

Immune regulation by histamine

Opinion

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Histamine is a potent bioamine with multiple activities in various pathological and physiological conditions. In addition to its well-characterised effects in the acute inflammatory and allergic responses, histamine regulates several aspects of antigen-specific immune response development. Histamine affects the maturation of dendritic cells and alters their T cell-polarising capacity. Histamine also regulates antigen-specific T helper 1 and T helper 2 cells, as well as related antibody isotype responses. Apparently, diverse effects of histamine on immune regulation are because of differential expression of four types of histamine receptors and their distinct intracellular signals.

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Abbreviations

DC	dendritic cell
HDC	histidine decarboxylase
HR	histamine receptor
IFN	interferon
IL	interleukin
OVA	ovalbumin
Th	T helper
TNF	tumour necrosis factor

Introduction

Histamine (β -imidazolyethylamine) is one of the most important mediators involved in various physiological and pathological conditions, including neurotransmission and numerous brain functions, secretion of pituitary hormones, regulation of gastrointestinal and circulatory functions and inflammatory reactions [1]. Histamine has been shown to potently influence the immune response [2,3^{••},4[•],5[•]]. Mast cells and basophils are the major source of granule-stored histamine. Histidine decarboxylase (HDC) synthesises histamine in mammals [6]. Several non-mast cell myeloid and lymphoid cell types that do not store histamine show high HDC activity and are capable of production of high amounts of histamine ([7,8], see also Update). These cells include platelets, dendritic cells and T cells [9,10[•],11]. The level of histamine is also controlled by the metabolising enzymes: diamine oxidase and histamine N-methyltransferase [12,13]. Recent investigations have generated much interest in the immune-regulatory mechanisms triggered

by histamine; however, diverse experimental systems have yielded conflicting data indicating either pro-inflammatory or anti-inflammatory effects of histamine, dependent upon predominance of a certain type of histamine receptor. This article reviews an important regulatory mechanism in the control of antigen-specific immune response by histamine, which may activate feedback regulation in a wide variety of physiological and pathological conditions.

Histamine receptors

The pharmacological effects of histamine are mediated through four types of membrane histamine receptors (HRs): H1R, H2R, H3R and H4R, all of which are heptahelical G-protein-coupled receptors (Table 1; [14–17]). Histamine receptors possess all structural features of G-protein-coupled receptors, including seven putative transmembrane domains, amino-terminal glycosylation sites, and phosphorylation sites for protein kinase A and protein kinase C. Stimulation of H1R and H2R activates G_q and G_s, respectively, whereas both H3 and H4 are coupled to G_{i/o} [1,18]. H1R and H2R are expressed on many cell types, including nerve cells, airway and vascular smooth muscle cells, hepatocytes, chondrocytes, endothelial cells, neutrophils, eosinophils, monocytes, dendritic cells, and T and B cells [1]. Activation of H1R produces signals through the Gq/11 family of G proteins, which are capable of communicating with T cell receptor-mediated signalling [19]. The primary signal from H1R is delivered through activation of phospholipase C with generation of inositol 1,4,5-triphosphate (Ins(1,4,5)P₃) and 1,2-diacylglycerol and increased cytosolic Ca²⁺ [20]. H2Rs are coupled both to adenylate cyclase and phosphoinositide systems; however, stimulation through H2R results primarily in cAMP formation. Remarkably, in most systems, histamine can exert both suppressive properties through H2R and enhancing effects through H1R activation. H3R is expressed on histaminergic neurons in the brain and on some peripheral tissues; however, the density of this receptor is rather low as compared to H1R or H2R [18,21]. H4R shares 37–43% homology with H3R. Its transcripts are mainly found on haematopoietic cells, including neutrophils, eosinophils and T helper (Th) cells, as well as on basophils and mast cells [22,23]. Its exact function is still unknown, but it activates cells by inhibition of cAMP accumulation and inducing increase in cytosolic calcium. The expression of HR may be affected during normal immune responses as well as in pathologies such as atherosclerosis, rheumatoid arthritis or allergic rhinitis [24,25].

