

Roles of histamine and its receptors in allergic and inflammatory bowel diseases

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Abstract

Mast cell has a long history of being recognized as an important mediator-secreting cell in allergic diseases, and has been discovered to be involved in IBD in last two decades. Histamine is a major mediator in allergic diseases, and has multiple effects that are mediated by specific surface receptors on target cells. Four types of histamine receptors have now been recognized pharmacologically and the first three are located in the gut. The ability of histamine receptor antagonists to inhibit mast cell degranulation suggests that they might be developed as a group of mast cell stabilizers. Recently, a series of experiments with dispersed colon mast cells suggested that there should be at least two pathways in man for mast cells to amplify their own activation-degranulation signals in an autocrine or paracrine manner. In a word, histamine is an important mediator in allergic diseases and IBD, its antagonists may be developed as a group of mast cell stabilizers to treat these diseases.

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INTRODUCTION

Allergic diseases including allergic asthma, allergic rhinitis, food allergy, drug allergy, and allergic atopic eczema/dermatitis syndrome, *etc.* are a group of common disorders which are regarded to be mediated by immunoglobulin (Ig) E. People at all ages in countries throughout the world suffer from

these diseases. The prevalence of allergy has shown an increase in the last few years. At present it affects about 30-40% of world population and has become one of the three key diseases in the 21st century.

Since last two decades, inflammation has been known as the main pathophysiological characteristics of allergy. Mast cells are major participants of allergic reactions, and their activation may be all that is sufficient and necessary for the rapid development of microvascular leakage and tissue edema in sensitized subjects exposed to allergen. Mast cell is a key source of potent mediators of allergic inflammation including histamine, neutral proteinases, proteoglycans, prostaglandin D₂, leukotriene C₄ and certain cytokines^[1]. Among them, histamine is the first mediator implicated in the pathophysiological changes of asthma when it was found to mimic several features of the disease, and James received the Nobel Prize for medicine in 1988 for his outstanding achievements in histamine research. Recently, some novel findings concerning histamine, mast cell and allergy or IBD have been reported and are summarized herein.

THE ROLES OF MAST CELLS IN ALLERGIC DISEASES

Mast cell has a long history of being recognized as an important mediator-secreting cell in allergic diseases. It has a high capacity to release an array of both preformed and newly generated mediators in response to environmental stimuli, especially allergen exposure. Cross linkage of IgE bound to high affinity receptors on mast cells not only results in the rapid release of autacoid mediators, but also the sustained synthesis and release of cytokines, chemokines and growth factors.

Mature mast cells are ubiquitous in human tissues and can thus participate in the processes of inflammation at different sites. Systemic anaphylaxis, a life-threatening disease, involves mast cell activation in multiple organs. In bronchial asthma, a disease characterized by widespread but potentially reversible bronchial obstruction, there are increased numbers of mast cells and a greater degree of continuous mast cell degranulation in bronchoalveolar lavage fluid from asthmatics compared with normal controls. Increased mast cell numbers and evidence for continuous degranulation of mast cells have been observed also in nasal lavage fluid and the nasal epithelium of the patients with allergic rhinitis.

Recent population surveys have estimated rates of prevalence of perceived food hypersensitivity of 12-20% in adults though this rate varied largely across different

countries (e.g., Spain, 4.6%; Australia, 19.1%) despite a common standardized methodology^[2]. Intestinal mast cells, as well as eosinophils, have been shown to be involved in the pathogenesis of food-allergy-related enteropathy.

Adverse drug reactions are common, but only 6-10% are immunologically mediated^[3]. Although allergic drug reactions are just one type of adverse reactions to medications, they are clinically very important because of the morbidity and mortality they cause. Allergic drug reactions may result in anaphylaxis, urticaria, bronchospasm and angioedema. During these reactions, allergic drugs cause direct histamine release from mast cells.

