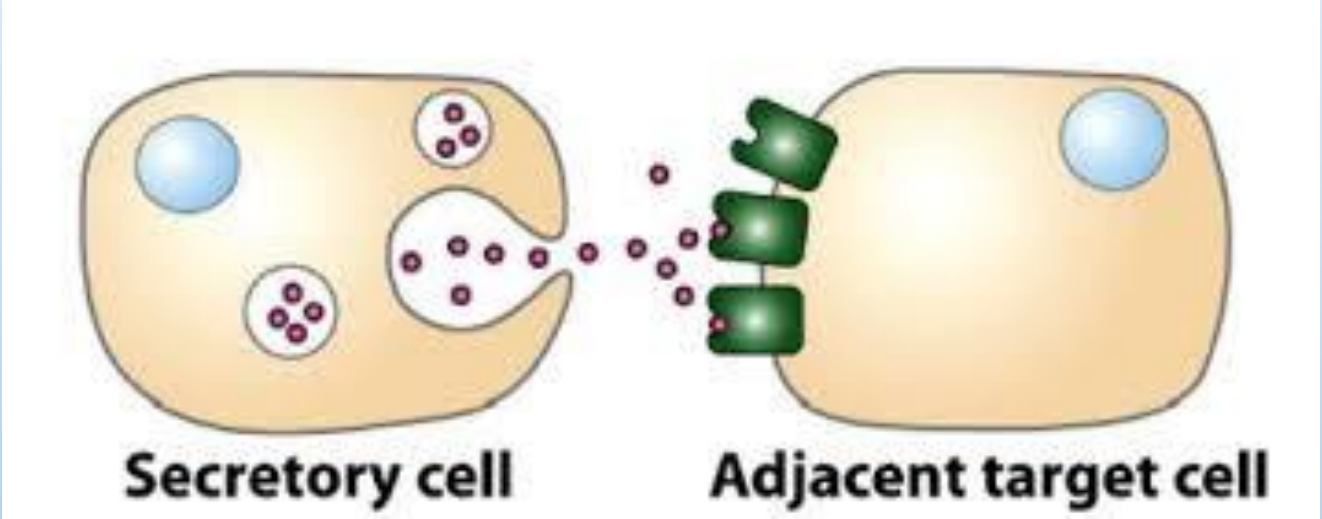
Autacoids

(part1)



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Definition

Autos - acos

Autacoids are chemical mediators that are synthesized and function in a localized tissue or area

participate in physiologic or pathophysiologic responses to injury.

They act only locally “local hormone.”

Autacoids normally do not function as the classical blood-borne hormones.

Autacoids are short-lived and rapidly degraded.

Class	Example
Biogenic Amines	**Histamine** Serotonin (5 HT)
Phospholipids Derived	**Prostaglandins** (Eicosanoids) , leukotrienes, Thromboxanes, Platelet activating factors (PAF)
Polypeptides	Angiotensin and Kinins (Bradykinin and Kallikidin)