The generation of HDC-deficient mice provided histamine-free systems to study the role of endogenous

Table 1**Histamine receptors.**

Histamine receptors	Expression	Intracellular signals	G proteins
H1	Nerve cells, airway and vascular smooth muscles, hepatocytes, chondrocytes, endothelial cells, neutrophils, eosinophils, monocytes, DC, T and B cells	PLC, Ca ⁺² , cGMP, cAMP, PLA2	Gα _o
H2	As above	cAMP, PLC, Ca ⁺² , c-fos	Gα _s and other GTP-related pathways
H3	Histaminergic neurons, eosinophils, DC, monocytes	Inhibition of cAMP, Ca ⁺²	Gi/o
H4	Low expression in peripheral tissues Eosinophils, neutrophils, DC, T cells, basophils, mast cells Low expression in nerve cells, hepatocytes, peripheral tissues	Inhibition of cAMP	Gi/o

histamine in a broad range of normal and disease processes. These mice showed a decreased number of mast cells and significantly reduced granule content, which suggests that histamine might affect the synthesis of mast cell granule proteins [26]. In addition, HDC-deleted mice showed significantly reduced IL-6 production with increased IL-6 receptor/gp130 expression [26].

The effect of histamine stimulation on immune regulation

The cells that are critical in the regulation of immune response (i.e. T cells, monocytes and dendritic cells) all possess histamine receptors on their surface and are capable of producing and secreting histamine. Indeed, it has been recently documented that histamine directly affects monocyte, dendritic cell, and T cell functions as well as antibody isotypes.

Monocytes and dendritic cells

In monocytes stimulated with bacterial products, histamine inhibits the production of IL-1-like activity, tumour necrosis factor (TNF)-α and IL-12, but enhances IL-10 secretion and self induction of IL-1α through H2R stimulation [27–29].

Endogenous histamine is actively synthesised during cytokine-induced dendritic cell (DC) differentiation and acts in an autocrine and paracrine way [30]. Inhibition of histamine synthesis by HDC affects the differentiation of DC.

It has also been demonstrated that histamine acting upon immature DCs changes their T cell-polarising capacity [5•,31•]. It remains controversial whether histamine significantly affects the maturation of DCs in terms of phenotypic changes or capacity to prime naïve T cells. Histamine induces increases in CD80, CD86 and MHC II [31•]. Immature and mature DCs expressed the mRNA for H1, H2 and H3 [5•,29,31•,32,33•,34]. There is some evidence that H4R mRNA is expressed in DCs (S Klunker, K Blaser, CA Akdis, unpublished data). Histamine induces intracellular Ca²⁺ transients, actin polymerisation and

chemotaxis in immature DCs. Maturation of DCs results in the loss of these responses; however, in maturing DCs, histamine dose-dependently enhances intracellular cAMP levels and stimulates IL-10 secretion while inhibiting production of IL-12. Specific histamine receptor agonists or antagonists reveal that Ca²⁺ transients, actin polymerisation and chemotaxis of immature DCs are because of stimulation of H1R and H3R subtypes. Modulation of IL-12 and IL-10 secretion by histamine involves the H2R and H3R exclusively [5•,29,31•,32,33•,34].