THE ROLES OF HISTAMINE IN ALLERGIC DISEASE

Since its discovery in 1911, histamine has been recognized as a major mediator in allergic diseases. Histamine is a primary amine synthesized from histidine in the Golgi apparatus, from where it is transported to the granule for storage in ionic association with the acidic residues of the glycosaminoglycans side chains of heparin and with proteinases. The histamine content of mast cells dispersed from human lung and skin is similar at 2-5 pg/cell, and the histamine stored ranges from 10 to 12 µg/g in both tissues. Following mast cell activation, histamine is rapidly dissociated from the granule matrix by exchange with sodium ions in the extracellular environment. Proteoglycans comprise the major supporting matrix of the mast cell granule with the sulfate groups binding to histamine, proteinases and acid hydrolases. As only mast cells and basophils contain histamine in man (apart from histaminergic nerve), and there are few basophils in human tissues, histamine can be used as a marker of mast cell degranulation.

The allergic process is believed to consist of two phases: early and late. The early phase reaction is mainly induced by histamine released from mast cells. Histamine is a potent vasoactive agent, bronchial smooth muscle constrictor, and stimulant of nociceptive itch nerves. In addition to its known effects on glands, vessels and sensory nerves, recent data have provided further evidence of histamine's proinflammatory actions^[4]. Histamine binding specific cell receptors produces clinical allergic symptoms. This mediator also activates neutrophils and eosinophils as well as being a chemoattractant for these cells^[5]. Histamine increases IL-8 level and evokes leukocyte rolling on endothelial cells. Thus histamine participates in both early and late-phase allergic responses.

ROLES OF HISTAMINE IN PATHOGENESIS OF IBD

Using segmental jejunal perfusion system with a two-balloon, six-channel small tube, Knutson and colleagues found that the histamine secretion rate was increased in patients with Crohn's disease compared with normal controls, and the secretion of histamine was related to disease activity, indicating strongly that degranulation of mast cells was involved in active Crohn's disease^[6]. The highly elevated mucosal histamine levels were also observed in allergic enteropathy and ulcerative colitis^[7]. Moreover, enhanced

histamine metabolism was found in collagenous colitis and food allergy^[8], and increased level of *N*-methylhistamine, a stable metabolite of the mast cell mediator histamine, was detected in the urine of patients with active Crohn's disease or ulcerative colitis^[9,10]. Since increased level of *N*-methylhistamine was significantly correlated to clinical disease activity, the above findings further strongly suggest the active involvement of histamine in the pathogenesis of these diseases.

Interestingly, mast cells originated from the resected colon of active Crohn's disease or ulcerative colitis were able to release more histamine than those from normal colon when being stimulated with an antigen, colon-derived murine epithelial cell-associated compounds^[11]. Similarly, cultured colorectal endoscopic samples from patients with IBD secreted more histamine towards substance P alone or substance P with anti-IgE than the samples from normal control subjects under the same stimulation^[12]. In a guinea pig model of intestinal inflammation induced by cow's milk proteins and trinitrobenzene sulfonic acid, both IgE titers and histamine levels were higher than normal control animals^[13].

As a proinflammatory mediator, histamine is selectively located in the granules of human mast cells and basophils and released from these cells upon degranulation. To date, a total of three histamine receptors H₁, H₂ and H₃ have been discovered in human gut^[14,15]. It proves that there are some specific targets that histamine can work on in intestinal tract. Histamine was found to cause a transient concentration-dependent increase in short-circuit current, a measure of total ion transport across the epithelial tissue in the gut^[16]. This could be due to that histamine interacts with H₁ receptors to increase the secretion of Na and Cl ions from epithelium^[17]. The finding that H₁-receptor antagonist pyrilamine was able to inhibit anti-IgE induced histamine release and ion transport^[18] suggested further that histamine is a crucial mediator responsible for diarrhea in IBD and food allergy. The ability of SR140333, a potent NK₁ antagonist in reducing mucosal ion transport, was most likely due to its inhibitory actions on histamine release from colon mast cells^[19].

HISTAMINE RECEPTORS

Histamine has multiple effects that are mediated by specific surface receptors on target cells. Four types of histamine receptors have now been recognized pharmacologically. Histamine receptors were first differentiated into H₁ and H₂ by Ash and Schild in 1966, when it was found that some responses to histamine were blocked by low doses of mepyramine (pyrilamine), whereas others were insensitive. A third histamine receptor subtype, termed H₃, was cloned in 1999 by Lovenberg and co-workers^[20] and the fourth histamine receptor subtype, termed H₄, was first reported in 2000 by Oda and co-workers^[21].