Function

1. Autacoids modulate blood flow in specific tissues.

2. Some autacoids modulate secretory processes, for example, histamine on gastric acid formation.

3. Autacoids modulate smooth muscle function.

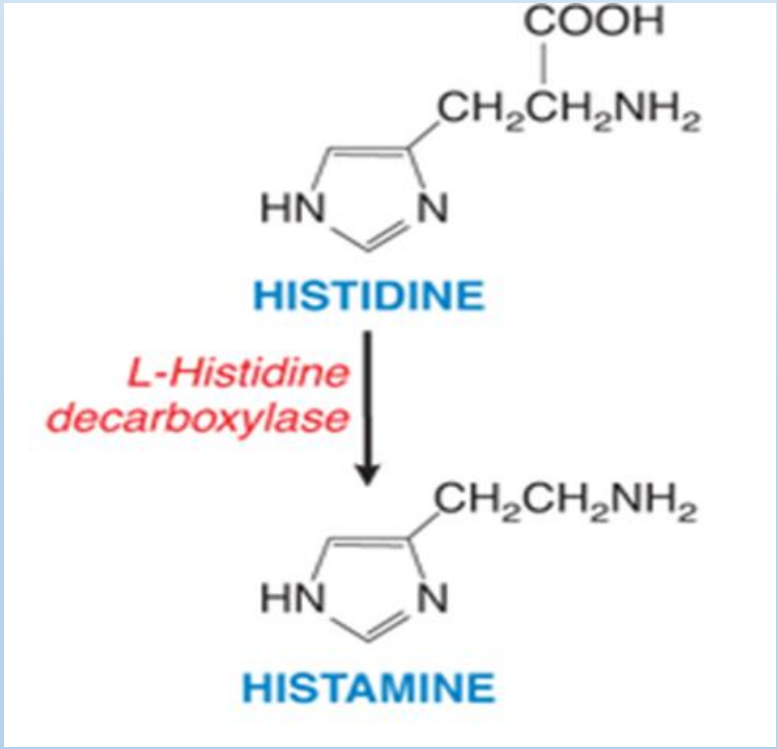
4. Autacoids play a key role in allergy, inflammation, smooth muscle function, pain, and certain types of drug reactions (Anaphylaxis).

