

Forum Minireview

Recent Advances in Molecular Pharmacology of the Histamine Systems: Immune Regulatory Roles of Histamine Produced by Leukocytes

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Abstract. Accumulating evidence has highlighted the importance of histamine in immune responses. The H₁ receptor is involved not only in allergic inflammatory reactions but also in augmentation of helper T cell (Th)1 responses, whereas H₂ receptor suppresses Th responses and participates in immune tolerance through interleukin-10 and transforming growth factor- β . Identification of the H₄ receptor, which binds to histamine with high affinity and of which expression is limited to the hematopoietic system, has enhanced the importance of histamine in immune responses. However, since a majority of previous studies has evaluated the effects of exogenous histamine, it remains largely unknown how endogenously produced histamine is involved in regulation of such kinds of immune responses. Insight into precise roles of histamine in the immune system can not be obtained without correct understanding of both the predominance of a certain type of histamine receptor and the regulation of histamine synthesis. Here we review a part of the recent progress in histamine research in the field of immunology with attention to the source of involved histamine.

Keywords: mast cell, IgE, histamine, histidine decarboxylase

Introduction

Histamine plays a diverse role in physiological and pathological responses by acting on its specific membrane receptors, H₁, H₂, H₃, and H₄. An array of recent studies highlights the important function of histamine in the immune system. The recently identified H₄ receptor has greatly expanded the field of histamine research, especially in the immune system, since this receptor subtype is primarily expressed in immune cells. Accumulating evidence has shed light on the complex regulatory roles of histamine in immune responses. Insight into precise roles of histamine in the immune system can not be obtained without correct understanding of both the predominance of a certain type of histamine receptor and the regulation of histamine synthesis. Here we review a part of the recent progress in histamine research in the field of immunology with attention to the source of involved histamine.

Inducible histamine synthesis in immune cells other than mast cells

A wide variety of studies has suggested that histamine is involved in regulation and modulation of immune responses. However, since a large part of these studies has evaluated the effects of exogenous histamine, it remains largely unknown how endogenously produced histamine is involved in regulation of such kinds of immune responses. Mast cells and basophils are the major source of stored histamine (1, 2). Granule-stored histamine is liberated upon various stimuli including IgE-mediated antigen stimulation, and this kind of histamine release, degranulation, is characterized by its rapid and transient nature. Pro-longed and continuous production of histamine was often observed in post-anaphylactic phase (3), which can not be attributed to transient release of histamine from mast cells and basophils. In contrast to the static granule-stored form, histamine with a dynamic property was designed as 'inducible or nascent' histamine (4), which is generally accompanied by induction of *l*-histidine decarboxylase

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(HDC), the rate-limiting enzyme for histamine synthesis in mammalian cells. Histamine synthesis in non-mast cells was first confirmed using W/W^V mice, which genetically lack mature mast cells, upon stimulation with a phorbol ester (5). Recent studies have indicated that the possible candidates for the source of 'inducible' histamine are activated macrophages and neutrophils (6–10). Since these cells were found to exhibit relatively high enzyme activity and release histamine spontaneously, they fulfill the requirement for 'inducible' histamine. Although histamine synthesis was also reported in Con A-activated T lymphocytes previously (11), further supporting evidence should be required to establish the concept of T cell-derived histamine.

