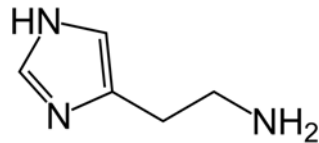


HISTAMINE AND ANTI-HISTAMINE DRUGS

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HISTAMINE [2-(4-imidazolyl)ethylamine]



First Synthesized in 1907
Pharmacological properties demonstrated in 1911
Extracted from tissues and named 1927 (Histo- = tissue + amine)
First antihistamine drugs 1943-44
Receptor subtypes characterized 1966-present

Histamine is an Autacoid (aut- = self, akos = cure); a molecule biosynthesized or secreted by a cell that exerts a pharmacological effect on neighboring cells; a “local hormone” It is also a neurotransmitter.

Histamine is found throughout the body, but in high concentrations in the brain, gut, skin, and lungs. It is concentrated in 3 main cell types; mast cells, enterochromaffin-like (ECL) cells and a variety of neurons.

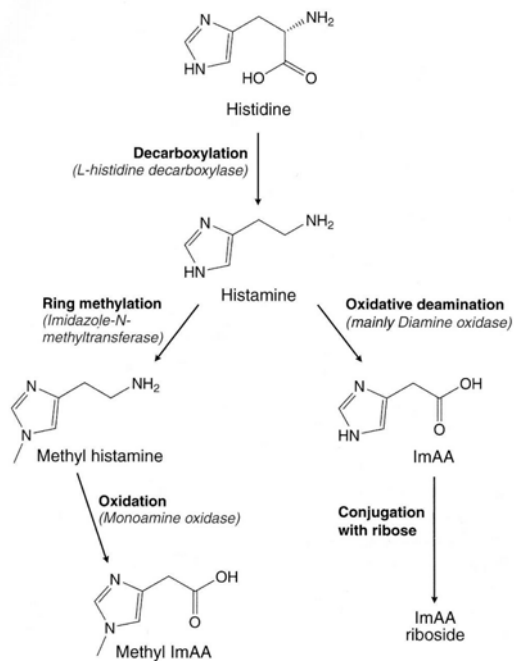


Figure 41-1. Histamine Synthesis and Degradation. Histamine is synthesized from histidine in a decarboxylation reaction catalyzed by L-histidine decarboxylase. The liver metabolizes histamine into inert byproducts. Histamine can be methylated on the imidazole ring or oxidatively deaminated. These degradation products can then undergo further oxidation or conjugation with ribose. Diamine oxidase is also known as histaminase. ImAA, imidazoleacetic acid.

Histamine receptors are found in tissues where histamine acts pharmacologically. There are currently 4 known types of histamine receptors.

TABLE 41-2 Histamine Receptor Subtypes

RECEPTOR SUBTYPE	POST-RECEPTOR MECHANISM	DISTRIBUTION
H1	Increased IP ₃ , DAG, and intracellular Ca ²⁺	Smooth muscle, vascular endothelium, brain (autoreceptor)
H2	Increased cAMP	Gastric mucosa, cardiac muscle, mast cells, brain
H3	Decreased Ca ²⁺ influx	CNS and some peripheral nerves

The pharmacological activity of histamine depends on the tissue and type of receptor that it activates

TABLE 41-1 Major Physiologic Actions of Histamine

TISSUE	EFFECT OF HISTAMINE	CLINICAL MANIFESTATIONS	RECEPTOR SUBTYPE
Lungs	Bronchoconstriction	Asthma-like symptoms	H1
Vascular smooth muscle	Post-capillary venule dilation Terminal arteriole dilation Venoconstriction	Rubor	H1
Vascular endothelial cells	Contraction and separation of endothelial cells	Edema, wheal response	H1
Nerves	Sensitization of afferent nerve terminals	Itchiness, pain	H1
Heart	Minor increase in heart rate and contractility	Minor	H2
Stomach	Increased gastric acid secretion	Peptic ulcer disease, heartburn	H2
CNS	Neurotransmitter	Circadian rhythms, wakefulness	H3

Mast cell histamine is a major mediator of the “immediate hypersensitivity response”, along with cytokines, prostaglandins, leukotrienes, heparin, and proteases.