Anaphylaxis

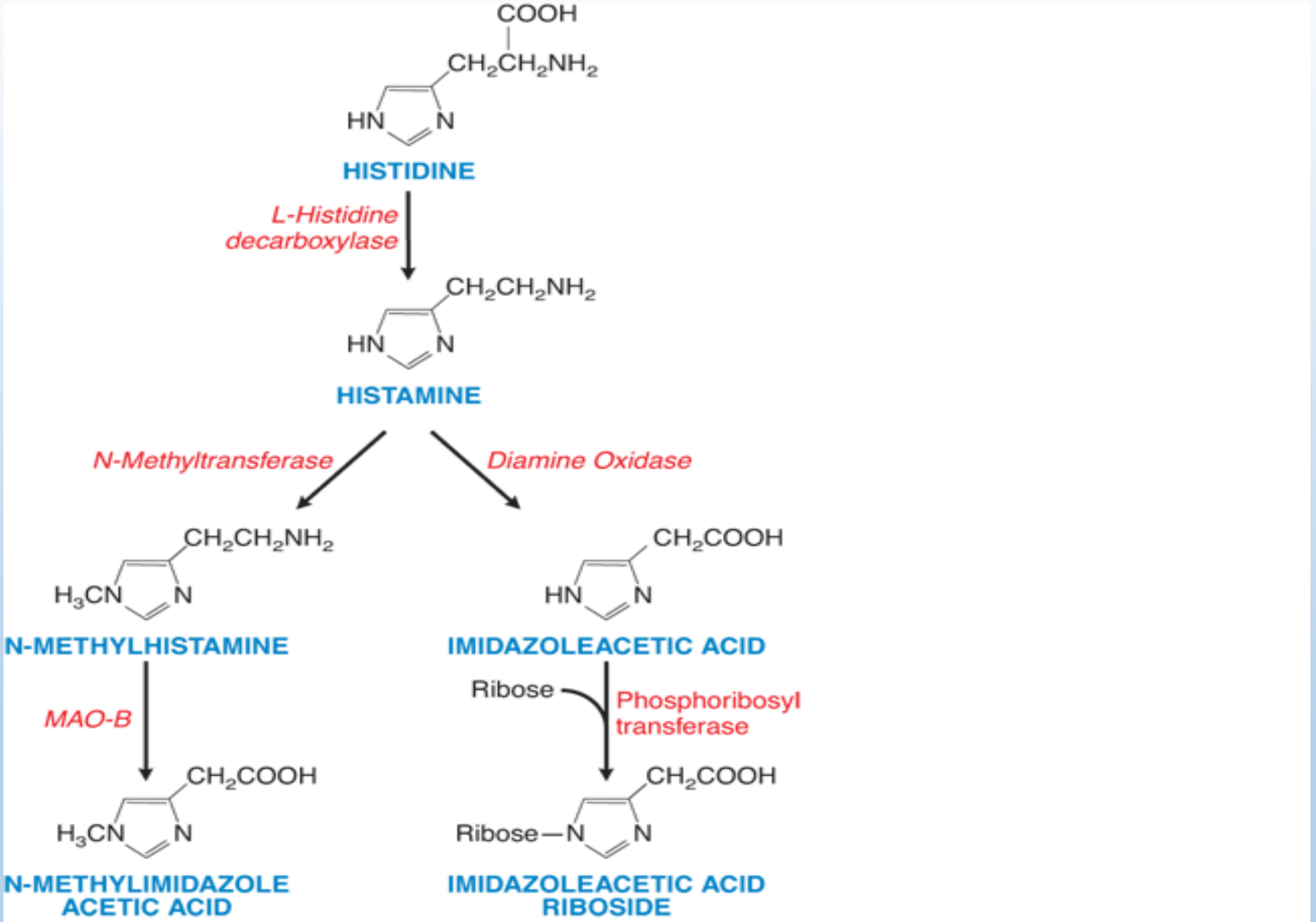
Histamine

1. Biosynthesis

Dietary **histidine** is decarboxylated by l-histidine decarboxylase to form **histamine**



2. Metabolism



Source: L. L. Brunton, B. A. Chabner, B. C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12ed.
www.accesspharmacy.com

3.storage sites

- Mast cells in **lungs**, **skin**, mucosal layer of the **stomach**

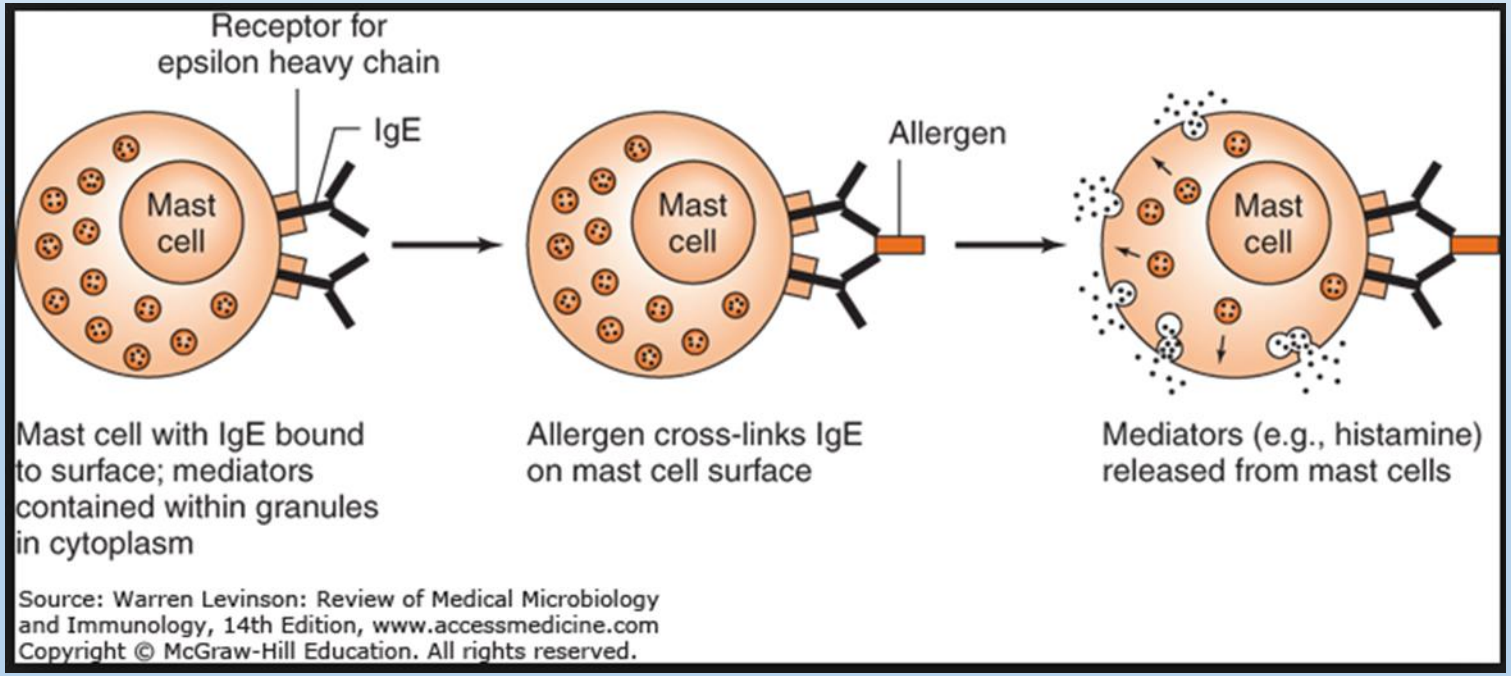
Mast cells are the primary cells that store histamine where it exists in a complex with heparin sulfate and chondroitin sulfate E in storage granules

