Autacoids

The term **Autacoid** derived from Greek word

- Autos = Self
- Akoid (Coid) = Medicinal agent or Remedy

Autacoid means **"Self remedy"**

Autacoids are heterogeneous chemical substances that are synthesized within the body and protect the body from some adverse situations by exerting its pharmacological action.

- Produced by wide variety of cells in the body and released locally
- Generally act locally at the site of synthesis or near the site of their release and degraded quickly
- They can't be placed in the group of classical hormones but may be called **"Local Hormones"**
- They are different from hormones in two important ways-hormones are produced by specific cells and are transported through circulation to act on distant target tissues.

Classification of Autacoids:

Autacoids can be classified into three groups. Such as-

1. **Amine autacoids:**

   Example: Histamine, Serotonin / 5- Hydroxy tryptamine (5-HT)

2. **Lipid derived autacoids:**

   Example: Eicosanoids (Prostaglandins (PG), Leuckotrines (LT)), Platelet activating factors (PAF))

3. **Peptide autacoids:**

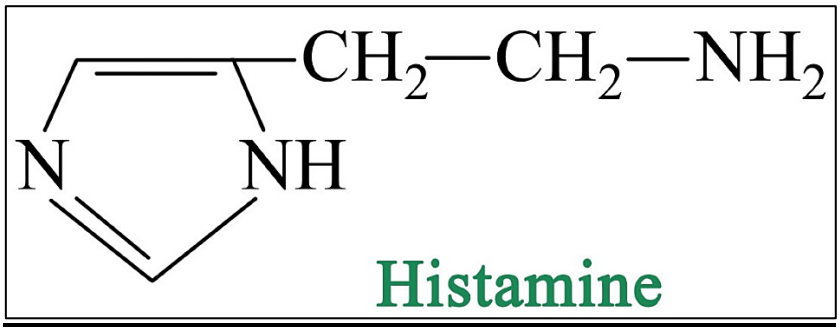
   Example: Angiotensin, Kinins

Functions of Autacoids:

- ✓ Moderate local circulation
- ✓ Influence the process of inflammation

Histamine

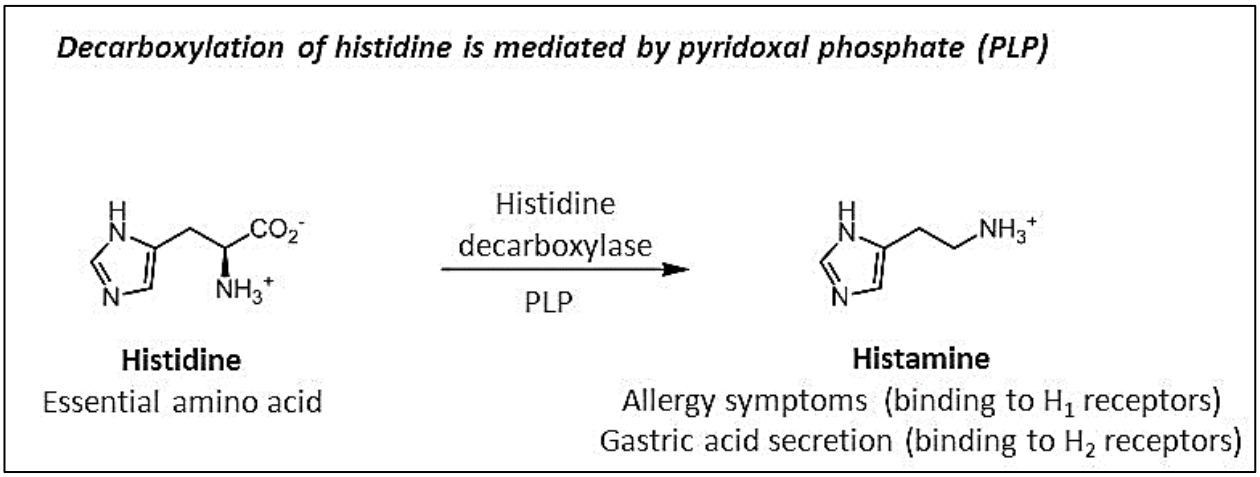
Histamine (Histo=Tissue), also called as **biogenic amine.**



It is a potent tissue amine widely distributed in plant and animal tissues and in the venoms of bees.

Synthesis:

In man, it is formed by decarboxylation of histidine.



- **Storage:** **Storage:**
  1. **Mast cell**
  2. **Basophil**
  3. **Epidermis of skin**
  4. **Cells in the gastric mucosa**
  5. **Neurons on the CNS**

After synthesis histamine stored in mast cell or in basophils of blood or in CNS. In mast cell, histamine bound with protein or high molecular weight heparin. Bounded form is biologically inactive

- **Release:** **Release of histamine:**
  1. **Immunologic release:** IgE medicated histamine release in type I hypersensitivity. This type of release also requires energy and calcium.
  2. **Physical factors:** scratch, burn, soap, exposure to sun, radiation
  3. **Chemical factors:** Dextran, polysaccharide, bile salts, lecithin, radio-contrast media.

