

Pharmacology 3rd year ---- college of Dentist Medicine

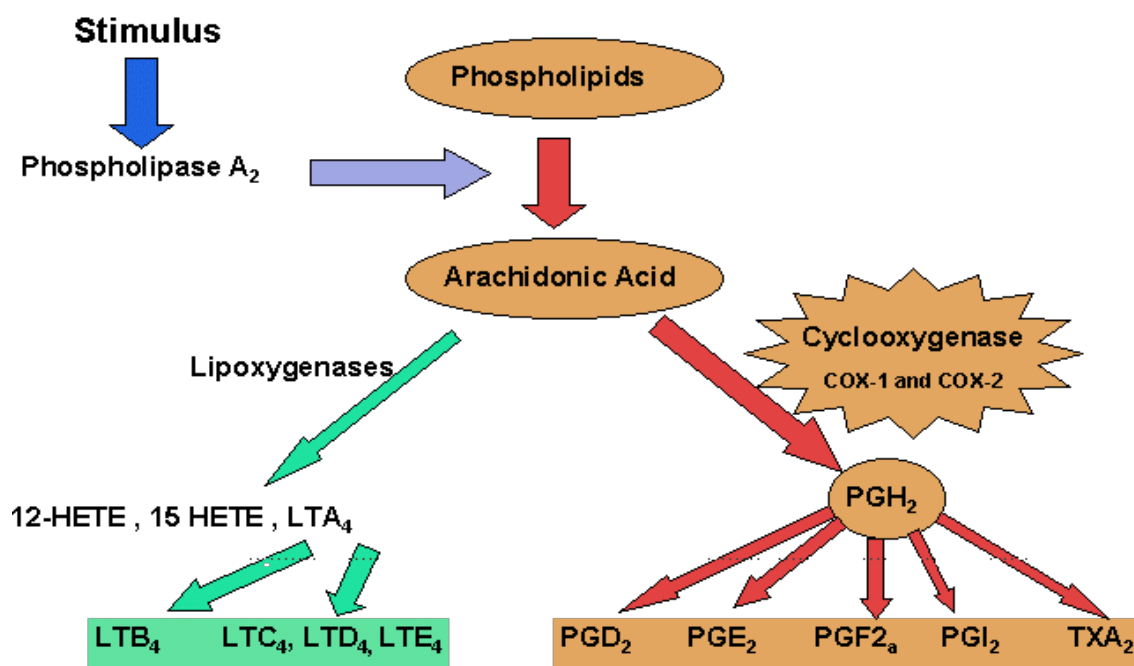
Autacoids and Autacoid Antagonists

- Prostaglandins, histamine, and serotonin belong to a group of compounds called autacoids.
- These heterogeneous substances have widely differing structures and pharmacologic activities.
- They all have the common feature of being formed by the tissues on which they act; thus, they function as local hormones.
- The autacoids also differ from circulating hormones in that they are produced by many tissues rather than in specific endocrine glands.

1-Prostaglandins:-

Prostaglandins are unsaturated fatty acid derivatives that act on the tissues in which they are synthesized and are rapidly metabolized to inactive products at the site of action.

