Pharmacology of Autocoids

Autocoids or Autacoids :-

Autacoids (Greek "self-remedy") is a collective term for various endogenous peptides, prostaglandins, leukotrienes, and cytokines. These are sometimes also called local hormones. They play important roles in physiologic processes and also have several pharmacological significances.

- Any imbalance in autocoids synthesis, release or in the transduction system contributes significantly to pathological conditions such as inflammation, allergy, hypersensitivity and ischemia- reperfusion.
- There are many autacoids which secreted in the body of animals like Histamine, Serotonin, Kinins and Ecosinids (Prostaglandins and leukotrines) and others.
- In our present lecture we shall focus individually on each previously listed autacoids and their origins, also the pharmacological effect of each one, in addition to their agonists and antagonists.

A- Histamine: is a biogenic amine (synthesized from histidine and stored in mast cells "tissue phagocytes" and basophils) throughout the body involved in local immune responses as well as regulating physiological function in the gut and acting as a neurotransmitter.

- There are at least four receptor populations, H_1, H_2, H_3, and H_4. and their distribution and their functions have been illustrated in the table below:

Type	Location	Function
H1	Brain , Sooth muscle , Heart , Endothelium	Causes vasodilation, bronchoconstriction, bronchial smooth muscle contraction, separation of endothelial cells (responsible for hives), and pain and itching due to insect stings; the primary receptors involved in allergic rhinitis symptoms and motion sickness.
H2	Chiefly on the parietal cells in stomach , Brain , Smooth muscle , Heart , Mast cell	Primarily stimulate gastric acid secretion.
H3	Brain , autonomic nerve endings ,endothelia	Decreased neurotransmitter release: histamine, acetylcholine, norepinephrine, serotonin .

❖ **Histamine agonists:**

Histamine: histamine injection is used to diagnose skin allergy (positive control).

Betazole : (histamine analog) is used to stimulate gastric acid secretion for diagnosis of hypochlorhydria.

❖ **Histamine antagonists:**

- **Diphenhydramine (Allrmine® or Benadryl®):**
  - It is H_1 receptor antagonist.
  - It is administrated orally or as injections.
  - It used for allergies and insect bites/stings; motion sickness and travel anxiety, organophosphate or carbamate poisoning; sedation, cough.
  - Side effects: lethargy, dry mouth, urinary retention. Less commonly emesis, diarrhea, and lack of appetite.
  - Overdose: excitement or seizure, lethargy, coma, respiratory depression, and death.

+ Other H_1 receptor blockers drugs include:-

- **Cyproheptadine.**
- **Chlorpheniramine**
- **Dimenhydrinate**
- **Loratidine**
- **Meclazine**

- **Cimetidine (Tagamet®), Rantidine (Zantac®) and Famotidine.**
  - They are H_2 receptor blockers.
  - They used for treatment of duodenal and gastric ulcers (in adult horses; ranitidine is also used in foals). Also they used as pre-anesthetic drugs for prophylaxis against aspiration of gastric juice.
- **Thioperamide**
  - Is a potent and selective H_3 and H_4 receptors blocker.
  - Its uses are not exceed the limitations of empirical purposes.
- **Cromolyn sodium**
  - It prevents the release of histamine, by preventing the degranulation of histamine from mast cell and basophil. (Unspecified histamine receptors blocker).
  - It used for treatment of allergic rhinitis, preventive management of asthma, allergic conjunctivitis, urticaria and ulcerative colitis.

B- Serotonin:

- Serotonin (5-hydroxytriptamine or 5-HT) is synthesized from dietary tryptophan.
- It is stored in the intestine (enterochromaffin cells), the CNS, and mast cells (rodents). It is also found concentrated in blood platelets.
- It does not cross the blood-brain barrier. However, since serotonin is synthesized in the CNS, it is also considered as a central neurotransmitter.

Physiological and pharmacological activities of Serotonin:

- Serotonin has a vasodilator effect on the vascular bed of skeletal muscles; it also stimulates bronchi and intestinal muscles. It has inotropic and chronotropic effects.
- Its CNS action is known to influence sleep-wake cycle, mood and behavior, intestinal motility, thermoregulation, platelet aggregation.