H₁ receptors

H₁ receptors have been cloned from cows, rats, guinea pigs and humans. The published sequences suggest that there are surprisingly large differences among species. H₁ receptors mediate most of the effects of histamine that are relevant to asthma. The cardinal features of asthma include smooth muscle spasm, mucosal edema, inflammation and mucous

secretion. It has been demonstrated that at least two of these features, bronchospasm and mucosal edema, can be caused by H₁-receptor stimulation. Northern analysis has demonstrated that there is a high level of expression of H₁ receptor messenger ribonucleic acid in lung.

Ocular allergy presents unsolved mysteries in molecular and cellular mechanisms, the recent understanding of the key role of the T helper type 2 cytokines, adhesion molecules and chemokines may provide future avenues for pharmacological targeting of releasable inflammatory mediators. More potent topical mast cell stabilizers and H₁ receptor antagonists have become commercially available for the management of the prevalent and benign forms of allergic conjunctivitis^[22]. Immunostimulatory DNA sequences present an innovative and promising route for the treatment of ocular allergy, but clinical studies are needed to demonstrate their efficacy in humans.

Bphs controls Bordetella pertussis toxin (PTX)-induced vasoactive amine sensitization elicited by histamine (VAASH) and has an established role in autoimmunity. Ma and co-workers^[23] reported that congenic mapping links Bphs to the histamine H₁ receptor gene (Hrh1/H₁R) and that H₁R differs at three amino acid residues in VAASH-susceptible and -resistant mice. Hrh1-/- mice are protected from VAASH, which can be restored by genetic complementation with a susceptible Bphs/Hrh1 allele, and experimental allergic encephalomyelitis and autoimmune orchitis due to immune deviation. Thus, natural alleles of Hrh1 control both the autoimmune T cells and vascular responses regulated by histamine after PTX sensitization.

H₂ receptors

H₂ receptors have been cloned from dogs and humans. Although H₂ receptors are present in the airway, their clinical relevance is unclear, because H₂ receptor antagonists have few measurable effects on airway function. Histamine stimulates an increase in cyclic AMP levels in lung fragments that is blocked by H₂ receptor antagonists, indicating that H₂ receptors are positively coupled to adenylyl cyclase in lung.

Atopic diseases such as allergic rhinitis and asthma are characterized by increases in Th2 cells and serum IgE antibodies. The binding of allergens to IgE on mast cells triggers the release of several mediators, of which histamine is the most prevalent. Mazzoni and co-workers reported that histamine, together with a maturation signal, acts directly upon immature dendritic cells (DCs), which express H₁ and H₂, two active histamine receptors. Histamine, acting upon the H₂ receptor for a short period of time, increased IL-10 production and reduced IL-12 secretion. As a result, histamine-matured DCs polarized naive CD4(+) T cells toward a Th2 phenotype, as compared with DCs that had matured in the absence of histamine. The Th2 cells favor IgE production, leading to increased histamine secretion by mast cells, thus creating a positive feedback loop that could contribute to the severity of atopic diseases^[24].

H₃ receptors

The identification of H₃ receptor cDNA allowed several groups to reveal the complexity of the histamine-mediated systems. Comparison of the cDNA with available genome

databases revealed that the gene encoding H₃ receptor is located on chromosome 20 and contains at least two introns. In rats, H₃ receptors consist of at least three functional isoforms, referred to as H_{3A}, H_{3B} and H_{3C}, which vary in the length of their third intracellular loop (I3) (136 104 and 88 amino acids respectively). In humans, H₃ receptor isoforms have been cloned, including one with an 80-amino-acid deletion of I3. Moreover, another isoform has been identified, in which the 80-amino-acid deletion is accompanied by an additional 8 amino acids at the C-terminal tail. Using reverse transcription polymerase chain reaction, the human isoforms have been found to be differentially expressed in various brain areas. The 80-amino-acid sequence located at the C-terminal portion of I3 plays an essential role in H₃ agonist-mediated signal transduction. The existence of multiple H₃ isoforms with different signal transduction capabilities suggests that H₃-mediated biological functions might be tightly regulated through alternative splicing mechanisms. Otherwise, histamine H₃ receptor activation inhibits neurogenic sympathetic vasoconstriction in porcine nasal mucosa, suggesting that histamine H₃ receptors may play a role in the regulation of vascular tone and nasal patency in allergic nasal congestive disease^[25].

