

HISTAMINE INTRODUCTION

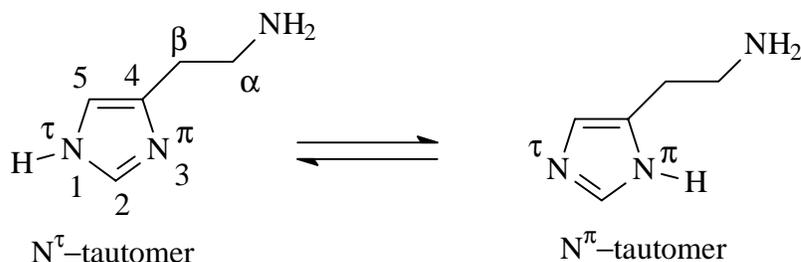
I. Introduction

Histamine is an β -imidazolylethylamine derivative that is present in essentially all mammalian tissues. The major physiological actions of histamine are centered on the cardiovascular system, nonvascular smooth muscle, exocrine glands and the adrenal medulla. In a general sense, histamine plays an important role as a “chemical messenger” component of the various pathways that have evolved in multicellular organisms allowing them to communicate efficiently and effectively. The involvement of histamine in the mediation of allergic and hypersensitivity reactions as well as in the regulation of gastric acid secretion has led to the development of important drug classes useful in the treatment of symptoms associated with allergic and gastric hypersecretory disorders.

Histamine exhibits a wide variety of both physiologic and pathologic functions in different tissues and cells as described in the **Pharmacology Notes**. The actions of histamine that are of interest from both a pharmacologic and therapeutic point of view include (1) its important but limited role as a chemical mediator of hypersensitivity reactions, (2) a major role in the regulation of gastric acid secretion and (3) an emerging role as a neurotransmitter in the CNS.

II. Histamine Chemistry and Stereochemistry

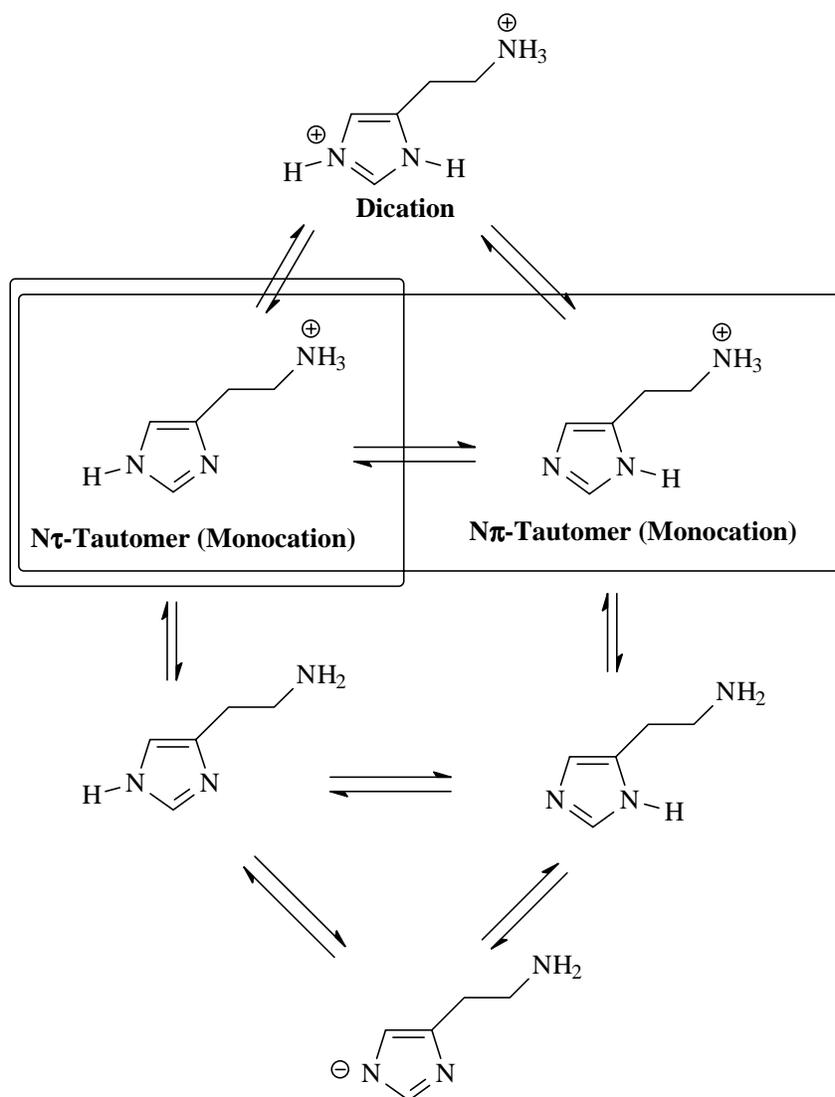
Histamine, known trivially as 4(5-)(2-aminoethyl)-imidazole, consists of an imidazole heterocycle and ethylamine side chain. The methylene groups of the aminoethyl side chain are designated as α and β . The side chain is attached, via the β -CH₂ group, to the 4-position of an imidazole ring. The imidazole N at position 3 is designated as the pros (π) N whereas the N at position 1 is termed the tele (τ) N. The side chain N is distinguished as $N\alpha$.