The stored histamine from the mast cells released by 2 ways mechanisms.

A. Immunological release (anaphylactic)

B. Chemical mediators (anaphylactoid)

Immunological release:

Allergen enter (Forgein body)

⬇

Immunological reaction (AG: AB Complex formation)

↓

Circulation in blood

↓

Basophiles, Neutrophilis engulf

↓

Cause neutralization

↓

Whenever same allergen re-exposed

↓

Activation of AG: AB complex

↓

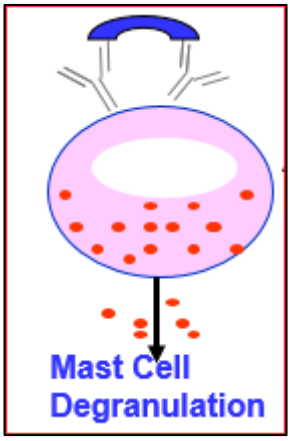
Reacts with mast cells

↓

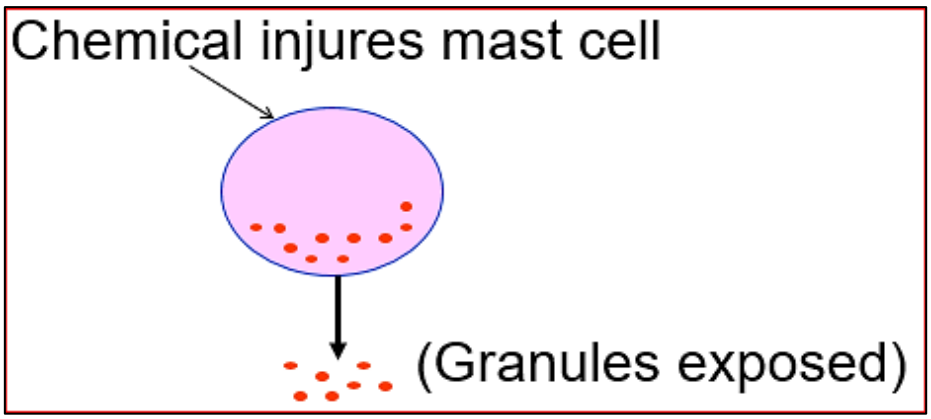
(Degranulation of mast cells)

↓

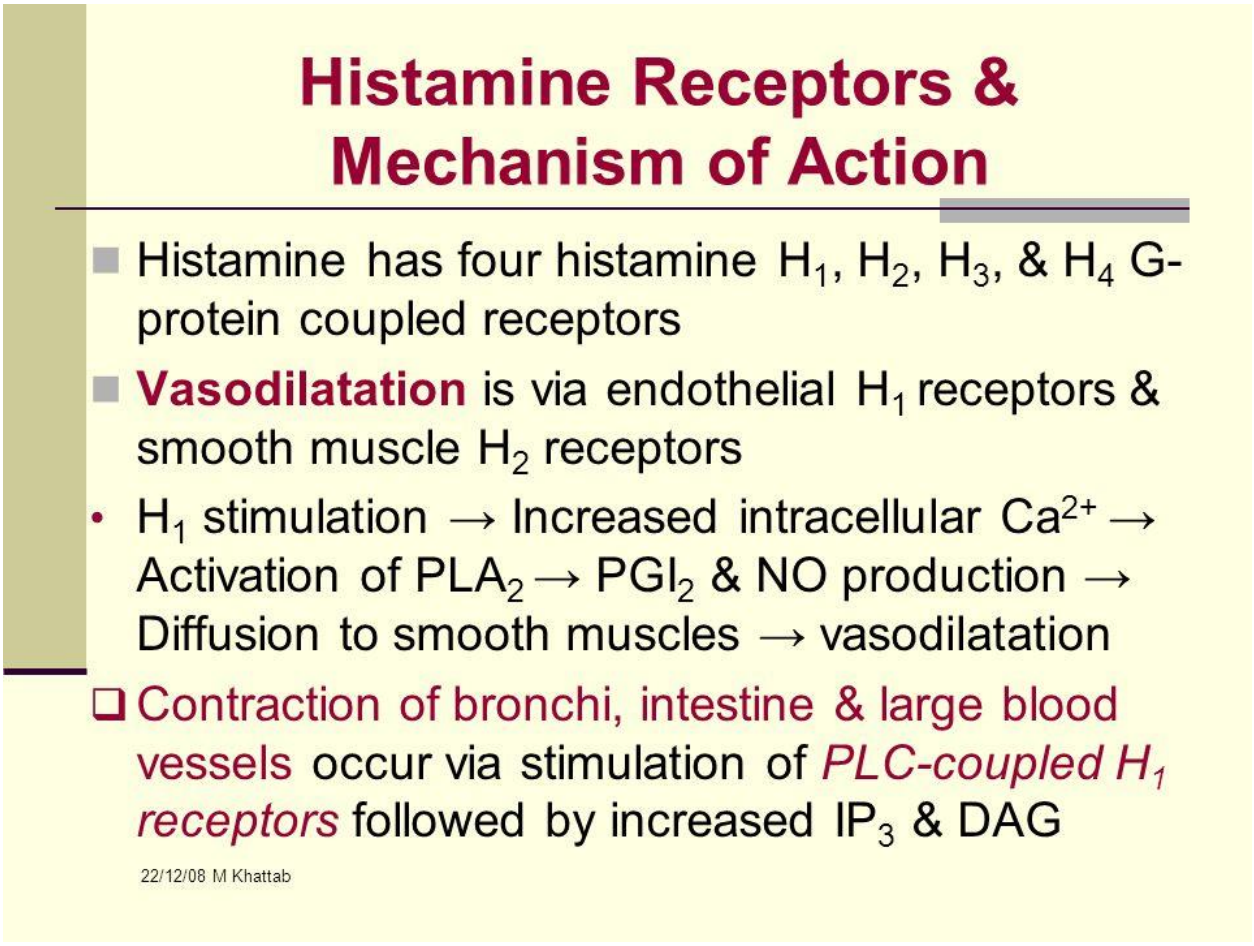
Spasmogens release ((Like Histamine, Serotonin (5HT), PGs, LT4, and Cytokines)