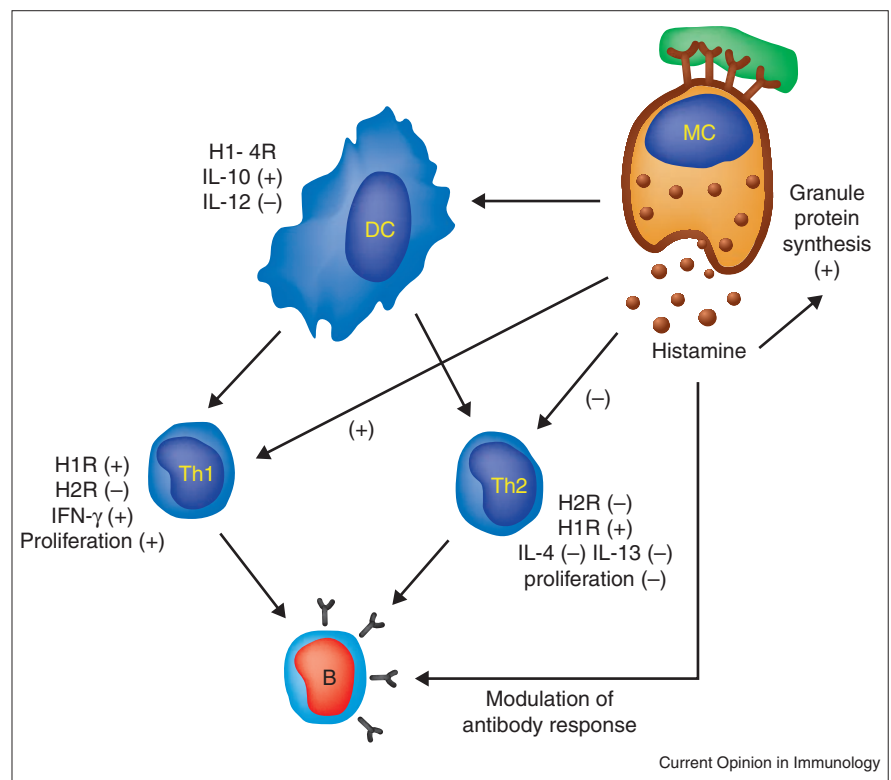
T cells

Naïve T cell precursors develop into at least two distinct subtypes of CD4⁺ cells, defined on the basis of their different cytokine profiles and functions. Th1 cells, which predominantly secrete IL-2, IFN-γ, and TNF-β are implicated in cell-mediated immunity, including inflammation, cytotoxicity and delayed-type hypersensitivity reactions. Th2 cells, which produce IL-4, IL-5 and IL-13, are associated with strong antibody responses and eosinophilia. Th2 cell-derived cytokines induce an immunoglobulin class switch to IgE [35]. The dysregulation of Th1 and Th2 responses results in various immunopathological conditions [36,37]. Atopic diseases are characterised by increases in Th2 cells and IgE antibodies. The diversity of Th1 and Th2 function is not predetermined, but depends on signals that drive the cells towards either subset. Histamine has been demonstrated to affect both Th1/Th2 balance and immunoglobulin synthesis [2,3••,38,39]. Interestingly, the interaction between histamine and the cytokines is mutual as some cytokines affect both production and release of histamine as well as histamine receptor expression [40].

There is conflicting evidence regarding the effect of histamine on Th1/Th2 balance. The above mentioned effects on DC favour histamine-induced development of Th2 cells. Several studies also show enhancement of Th2-type cytokine production by histamine [38–42]; however, recent data account for a complexity of this model, because the effect of histamine is dependent on the expression of certain histamine receptor types on the cell surface [2,3••,31].

Figure 1

Immunoregulation by histamine. Dendritic cells (DCs) express four types of histamine receptors. Histamine upregulates IL-10 and downregulates IL-12 production by human monocyte-derived DC. Th1 cells show predominant, but not exclusive, expression of H1R, whereas Th2 cells show upregulation of H2R. Histamine induces increased proliferation and IFN- γ production in Th1 cells. Th2 cells express predominant H2R, which acts as the negative regulator of proliferation, IL-4 and IL-13 production. Histamine enhances Th1-type responses by triggering the histamine receptor type 1 (H1R), whereas both Th1- and Th2-type responses are negatively regulated by H2R. Histamine plays a role in mast cell (MC) granule protein synthesis. B cell (B) antibody response is also modulated by histamine.



It has been demonstrated that differential patterns of histamine receptor expression on Th1 and Th2 cells determine reciprocal responses following histamine stimulation [3•]. Th1 cells show predominant, but not exclusive, expression of H1R, whereas Th2 cells show upregulation of H2R. Histamine enhances Th1-type responses by triggering the H1R (see also Update), whereas both Th1- and Th2-type responses are negatively regulated by H2R, because of activation of different biochemical intracellular signals [3•]. In mice, deletion of H1R results in suppression of IFN- γ and dominant secretion of Th2 cytokines (IL-4 and IL-13). H2R-deleted mice show upregulation of both Th1 and Th2 cytokines. In addition, IL-3 stimulation significantly increases H1R expression on Th1, but not on Th2 cells. IL-3 plays an important role in T cell regulation of mast cell and basophil development [43]. The increase in H1R expression on Th1 cells by IL-3 may account for negative feedback regulation because of the anti-allergic role of Th1 cells.

