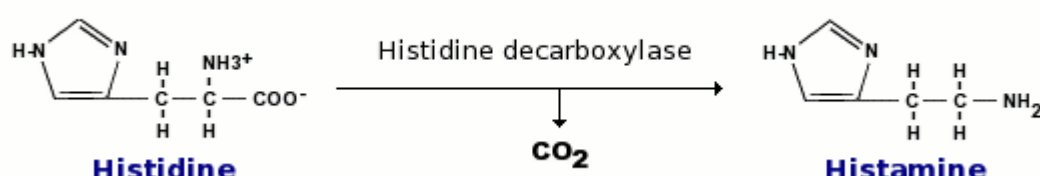


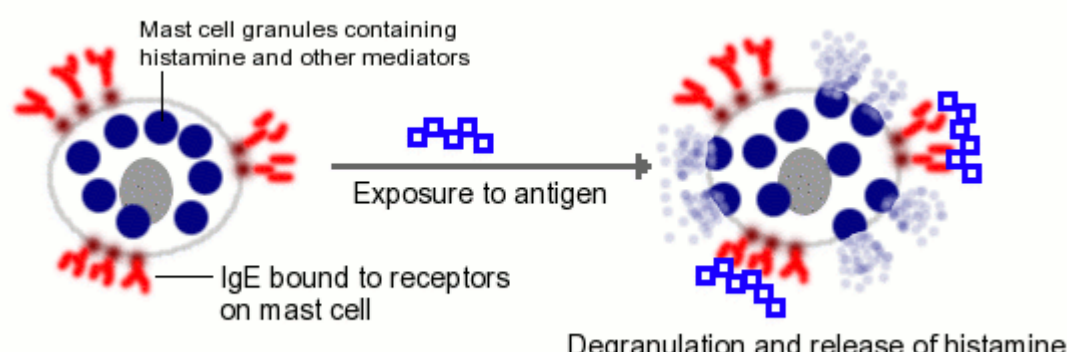


Histamine and Histamine Receptors

Histamine is a small molecule derived from the decarboxylation of the amino acid histidine. It is destroyed by the enzyme diamine oxidase (histaminase), 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.

An interesting illustration of the systemic effects of histamine is scombroid fish poisoning. Essentially histamine poisoning, this disorder is seen following consumption of fish, commonly tuna or mackerel, that have spoiled and within which bacteria have generated abundant quantities of histamine from histidine in muscle protein. Consumption of such spoiled fish results in the rapid development of a variety of clinical signs, including headache, sweating, diarrhea, a flushed face, and vomiting, all resulting from systemic exposure to histamine. The lesson here: keep fish refrigerated!



Allergic and Inflammatory Reactions

Histamine plays a pivotal 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. Clinical manifestations of histamine release vary from life-threatening anaphylactic reactions, to urticaria (hives), to local wheal and flare reactions. The image on the right shows a dog with hives due to a drug allergy.



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 frank 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, macrophages and a variety of hematopoietic cells. 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 histamine 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, bronchoconstriction 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 histamine 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.

Receptor Type	Major Tissue Locations	Major Biologic Effects
H ₁	smooth muscle, endothelial cells	acute allergic responses
H ₂	gastric parietal cells	secretion of gastric acid
H ₃	central nervous system	modulating neurotransmission
H ₄	mast cells, eosinophils, T cells, dendritic cells	regulating immune responses

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.

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