Chemical Release:



Mechanisms of Action:



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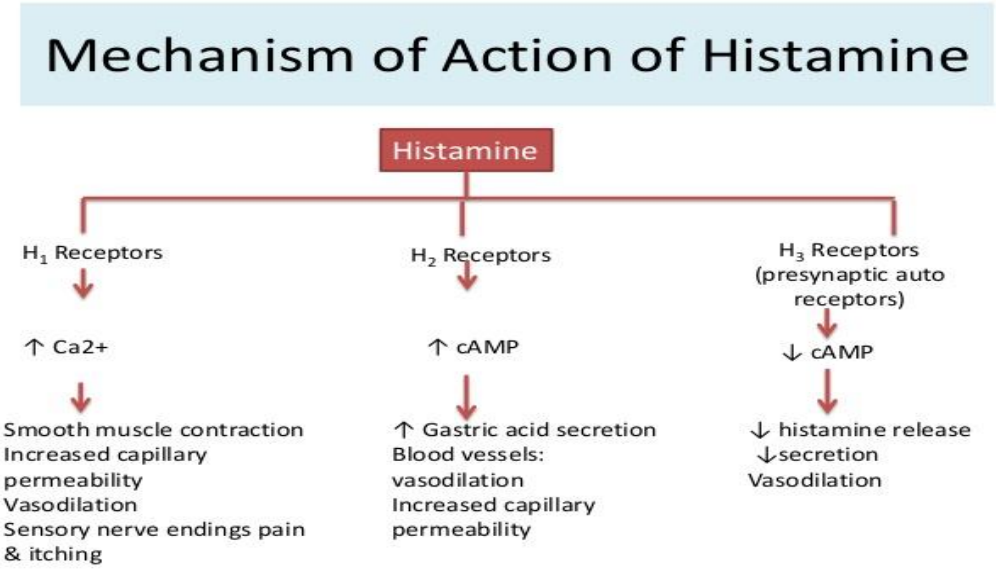


It acts on 2 major types of receptors

1. **H_1 receptor mediated:**

   Stimulation of H_1 receptors results in **smooth muscle contraction**, **increased vascular permeability**, and **mucus production**. These effects are blocked competitively by H1 antagonists.

2. **H_2 receptor mediated:**

Activation of H_2 receptors increases gastric acid production, and this effect is blocked by H_2 blockers such as cimetidine.

Both types of receptors are involved in vascular dilatation and edema formation.

Pharmacological Actions:

- **Cardiovascular system:** Histamine produces relaxation of blood vessels resulting in fall in blood pressure.
- **Smooth Muscles:** Histamine directly stimulates the smooth muscles of various tissues including the bronchi and uterus. Histamine-induced bronchospasm is effectively antagonized by adrenaline.
- **Exocrine Glands:** It is a powerful stimulant of HCl secretion by the gastric mucosa.
- **Miscellaneous** actions include induction of itching and pain.