❖ **Serotonin agonists:**

- **Buspirone:**

  - Is used to stop inappropriate urination in cats and to treat "social" anxiety (e.g., changes in the family pack) in dogs

❖ **Serotonin antagonists**

- **Ondansetron, Alosetron and Cilansetron**
  - They are used in treatment of irritable bowel syndrome.
  - Also they are used in the prevention and treatment of nausea and vomiting. They are particularly effective in controlling the nausea and vomiting produced by cancer chemotherapy.

❖ **Serotonin reuptake inhibitors:**

These drugs regulate serotonin turnover.

- **Clomipramine:**
  - It is a *tricyclic antidepressant* is thought to act by blocking serotonin re-uptake by neurons and hence increasing serotonin levels in the brain and decreasing the level of fear and anxiety.

- **Imipramine**

- It used to inhibit urinary incontinence in dogs and narcolepsy and ejaculatory dysfunction in horses.

3- Kinins: A (kinin) is any of various structurally related polypeptides, such as bradykinin and kallikrein. They are members of the autacoid family.

Physiological activities of Kinins:

- Influence smooth muscle contractions.
- Increase blood flow throughout the body.
- Increase the permeability of small capillaries.
- Stimulate pain receptors.

❖ **Pharmacological uses of kinins inhibitors**

The recent studies show promises to use kinins inhibitors in treatment of pencreatitis , sepsis and brain edema, while in human a new studies on new experimental kinins inhibitors may create a new pharmacological agents to treat acute attacks of hereditary angioedema.

4- Eicosanoids:

The Eicosanoids, {prostaglandins, thromboxane, prostacyclin, and leukotrienes}, are formed in the organism from arachidonic acid, a C20 fatty acid with four double bonds (eicosatetraenoic acid).

- Synthesis of prostaglandins (PG), prostacyclin, and thromboxane proceeds via intermediary cyclic endoperoxides.
- The letters following PG (D, E, F, G, H, or I) indicate differences in substitution with hydroxyl or keto groups; the number subscripts refer to the number of double bonds, and the Greek letter designates the position of the hydroxyl group at C_9 (the substance shown is PGF2α).
- PG are primarily inactivated by the enzyme {15-hydroxyprostaglandindehydrogenase}. Inactivation in plasma is very rapid; during one passage through the lung, 90% of PG circulating in plasma are degraded. PG are local mediators that attain biologically effective concentrations only at their site of formation.

Physiological activities of Eicosanoids:

- Nociceptors\ PG increase sensitivity of sensory nerve fibers towards ordinary pain stimuli, i.e., at a given stimulus strength there is an increased rate of evoked action potentials.
- Thermoregulation\ PG raise the set point of hypothalamic (preoptic) thermoregulatory neurons; body temperature increases (fever).
- Vascular smooth muscle\ PGE2 and PGI2 produce arteriolar vasodilation; PGF2α, venoconstriction.
- Gastric secretion\ PG promote the production of gastric mucus and reduce the formation of gastric acid.
- Menstruation. PGF2α is believed to be responsible for the ischemic necrosis of the endometrium preceding menstruation. The relative proportions of individual PG are said to be altered in dysmenorrheal and excessive menstrual bleeding. Uterine muscle. PG stimulate labor contractions.
- Bronchial muscle\ PGE2 and PGI2 induce bronchodilation; PGF2α causes constriction.
- Renal blood flow\ when renal blood flow is lowered, vasodilating PG are released that act to restore blood flow.
- Thromboxane and prostacyclin play a role in regulating the aggregability of platelets and vascular diameter.
- Leukotrienes (*Discussed in Respiratory sys. Lecture*) increase capillary permeability and serve as chemotactic factors for neutrophil granulocytes. As "slow-reacting substances of anaphylaxis," they are involved in allergic reactions; together with PG, they evoke the spectrum of characteristic inflammatory symptoms: redness, heat, swelling, and pain.