H₄ receptors

The discovery of the histamine H₄ receptor adds a new chapter to the histamine story. The H₄ receptor is a G protein-coupled receptor and is most closely related to the H₃ receptor, sharing 58% identity in the transmembrane regions. The gene encoding the H₄ receptor was discovered initially in a search of the GenBank databases as sequence fragments retrieved in a partially sequenced human genomic contig mapped to chromosome 18^[26]. About the histamine-binding site of H₄ receptor, Shin reported that Asp94 (3.32) in transmembrane region (TM) 3 and Glu182 (5.46) in TM5 are critically involved in histamine binding. Asp94 probably serves as a counter-anion to the cationic amino group of histamine, whereas Glu182 (5.46) interacts with the N(τ) nitrogen atom of the histamine imidazole ring via an ion pair. These results resemble those for the analogous residues in the H₁ histamine receptor but contrast with findings regarding the H₂ histamine receptor. It indicates that although histamine seems to bind to the H₄ receptor in a fashion similar to that predicted for the other histamine receptor subtypes, there are also important differences that can probably be exploited for the discovery of novel H₄-selective compounds^[27]. H₄ receptor exhibits a very restricted localization, expression is primarily found in intestinal tissue, spleen, thymus and immune active cells, such as T cells, mast cells, neutrophils and eosinophils. It suggests an important role for the H₄ receptor in the regulation of immune function and offers novel therapeutic potentials for histamine receptor ligands in allergic and inflammatory diseases^[28].

THE EFFECTS OF HISTAMINE RECEPTOR ANTAGONISTS ON HISTAMINE RELEASE FROM MAST CELLS

Today, according to action on different receptors, the histamine

receptor agonists (Table 1) and antagonists (Table 2) are classified into four subtypes, respectively. Among H₁ receptor antagonists, the first generation antihistamines have considerable sedative effects caused by their ability to cross the blood-brain barrier. The second generation of antihistamines to emerge in the market is devoid of these sedative effects. The third generation antihistamines, metabolites of the earlier drugs, have demonstrated no cardiac effects of the parent drugs and are at least potent^[29].

Table 1 Agonists of histamine receptors

Receptor subtype	Agonists
H ₁	Dimethylhistaprodifen ^[30] , methylhistaprodifen ^[30] , histaprodifen ^[30,31] , histamine-trifluoromethyl-toluidine ^[32] , 2-thiazolyethylamine ^[33] , 2-(3-trifluoromethylphenyl) histamine ^[34] , 2-phenylhistamines ^[31] , 2-pyridylethylamine ^[35]
H ₂	Dimaprit ^[30,34]
H ₃	Imetit ^[32] , alpha-methylhistamine ^[33,34]
H ₄	Clobenpropit ^[32] , imetit ^[32]

Table 2 Antagonists of histamine receptors

Receptor subtype	Antagonists
H ₁	First-generation Azatadine, clemastine, chlorpheniramine (chlorphenamine maleate), diphenhydramine, dexchlorpheniramine, hydroxyzine, mepyramine (pyrilamine), promethazine, terfenadine (teldane), triprolidine ^[35-37] Second-generation Acrivastine ^[37,38] , astemizole (hismanal) ^[38] , azelastine ^[38] , cetirizine (virilx, zirtek, zyrtec) ^[39-41] , chlorpheniramine ^[42,43] , desloratadine ^[44,45] , ebastine ^[37,44] , emedastine ^[37] , epinastine ^[41,46] , homochlorcyclizine ^[47] , ketotifen ^[41,48] , levocabastine ^[46] , loratadine (claritin, clarityne) ^[41,44,49] , olopatadine ^[41,50] , mequitazine ^[47] , mizolastine ^[47] , pseudoephedrine ^[51,52] , rupatadine ^[53,54] , tripeleminamine (pyribenzamin) ^[55] Third-generation Fexofenadine ^[37,44,56] , levocetirizine ^[37,39]
H ₂	First-generation Cimetidine ^[57] , metiamide ^[58] Second-generation Ranitidine (1979) ^[59] , omeprazole (1982) ^[60] Third-generation Famotidine ^[61] , ebrotidine ^[62] , lafutidine ^[63,64] , niperotidine ^[60] , nizatidine ^[60] , potentidine ^[65] , roxatidine ^[60] , zolantidine ^[58]
H ₃	A-304121 ^[66] , A-317920 ^[66] , 4-(aminoalkoxy) benzylamines ^[67] , ciproxifan ^[66] , clobenpropit ^[68] , D-alanine-piperazine-amides ^[69] , imidazopyridine ^[70] , indole ^[70] , indolizine ^[70] , 4'-[(NR1R2-1-yl)]-propoxy-biaryl-4-carboxamides ^[70] , pyrazolopyridine ^[71] , 1-(4-(phenoxy)methyl)benzyl piperidines ^[72] , SCH 79687 ^[73] , thioperamide ^[68,74]
H ₄	JNJ 7777120 ^[75,76] , thioperamide ^[77]