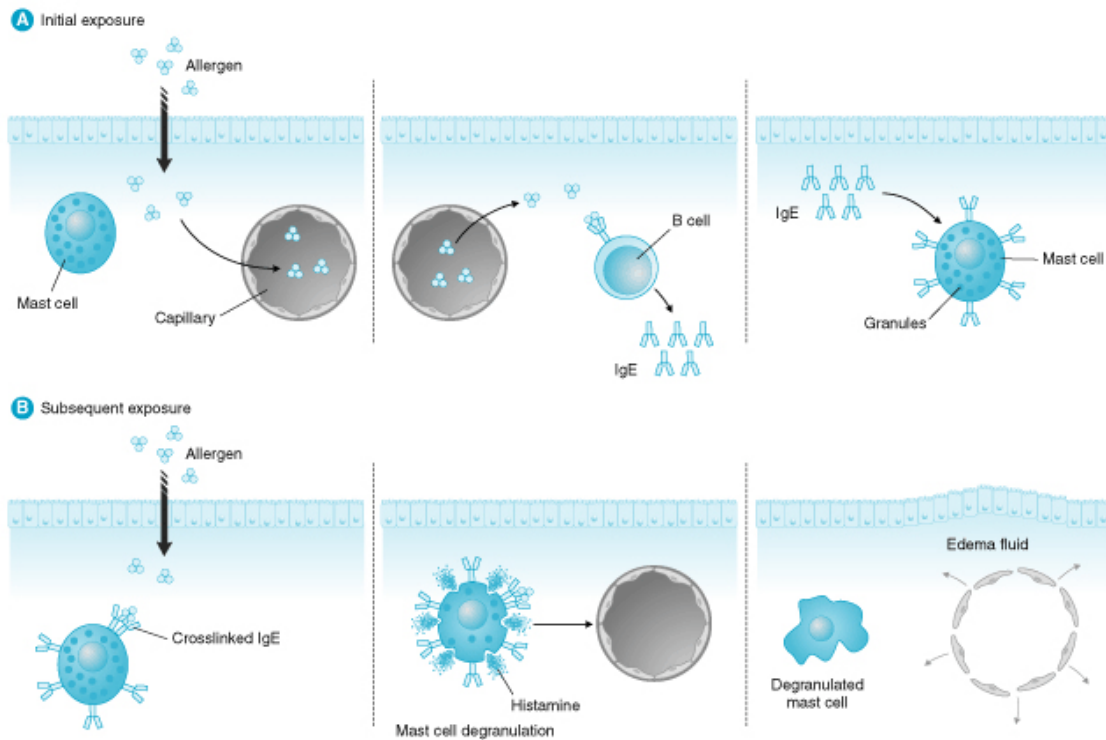


Figure 41-2 Pathophysiology of the IgE-Mediated Hypersensitivity Reaction. Allergen-induced mast cell degranulation requires two separate exposures to the allergen. **A.** On initial exposure, the allergen must penetrate mucosal surfaces so that it can encounter cells of the immune system. Activation of the immune response causes B lymphocytes to secrete allergen-specific IgE antibodies. These IgE molecules bind to Fc receptors on mast cells, leading to sensitization of the mast cells. **B.** On subsequent exposure, the multivalent allergen crosslinks two IgE/Fc receptor complexes on the mast cell surface. Receptor crosslinking causes the mast cell to degranulate. Local histamine release results in an inflammatory response, shown here as edema.

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Degranulation and histamine release can be triggered by antigen-IgE interaction, or by direct chemical stimulation of mast cells.

Result of release of Mast cell histamine: Vasodilation, Increased vascular permeability, stimulation of local pain-sensing neurons = redness, swelling, stinging or itching

Beneficial consequences of histamine release: increased local circulation, increased capillary permeability, increased leukocyte mobilization and chemotaxis, sensation of foreign object (all help fight infection)

Harmful consequences of histamine release: pain, itching, swelling, drop in blood pressure (shock), bronchoconstriction, tracheal swelling.

ALL PHARMACOLOGICAL MODULATION OF HISTAMINE ACTIVITY IS AIMED AT BLOCKING IT (ANTIHISTAMINE DRUGS)

TABLE 41-3 Strategies of Histamine Pharmacology

STRATEGY	EXAMPLE OF PHARMACOLOGIC AGENT	EXAMPLE OF DISEASE TREATED
Administer drug to counter the pathologic effect of histamine	Epinephrine	Anaphylaxis
Prevent mast cell degranulation	Cromolyn, nedocromil	Asthma
Histamine receptor antagonist	Diphenhydramine Cimetidine, ranitidine	Allergies Ulcers, heartburn

Indirect antihistamine activity:

Cromolyn (blocks degranulation)

Epinephrine (counteracts its physiological activity)

Vasoconstriction

Bronchodilation

Increased cardiac output

(Little or no effect on vascular permeability)

Direct antihistamine activity (Histamine antagonists)

The first antihistamine drugs were used as “anti-allergy” drugs to block histamine mediation of the immediate hypersensitivity response. These act primarily at H1 receptors, and are known as the “First Generation” antihistamines

TABLE 26-2. Pharmacologic Properties of Selected Histamine H1 Receptor Antagonists

Drug	Duration of Action (Hours)	Sedative Effects	Antiemetic Effects	Anticholinergic Effects
First-generation antihistamines				
Chlorpheniramine	6	Medium	None	Medium
Dimenhydrinate	8	High	Medium	High
Diphenhydramine	8	High	Medium	High
Hydroxyzine	6	High	High	Medium
Meclizine	12	Medium	High	Medium
Promethazine	12	High	High	High
Second-generation antihistamines				
Cetirizine	24	Low	None	Very low
Fexofenadine	12	Very low	None	Very low
Loratadine	24	Very low	None	Very low
Intranasal antihistamines				
Azelastine	12	Low	None	Very low

