Chapter 9

Histamine, Immune Cells and Autoimmunity

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Abstract

Histamine is one of the most versatile biogenic amines with multiple roles during the immune response and in allergic disorders. With four distinct G protein-coupled receptors (H_1R, H_2R, H_3R and H_4R), intracellular histamine binding sites (most likely members of the cytochrome P450 family) as well as a membrane transporter (Organic Cation Transporter; OCT3) expressed in various immunocompetent cells, it can entertain a complex network of interactions. These signaling pathways are expressed differentially, depending on the stage of differentiation or activation of target cells, thus adding a further degree of complexity to the system. For this reason, published data are sometimes conflicting and varying according to the particular cell type or responses analyzed and the experimental approaches used. On the other hand, histamine is generated by several cells during the immune response, not only through release of intracellular stores in mast cells or basophils in response to IgE-dependent or -independent stimuli, but also through neosynthesis catalyzed by histidine decarboxylase (HDC) in a number of hematopoietic cells that secrete the amine immediately without prior storage. These features enable histamine to tune the fine balance between immunity and tolerance by affecting dendritic cells, immunoregulatory cells, T-cell polarization and cytokine production, making the way for new pharmacological strategies to control immune reactivity during immune disorders, such as autoimmunity.

Introduction

Histamine (2-(imidazol-4-yl) ethylamine) was discovered in 1910 by Sir Henry Dale,[1] due to its ability to constrict guinea-pig ileum. At present, it is considered the biogenic monoamine with the broadest spectrum of activities in various physiological and pathological situations. Thus, it performs neurotransmitter functions in the central nervous system, regulates peripheral vasoactivity as well as acid secretion in the stomach and modulates immune responses, inflammation and hematopoiesis. These effects are mediated through four distinct histamine receptors (H_1R, H_2R, H_3R and H_4R), which are heptahelical, G-protein-coupled molecules expressed either ubiquitously (H_1R and H_2R) or predominant in particular tissues (H_3R in the brain and H_4R in the hematopoietic system). The multiple activities of histamine and its receptors have been extensively reviewed.[2-8]

Histamine is synthesized by a unique enzyme, histidine decarboxylase (HDC) (EC.4.1.1.22) that requires pyridoxal-5-phosphate as a cofactor. The HDC gene is located on chromosome 15 in humans and chromosome 2 in mice and its expression is controlled by various lineage-specific transcription factors.[2] Recently, several findings have shed a new light on the contribution of histamine to the regulation of the immune response, namely 1) cloning of a H_4R expressed in hematopoietic

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cells, 2) demonstration of histamine synthesis in immuno-competent cells other than mast cells or basophils, 3) identification of OCT3 as a transporter through which intracellular histamine levels can be increased to inhibit basophil functions and 4) evidence for a histamine-cytokine connection.[2] These properties enable histamine to modulate the fine balance that prevents the rupture of immune tolerance toward various tissue autoantigens leading to autoimmunity. We will discuss this issue later in this chapter, once we have dealt with the cellular sources of histamine and its effect on target cells involved in the immune response.

Histamine and Immune Cells

Basophils and mast cells have long been considered the unique source of histamine among the cells of the immune system. They remain the most proficient producers of this biogenic amine, since they can store and release in response to IgE-dependent or independent stimuli. However, it has been established that a number of other immuno-competent cells can express high levels of inducible HDC activity and secrete the newly synthesized histamine immediately rather than storing it in specific granules. This property is shared by dendritic cells, neutrophils and monocytes/macrophages and lymphoid cells that generate histamine in response to various stimuli, making it available in the microenvironment, ready to modulate the biological activities of other immune cells and hence the orientation of the immune response.