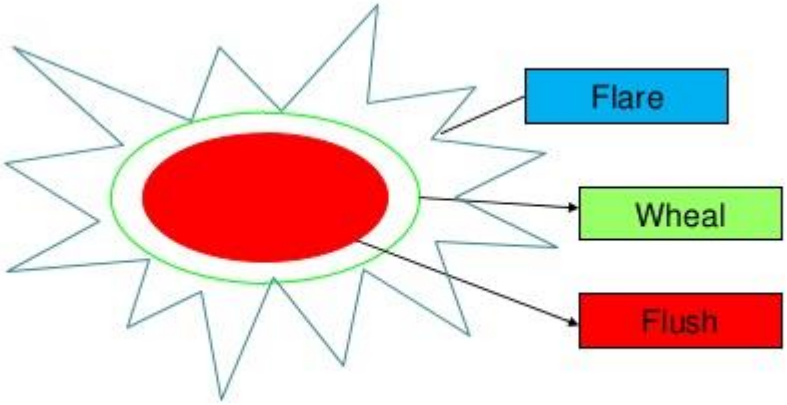
Histamine has no valid therapeutic use currently. But it plays very important role in various forms of allergic reactions.

Triple response:

In sensitive (allergic) person, when Histamine injected intradermally, a triple response is produced.

It is characterized by an immediate redding of skin (Flush) due to vasodilatation, formation of edematous patch (Wheal) due to exudation of fluid from capillaries and venules due to increased permeability and a red irregular halo surround the wheal (Flare) due to vasodilatation through the release of vasodilatory neuromediators.

- Histamine inj intradermally, atypical triple response is produced
- It characterized by an immediate redding of skin (Flush) , formation of edematous patch (Wheal) and a red irregular halo surround the wheal (Flare)



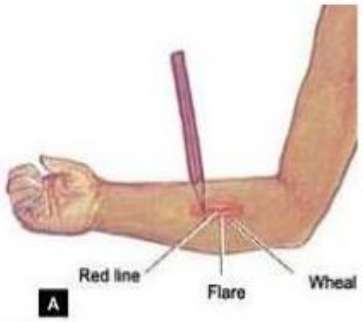
Rubor

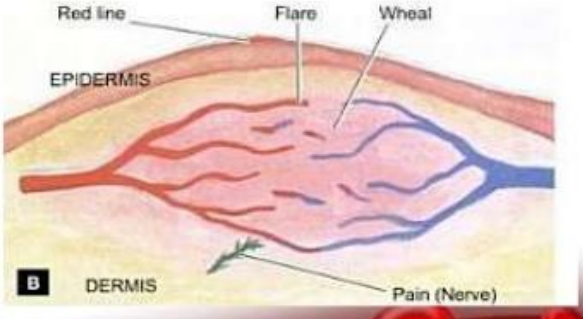
Redness is due to

VASODILATION (DUE TO RELEASE OF MEDIATORS)

INCREASED BLOOD SUPPLY

TRIPLE RESPONSE OF LEWIS(1924)





Antihistaminic Drugs:

Generation	Characteristic	Name of Drug
1.First generation or sedative	Small ,lipophilic molecules that could cross the BBB	Alimemazine, chlorphenamine, clemastine, cyproheptadine, hydroxyzine, ketotifen.
2.Second generation or non sedative	Modifications of the first generation	Acrivastine, cetirizine, loratadine, mizolastine, astemizole
3.Third generation	Safer,farster acting or more potent than second generation drugs	fexofenadine, levocetirizine, desloratadine. Rupatadine and ebastine

Antihistamine may be defined as the chemical agents or drugs that are generally used against histamine to counteract the activity of histamine competitively on various receptor sites.

These drugs competitively block histamine receptors and are of two types:

1. **H_1 receptor antagonists / H_1 Blockers:**

   Drugs which selectively and competitively antagonize most of the actions of histamine that are mediated by H_1 – receptor are called H_1 – receptor antagonists or H_1 blockers.

   Example: Diphenhydramine, promethazine, loratadine, cetirizine etc.