Figure 2 : Biosynthesis of eicosanoids

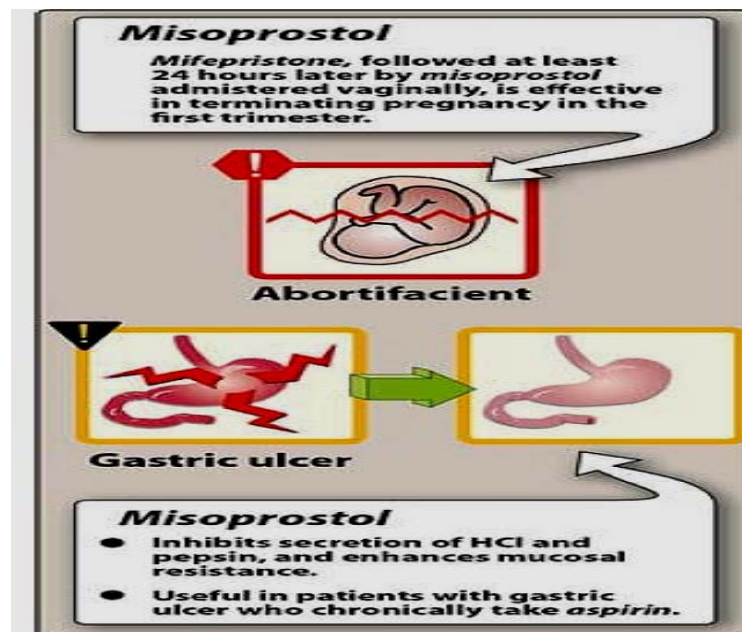


Therapeutic uses of prostaglandins:-

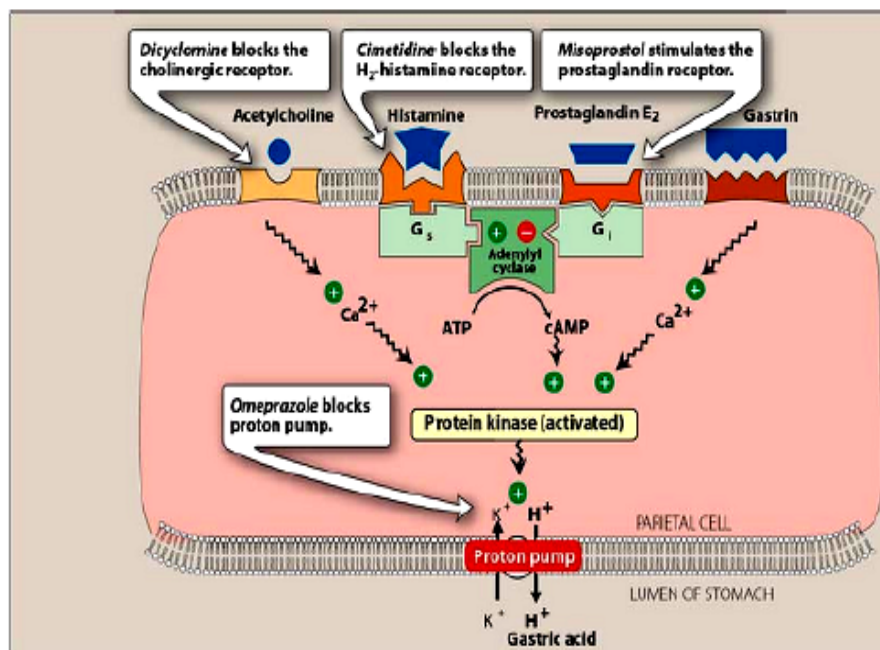
Systemic administration of prostaglandins evokes multiple effects a fact that limits the therapeutic usefulness of these agents.

Abortion: Several of the prostaglandins find use as abortifacients (agents causing abortions). The most effective option available involves oral administration **mifepristone** (antiprogestational effects) followed at least 24 hours later by the synthetic prostaglandin E₁ analog **misoprostol** administered

vaginally .Infection, hemorrhage, and retained tissue are among the more common complications.



Peptic ulcers: Misoprostol is sometimes used to inhibit the secretion of gastric acid and to enhance mucosal resistance to injury in patients with gastric ulcer.



2-Histamine:-

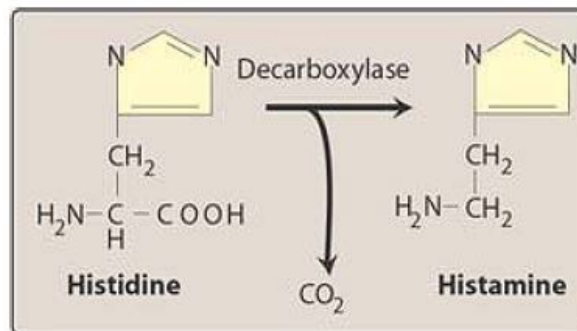
Histamine is a chemical messenger that mediates a wide range of cellular responses, including allergic and inflammatory reactions, gastric acid secretion. Histamine has no clinical applications.

