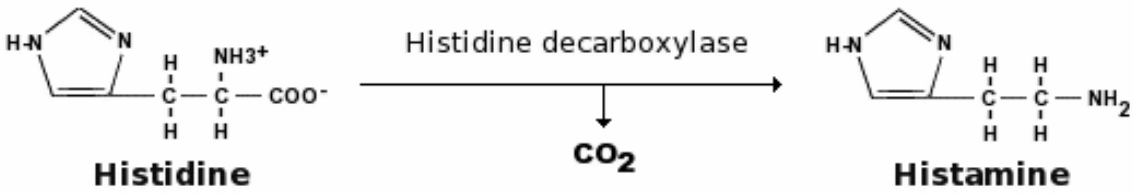
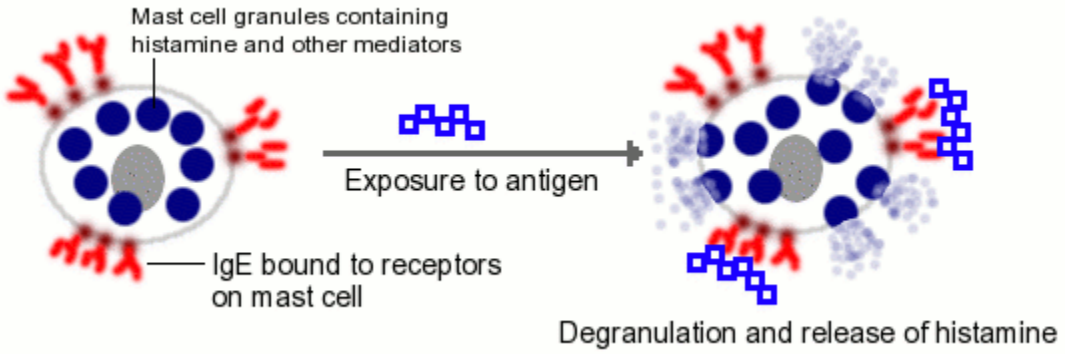
HISTAMINE AND ANTIHISTAMINERGIC DRUGS:

Histamine is a small molecule derived from the decarboxylation of the amino acid histidine. It is destroyed by the enzyme diamine oxidase (histiminase), which is also involved in the metabolism of other bioactive amines.



Histamine is synthesized in all tissues, but is particularly abundant in skin, lung and gastrointestinal tract. Mast cells, which are present in many tissues, are a prominent source of histamine, but histamine is also secreted by a number of other immune cells. Mast cells have surface receptors that bind immunoglobulin E, and when antigen crosslinks IgE on the mast cell surface, they respond by secreting histamine, along with a variety of other bioactive mediators.



PHYSIOLOGIC EFFECTS OF HISTAMINE

Histamine is best known as a mediator of allergic reactions, but it is now recognized to participate in numerous other normal and pathologic processes. The sensitivity and response of a particular cell to histamine depends upon which type of histamine receptor is present on that cell.

ALLERGIC AND INFLAMMATORY REACTIONS

Histamine plays a prominent role in many types of allergic and inflammatory processes, including both acute and delayed hypersensitivity reactions.

The source of histamine in such cases is tissue mast cells. The magnitude of such problems depends on the route of exposure (local versus systemic), sites of exposure (e.g. inhaled versus cutaneous), the dose of allergen, and the degree of previous sensitization to the allergen.

Many of the signs of allergic reaction result from the ability of histamine to affect blood vessels, inducing increased blood flow, vasodilation and increased vascular permeability.

REGULATION OF IMMUNE RESPONSES

In addition to allergic reactions, histamine has significant effects on many aspects of immune reactions by binding to its diverse group of receptors expressed variously on B and T lymphocytes, dendritic cells, and macrophages. Among other things, histamine influences immune cell maturation and activation, secretion of several cytokines, and chemotactic responses of cells.

SECRETION OF GASTRIC ACID

Hydrochloric acid is secreted in abundance by parietal cells embedded in the epithelium of the stomach. One of the principle stimuli for secretion of acid by parietal cells is histamine, secreted from neighboring enterochromaffin cells. The histamine receptor on parietal cells is the H2 type, and blocking the binding of histamine to this receptor is a widely used method for suppressing gastric acid secretion.

SMOOTH MUSCLE CONTRACTION

Smooth muscle around bronchi in the lungs and within the intestinal tract respond to histmine stimulation by contraction, although the magnitude of response varies considerably among species. These effects also depend on which receptor is being bound by histamine; for example, the H2 receptor mediates bronchodilation. One of the first bioassays for histamine involved measuring contraction of guinea pig intestinal muscle. These effects on smooth muscle are manifest in a number of allergic reactions, for example, bronchocontriction in response to inhaled allergens.

EFFECTS IN THE NERVOUS SYSTEM

Histamine acts as a neurotransmitter within the central nervous system. The (histaminergic) neurons that secrete histmine are localized in small regions of the hypothalamus, but those neurons send axons widely throughout the brain. Histamine appears to modulate a number of important processes in the brain, including wakefulness, cognitive ability and food consumption.

Histamine Receptors and Receptor Antagonists

Four histamine receptors have been identified, all of which are G protein-coupled receptors. These different receptors are expressed on different cell types and work through different intracellular signalling mechanisms, which explains, at least at a simple level, the diverse effects of histamine in different cells and tissues.

