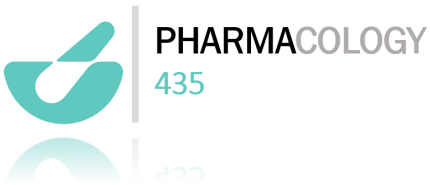
PHARMACOLOGY

Autocrine and Paracrine Mediators and their Antagonists

OBJECTIVE:

- 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 the amino acid histidine
Stored in vesicles

Histidine —**decarboxylase**→ **histamine**

Storage sites:

1. Mast cells **(highest storage amounts)**
2. Basophils
3. Skin
4. Lung
5. Intestinal Mucosa
6. Stomach
7. Brain

Releasing:

- Primary mechanism, during allergic reactions on sensitizing (**IgE antibody** interacts with **antigen** on the surface of mast cells) (Type I hypersensitivity)
- Mast cells degranulate and release histamine which leads to allergic reactions.
- It has some role in acute inflammation or injury (it causes local **vasodilatation** (also increased vascular permeability)) and leakage of plasma ,antibodies 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 and hives** (hives are also known as urticaria : a transient condition of the skin, usually caused by an allergic reaction, characterized by pale or reddened irregular, elevated patches بقعةand severe itchingحكه)

- **Hypotension** (decreased blood pressure due to vasodilatation)
- **Tachycardia** (An abnormally rapid heart rate)
- **Flushing**(Of a person's skin, face, etc. become red and hot, typically as the result of illness or strong emotion)

- **Headache, visual disturbances and increased skin temperature**

- **Excessive secretion of gastric acids and diarrhea**
- **Bronchoconstriction and dyspnea** (Difficult or labored breathing)

Histamine receptors antagonists :

Physiologic antagonists:

Reduce the effects

e.g. epinephrine

Specific receptor blockage:

Blocking of histamine receptors.

Note:

1. **epinephrine** which acts on different receptors but produces an **opposite** effects to histamine especially in **anaphylaxis**.
2. **Specific histamine blockers** are indicated in particular receptor stimulations.

First generation H1 receptor Blockers.

- Can cross the BBB act on sleep (sedative)
- Short period of action so they must be administered often

e.g. Diphenhydramine
Cyclizine
Promethazine

second generation H1 receptor Blockers.

- Non-sedative
- Longer duration of action so they are administered once a day

e.g. Loratidine
Citrizine

Diphenhydramin (First generation) → **H_1 antagonists (Blockers)**

- **Has a sedating effect**

Clinical uses :

- Insomnia
- Motion
- Rhinitis and hay fever

Loratadine (Second generation) → **H_1 antagonists**

- **Non-sedating effect**

Clinical uses :

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

Cimetidine → **H_2 antagonists**

- Histamine play a role in the formation and secretion of **HCl**
- Activated by **H2** receptor
- Blocker of H2 receptor inhibit gastric acid secretion
- Used for the treatment of **peptic ulcers** and **Gastritis**

Betahistine → **H_3 antagonists**

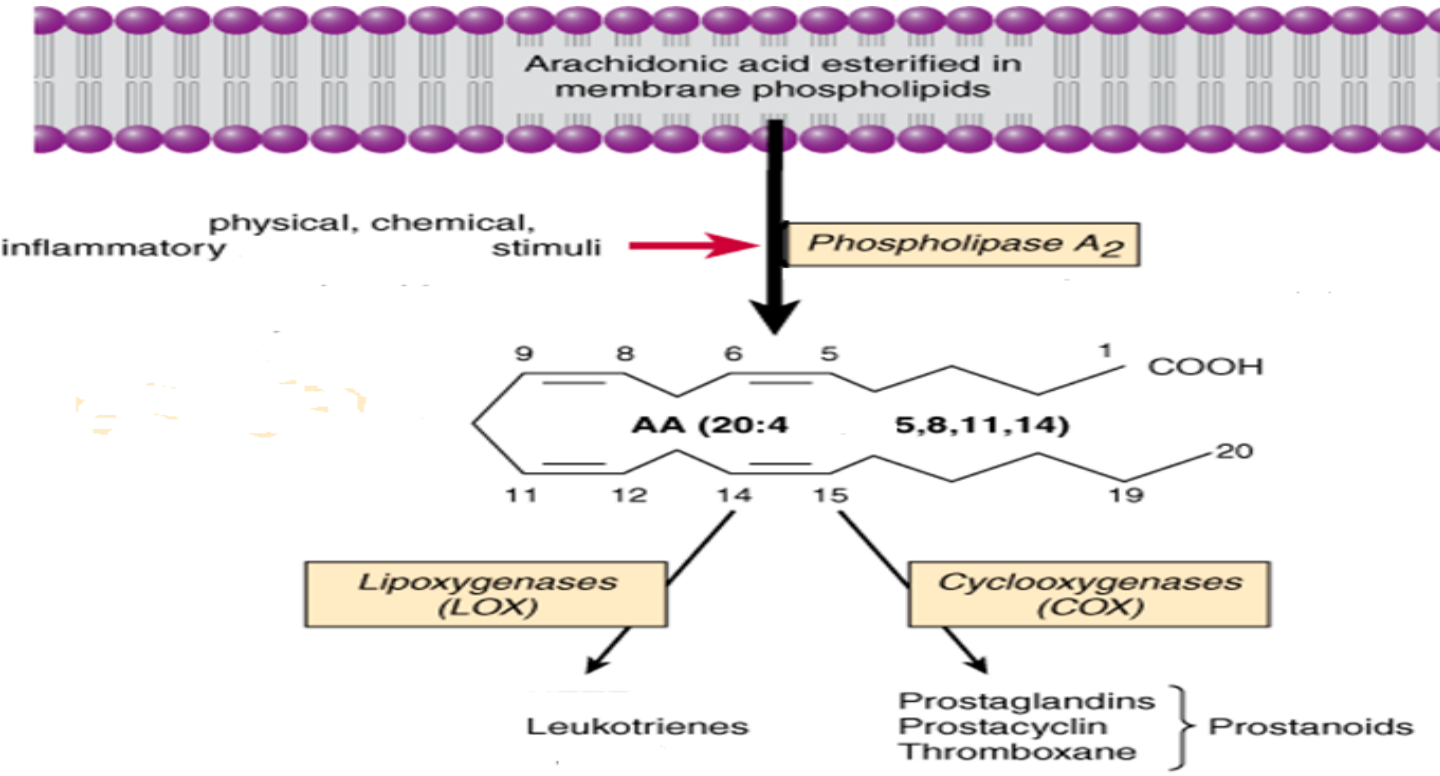
Its effect produced is **dilatation of blood vessels in inner ear**.