Location, synthesis, and release:-

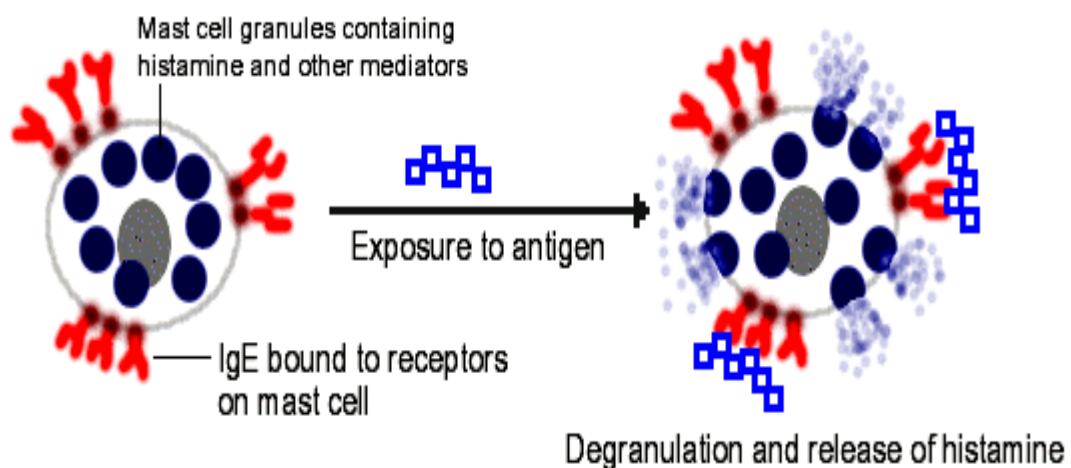
Location:

- Histamine occurs in practically all tissues.
- found in lung, skin, and the gastrointestinal tract .
- It is found at high concentration in mast cells or basophils.
- Histamine also occurs as a component of venoms and in secretions from insect stings.

Synthesis: Histamine is an amine formed by the decarboxylation of the amino acid histidine by histidine decarboxylase .



Release of histamine: The release of histamine may be the primary response to some stimuli. Stimuli causing the release of histamine from tissues include the
1- destruction of cells as a result of cold, bacterial toxins, bee sting venoms, or trauma. **2-** Allergies and anaphylaxis can also trigger release of histamine.



Mechanism of action:-

- Histamine released in response to various stimuli exerts its effects by binding to one or more of four types of histamine receptors- H_1 , H_2 , H_3 , and H_4 receptors.
- H_1 and H_2 receptors are widely expressed and are the targets of clinically useful drugs.

- All types of histamine receptors act by way of G protein-mediated second-messenger systems.

The H₁ receptors

- Are important in producing smooth muscle contraction and increasing capillary permeability .
- Histamine promotes vasodilation by causing vascular endothelium to release **nitric oxide**.
- This chemical diffuses to the vascular smooth muscle, where it stimulates cyclic guanosine monophosphate (cGMP) production, causing vasodilation.

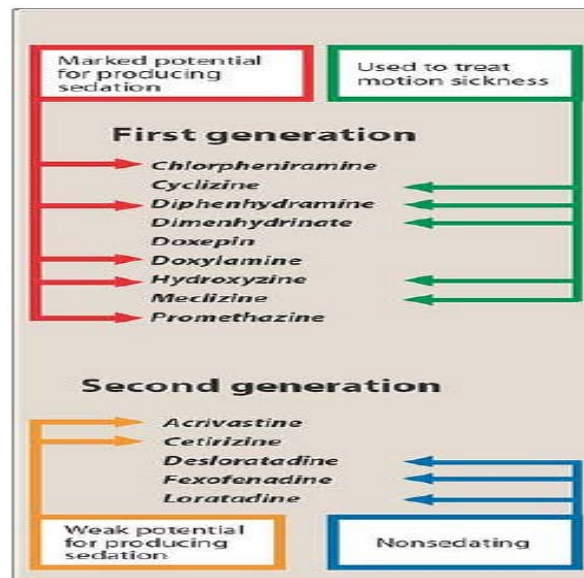
Histamine H₂ receptors mediate gastric acid secretion.