Histamine and Dendritic Cells

Dendritic cells (DCs) are professional antigen-presenting cells of lymphoid or myeloid origin, present in a variety of tissues. Immature DCs are activated by pathogens and cytokines that promote their final maturation into the DC1 or DC2 phenotype and their migration into lymphoid organs where they activate resting T-lymphocytes and produce cytokines that determine the differentiation of $CD4^+$ T cells into different helper subsets. DCs express H_1R, H_2R and H_4R, while H_3R expression is low or undetectable.[9-13] Histamine modulates their typical functions, such as chemotaxis,[11,12] antigen uptake and cross-presentation,[9] cytokine and chemokine production[14-16] as well as their ability to drive $CD4^+$ T-cell differentiation[14,16] by targeting one or several of its receptors, depending on their respective surface expression. In this context, several investigators have examined the effect of histamine on the capacity of DCs to promote the transformation of naïve $CD4^+$ T cells into Th1, Th2 or Th17 cells. They established that the amine inhibits IL-12 p70 and increases IL-10 production through H_1R, H_2R and/or H_4R activation, thus favoring the development of Th2 cells.[12,14,16,17] Histamine induces chemotaxis of human immature DCs by targeting H_1R and H_2R,[15] while chemotaxis of murine bone marrow-derived DCs is enhanced via the H_4R, as assessed in vitro as well as in a skin model in vivo.[11] This receptor is also implicated in the enhancement of the cross-presentation of antigen by MHC-class I molecules induced by exposure of immature DCs to histamine,[9] while its positive effect on antigen uptake and endocytosis is mediated through the H_2R subtype.[9] These data suggest that histamine can enhance the ability of extracellular antigens to activate $CD8^+$ T-cell-mediated responses by targeting DCs. Its effect is restricted to soluble antigens, while particulate antigen cross-presentation or uptake by dendritic cells is not affected.[18] Not only does histamine influence DC polarization to skew the differentiation of naive T cells toward a Th2 profile, but it also enhances Th2 cell recruitment by inducing Th2-attracting chemokines (CCL17 and CCL2), while inhibiting their Th1 counterpart (CXCL10).[18]

Plasmacytoid DCs (pDCs) constitute another subset of professional antigen-presenting cells and are a major source of IFNα. Similarly to what happens in myeloid DCs, histamine modulates their cytokine production through H_2R. Indeed, the presence of histamine during stimulation of pDCs by live flu virus or CpG oligodeoxynucleotides markedly decreases their IFNα and TNFα production.[19] This may explain why viral infections in atopic children are associated with low levels of Type I IFN. In striking contrast with functional H_1R and H_2R expression by myeloid DCs and dermal dendritic cells, Langerhans cells lack both receptors, probably because their expression is inhibited by TGFß1, which is required for the differentiation of these cells.[20]

Interestingly, previous studies have demonstrated that DCs themselves can produce histamine, which could in turn modulate the expression of DC markers in an autocrine or paracrine manner.[21] It is tempting to speculate that during inflammatory processes DCs can produce sufficient amounts of histamine to act similarly, since it has been reported that histamine production by DCs is increased under such circumstances.[22] In support of such a contribution to antigen presentation and regulation of Th1/Th2 $CD4^+$ T-cell differentiation, it has been described that the antigen-presenting capacity and the cytokine production profile are altered in spleen DCs from HDC-deficient mice, leading to preferential Th1 development.[23]

Histamine and T Cells

It is currently acknowledged that histamine can influence T helper cell differentiation by targeting DCs. This notion is supported by the decreased allergic airway inflammation in an allergic asthma model carried out in mice in which the H_4R was either disrupted or blocked by a specific antagonist.[22] These data are reminiscent of a similar effect described in mice lacking HDC or injected with histamine-binding proteins.[24-26]

On the other hand, histamine receptors are also expressed by T cells, which respond directly to the amine. Indeed, Th1 cells display predominantly the H_1R, through which histamine enhances their typical functions, while the H_2R that mediates the inhibitory effect of histamine on Th2 as well as on Th1 cells is preferentially associated with the Th2 subset.[27,28] In agreement with these data, H_1R-deficient mice produce low levels of IFNγ together with high amounts of Th2-derived cytokines, while both Th1- and Th2-type cytokine synthesis is increased in their H_2R-deficient counterpart. Although IL-17 production is diminished during the asthmatic response in H_4R-deficient mice,[24] no formal demonstration of the effect of histamine on Th17 cell differentiation has been provided as yet. Conversely, it has been shown that histamine does not affect Th17 cell differentiation in a model involving mast cells.[29]

$CD8^+$ T cells are also sensitive to histamine as demonstrated by their increased IL-16 production in response to H_2R or H_4R engagement[30] and by their reduced IFNγ production in H_1R- or H_2R-deficient mice.[31]