IgE-mediated induction of histamine synthesis in mast cells

Since mast cells and basophils are the dominant source of stored histamine, the regulation of histamine synthesis in these cells is critical for immune modulation by histamine. A recent topic in this field is 'monomeric IgE'-induced histamine synthesis in murine cultured mast cells. Interleukin-3 (IL-3)-dependent bone marrow-derived mast cells (BMMCs) were found to be activated by certain IgE clones in the absence of the specific antigen, leading to their survival, cytokine secretion, histamine synthesis, adhesion, and migration (Review in reference 12). A drastic and transient induction of HDC (approximately 200-fold in activity) was found in BMMCs stimulated by IgE alone, which was much higher than that upon antigen stimulation, and this induction resulted in the increase in stored histamine (13). A recent study demonstrated that the anti-apoptotic effects of monomeric IgE on BMMCs were largely mediated by IL-3 in an autocrine fashion (14). Although IL-3 was found to have a potential to induce HDC in bone marrow cells (15), monomeric IgE-induced histamine synthesis may not be mediated by IL-3 (14). Since induction of histamine synthesis also occurs upon IgE-mediated antigen stimulation, it remains controversial whether these two modes of FcεRI activation share a common signaling pathway. However, recent studies have revealed the qualitative differences between them: 1) monomeric IgE-induced Ca²⁺ influx is mediated by a distinct channel from that activated upon antigen stimulation (16), and 2) PKCβII plays a critical role in monomeric IgE-induced histamine synthesis in mast cells, but not upon antigen stimulation (17). Since only small levels of increase in histamine synthesis by monomeric IgE were found both in purified rat peritoneal mast cells and in vitro matured BMMCs, stimulating effects of monomeric IgE on mast cells may be

limited to immature mast cells (16). However, it is likely that monomeric IgE-induced histamine synthesis exacerbates the symptoms of chronic allergy, since drastic increases in the levels of serum IgE are often observed in such diseases.

Effects of histamine on immune cells

Monocytes and dendritic cells

Recent studies have demonstrated that histamine has a potential to modulate maturation and function of monocytes and dendritic cells. Although activated monocytes and dendritic cells may have a potential to produce histamine, a majority of researches in this field was performed with exogenously added histamine. In human monocytes, histamine was found to suppress the production of tumor necrosis factor-α (TNF-α) and IL-12 and to enhance the production of IL-10 in response to Toll-like receptor ligands by acting on the H₂ receptor (18–20). Similar suppression of IL-12 and augmentation of IL-10 production was observed in human monocyte-derived dendritic cells, which leads to acquisition of DC2 phenotype that drives the development of helper T cell (Th)2 cells (21, 22). Recently, involvement of the H₄ receptor in suppression of IL-12 was also reported (23). In addition, expression of co-stimulatory molecules such as CD80, CD86, and MHC class II, and several chemokines was enhanced by histamine exclusively in immature dendritic cells via the H₁ and H₂ receptors (24). Very recently, Jawdat et al. demonstrated that Langerhans cell migration to the draining lymph node upon the cutaneous IgE/antigen stimulation is mast cell-dependent and is blocked by an H₂-receptor antagonist, cimetidine (25). This result obtained in vivo strongly indicates the significance of mast cell-derived histamine in efficient antigen presentation by Langerhans cells in the draining lymph node. In the *P. acnes*-primed and LPS-induced hepatitis model, endogenous production of histamine by Kupffer cells/macrophages was found to play a protective role by acting on the H₂ receptors (8). These two studies were performed with attention to endogenous histamine synthesis, with mast cells in the former case and Kupffer cells/macrophages in the latter.

T cells and antibody responses

One of the most important findings in the recent progress in histamine research is the modulation of Th responses by histamine via the H₁ and H₂ receptors. Jutel et al. demonstrated that histamine enhances Th1-type responses by acting on the H₁ receptor, which is predominantly expressed in the Th1 cells, whereas histamine suppresses both Th responses by acting on