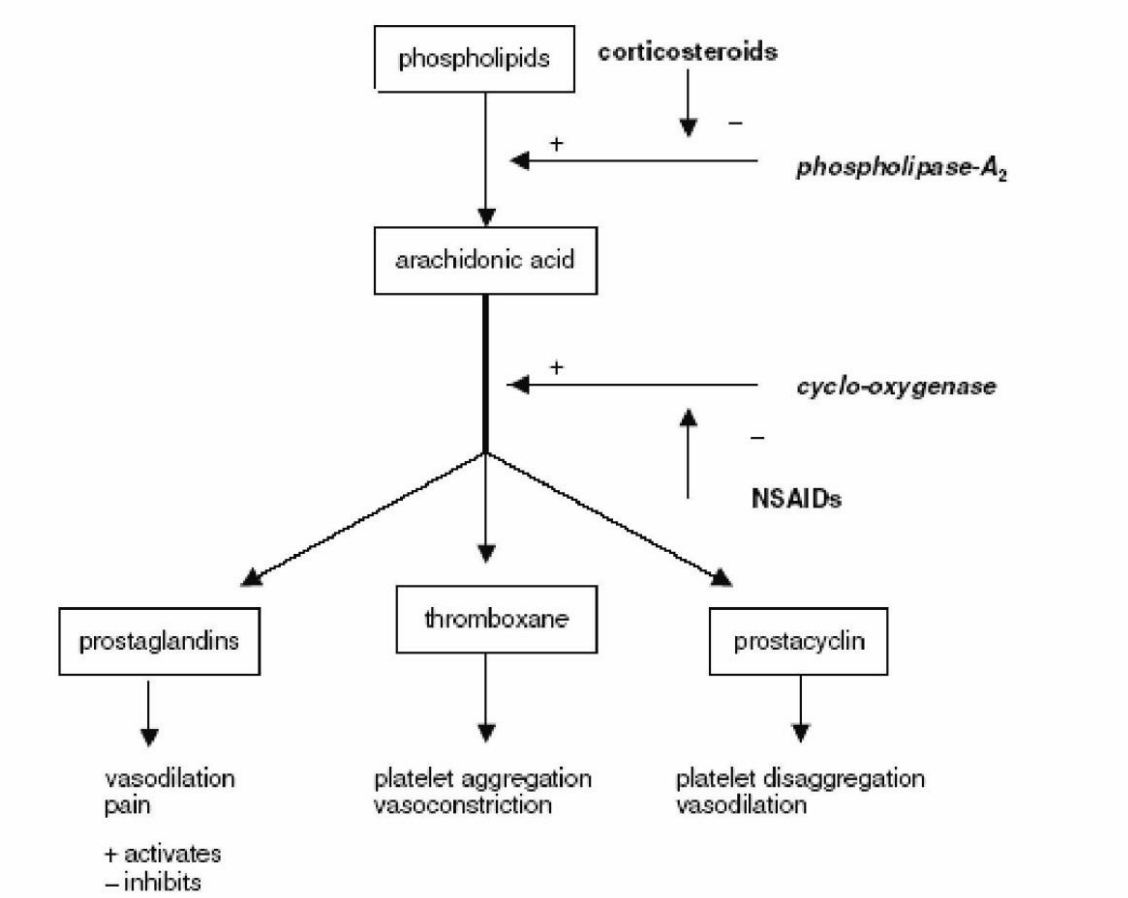
Therapeutic applications of Prostaglandins:

- ✓ PG derivatives are used to: induce labor or to interrupt gestation.
- ✓ In the therapy of peptic ulcer.
- ✓ PG derivatives are used in peripheral arterial disease.

❖ **Eicosanoids antagonists:**

- **Prostaglandins Inhibitors:**

Generally, prostaglandins can be inhibiting via preventing their synthesis from the sources, and we can follow the synthesis of the prostaglandins by this simple sketch:-



From the sketch above we can divide prostaglandins inhibitors to:

1- ***Phospholipase A_2 inhibitors***: - these drugs are inhibit the turning of the phospholipids in the cell wall to arachidonic acid via inhibition of Phospholipase A_2 whom responsible of this conversion. Example: Corticosteroids.

2- ***Cyclooxygenase (COX) inhibitors***: these drugs are inhibit the turning of the arachidonic acid to prostaglandins through inhibition of cyclooxygenase (COX) whom responsible of this conversion. Example: Non-steroidal anti-inflammatory drugs (N - $said_s$ or NSAIDs). So that we can say that the NSAIDs can inhibit the synthesis of thromboxane and prostacyclins.