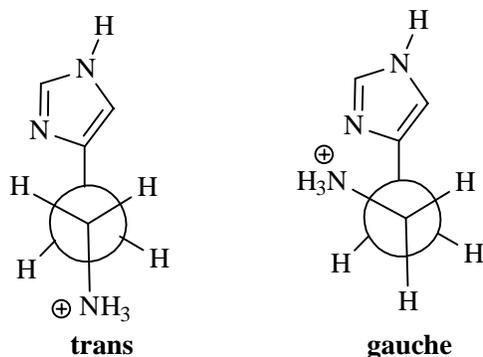
Histamine is a basic organic compound ($N\pi$, $pK_{a1}=5.80$; $N\alpha$, $pK_{a2}=9.40$ and $N\tau$, $pK_{a3}=14.0$) capable of existing as a mixture of different ionic and uncharged tautomeric species as shown in the Figure below. Histamine has been found to exist almost exclusively (96.6%) as the monocationic conjugate species ($N\alpha$ as NH_3^+) at physiologic pH (7.4). The ratio of the concentrations of the tautomers $N\tau$ -H/ $N\pi$ -H has been calculated to be 4.2 indicating that in aqueous solution 80% of the histamine monocation exists as $N\tau$ -H and 20% as $N\pi$ -H.

Structure-activity relationship studies suggest that the α - NH_3^+ monocation is important for agonist activity at histamine receptors and that transient existence of the more lipophilic uncharged histamine species may contribute to translocation of cell membranes. Other studies support the

proposal that the $N\pi$ -H tautomer of the histamine monocation is the pharmacophoric species at the H_1 -receptor while a 1,3-tautomer system is important for selective H_2 -receptor agonism.



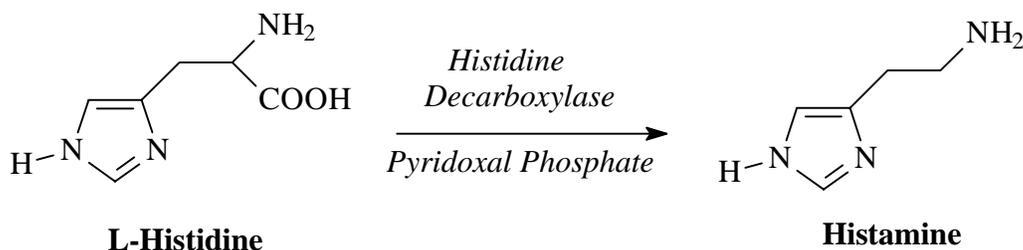
Histamine is an achiral molecule, however, histamine receptors are known to exert a high degree of stereoselectivity toward chiral ligands. Molecular modeling and steric-activity relationship studies of the influence of conformational isomerism on the activity of histamine suggest the importance of trans-gauche rotameric structures in the receptor activities of this substance. Studies with conformationally-restricted histamine analogues suggest that, while the trans rotamer of histamine possesses affinity for both H_1 and H_2 histamine receptors, the gauche conformer does not act at H_2 -sites.