Role in allergy and anaphylaxis:-

The symptoms resulting from intravenous injection of histamine are similar to those associated with anaphylactic shock and allergic reactions. These include 1- contraction of smooth muscle, 2- stimulation of secretions, 3- dilation and increased permeability of the capillaries, and 4- stimulation of sensory nerve endings.

H₁ Antihistamines:-

- The term antihistamine, refers to the classic H₁-receptor blockers.
- These compounds do not influence the formation or release of histamine; rather, they block the receptor-mediated response of a target tissue.
- **The H₁-receptor blockers can be divided into first- and second-generation drugs.**



- **The older first-generation drugs are still widely used because they are effective and inexpensive.**

- Most of these drugs penetrate the CNS and cause sedation. They tend to interact with other receptors, producing a variety of unwanted adverse effects.
- By contrast, **the second-generation** agents are specific for H₁ receptors, and because they do not penetrate the blood-brain barrier, they show less CNS toxicity than the first-generation drugs.
- Among these agents **desloratadine** , **fexofenadine** , and **loratadine** show the least sedation.

Therapeutic uses:-

Allergic and inflammatory conditions:

- H₁-receptor blockers are useful in treating allergies caused by antigens acting on immunoglobulin E antibody-sensitized mast cells.
- For example, antihistamines are the drugs of choice in controlling the symptoms of allergic rhinitis and urticaria, because histamine is the principal mediator.

Motion sickness and nausea:

- certain H₁-receptor blockers, such as **diphenhydramine** , **dimenhydrinate** , **cyclizine** , **meclizine** , and **hydroxyzine** , are the most effective agents for prevention of the symptoms of motion sickness.
- The antihistamines prevent or diminish vomiting and nausea mediated by both the chemoreceptor and vestibular pathways.
- The antiemetic action of these medications seems to be due to their blockade of central H₁ and muscarinic receptors.

Somnifacients:

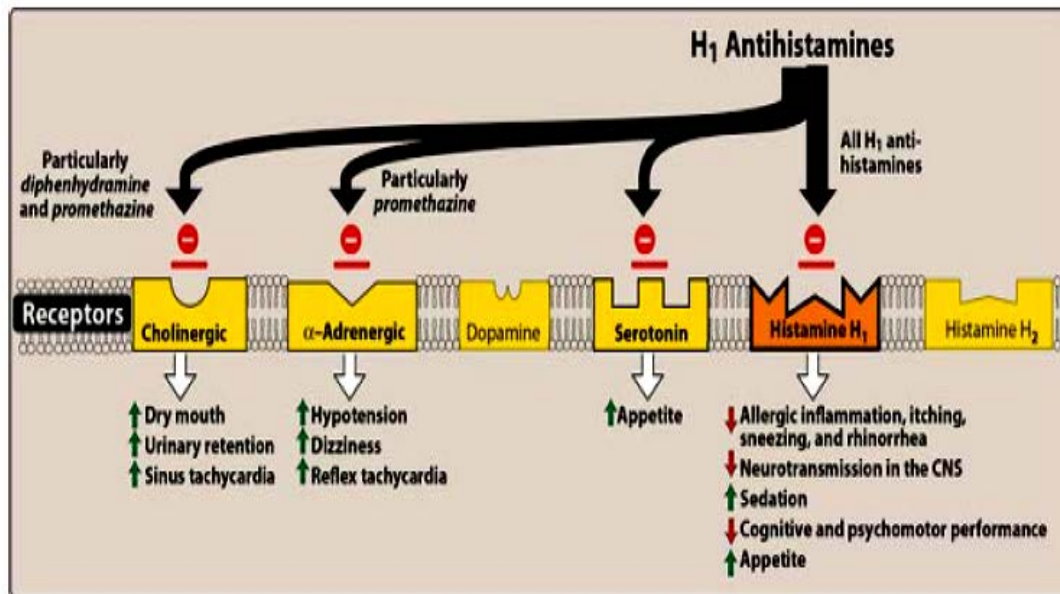
- Many first-generation antihistamines, such as **diphenhydramine** and **doxylamine** , have strong sedative properties and are used in the treatment of insomnia .
- The use of first-generation H₁ antihistamines is contraindicated in the treatment of individuals working in jobs where wakefulness is critical.