Endogenous production of histamine by $CD4^+$ and $CD8^+$ T cells has been described following mitogen stimulation.[31-32] Although HDC has been detected in the Jurkat cell line,[33] normal T cells need to be purified more thoroughly to confirm their histamine production since this could easily be generated by a few contaminating basophils or basophil precursors (less than 1%). This explanation is particularly likely in view of the authors' claim that IL-3 and GM-CSF, two cytokines well known for their effect on this lineage, increase histamine production in the lymphocyte preparation, even in the absence of mitogen.[32] Indeed, it has been documented long ago that splenic nonT non-B cells,[34] presently identified as basophils[35,36] increase their histamine synthesis in response to IL-3 and GM-CSF, both produced by ConA-stimulated lymphocytes.[37-39]

Histamine and Immunoregulatory T Cells

The immunosuppressive functions of histamine have been known for a long time and were initially ascribed to its ability to induce IL-10 production, a strong immunosuppressive or immunoregulatory cytokine. As mentioned above, histamine targets dendritic cells or Th2 cells to increase their production of IL-10, which can in turn enhance the suppressive effect of TGFβ on T cells.[40] More recently, the effect of histamine on immunoregulatory T cells, such as $CD4^+CD25^+Foxp3^+$ (Treg) and NKT cells, has been investigated in an allergic asthma model. This study established that histamine acted as a chemoattractant of T cells by activating their H_1R or H_4R. However, those recruited through the H_1R were mainstream T-lymphocytes, whereas those targeted via the H_4R belonged mostly to the $CD4^+CD25^+Foxp3^+$ T-cell subset that suppressed autologous T-cell proliferation in an IL-10-independent fashion. These regulatory T cells accumulated in the lung following instillation of H_4R agonist and might be responsible for the inhibition of allergic asthma in this model.[41] However, the apparent discrepancy between this result and a similar alleviation of disease syndromes reported after treatment with a specific H_4R antagonist[25] needs to be clarified,

even though the route of administration differs between the two protocols (local for the agonist versus systemic for the antagonist).

iNKT cells, another immunoregulatory T-cell subset, constitute a distinctive population of mature T-lymphocytes positively selected by the nonpolymorphic MHC class-I-like molecule, CD1d. They co-express a highly restricted T-cell receptor (TCR) repertoire, composed of a single invariant Vα14Jα18 chain in mice and a Vα24Jα18 chain in humans, preferentially paired with a limited TCR Vβ chain repertoire that specifically recognizes glycolipids. iNKT cells are implicated in the control of several immune responses, most likely because of their capacity to promptly produce cytokines, such as IL-4 and IFN-γ.[42-44] Histamine has been shown to target this cell population by modulating their cytokine production. Indeed, iNKT cells from HDC-deficient mice generate less cytokines in response to their specific ligand αGalCer than their wild-type counterpart. Administration of histamine restores a normal production, through H_4R engagement. Indeed, this conclusion is supported by the fact that the functional recovery no longer occurs when the receptors are blocked by a specific antagonist and a similar deficit in iNKT-cell-derived cytokine production is found in H_4R- and HDC-deficient mice.[45] Although the exact mechanism through which histamine exerts this positive effect has not been elucidated, these data underscore once again the importance of mutual interactions between histamine and cytokines, whatever the target cells.[2,46]

Histamine and B Cells

Anti-IgM-induced B cell proliferation in mice is increased in the presence of histamine and diminished in H_1R-deficient mice, suggesting that H_1R activation can amplify B cell receptor signaling. Concerning the antibody response to T-cell-dependent antigens, two different results have been reported, namely an increase of ovalbumin-specific IgE and IgG1 antibody production in H_1R-deficient mice and a decreased IgE and IgG3 production in H_2R-deficient mice. In the latter, ovalbumin-specific IgE levels dropped, in spite of the enhanced IL-4 and IL-13 production, because of the high inhibitory concentration of IFNγ. This finding supports the idea that H_1R and Th1 responses prevail over humoral responses.[29,47]

