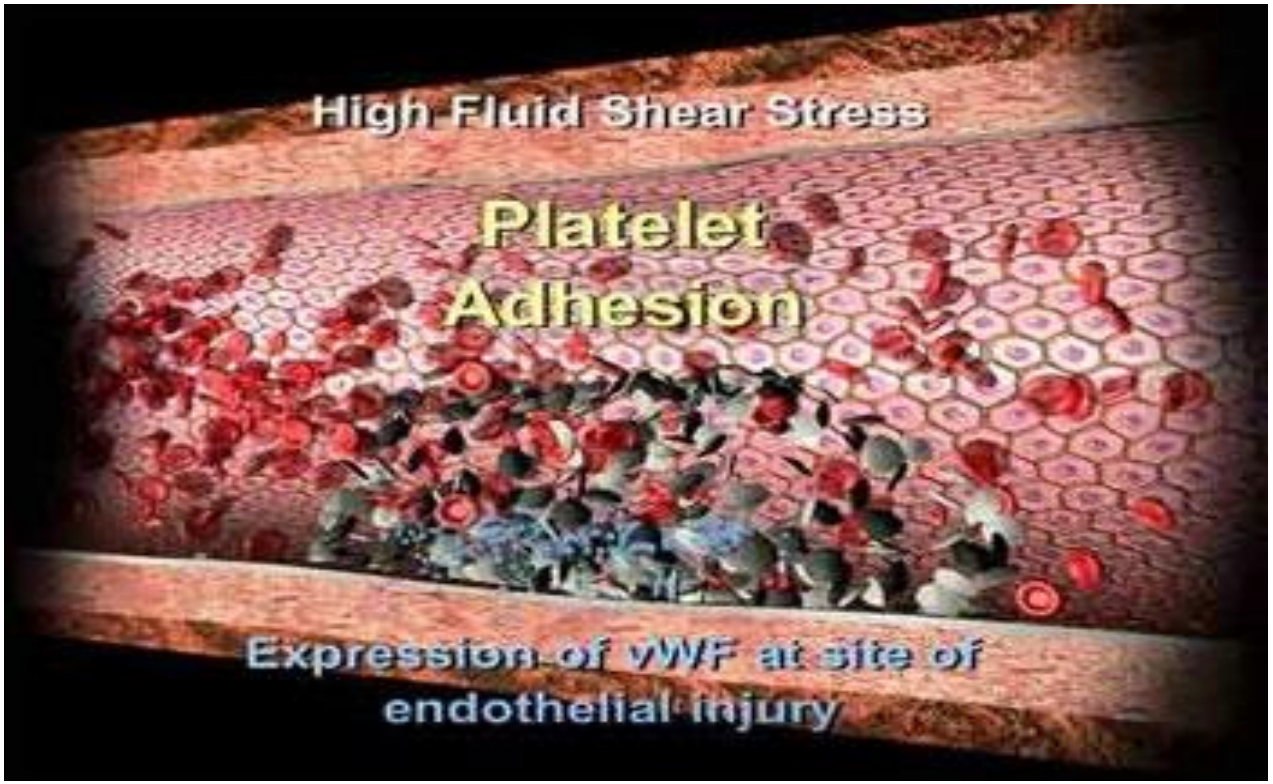


Potent vasoconstrictor.

Blood:

TXA2

a potent inducer of platelet aggregation.



Prostaglandins

inhibit platelet aggregation

INFLAMMATION:

- **Both play important role in inflammatory reactions.**

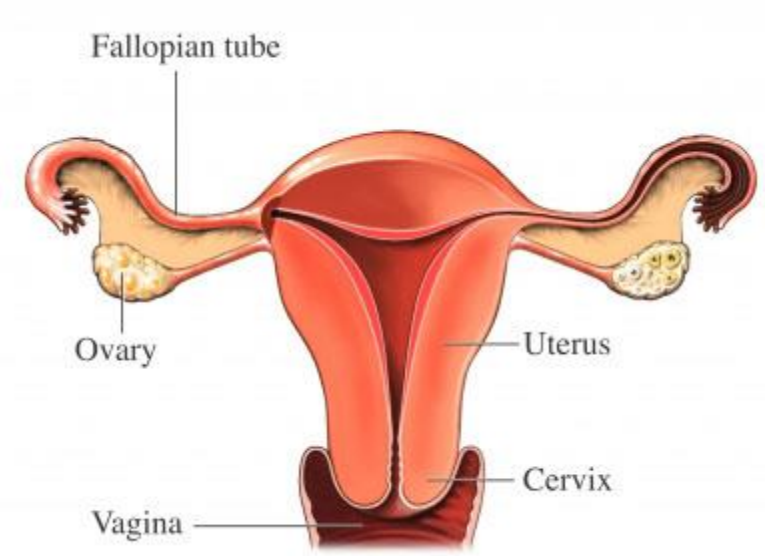
-**Prostaglandins** **(bronchorelaxation)**

BRONCHIAL SMOOTH MUSCLE:

-**Thromboxane**

(bronchoconstriction)

Uterine smooth muscle:

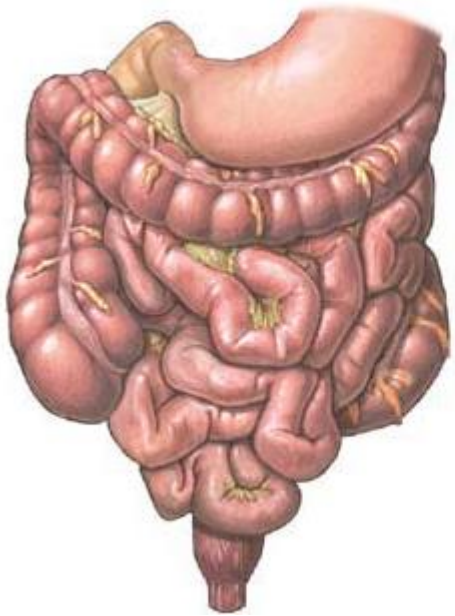


Prostaglandins increase uterine contractions →
Menstruation/ Dysmenorrhea/ Labor contractions

GIT SMOOTH MUSCLE:

- **Prostaglandins**

↑GIT motility



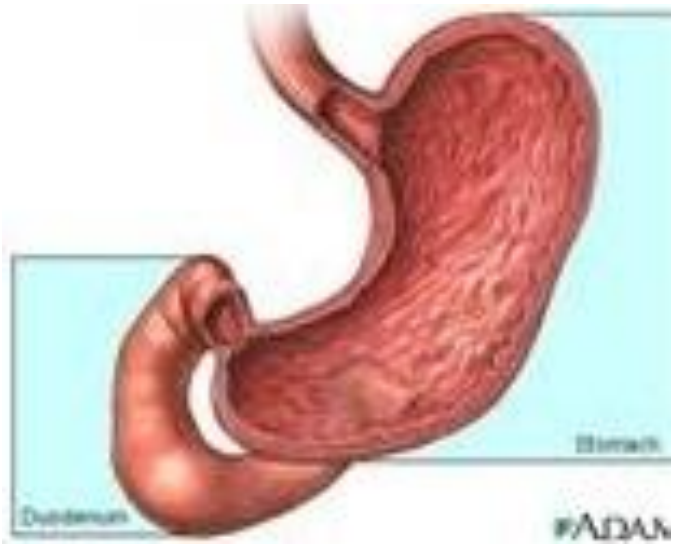
Gastrointestinal tract

GIT secretions:

Prostaglandins

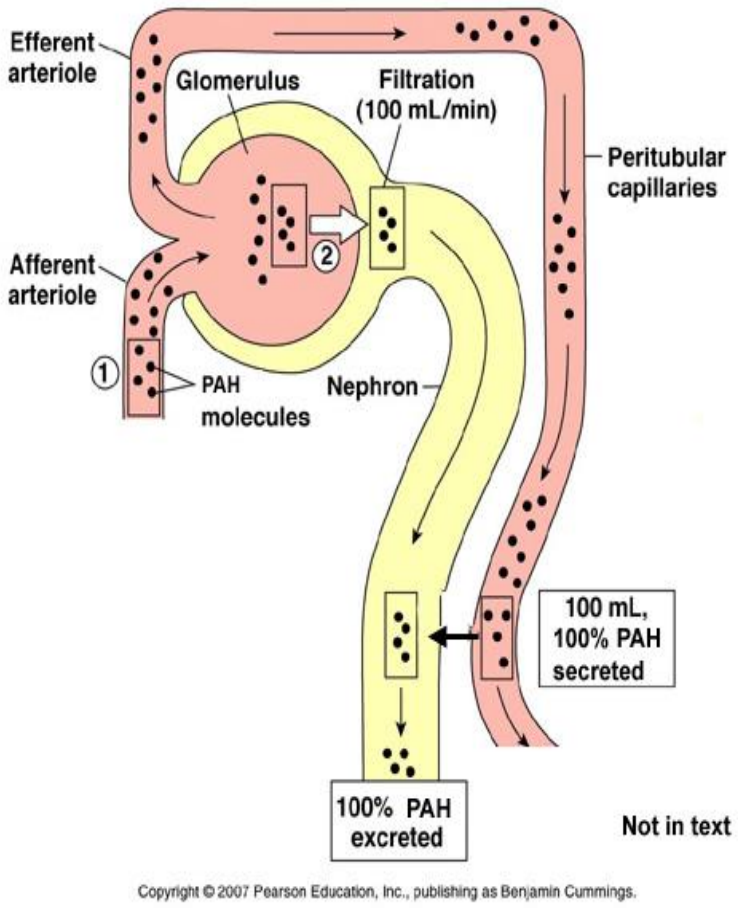
↓ acid secretion

↑ Mucin secretion



KIDENY

Prostaglandins
increase renal blood flow and and may cau diuresis.