Among them, H₁ receptor antagonists loratadine and terfenadine were able to inhibit IgE-induced histamine release from human mast cells^[78], which may at least partially

explain their potent antiallergic activity^[79]. However, the extent of H₁ receptor antagonists binding to mast cells is quite different. Wescott *et al*^[80], reported tripeleminamine > pyrilamine > diphenhydramine in binding H₁ receptor.

Fexofenadine, an effective H₁ antihistamine, is the active metabolite of terfenadine, but they had different effects on histamine and tryptase release from mast cells. Terfenadine inhibited release of histamine and tryptase from mast cells during the early allergic response, whereas fexofenadine did not^[81].

In combination with H₁ antihistamines, H₂ antihistamines famotidine, ranitidine or cimetidine suppressed effectively the chronic swelling. It is deduced that simultaneous blockage of both histamine H₁ and H₂ receptors may be necessary for sufficient inhibition of the microvascular permeability increase in some kinds of anaphylactic reactions, and that histamine, mainly interacting with H₂ receptors, may play an important role in activation of a certain phase of chronic inflammation where mast cell degranulation is involved^[82]. Metiamide, one H₂ receptor antagonist, can reduce the histamine release from secreting mast cells in mast-cell mediated angiogenesis^[83]. H₃ antagonists, thioperamide and clobenpropit combined with H₁ antihistamine loratadine, not the H₂ antagonist ranitidine, reduced nasal congestion^[84] in mast cell-deficient mice, indicating that its action was not associated with mast cell degranulation^[85].

THE HYPOTHESIS OF SELF-AMPLIFICATION MECHANISM OF MAST CELL DEGRANULATION

Tryptase has been proved to be a unique marker of mast cell degranulation *in vitro* as it is more selective than histamine to mast cells. Inhibitors of tryptase^[86,87] and chymase^[88] have been discovered to possess the ability to inhibit histamine or tryptase release from human skin, tonsil, synovial^[89] and colon mast cells^[90], suggesting that they are likely to be developed as a novel class of mast cell stabilizers. Recently, a series of experiments with dispersed colon mast cells suggested that there should be at least two pathways in man for mast cells to amplify their own activation-degranulation signals in an autocrine or paracrine manner, which may partially explain the phenomena that when a sensitized individual contacts allergen only once the local allergic response in the involved tissue or organ may last for days or weeks. These findings included that both anti-IgE and calcium ionophore were able to induce significant release of tryptase and histamine from colon mast cells, histamine is a potent activator of human colon mast cells and the agonists of PAR-2 and trypsin are potent secretagogues of human colon mast cells. Since tryptase was reported to be able to activate human mast cells^[86] and H₁ receptor antagonists terfenadine and cetirizine^[78] were capable of inhibiting mast cell activation, the hypothesis of mast cell degranulation self-amplification mechanisms is that mast cell secretagogues induce mast cell degranulation, and release of histamine, which then stimulates the adjacent mast cells or positively feedbacks to further stimulate its host mast cells through H₁ receptors, whereas released tryptase acts similarly to histamine, but through its receptor PAR-2 on mast cells.

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