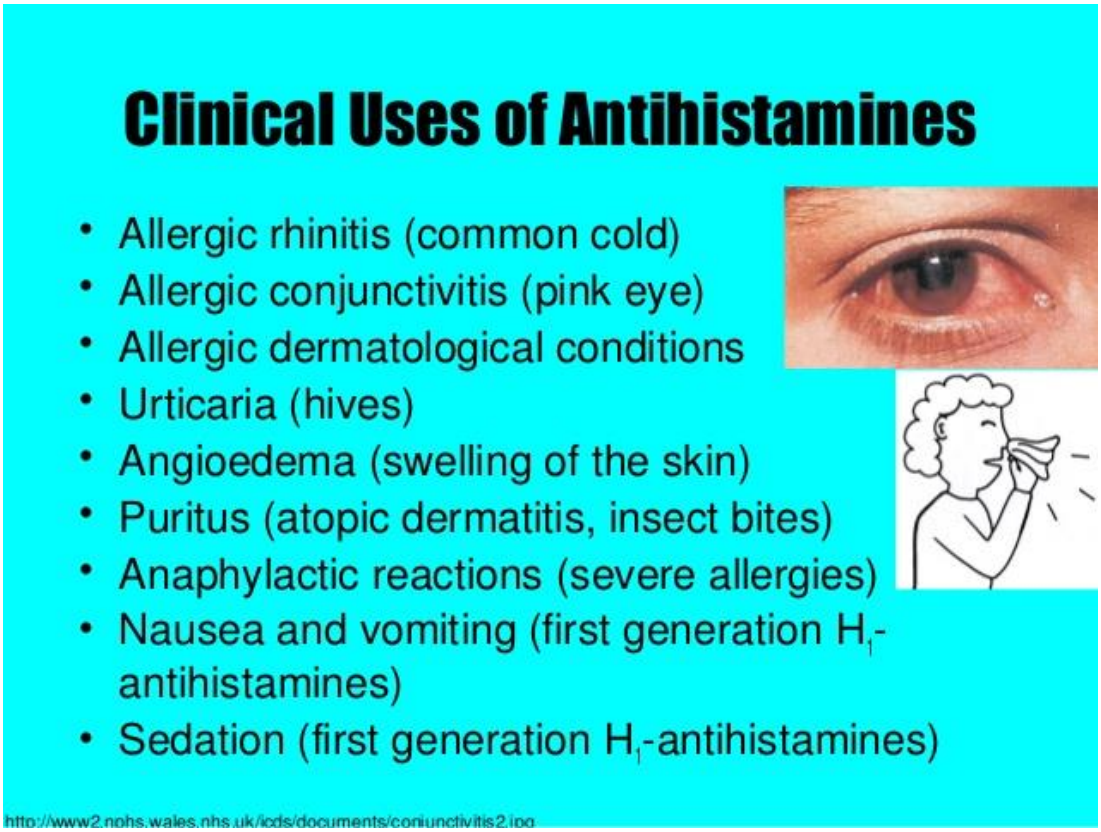
2. **H_2 receptor antagonists / H_2 Blockers:**

   Drugs which selectively and competitively antagonize most of the actions of histamine that are mediated by H_2 – receptor are called H_2 – receptor antagonists or H_2 blockers.

   Used in the treatment of acid-peptic disease.

   Example: Ranitidine, cimetidine etc.

Therapeutic Uses:



- **Allergic Disorders**
- **Other uses:** Diphehydramine and promethazine are used as hypnotics.

Adverse Effects:

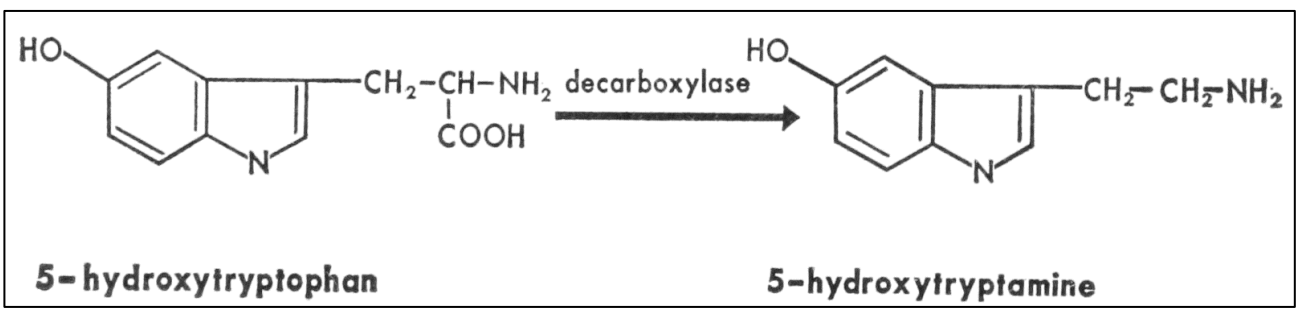
Usually mild. Most common is sedation. The most common anticholinergic adverse effect is dryness of the mouth. They may themselves occasionally cause allergic reactions.