III. Histamine Biosynthesis, Storage, Release and Metabolism

Knowledge of the biodisposition of histamine is important to understanding the involvement of this substance in various pathophysiology as well as the actions of various ligands that either enhance or block the actions of histamine. Each of the steps in the “life cycle” of histamine represents a potential site for pharmacological intervention.

Histamine is synthesized in cytoplasmic granules of its principle storage cells, mast cells and basophils. Histamine is formed from the naturally-occurring amino acid, *S*-histidine via the catalysis of either the pyridoxal phosphate-dependent enzyme histidine decarboxylase (HDC, EC 4.1.1.22) or aromatic amino acid decarboxylase as shown below. Substrate specificity is higher for HDC. Inhibitors of HDC include α -fluoromethylhistidine (FMH) and certain flavanoids, however no HDCIs have proved useful clinically.

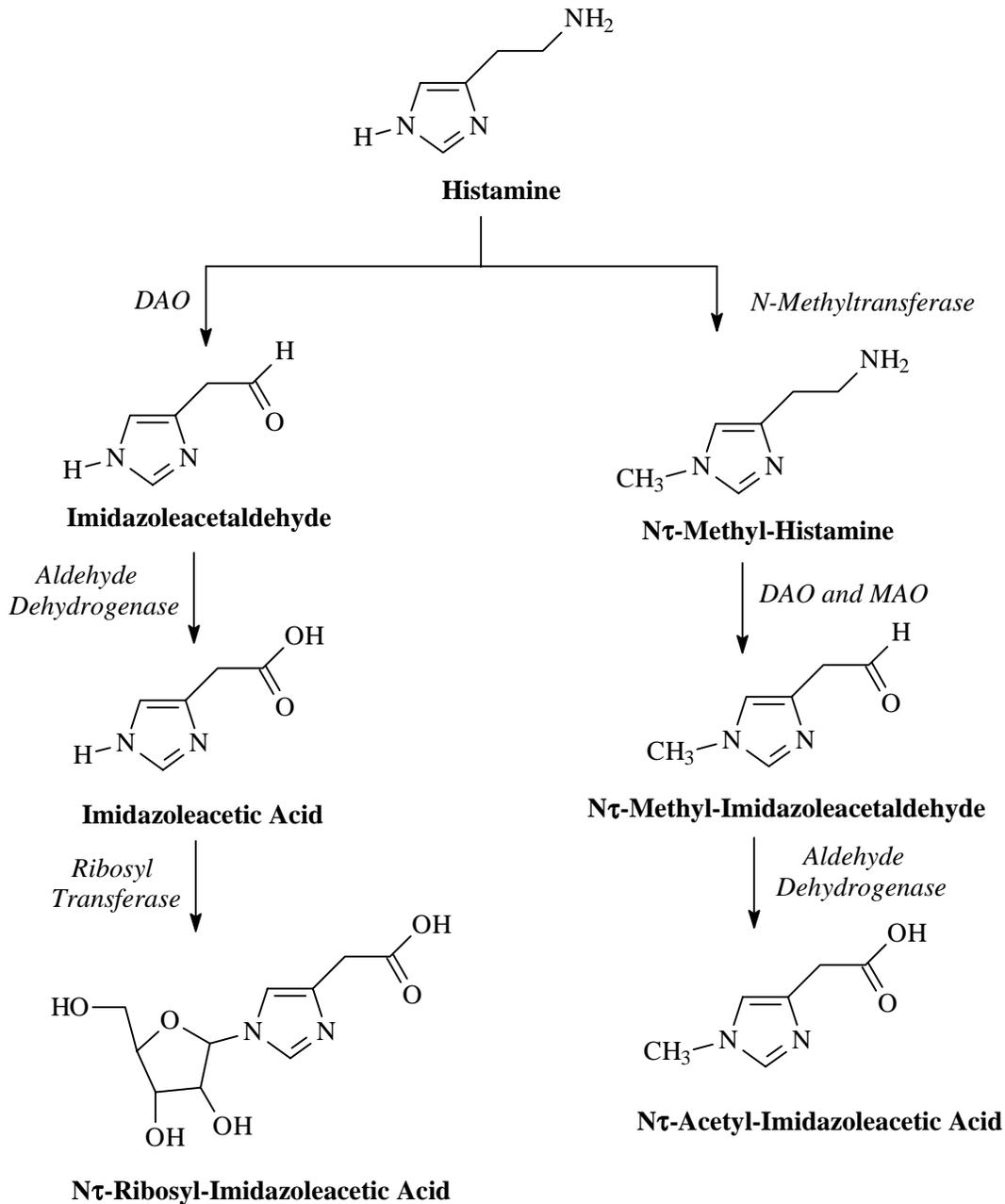


Histamine is found in almost all mammalian tissues in concentrations ranging from 1 to >100 mg/g. This substance is in particularly high concentration in skin, bronchial and intestinal mucosa. It is found in higher concentrations in mammalian cerebrospinal fluid than in plasma and other body fluids.

Most histamine is synthesized and stored in mast cells and basophil granulocytes. Protein-complexed histamine is then stored in secretory granules and released by exocytosis in response to a wide variety of immune (antigen and antibody) and non-immune (bacterial products, xenobiotics, physical effects and cholinergic effects) stimuli. The release of histamine as one of the mediators of hypersensitivity reactions is initiated by the interaction of an antigen-IgE