Moreover, it has been shown that histamine stimulation induced IL-10 secretion through H2R [44]. IL-10 is a suppressor cytokine and major regulatory agent of inflammatory responses. IL-10 is a general inhibitor of proliferative and cytokine responses in T cells and is produced by mononuclear phagocytes [45,46], natural killer cells [47] and by both Th1- and Th2-type lymphocytes [48]. It can suppress T cells by inhibiting the CD28 signal transduction pathway [49]. Thus, histamine-induced IL-10 production in both DC and T cells accounts

for an important regulatory mechanism in the control of inflammatory functions through histamine.

It should be noted, however, that histamine contributes to the progression of allergic-inflammatory responses by enhancement of the secretion of several pro-inflammatory cytokines, such as IL-1 α , IL-1 β and IL-6, as well as chemokines, such as RANTES or IL-8, both in several cell types and local tissues [27,50–52]. On the contrary, production of TNF- α is inhibited by histamine [53].

Antibody responses

In mice, histamine enhances anti-IgM-induced proliferation of B cells, which is abolished in H1R-deleted mice. In addition, anti-IgM-induced B cell proliferation is decreased in H1R-deleted mice. In H1R-deleted mice antibody production against a T cell-independent antigen-TNP-Ficoll is decreased [2], suggesting an important role of H1R signalling in responses triggered from B cell receptors. Interestingly, B cell proliferative responses to lipopolysaccharide, IL-4 or CD40 were apparently normal in H1R-deleted mice. Antibody responses to T cell-dependent antigens, such as ovalbumin (OVA) show a different pattern. Recently, OVA-specific antibody production in H1R- and H2R-deleted mice was reported [3•]. H1R-deleted mice produced high OVA-specific IgG1 and IgE in comparison to wild-type mice. By contrast, H2R-deleted mice showed decreased serum levels of OVA-specific IgG3 and IgE in comparison to wild-type

mice and H1R knockout mice. Although T cells of H2R knockout mice secreted increased IL-4 and IL-13, OVA-specific IgE was suppressed in the presence of highly increased IFN- γ [3**]. Thus, H1R and related Th1 response may play the dominant role in the suppression of humoral immune response.

Conclusions and future perspectives

Over the past few years, histamine research provided significant evidence for the capacity of this small molecule to exert various immunoregulatory functions. Histamine, and four different known HRs display a very complex system with distinct functions of receptor subtypes and their differential expression, which changes according to the stage of cell differentiation as well as microenvironmental influences. In particular, the generation of H1R-, H2R- and HDC-deleted mice has brought new insights to the understanding of interactions of the immune system cells and histamine. Studies on several disease models using these mice may help to better understand where and how histamine and relevant receptors play a role in the complexity of the system.

Recent findings provide new insights into the actions of antihistamines, which were previously designated non-H1R-mediated suppressive effects in allergic-inflammatory response, and now can be explained by receptor-mediated actions on immune-competent cells. Accordingly, it has been shown that combination of allergen specific immunotherapy and antihistamine treatment increased the efficacy of treatment, possibly through interaction with histamine receptors on the immune system [54*]. These insights may provide new therapeutic strategies aiming at restoration of homeostasis with a balance between mediator secretion and receptor expression. Modified use of HR antagonists or the use of selective agonists should be considered for the future treatment strategies.

Update

IgE binding to the Fc ϵ RI on IL-3 dependent mouse bone marrow-derived mast cells induces the expression of HDC through a signalling pathway distinct to that operating during antigen-stimulated Fc ϵ RI activation [55].

Recently, the H1R gene was identified as *Bphs*, an autoimmune disease locus [56]. H1R differs at three amino acid residues in autoimmune orchitis and allergic encephalomyelitis-susceptible and resistant mice. T cells from H1R^{-/-} mice produce significantly less IFN- γ and increased IL-4 (Th2-biased) associated with significantly less severe autoimmune disease.

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