the H₂ receptor (26). Suppression of interferon- γ (IFN- γ) production and dominant secretion of Th2 cytokines were observed in the H₁ receptor deficient mice, whereas total up-regulation of both Th cytokines was observed in the H₂-receptor-deficient mice. Although augmented production of IL-4 and IL-13 was observed in the H₂-receptor-deficient mice, IgE production was suppressed due to the increased production of IFN- γ in the ovalbumin-induced allergy model, indicating the potent role of H₁ receptor-related Th1 responses in suppression of humoral responses (26). A recent finding that an autoimmune-disease-related gene, *Bphs*, encodes the H₁ receptor makes perfect sense in interpretation of the immunological role of this receptor (27). Indeed, the H₁-receptor-deficient mice showed delayed onset and decreased sensitivity in experimental allergic encephalomyelitis. Furthermore, histamine was found to enhance anti-IgM-induced proliferation of B cells by acting on the H₁ receptor. Furthermore, antibody production against a T cell-independent antigen was significantly decreased in the H₁-receptor-deficient mice (28). In case of T cell-dependent antigen, higher levels of specific IgG1 and IgE production was observed in the H₁-receptor-deficient mice (26). It remains to be clarified what kinds of cells produce histamine that affects the Th responses and antibody production.

Tumor immunity

Several H₂ receptor antagonists, especially cimetidine, have been found to have a suppressive effect on tumor development (29, 30). Recent concepts for the function of histamine in immune responses can provide a good explanation for the anti-tumoral effects of the H₂ antagonists. As described above, the H₂ receptor is involved in suppression of Th responses in helper T cells. In addition, histamine was found to induce the production of IL-10 from dendritic cells and Th2 cells and to enhance the immune suppressive effects of transforming growth factor- β on T cells, both of which are mediated by the H₂ receptors (21, 31, 32). Although the main source of histamine involved in suppression of tumor immunity remains unknown, Takahashi et al. demonstrated using an experimental tumor model with HDC-deficient mice and a stable tumor cell line expressing HDC that local synthesis of histamine in the tumor tissues suppresses the local expression of cytokines, such as IFN- γ , TNF- α , and lymphotoxin- β , by acting on the H₂ receptor (33, 34).

Eosinophils

Although eosinophil migration induced by histamine via the H₁ receptor was previously reported, recent studies revealed that the H₄ receptor plays a critical role

in eosinophil migration (35). H₄-receptor-mediated migration was also reported in neutrophils, dendritic cells, and mast cells (23, 36, 37). The H₄ receptor is coupled with a heterotrimeric G protein, Gi, and triggering of the H₄ receptor induces Ca²⁺ influx, which is reminiscent of chemokine receptors. Indeed, since liver-expressed chemokine/CC chemokine ligand 16 was reported to be a functional ligand for the H₄ receptor in eosinophil migration, involvement of this chemokine should be noted in evaluation of H₄-receptor-mediated chemotaxis in vivo (38).

Mast cells and basophils

Although little attention has been paid to the autocrine effects of histamine on mast cells and basophils, recent studies shed light on the role of histamine in mast cells and basophils. In HDC-deficient-mice, peritoneal and skin mast cells exhibited aberrant granules with very low electron density, indicating the drastic decrease in the granule contents such as granule proteases and sulfated proteoglycans (39). Although critical roles of histamine in cutaneous and systemic anaphylaxis have been documented using the HDC-deficient mice (40, 41), there remains a possibility that decreased granule constituents, such as proteases, make some contribution to the relief of anaphylaxis in the mutant mice. Further studies on the impact of absence of histamine on mast cell function should be required to comprehend in detail how histamine regulates allergic responses through maturation of tissue mast cells. Effects of histamine were also reported in the migration of mast cells, which were mediated exclusively by the H₄ receptor (37).

Since fetal liver tissues were found to express high levels of HDC, which was rapidly diminished after birth (42), involvement of histamine in hematopoiesis has been focused on. An adult hematopoietic organ, bone marrow, contains certain kinds of cells that can produce histamine in response to IL-3 (43, 44). The role of IL-3-induced histamine synthesis in bone marrow remains to be clarified. However, a recent study depicted a unique circuit of newly synthesized histamine and its role in basophil precursors (45). This study demonstrated that bidirectional transport of histamine is mediated largely by organic cation transporter 3 (OCT3) in the plasma membranes of the Fc ϵ RI⁺, c-kit⁺ bone marrow cells, and strongly indicated that intracellular accumulated histamine in the OCT3-deficient cells has suppressive effects on expression of HDC, IL-4, and IL-6. This system may contribute not only to feedback inhibition of histamine synthesis but also to suppression of Th2 cytokine production by immature basophils. Histamine transport across the plasma membrane was also reported in the other studies, indicating the involvement of OCT2