Pharmacokinetics:-

- H₁-receptor blockers are well absorbed after oral administration, with maximum serum levels occurring at 1 to 2 hours.
- H₁-receptor blockers have high bioavailability and are distributed in all tissues, including the CNS.
- The duration of action for many oral H₁ antihistamines is at least 24 hours, facilitating once-daily dosing.

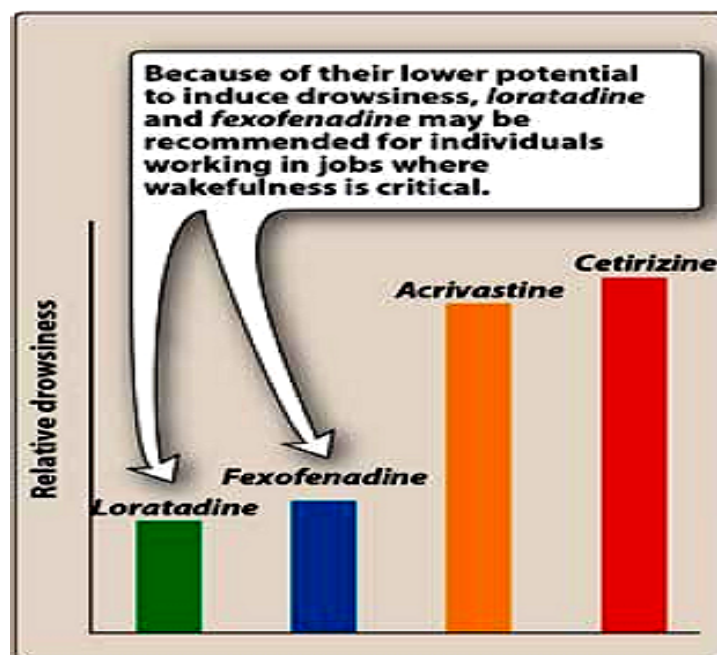
Adverse effects:-

- First-generation H₁-receptor blockers have a low specificity; that is, they interact not only with histamine receptors but also with 1-cholinergic receptors, 2- α -adrenergic receptors, and 3-serotonin receptors .



Sedation:

- First-generation H₁antihistamines, such as **chlorpheniramine** , **diphenhydramine** , and **promethazine** , bind to H₁ receptors and block the neurotransmitter effect of histamine in the CNS.
- The most frequently observed adverse reaction is sedation .
- Second-generation H₁ antihistamines are specific for H₁ receptors and penetrate the CNS poorly. They show less sedation and other CNS effects.



Drug interactions:

- Interaction of H₁-receptor blockers with other drugs can cause serious consequences, such as potentiation of the effects of all other CNS depressants, including alcohol.

Histamine H₂-Receptor Blockers:-

- Histamine H₂-receptor blockers have little, if any, affinity for H₁ receptors.
- Although antagonists of the histamine H₂ receptor (H₂ antagonists) block the actions of histamine at all H₂ receptors, their chief clinical use is as inhibitors of gastric acid secretion in the treatment of ulcers and heartburn.
- By competitively blocking the binding of histamine to H₂ receptors, these agents reduce intracellular concentrations of cAMP and, thereby, secretion of gastric acid.
- The four drugs used -**cimetidine, ranitidine, famotidine. nizatidine.**