Histamine and Monocytes/Macrophages

Histamine decreases p40 and p70 IL-12 and increases IL-10 production through the H_2R in lipopolysaccharide (LPS)-stimulated whole blood cells or purified monocytes.[48,49] These data are reminiscent of the work of Rocklin et al. who demonstrated the presence several years ago of a histamine-induced suppressor T-cell factor derived from monocytes,[50] which, in the light of the present data, could be identical with IL-10. Histamine also inhibits LPS-induced TNFα production by human peripheral blood monocytes via its H_2R.[51] Conversely, it fails to prevent LPS-induced upregulation of TNFα expression in macrophages or even increases its secretion by modulating the TNFα-converting enzyme (TACE) via H_1R.[52] A distinctive effect of histamine on monocytes and macrophages is also observed in terms of Ca^{++} influx and IL-8 production in response to H_1R stimulation, which takes place only in macrophages.[53] Furthermore, decreased lectin-like oxidized low-density receptor-1 (LOX-1) gene expression associated with upregulation of monocyte-chemoattractant protein-1 (CCL2) and its receptor CCR2 via H_2R engagement occurs in monocytes but not in macrophages.[54,55] This differential modulation is explained by a switch in histamine receptor expression from H_2R to H_1R during maturation of monocytes into macrophages.[52,53] In apparent contradiction, it has recently been shown that CCL2 synthesis and secretion by monocytes is downregulated by histamine through H_4R.[56]

The decreased TNFα production by LPS-induced monocytes in the presence of histamine might result from its ability to reduce the surface expression of CD14, but not TLR4.[57] The modulation of CD14 probably occurs through posttranscriptional events, since mRNA levels remained unchanged. However, histamine does not downregulate this surface marker during GM-CSF- and IL-4-induced differentiation of monocytes into dendritic cells that continue to express CD14 but not CD1a.[58] It is also noteworthy that histamine diminishes IL-18- induced IFNγ, TNFα and IL-12 production by human PBMC. IL-18 exerts this effect through upregulation of ICAM on monocytes, which

is prevented by histamine via the H_2R.[59] In addition, it has also been demonstrated that histamine increases the lifespan of monocytes by protecting them against apoptosis in response to CD95/Fas ligation, dexamethasone or serum deprivation. These effects are explained by upregulation of Bcl-2 and Mcl-1 and inhibition of caspase 3 activation and could be partially mediated through histamine-induced IL-10 production.[60]

HDC expression increased during maturation of monocytes into macrophages,[55] in agreement with other reports on histamine synthesis in the differentiated population.[54,61] In addition, it has been shown that mouse peritoneal macrophages as well as the macrophage cell line, RAW264.7 can take up histamine and release it when its extracellular concentrations drop.[62] Whatever the exact mechanism, these data suggest that histamine originating from macrophages could contribute to their deleterious effects during inflammatory pathologies, such as in atherosclerosis.[55]

Histamine and Basophils/Mast Cells

Mast cells and basophils compose the main population of cells in which histamine can be stored to be promptly liberated upon stimulation. Mast cells reside in various tissues of the organism, conversely to basophils, which represent the mobile pool of the amine. Both cells derive from $CD34^+$ hematopoietic stem cells. Mast cells leave the bone marrow as immature precursors and complete their differentiation in peripheral tissues. Conversely, basophils enter the circulation only when they have achieved full maturation in the bone marrow. It is generally accepted that mast cells and basophils represent distinct cell lineages derived from different progenitors. However, some data argue in favor of a mast cell/basophil progenitor, such as the expression of a common antigen recognized by the antibody 97A6, shared by mature basophils and mast cells, as well as their precursors[63] and the identification of cells with metachromatic granules combining the features of both basophils (blood location, segmented nuclei and expression of Bsp1, a basophil specific antigen) and mast cells (c-kit, tryptase and chymase expression) in the peripheral blood of patients with asthma, allergy and allergic drug reactions.[64] Mast cells and basophils are regarded as key effector cells in IgE-associated immediate hypersensitivity reactions and allergic disorders, while basophils though described over a century ago, remain enigmatic as to their physiological functions. However, recent data suggest that they may play an important role during helminth infections and are more efficient than mast cells in producing IL-4 together with histamine, which both facilitate Th2 differentiation.[65] Mast cells and basophils share the expression of FcεRI, a tetramer composed of one α, β and two γ chains ($\alpha\beta\gamma_2$). Cross-linking of FcεRI-bound IgE with antigen, initiates degranulation with subsequent release of stored mediators, such as histamine, de novo synthesis of pro-inflammatory lipid mediators and production of cytokines and chemokines. In these conditions, the amount of histamine liberated into the microenvironment may reach millimolar levels. This process is enhanced by high concentrations of IgE, which upregulate membrane FcεRI expression. In addition, recent data indicate that monomeric IgE can increase survival of mast cells without cross-linking, by rendering them resistant to apoptosis. This type of stimulation is efficient enough to induce cytokine production and increased HDC activity through a signaling pathway distinct from the one triggered by antigen-induced FcεRI cross-linking.[66]