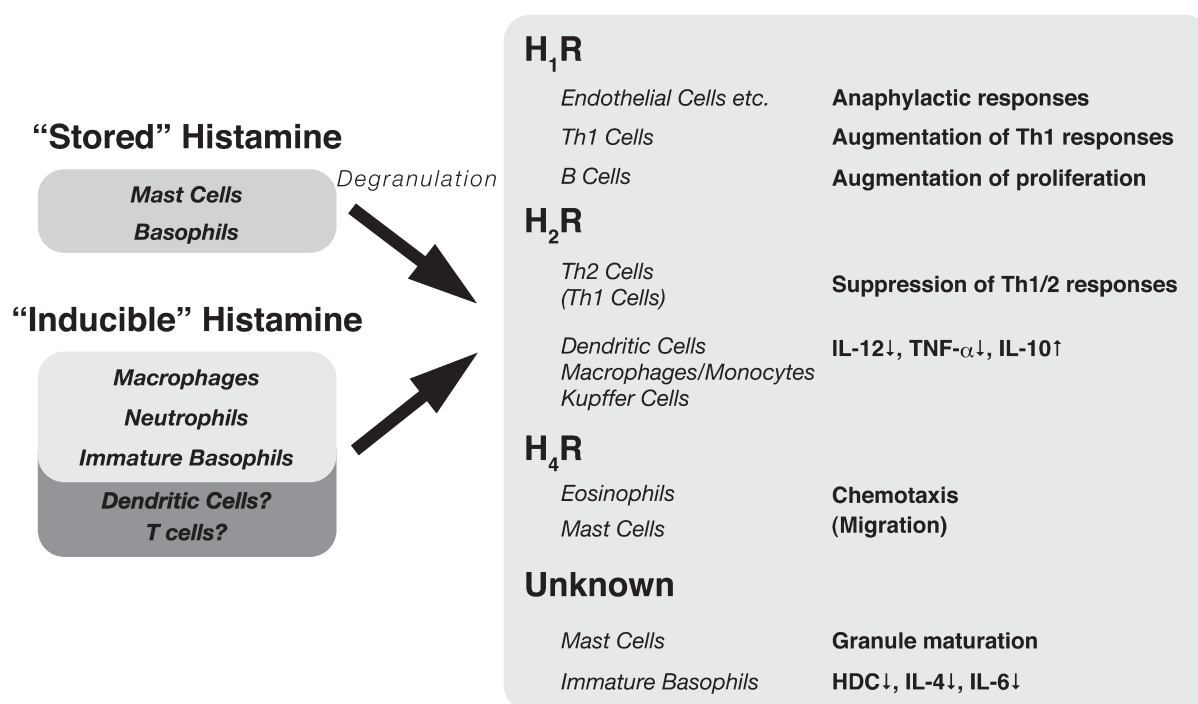


Fig. 1. Immune regulation by histamine produced by various leukocytes. Recent studies have greatly expanded the area of immune responses that are regulated by histamine. In parallel, various kinds of leukocytes, such as macrophages and neutrophils, have been found to have a potential to produce histamine. Integration of these results should improve our understanding of the function of histamine in immune responses.

and an unknown system other than the OCT/OCTN family in addition to OCT3 (46, 47).

Concluding remarks

Accumulating evidence has suggested that histamine plays a modulatory role in immune responses. The H₁ receptor is involved not only in allergic inflammatory reactions but also in augmentation of Th1 responses, whereas the H₂ receptor suppresses Th responses and participates in immune tolerance through IL-10 and TGF-β. Identification of the H₄ receptor, which binds to histamine with high affinity and of which expression is limited to the hematopoietic system, has enhanced the importance of histamine in immune responses. Indeed, recent progress in this field has deepened our understanding of the role of histamine in regulation of immune responses (Fig. 1). It should be critical for making a big picture to reveal when and how histamine is synthesized and functions in immune responses.