5-Hydroxytryptamine (Serotonin)

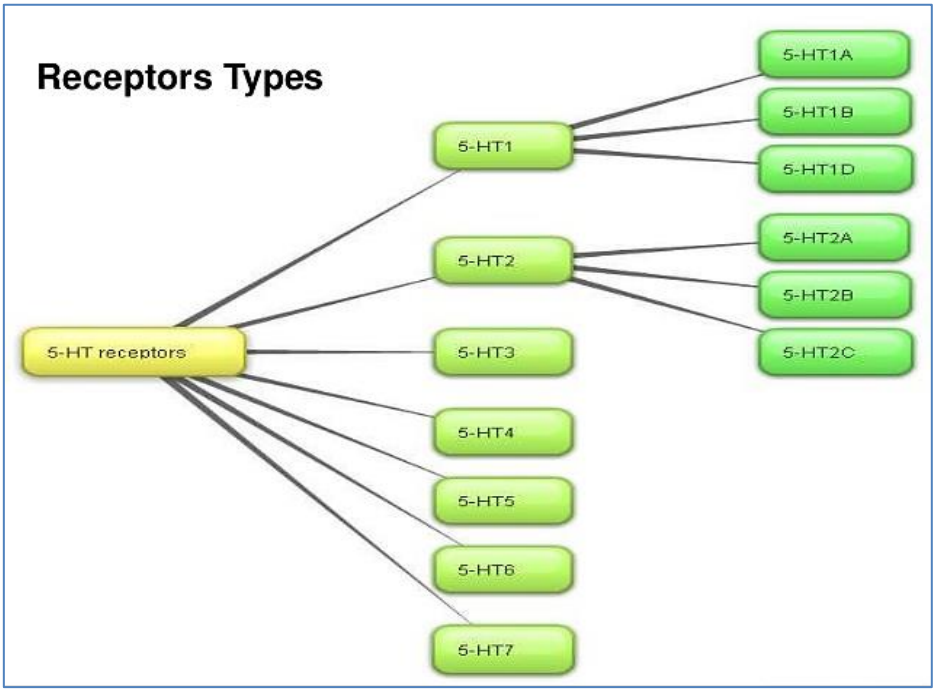
It is widely distributed in plants and animals. Highest concentration in mammals is found in the pineal gland (small endocrine gland in the vertebrate brain), acting as a precursor for melatonin (Hormone made by the pineal gland which helps to control sleep and wake cycles). Serotonin is manufactured in the brain and the intestines. The majority of the body's serotonin, between 80-90%, can be found in the gastrointestinal tract (enterochromaffin cells). It can also be found in the blood platelets

It is synthesized from the amino acid tryptophan and acts on several types of receptors.

Synthesis:



Serotonin receptors:



SEROTONIN RECEPTORS

Family	Type	Mechanism	Potential
5-HT$_1$	G-protein coupled.	Decreasing cellular levels of cAMP.	Inhibitory
5-HT$_2$	G protein coupled.	Increasing cellular levels of IP_3 and DAG.	Excitatory
5-HT$_3$	Ligand-gated Na^+ and K^+ cation channel.	Depolarizing plasma membrane.	Excitatory
5-HT$_4$	G-protein coupled.	Increasing cellular levels of cAMP.	Excitatory
5-HT$_5$	G-protein coupled.	Decreasing cellular levels of cAMP.	Inhibitory
5-HT$_6$	G-protein coupled.	Increasing cellular levels of cAMP.	Excitatory
5-HT$_7$	G-protein coupled.	Increasing cellular levels of cAMP.	Excitatory

Pharmacological Actions:

- It stimulates smooth muscles causing contraction of bronchial and intestinal smooth muscle.
- Serotonin is widely distributed in the CNS, serving as a neurotransmitter. It is involved in thermoregulation, behavioral pattern (mood, eating behavior). It is known as **happy molecule**.

Serotonin Agonists:

Buspirone, a serotonin agonist, is a useful effective anxiolytic agent.

Serotonin Antagonists:

- **Cyproheptadine:** It is mainly used to relieve the itching associated with skin disorders such as allergic dermatitis.
- **Ondansetron:** It is specific 5-HT_3 receptor antagonist. Given orally or intravenously, it is useful in the management of nausea and vomiting associated with cytotoxic therapy.

Lipid derived autacoids (Eicosanoids and Platelet activating factors)