- **Basophils**

- also found in CNS where it act as a neurotransmitter

4. Release

- a. Immune release.
- b. Drug-induced release
- c. Plant and animal stings
- d. Physical injury



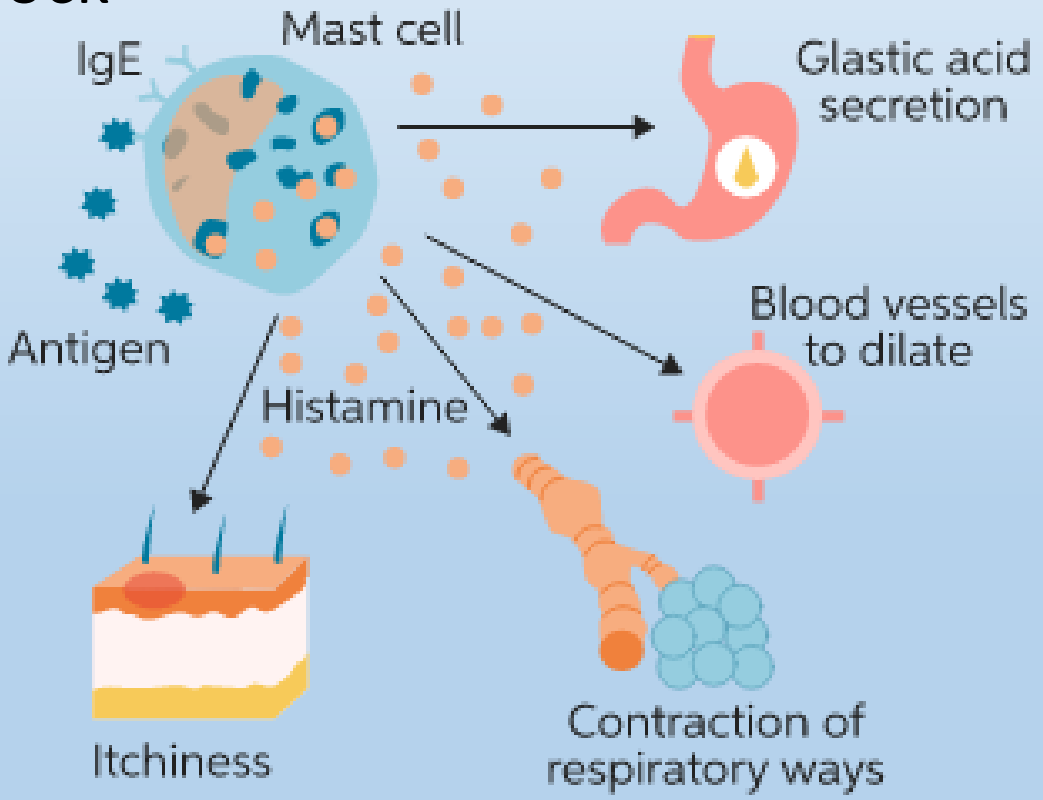
5. Physiologic and pathologic roles

a. Gastric acid secretion

b. Allergic reactions and anaphylactic shock

c. Inflammation

d. Neurotransmission



6. Pharmacologic effects

a. Cardiovascular system
b. Respiratory system
c. Glandular tissue
d. CNS
e. Intradermal tissue

Antihistamines

Therapeutically useful antihistamine drugs are H_1-antihistamines and H_2 antihistamines

H_1-antihistamine:

first type of antihistaminic drugs

classical antihistaminic

act as competitive antagonists/inverse agonists of histamine receptors

first-generation H_1-antihistamines

diphenhydramine, dimenhydrinate, hydroxyzyline, chlorpheniramine, meclizine, promethazine, and **cyproheptadine**.