complex with the membrane of a histamine-storage cell. This interaction triggers activation of intracellular phosphokinase C (PKC) and accumulation of inositol phosphates, diacylglycerols and Ca^{++} . Exocytotic release of histamine follows the degranulation of histamine storage cells. Histamine is

released from mast cells in the gastric mucosa by gastrin and acetylcholine. Neurochemical studies also suggest that histamine is stored in selected neuronal tracts in the CNS.

Histamine Metabolism

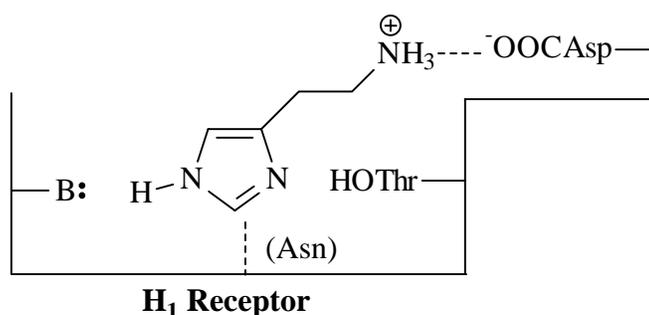


Three principle ways exist for terminating the physiological effects of histamine. Cellular uptake: Na^+ -dependent process in rabbit gastric glands and the histamine is metabolized once in the cell. Desensitization of cells; some H_1 -receptor-containing tissues exhibit a homogeneous loss of sensitivity to the actions of histamine perhaps as a result of receptor modification. Metabolism, the most common pathway for terminating histamine action, involves enzymatic inactivation. The enzyme histamine N-methyltransferase (HMT, EC 2.1.1.8) is widely and ubiquitously distributed among mammalian tissues and catalyzes the transfer of a methyl group from S-adenosyl-L-methionine (SAM) to the ring Nτ-nitrogen of histamine producing Nτ-methylhistamine and S-

adenosyl-L-homocysteine. Histamine is also subject to oxidative deamination by diamine oxidase (DAO, EC 1.4.3.6) yielding imidazole acetic acid, a physiologically inactive product, excreted in the urine. Similarly, $N\tau$ -methylhistamine is converted by both DAO and monoamine oxidase (MAO) to N -methyl imidazole acetic acid. These metabolites may also be conjugated with ribose. **These pathways are summarized on the previous page.**