References

- 1 Riley JF, West GB. The presence of histamine in tissue mast cells. *J Physiol.* 1953;120:528–537.
- 2 Code CF, Mitchell RG. Histamine in eosinophils and basophils in the blood. *J Physiol.* 1957;136:449–468.
- 3 Hirasawa N, Ohuchi K, Kawarasaki K, Watanabe M, Tsurufuji S. Occurrence of histamine-production-increasing factor in the postanaphylactic phase of allergic inflammation. *Int Arch Allergy Immunol.* 1989;88:386–393.
- 4 Kahlson G, Rosengren E. New approaches to the physiology of histamine. *Physiol Rev.* 1968;48:155–196.
- 5 Taguchi Y, Tsuyama K, Watanabe T, Wada H, Kitamura Y. Increase in histidine decarboxylase activity in skin of genetically mast-cell-deficient *W/W^v* mice after application of phorbol myristate 13-acetate: Evidence for the presence of histamine-producing cells without basophilic granules. *Proc Natl Acad Sci USA.* 1982;79:6837–6841.
- 6 Takamatsu S, Nakashima I, Nakano K. Modulation of endotoxin-induced histamine synthesis by cytokines in mouse bone marrow-derived macrophages. *J Immunol.* 1996;156:778–785.
- 7 Ghosh AK, Hirasawa N, Ohtsu H, Watanabe T, Ohuchi K. Defective angiogenesis in the inflammatory granulation tissue in histidine decarboxylase-deficient mice but not in mast cell-deficient mice. *J Exp Med.* 2002;195:973–982.
- 8 Yokoyama M, Yokoyama A, Mori S, Takahashi HK, Yoshino T, Watanabe T, et al. Inducible histamine protects mice from P. acnes-primed and LPS-induced hepatitis through H2-receptor stimulation. *Gastroenterology.* 2004;127:892–902.
- 9 Shiraishi M, Hirasawa N, Oikawa S, Kobayashi Y, Ohuchi K. Analysis of histamine-producing cells at the late phase of allergic inflammation in rats. *Immunology.* 2000;99:600–606.
- 10 Tanaka S, Deai K, Konomi A, Takahashi K, Yamane H,