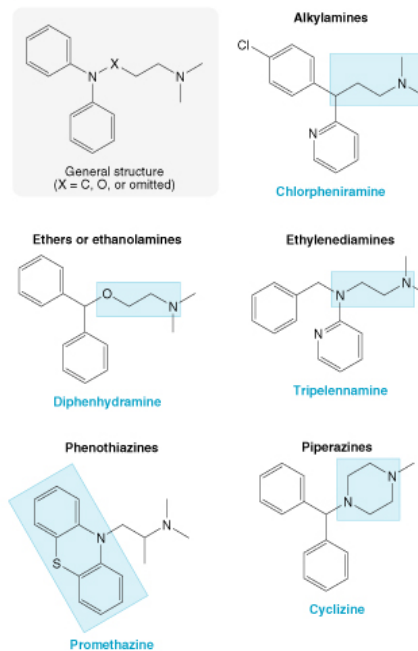


Figure 41-3 Structure of First-Generation Histamine H1 Receptor Antagonists. The general structure of the first-generation H1 receptor antagonists consists of a substituted ethylamine backbone with two terminal aromatic rings (Note the similarity between the ethylamine moiety in these antagonists and the ethylamine side chain of histamine shown in Fig. 41-1). Each of the five subclasses is a variation on this general structure. First-generation H1 antagonists are neutral compounds at physiologic pH and readily cross the blood–brain barrier. In contrast, second-generation H1 antagonists (e.g., loratadine, cetirizine, fexofenadine) are ionized at physiologic pH and do not appreciably cross the blood–brain barrier (not shown). This difference in blood–brain barrier penetration underlies the differential extent of sedation associated with use of the first- and second-generation H1 antagonists.

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Major side effects: Sedation, Anticholinergic (antimuscarinic) activity
Dry mouth

Ability to block H1 receptors in the CNS makes these drugs useful as mild sedatives and mild anti-nausea drugs (e.g. motion sickness) – their second major therapeutic application.

“Second generation” antihistamines also act at H1 receptors, but have much less antimuscarinic and sedative side effects.

“Third generation” antihistamines: Second generation drugs with decreased cardiac side effects

H2 antagonists:

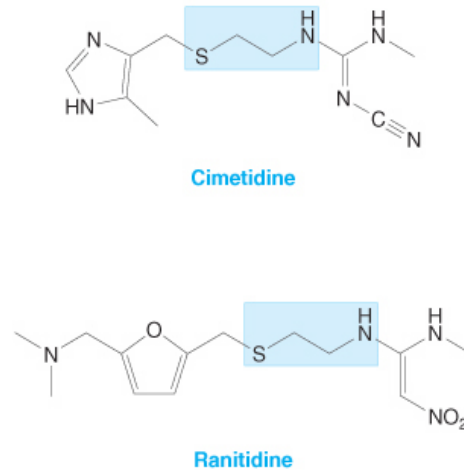


Figure 41-4 **Structure of Histamine H2 Receptor Antagonists.** H2 receptor antagonists have a thioethanolamine backbone (highlighted in blue box) that is N-substituted with a bulky side chain and terminates in a single five-membered ring. (Compare the bulky N-substituted side chain of the H2 antagonists with the simple tertiary amine of the H1 antagonists in Fig. 41-3, and compare the small five-membered imidazole or furan ring of the H2 antagonists with the pair of bulky aromatic rings of the H1 antagonists.) These structural differences enable cimetidine, ranitidine, and other H2 antagonists to bind selectively to H2 receptors in the gastric mucosa and, thereby, to decrease the production of gastric acid.

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Major use of H2 antagonists is to block the stimulation by histamine of H2 receptor-mediated acid secretion in the stomach. H2 histamine antagonists are very effective in treatment of gastric hyperacidity and peptic ulcer disease.

Histamine antagonists that selectively target H3 and H4 receptors have potential therapeutic applications, but these have no current defined clinical use.

MAJOR DRUGS TO KNOW:

First Generation H1 antagonists:

Diphenhydramine (Benadryl, etc. OTC)

Chlorpheniramine (Chlor-trimetron, etc. OTC)

Promethazine (Phenergan, etc. OTC)

Antiemetic and Motion Sickness:

Promethazine

Meclizine (Bonine OTC)

Dimenhydrinate (Dramamine OTC) (salt of diphenhydramine and chlorotheophylline)

Second Generation H1 antagonists:

Loratadine (OTC)

Fexofenadine (Rx)

H2 antagonists:

Cimetidine (OTC)

Famotidine (OTC)

Ranitidine (OTC)

Not Histamine Receptor Antagonists:

Cromolyn

Epinephrine