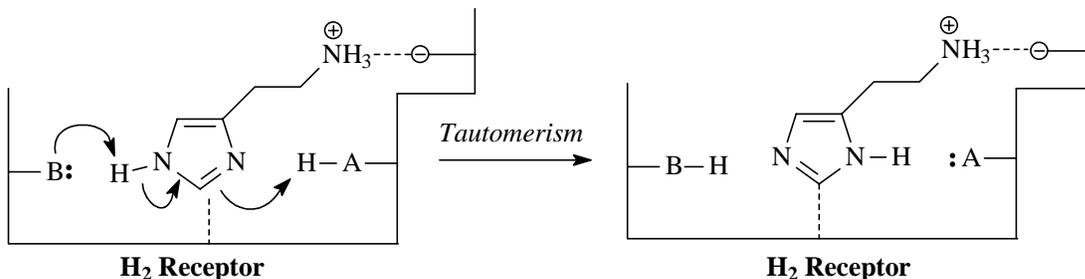
IV. Histamine receptors

Once released, the physiological effects of histamine are mediated by specific cell-surface receptors. Extensive pharmacological analysis suggests the existence of three different histamine-receptor subtypes, H_1 , H_2 and H_3 . Histamine H_1 -receptors mediate smooth muscle contraction, increased vascular permeability, pruritus, prostaglandin generation, decreased atrioventricular conduction time accompanied by tachycardia and activation of vagal reflexes. Histamine H_1 -receptors are $G_{q/11}$ -protein-linked receptors which, when activated, give stimulate phospholipase C (PLC) resulting in a rise intracellularly to the second messengers inositol triphosphate (IP_3) and diacylglycerol (DAG). These actions result in increased intracellular calcium and protein kinase C activities. The structure of the H_1 -receptor has been determined and shown to display several important features that distinguish it from the H_2 -receptor.⁸ The H_1 -receptor contains seven hydrophobic transmembrane domains (TMs) characteristic of most G-protein receptors. Analysis of the primary structure of this receptor indicates the presence threonine and asparagine residues in TM5 proposed to serve as the histamine-imidazole binding site and an aspartate residue in TM3 thought to interact ionically with the histamine α - NH_3^+ monocation. A structural requirement for H_1 -receptor agonism is the presence of an "aromatic" nitrogen with a nonbonded pair of electrons oriented a to the point of attachment of the ethylamine side chain, i.e, $N\pi$ in the case of histamine.



H_2 -receptors are located on the cell membrane of acid-secreting cells (parietal) of the gastric mucosa and mediate the gastric acid secretory actions of histamine. The physiologic and pharmacologic effects of H_2 -receptor ligands are mediated by a stimulatory G_s -protein coupled receptor which, in turn, activates the adenylate cyclase/cyclic adenosine monophosphate (AMP) intracellular second messenger system. The H_2 -receptor has been cloned and, similar to the H_1 -site, found to consist of seven hydrophobic TMs. Examination of the primary structure of the H_2 -receptor has led to the proposal that an aspartate residue in TM3 is the primary binding site for the cationic nitrogen of histamine and that a threonine and an aspartate residue in TM5 may be important for hydrogen bonding with the nitrogen atoms of the imidazole ring of histamine. It has been further proposed that tautomerism of the imidazole ring of histamine or isosteric structural features of other

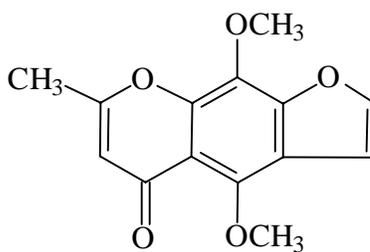
H₂-agonists is an important component of the ability of agonist ligands to activate this receptor system as shown below:



The most recently described receptor for histamine, the H₃-receptor, is proposed to function as a neural autoreceptor (presynaptic) serving to modulate histamine synthesis and release in the CNS. Subsequent studies have also located H₃-sites in peripheral tissue including the gastric mucosa where this receptor may negatively control gastric acid secretion and on the cardiac sympathetic terminals in the myocardium. Isolation and characterization of the H₃-receptor protein as well as identification of transmembrane signaling are just beginning. It appears this receptor is linked to G proteins that may be coupled to adenylate cyclase and inhibit this enzyme resulting in decreased cyclic AMP levels and decreased histamine release.