These drugs are unionized drugs at physiological pH and easily cross the blood–brain barrier (BBB). Therefore, they produce CNS side effects, in particular, sedation.

Second-generation H_1-antihistamines

loratadine (Claritin®), cetirizine (Zyrtec®), and fexofenadine (Allegra®)

This class of drugs is ionized at physiological pH and is difficult to cross BBB

Pharmacologic effects of H_1-antihistamines

- **(1) Relaxation** of contracted bronchiolar smooth muscle.
- **(2) Relaxation** of contracted intestinal smooth muscle.
- **(3) Inhibition** of histamine-induced vasodilation and increased capillary permeability and thereby blocking formation of edema and wheals.
- **(4) Inhibition** of itch sensation by prevention of stimulation of sensory nerves. Many H_1-antihistamines have a potent **local anesthetic action** that may contribute to their inhibition of itching and pain.
- **Note**: **H1-antihistamines alone are not effective for treatment of systemic anaphylaxis because large amount of other autacoids are released during anaphylaxis.**

- **Sedation** is a common effect of first-generation H_1 -antihistamines but sedation does not correlate with their potency for inhibiting H_1-receptors. Sedation may be a desirable/undesirable effect and can be expected to be additive to other CNS depressants.
- **Antimuscarinic effects** are prominent for some H_1-antihistamines, for example, **diphenhydramine** and **promethazine**, which decrease secretions and relax smooth muscles.
- **Antimotion sickness (antiemetic) effects.** This effect is due to the inhibition of histaminergic signals from the vestibular nucleus to the vomiting center in the medulla. All H_1-antihistamine have this effect, but some of them (diphenhydramine, dimenhydrinate, and meclizine) have more potent antimotion sickness effect than others in the group.

Adverse effects

- **(1)** CNS depression (lethargy, somnolence, ataxia) are the most common but they may diminish with time. The performance of working dogs may be adversely affected.
- **(2)** Antimuscarinic effects (dry mouth, urinary retention) occur with many H_1-antihistaqmines. They should be used with caution in patients with angle closure glaucoma.
- **(3)** In high doses CNS stimulation is possible, for example, pyrilamine in the horse.
- **(4)** Some individuals could develop allergy to the use of H_1-antihsitamines.
- **(5)** Drug tolerance

H_2-antihistamines

H_2-antihistamines contain imidazole ring with uncharged side chains and are smaller than H_1-antihistamines

These drugs are inhibitors of gastric acid secretion.

They have little action on H_1-receptors.

- cimetidine
- ranitidine
- nizatidine
- famotidine

- **Pharmacologic effects**. H_2-antihistamines competitively inhibits histamine (H_2-receptors) in parietal cell and thereby decreases gastric acid production during basal conditions and when stimulated by food, vagal activity, pentagastrin, gastrin, or histamine.

- **Therapeutic uses**. H_2-antihistamines are administered orally to treat gastric, abomasal and duodenal ulcers, drug-induced erosive gastritis, duodenal gastric reflux, and esophageal reflux.

❖ Cimetidine is least potent among the four H_2-antihistamines. Lack of therapeutic effect of cimetidine has been reported in dogs.

❖ Cimetidine can inhibit the hepatic cytochrome P450 enzymes. It may reduce the metabolism of other drugs, which undergo hepatic metabolism, thereby elevating and prolonging their concentration in the plasma

Cromolyn sodium

inhibits the release of histamine and other autacoids from mast cells.

It **does not** inhibit H_1– and H_2-receptors, but opens chloride channel to hyperpolarize the cells

(1) It is primarily used to treat pulmonary and nasal allergic reactions

(2) It is not well absorbed from the gut and has no clinical use when given orally.

(3) It is used in a prophylactic manner.

(4) It has been used in the horse where it is nebulized and delivered via a face mask.

(5) The 4% eye drop is used to control allergic conjunctivitis.

Histamine