- Sugimoto Y, et al. Expression of L-histidine decarboxylase in granules of elicited mouse polymorphonuclear leukocytes. *Eur J Immunol.* 2004;34:1472–1482.
- 11 Aoi R, Nakashima I, Kitamura Y, Asai H, Nakano K. Histamine synthesis by mouse T lymphocytes through induced histidine decarboxylase. *Immunology.* 1989;66:219–223.
 - 12 Kawakami T, Kitauro J. Mast cell survival and activation by IgE in the absence of antigen: A consideration of the biological mechanisms and relevance. *J Immunol.* 2005;175:4167–4173.
 - 13 Tanaka S, Takasu Y, Mikura S, Satoh N, Ichikawa A. Antigen-independent induction of histamine synthesis by immunoglobulin E in mouse bone marrow derived mast cells. *J Exp Med.* 2002;196:229–235.
 - 14 Kohno M, Yamasaki S, Tybulewicz VL, Saito T. Rapid and large amount of autocrine IL-3 production is responsible for mast cell survival by IgE in the absence of antigen. *Blood.* 2005;105:2059–2065.
 - 15 Schneider E, Pollard H, Lepault F, Guy-Grand D, Minkowski M, Dy M. Interleukin 3 and granulocyte-macrophage colony stimulating factor induce de novo synthesis of histidine decarboxylase in hematopoietic progenitor cells. *J Immunol.* 1987;139:3710–3717.
 - 16 Tanaka S, Mikura S, Hashimoto E, Sugimoto Y, Ichikawa A. Ca^{2+} influx-mediated histamine synthesis and IL-6 release in mast cells activated by monomeric IgE. *Eur J Immunol.* 2005;35:460–468.
 - 17 Liu Y, Furuta K, Teshima R, Shirata N, Sugimoto Y, Ichikawa A, et al. Critical role of PKC β II in activation of mast cells by monomeric IgE. *J Biol Chem.* 2005;280:38976–38981.
 - 18 Vannier E, Miller LC, Dinarello CA. Histamine suppresses gene expression and synthesis of tumor necrosis factor alpha via histamine H_2 receptors. *J Exp Med.* 1991;174:281–284.
 - 19 Elenkov IJ, Webster E, Papanicolaou DA, Fleisher TA, Chrousos GP, Wilder RL. Histamine potently suppresses human IL-12 and stimulates IL-10 production via H_2 receptors. *J Immunol.* 1998;161:2586–2593.
 - 20 van der Pouw Kraan TC, Snijders A, Boeijs LC, de Groot ER, Alewijnse AE, Leurs R, et al. Histamine inhibits the production of interleukin-12 through interaction with H_2 receptors. *J Clin Invest.* 1998;102:1866–1873.
 - 21 Mazzoni A, Young HA, Spitzer JH, Visintin A, Segal DM. Histamine regulates cytokine production in maturing dendritic cells, resulting in altered T cell polarization. *J Clin Invest.* 2001;108:1865–1873.
 - 22 Caron G, Delneste Y, Roelandts E, Duez C, Bonnefoy JY, Pestel J, et al. Histamine polarizes human dendritic cells into Th2 cell-promoting effector dendritic cells. 2001;167:2682–3686.
 - 23 Gutzmer R, Diestel C, Mommert S, Köther B, Stark H, Wittmann M, et al. Histamine H_4 receptor stimulation suppresses IL-12p70 production and mediates chemotaxis in human monocyte-derived dendritic cells. *J Immunol.* 2005;174:5224–5232.
 - 24 Caron G, Delneste Y, Roelandts E, Duez C, Herbault N, Magistrelli G, et al. Histamine induces CD86 expression and chemokine production by human immature dendritic cells. *J Immunol.* 2001;166:6000–6006.
 - 25 Jawdat DM, Albert EJ, Rowden G, Haidl ID, Marshall JS. IgE-mediated mast cell activation induces Langerhans cell migration in vivo. *J Immunol.* 2004;173:5275–5282.
 - 26 Jutel M, Watanabe T, Klunker S, Akdis M, Thomot OAR, Malolepszy J, et al. Histamine regulates T-cell and antibody responses by differential expression of H_1 and H_2 receptors. *Nature.* 2001;413:420–425.
 - 27 Ma RZ, Gao J, Meeker ND, Fillmore, PD, Tung KS, Watanabe T, et al. Identification of Bphs, an autoimmune diseases locus, as histamine receptor H_1 . *Science.* 2002;297:620–623.
 - 28 Banu Y, Watanabe T. Augmentation of antigen receptor-mediated responses by histamine H_1 receptor signaling. *J Exp Med.* 1999;189:673–682.