Used in treatment of :

- vertigo and Balance disturbances.
- May produce headache and insomnia

Eicosanoid :

- Signaling molecules
- These are 20 carbon atom fatty acids.
- Arachidonic acid (AA) found inside the phospholipids (PL). AA freed from PL by Phospholipase A2.
- Cyclooxygenase (COX) generate the Prostaglandins, Prostacyclins and Thrombaxane A2 (TXA2) from arachidonic acid.
- Lipoxygenase (LOX) generate the Leukotrienes from arachidonic acid.
- **Corticosteroids inhibit phospholipase A2.**
- **Zileuton inhibit lipoxygenase.**
- **NSAIDs inhibit cyclooxygenase**



Prostaglandin (PG):

Major Characteristics :

- First found in semen, they have since been found in cells throughout the body and in menstrual fluid.
- Found In Almost Every Tissue In Humans.
- Contains 20 Carbon Atoms.

The Actions of PG :

- Causes **Vasodilatation** of Vascular Smooth Muscle Cells (Contraction of Uterus).
- **Inhibit** The Aggregation of Platelets.
- Sensitize Neurons To Cause Pain
- Induce Labor
- **Decrease** intraocular pressure, blood pressure
- Acts On Thermoregulatory Center of Hypothalamus To Produce Fever.
- Acts On Kidney To Increase Glomerular Filtration.
- Acts On Parietal Cells of Stomach To Prevent Gastric Mucosa.
- Control Cell Growth.
- Regulate Hormones, Calcium, Inflammation.

The Clinical Uses of Prostaglandin :

- **ABORTION**

Technique In Pregnancies, Induce Abortion In **First Trimester**. After 30 Minutes of Injection Of Pg "$F_{2\alpha}$", Contraction Begins and Abortion Takes Place Within 19 to 20 Hours.

- **POSTPARTUM HAEMORRHAGE**

Vasoconstriction and Increase Uterine Muscle Contraction.

Effector	Prostaglandins	Thromboxane A2
Vascular smooth muscles	Potent vasodilators	Potent vasoconstrictor
Blood	Inhibit platelet aggregation	Induce platelet aggregation
inflammation	Both play important role in inflammatory reactions	
Bronchial smooth muscle	bronchorelaxation	bronchoconstriction
Uterine smooth muscle	increase uterine Constriction→ Dysmenorrhea /Labor Constriction	----------
GIT smooth muscle	↑GIT motility	----------
GIT secretions	↓ acid secretions ↑ Mucin secretions	----------
Kidney	increase renal blood flow and may cause diuresis.	----------
Central and peripheral nervous systems	Fever	----------

Clinical uses of prostaglandins analogs

(synthetic prostaglandins)

Prostaglandins analogs	Treatment of	
Carboprost	**Abortion** : induce abortion in first trimester	**Postpartum haemorrhage :** • Vasoconstriction. • Increase uterine muscle contraction
Latanoprost	Using as eye drops To treat **open angle glaucoma** • Reduce IOP (intraocular pressure: (fluid inside the eye). • Enhancing outflow of the aqueous humor.	
Misoprostol	**Peptic ulcer**	

THANK YOU FOR CHECKING OUR WORK

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