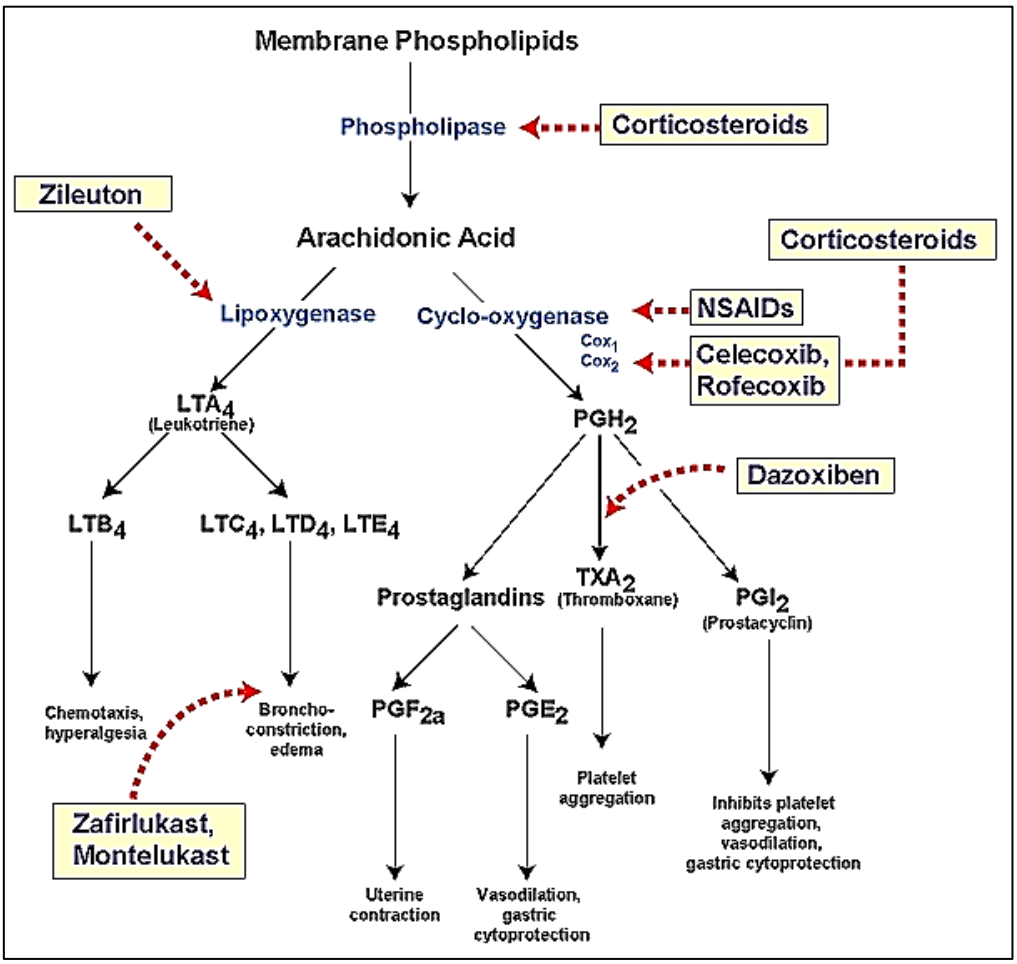
A. Eicosanoids:

'Eicosa' means 20 indicating a 20C structure and **'enoids'** indicates double bond. Other than some exceptions, eicosanoids are derived from the **Arachidonic acid** which has **20C atoms** and contains **4 double bonds.**

Prostaglandins:

Some compounds of eicosanoid group cause uterine contraction and come from the word prostate. So they are named Prostaglandins. Human seminal fluid is the richest known source, but they are also present in various tissues. PGE_2 and PGF_2 are the two main prostaglandins.

Synthesis of important prostaglndins and leukotrienes:



Pharmacological Actions:

- **Uterus:** PGE_2 and PGF_2 cause uterine contraction and are known to be important in the initiation and maintenance of labor.
- **GIT:** They increase intestinal motility. PGE_2 inhibits gastric acid secretion and acts as mucoprotective agent.
- **CVS:** PGE_2 is a vasodilator whereas PGF_2 is a vasoconstrictor.
- **Platelets:** Thromboxane (T_XA_2) causes platelet aggregation. PGI_2 is a potent inhibitor of platelet aggregation.
- **Miscellaneous:** Prostaglandins are important in pain generation and perception.

B. Platelet activating factors (PAF)

PAF is a phospholipid. Synthesis of PAF occurs in eosinophil, mast cells, neutrophil, platelets, macrophages and some kidney cells.

Pharmacological effects:

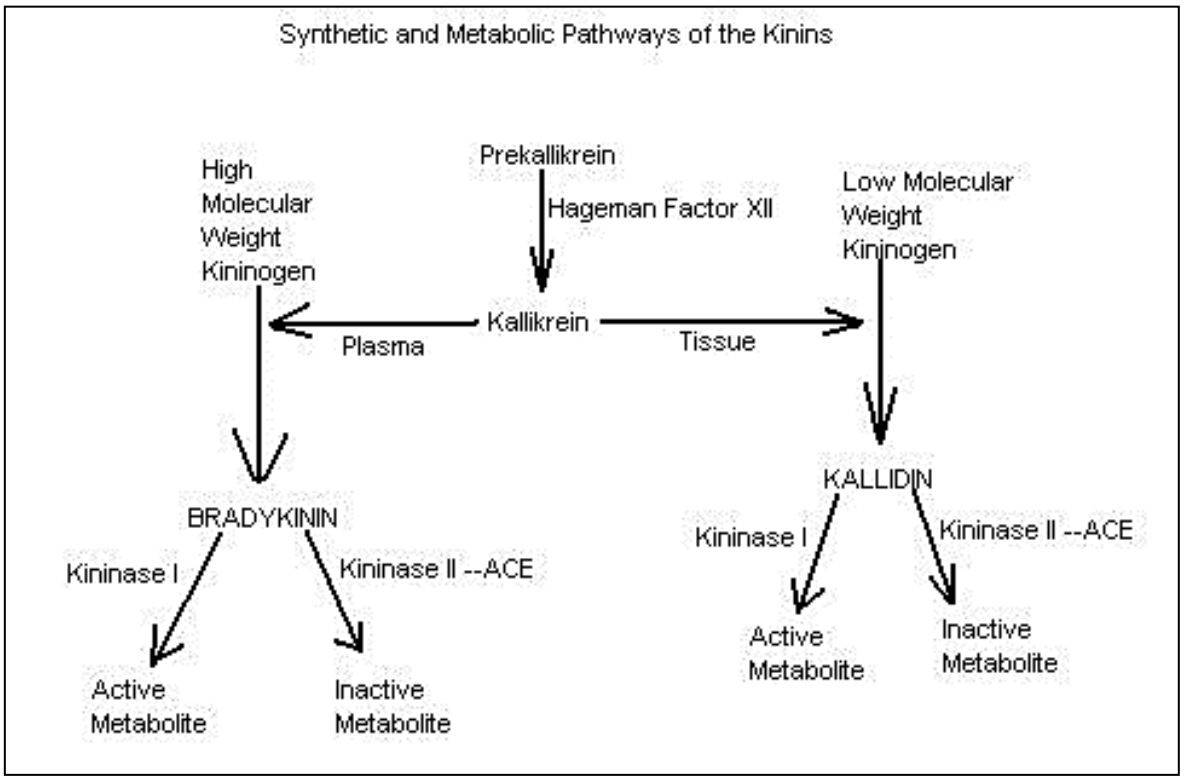
- **CVS:** They are potent vasodilators.
- **Blood:** Platelet aggregation is favored by PAF.

- **Smooth muscle:** They cause uterine contraction, GIT contraction, Bronchial muscle contraction.

Peptide autacoids

Two closely related peptide autacoids are Bradykinin and Kallidin (also known as Lysylbradykinin). They are found in the human body. They are formed from their precursors (Kininogen) under appropriate condition and almost immediately within a couple of seconds destroyed.

Biosynthesis:



Functions of Bradykinin and Kallidin:

1. Bradykinin causes local vasodialtion and increased capillary permeability, all of which promotes its role as an agent through which inflammation develops.
2. On smooth muscle, bradykinins cause contraction.
3. Kinins can cause local edema and local pain seen in rhinitis and angioedema.

4. **Anaphylactic reactions:** Anaphylactic reactions in the peri-operative period are often serious and potentially life-threatening conditions, involving multiple organ systems in which the clinical manifestations are the consequence of the release of preformed mediators from mast cells and basophils. Anaphylaxis is an immune mediated type I allergic reaction following the massive release of mediators from mast cells and basophils as a response to an allergen.
5. **Anaphylactoid reactions:** Anaphylactoid reactions are defined as those reactions that produce the same clinical picture with anaphylaxis but are not IgE mediated, occur through a direct nonimmune-mediated release of mediators from mast cells and/or basophils or result from direct complement activation. The occurrence of these reactions during anesthesia, although quite rare, remains a major concern for the anesthesiologists. Thus, the need for systematic screening before surgery and the awareness and expert advice to anaesthesiologists seems to be very critical.
6.
7. **Advantage of second generation antihistamines:** Second-generation antihistamines, being more lipophobic, offer the advantages of a lack of CNS and cholinergic effects such as sedation and dry mouth, which are commonly seen in first-generation antihistamines.

8. **Difference between first generation and second-generation antihistamines:** H1 antihistamines are mostly used to treat allergic reactions and mast cell-mediated disorders. While the first-generation H1 antihistamines have a central effect and, thus, are also used as sedatives, second-generation H1 antihistamines have fewer central effects and are used primarily as antiallergenic drugs.

9. **Vasoconstrictor:** Vasoconstrictors are useful additives to local anesthetic solutions. They can enhance the duration and quality of the anesthetic block while also decreasing surgical blood loss. Precautions must be taken, however, when using vasoconstrictors with certain patients, especially those with cardiovascular disease. Several drug interactions must also be considered before administration of a local anesthetic with a vasoconstrictor, and special care must be taken when injecting such preparations in patients on nonspecific beta-adrenergic blockers, tricyclic antidepressants, catechol-O-methyltransferase inhibitors, cocaine, and certain general anesthetics. Lastly, in the patient with true sulfite allergy, local anesthetics without a vasoconstrictor should be used.