V. Inhibitors of Histamine Release

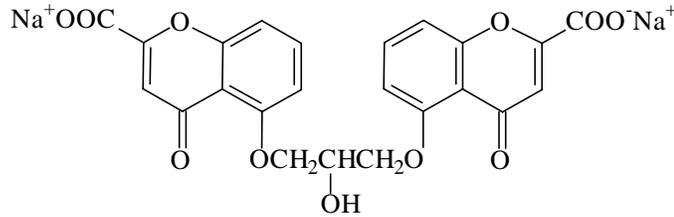
The discovery of the bronchodilating activity of the natural product khellin led to the development of the bis(chromones) as compounds that inhibit the release of histamine and other mediators of inflammation. The first therapeutically significant member of this class was cromolyn sodium. Further research targeting more effective agents resulting in the introduction of nedocromil more recently. The structures, chemical properties and pharmacologic profiles are provided in the monographs that follow.



Khellin

- **Cromolyn Sodium, USP.** Disodium 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane (*Intal*[®]). The pKa of cromolyn is 2.0. Cromolyn belongs to a completely novel class of compounds and bears no structural relationship to other commonly used antiasthmatic compounds. Unlike its naturally occurring predecessor (khellin), cromolyn is not a smooth-muscle relaxant or a bronchodilator. **It has no intrinsic bronchodilator, antihistaminic, or antiinflammatory action.**

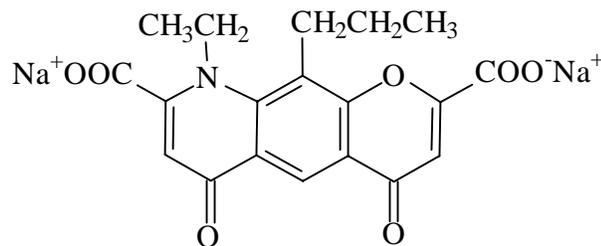
Cromolyn inhibits release of histamine, leukotrienes, and other potent substances from mast cells during allergic responses. Apparently, its action is on the mast cell after the sensitization stage but before the antigen challenge. It does not seem to interfere with the antigen-antibody reaction, but it seems to suppress the responses to this reaction.



Cromolyn Sodium

Although growing evidence indicates that the mechanism of action is not all mast cell related, the benefits of the drug in asthma are exclusively prophylactic. It is of no value after an asthmatic attack has begun (status asthmaticus). Cromolyn is also indicated for the prevention and treatment of the symptoms of allergic rhinitis. In order for cromolyn to be effective it must be administered at least 30 minutes prior to antigen challenge, and administered at regular intervals (see dosing information below). Overuse of cromolyn results in tolerance. **It is not orally effective.**

- **Nedocromil Sodium, USP.** Disodium 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-4H-pyrano[3,2-g]quinoline-2,8-dicarboxylate (Tilade[®]).
- Nedocromil is structurally related to cromolyn and displays similar, but broader pharmacological actions. This drug prevents the release of inflammatory, chemotactic and smooth muscle contracting mediators from the inflammatory cells implicated in asthma including neutrophils, eosinophils, monocytes, platelets and mast cells. Nedocromil also suppresses neuronal reflexes, including C-fiber response in the lung implicated with bronchoconstriction and blocks the immunologic and non-immunologic activation of mast cells. As a result of these actions, this drug inhibits not only the acute bronchoconstrictor response to inhaled irritants, but also the delayed asthmatic or inflammatory response. The superiority of nedocromil over cromolyn in the treatment of asthma has been established in a number of comparative clinical trials.



Nedocromil sodium