HISTAMINE RECEPTOR TYPES AND THEIR FUNCTIONS

Receptor Type	Major Tissue Locations	Major Biologic Effects
H_1	smooth muscle, endothelial cells and CNS	Acute allergic responses such as vasodilation, broncho constriction, also involved in allergic rhinitis symptoms, motion sickness; sleep regulation.
H_2	gastric parietal cells	secretion of gastric acid
H_3	central nervous system	modulating neurotransmitter (histamine, noradrenaline and acetylcholine release
H_4	Mast cells, eosinophils, T cells, dendrites	regulating immune responses

CONDITIONS THAT RELEASE HISTAMINE

1. Tissue injury: Any physical or chemical agent that injures tissue, skin or mucosa are particularly sensitive to injury and will cause the immediate release of histamine from mast cells.
2. Allergic reactions
3. Drugs and foreign compounds (morphine, dextran, antimalarial drug, antibiotic, Tetracyclines, Penicillines.

GENERAL MECHANISM OF ACTION OF ANTIHISTAMINES:

- Blocks action of histamine at receptor
- Competes with histamine for binding
- Displaces histamine from receptor
- Most beneficial when given early

HISTAMINE VS ANTIHISTAMINE:

1. **CARDIOVASCULAR EFFECTS**

   Histamine

   dilation of small blood vessels / increased permeability

   Antihistamine

   prevents dilation / prevents increased permeability

2. **SMOOTH MUSCLE EFFECTS**

   Histamine

   Stimulates exocrine glands (salivary, gastric, lacrimal, & bronchial secretions)

   Antihistamine

   prevents: salivary, gastric, lacrimal, & bronchial secretions

3. **IMMUNE EFFECTS**

   Histamine

   mast cell release: histamine & other substances released

   Antihistamine

   bind to receptors and prevents histamine from eliciting a response

FIRST GENERATION ANTIHISTAMINES

- **Piperazines, phenothiazines, Piperadines**

SECOND GENERATION ANTIHISTAMINES

Generally do not cause the sedation and drying seen in first generation antihistamines
Do not cross the blood-brain barrier as readily as First Generation compounds
Lipophobicity, Large molecular size,Electrostatic charge.

- **Seldane, loratidine, fexofenadine**

The first histamine antagonists - antihistamines - competitively blocked the binding of histamine to H1 receptors, and have been used for many years in "cold pills" and sleeping aids. Examples of H1 receptor antagonists include diphenhydramine (Benadryl) and loratadine (Claritin). Interestingly, discovery of new histamine receptors largely followed the findings that the H1 antagonists did not block all actions of histamine. For example, H1 receptor antagonists do not effect secretion of gastric acid because that response is due to binding of histamine to H2 type receptors; mitigating gastric acid secretion requires an H2 receptor antagonist. Receptor antagonists for H3 and H4 receptors are being avidly investigated because of their potential benefit for function of brain and immune system.

CONTROL OF APPETITE

Weight gain is often experienced by patients receiving H1 antihistamines or tricyclic antidepressants that have potent H1-receptor antagonist properties. This may reflect an inhibition of feeding exerted by histamine neurons that project to the ventromedial and paraventricular hypothalamic nuclei, as shown by the effects of histamine synthesis inhibitors or H3-receptor ligands. In addition, the extracellular concentration of the amine in rat hypothalamus increases during feeding.

POTENTIAL ROLE IN NEUROPSYCHIATRIC ILLNESSES

Research have shown that elevated levels of methyl histamine in cerebrospinal fluid (CSF) suggest increased central histaminergic activity in patients with chronic schizophrenia.

Post mortem studies of basal ganglia from patients with Parkinson's disease or in a rodent model of this disease showed no change in the activity of the histamine-synthesizing enzyme.

Patients with Alzheimer's disease show numerous neurofibrillary tangles and typical senile plaques in the tuberomammillary area. It is not clear, however, whether the number of histamine-immunoreactive neurons is decreased. In addition, it may be significant that 9-amino-1,2,3,4-tetrahydroacridine (THA), an anti cholinesterase that was found to be useful in Alzheimer's disease, is also a rather potent inhibitor of histamine methylation. In addition, an H_3-receptor antagonist improved learning deficits in mice.

The effects of antipsychotics at dopamine receptors strongly suggested the role of dopamine in schizophrenia. In contrast, the interactions of psychotropic drugs with histamine receptors are of limited help for deducing the role of histaminergic neurons in psychiatric illnesses. Over a decade ago it was proposed that the cerebral H_2 receptor are an important target for most tricyclic and other antidepressant drugs that interact with relatively high affinity with the receptor coupled to the cyclase.

A number of side effects (e.g., sedation or weight gain) of several antidepressant drugs, as well as some neuroleptics, are attributable to the blockade of cerebral H_1 receptors. The affinity of the atypical antipsychotic drug clozapine at the H_3 receptor is in the same range as at D2/D3 dopamine receptors.

Intra-cerebral injection of histamine in the cat ventro-lateral hypothalamus, where the density of histaminergic axons is high, increased wakefulness via stimulation of postsynaptic H1 receptors