 - 29 Matsumoto S. Cimetidine and survival with colorectal cancer. *Lancet.* 1995;346:115.
 - 30 Morris DL, Adams WJ. Cimetidine and colorectal cancer-old drug, new use? *Nat Med.* 1995;1:1243–1244.
 - 31 Osna N, Elliott K, Khan MM. Regulation of interleukin-10 secretion by histamine in Th2 cells and splenocytes. *Int Immunopharmacol.* 2001;1:85–96.
 - 32 Kunzmann S, Mantel PY, Wohlfahrt J, Akdis M, Blaser K, Schmidt-Weber C. Histamine enhances TGF- β 1-mediated suppression of Th2 responses. *FASEB J.* 2003;17:1089–1095.
 - 33 Takahashi K, Tanaka S, Ichikawa A. Effect of cimetidine on intratumoral cytokine expression in an experimental tumor. *Biochem Biophys Res Commun.* 2001;281:1113–1119.
 - 34 Takahashi K, Tanaka S, Furuta K, Ichikawa A. Histamine H_2 receptor-mediated modulation of local cytokine expression in a mouse experimental tumor model. *Biochem Biophys Res Commun.* 2002;297:1205–1210.
 - 35 Ling P, Ngo K, Nguyen S, Thurmond RL, Edwards JP, Karlsson L, et al. Histamine H_4 receptor mediates eosinophil chemotaxis with cell shape change and adhesion molecule upregulation. *Br J Pharmacol.* 2004;142:161–171.
 - 36 Takeshita K, Bacon KB, Gantner F. Critical role of L-selectin and histamine H_4 receptor in zymosan-induced neutrophil recruitment from the bone marrow: comparison with carrageenan. *J Pharmacol Exp Ther.* 2004;310:272–280.
 - 37 Hofstra CL, Desai PJ, Thurmond RL, Fung-Leung WP. Histamine H_4 receptor mediates chemotaxis and calcium mobilization of mast cells. *J Pharmacol Exp Ther.* 2003;305:1212–1221.
 - 38 Nakayama T, Kato Y, Hieshima K, Nagakubo D, Kunori Y, Fujisawa T, et al. Liver-expressed chemokine/CC chemokine ligand 16 attracts eosinophils by interacting with histamine H_4 receptor. *J Immunol.* 2004;173:2078–2083.
 - 39 Ohtsu H, Tanaka S, Terui T, Hori Y, Makabe-Kobayashi Y, Pejler G, et al. Mice lacking histidine decarboxylase exhibited abnormal mast cells. *FEBS Lett.* 2001;502:53–56.
 - 40 Ohtsu H, Kuramasu A, Tanaka S, Terui T, Hirasawa N, Hara M, et al. Plasma extravasation induced by dietary supplemented histamine in histamine-free mice. *Eur J Immunol.* 2002;32:1698–1708.
 - 41 Makabe-Kobayashi Y, Hori Y, Adachi T, Ishigaki-Suzuki S, Kikuchi Y, Kagaya Y, et al. The control effect of histamine on body temperature and respiratory function in IgE-dependent systemic anaphylaxis. *J Allergy Clin Immunol.* 2002;110:298–303.
 - 42 Burkhalter A. The formation of histamine by fetal rat liver. *Biochem Pharmacol.* 1962;11:315–322.
 - 43 Schneider E, Pollard H, Lepault F, Guy-Grand D, Minkowski M, Dy M. Histamine-producing cell-stimulating activity: interleukin 3 and granulocyte-macrophage colony-stimulating factor induce de novo synthesis of histidine decarboxylase in hematopoietic progenitor cells. *J Immunol.* 1987;139:3710–3717.

- 44 Schneider E, Lemoine F, Breston-Gorius J, Machavoine F, Arnould A, Crammer E, et al. IL-3-induced coexpression of histidine decarboxylase, IL-4, and IL-6 mRNA by murine basophil precursors. *Exp Hematol*. 1999;27:1010–1018.
- 45 Schneider E, Machavoine F, Pléau J-M, Bertron A-F, Thurmond RL, Ohtsu H, et al. Organic cation transporter 3 modulates murine basophil functions by controlling intracellular histamine levels. *J Exp Med*. 2005;202:387–393.
- 46 Gründemann D, Liebich G, Kiefer N, Köster S, Schömig E. Selective substrates for non-neuronal monoamine transporters. *Mol Pharmacol*. 1999;56:1–10.
- 47 Tanaka S, Deai K, Inagaki M, Ichikawa A. Uptake of histamine by mouse peritoneal macrophages and a macrophage cell line, RAW264.7. *Am J Physiol Cell Physiol*. 2003;285:C592–C598.

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