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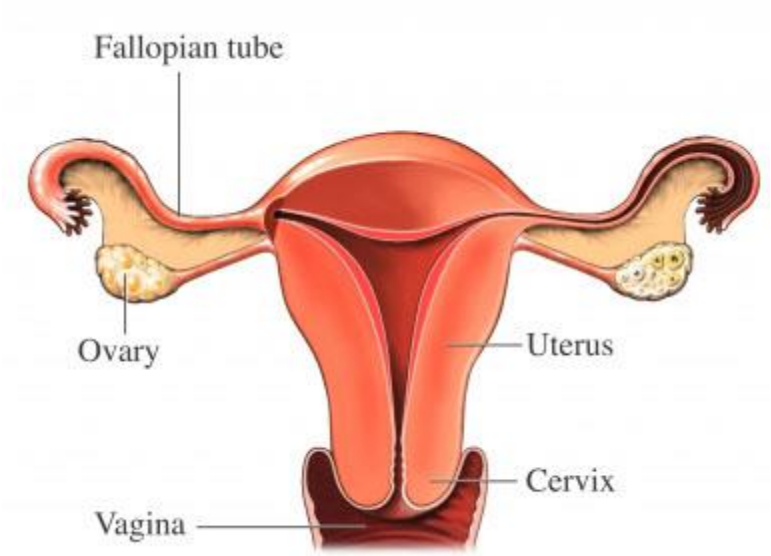
Central and peripheral nervous systems

– Fever

Clinical uses of prostaglandins analogs

- （ **Synthetic prostaglandins** ）

Carboprost



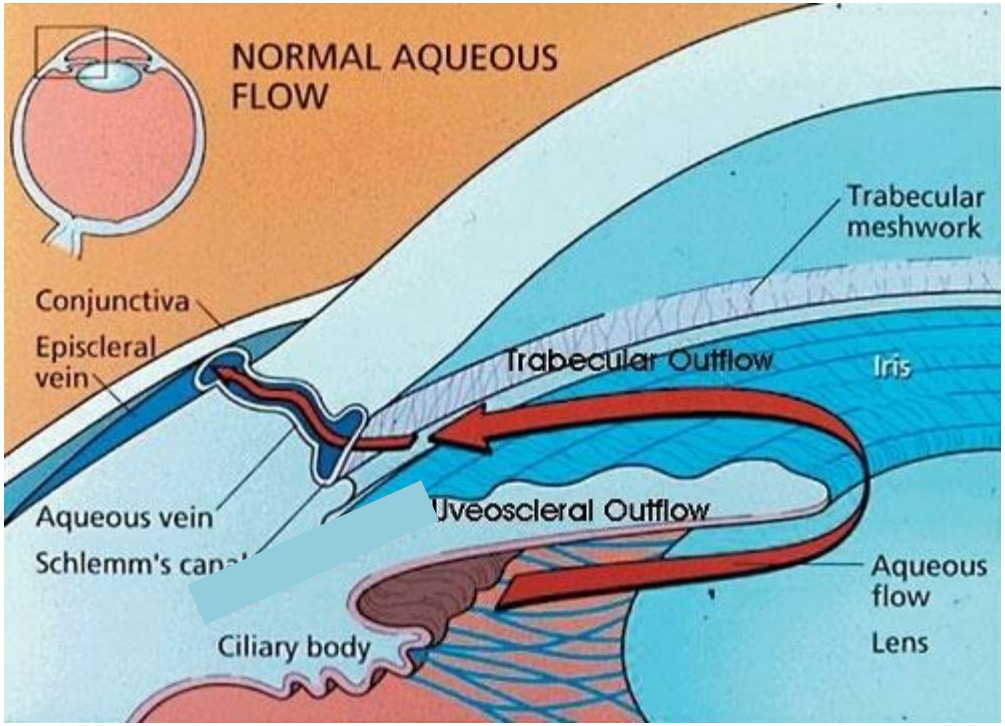
1) Abortion

Induce abortion in first trimester.
Induce labor in case if its over due

2) Treatment of postpartum haemorrhage

(vasoconstriction + ↑uterine muscle contraction)

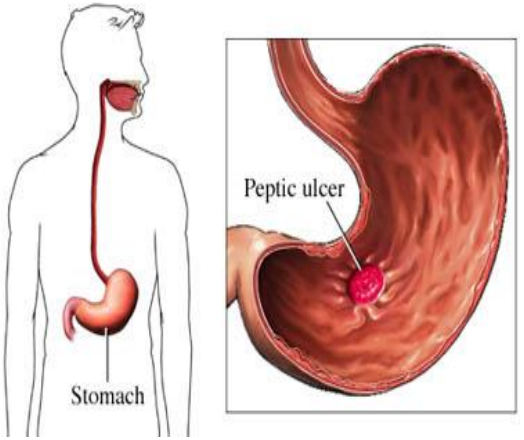
LATANOPROST



eye drops /in treatment of open angle glaucoma.

↓ IOP by enhancing outflow of the aqueous humar)

Misoprostol



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Treatment of Peptic ulcer

Thank you