Although basophils and mast cells are primarily a source of histamine, they also express histamine receptors (H_1R, H_2R and H_4R) and transporters (OCT3) and could therefore be targeted by the amine in an autocrine or paracrine manner. For instance, the H_4R seems to be involved in the control of mast cell chemotaxis since this biological activity is induced by receptor engagement in vitro and results in a change of tissue localization in vivo.[67,68] Histamine also synergizes with chemoattractants, such as CXCL12 by targeting the H_4R on mast cell precursors.[69] Histamine does not seem to affect degranulation in either cell. However, in basophils, histamine exerts a negative control on its own synthesis and that of associated cytokines (IL-4, IL-6 and IL-13). This effect is not mediated through classical receptors, but results from increased intracytosolic histamine levels under the control of the organic cation transporter, OCT3. When intracellular histamine attains a critical level, it inhibits the transcription of HDC and cytokine genes[70] by a mechanism not clearly identified as yet, but most likely related to molecules of the CYP450 family[71,72] (Fig. 1).

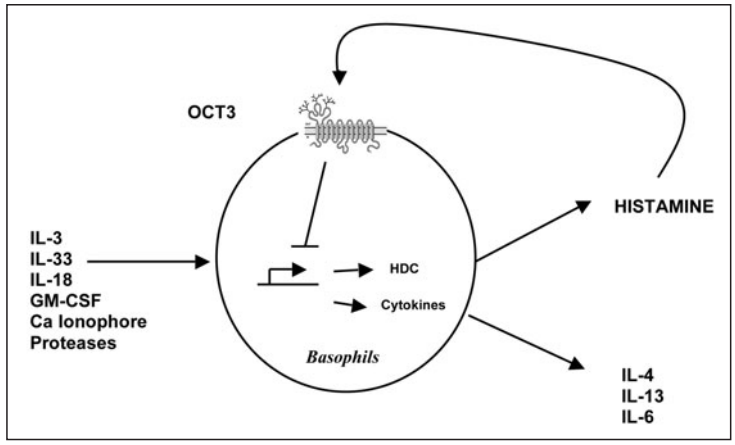


Figure 1. Basophils: a typical cell at the crossroad between cytokines and histamine. IL-3 and some other cytokines increase histamine synthesis as well as pro-Th2 cytokine production by basophils. When extracellular levels of histamine are high, histamine is taken up by OCT3 and inhibits its own synthesis and those of associated cytokines.

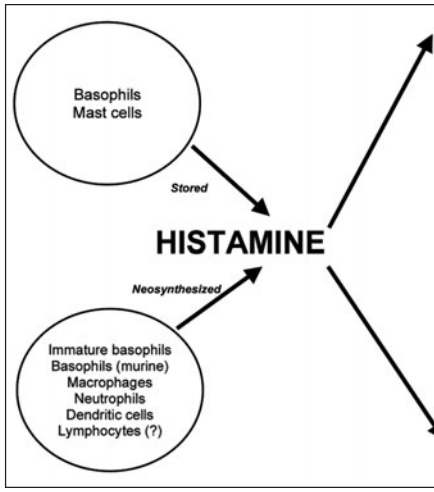
Histamine and Eosinophils/Neutrophils

As stated above for mast cells, histamine is also a potent chemoattractant for eosinophils via H_4R activation. Likewise, changes in eosinophil shape and increases in expression of adhesion molecules like CD11b/CD18 (Mac1) and CD54 (ICAM-1) appear to be mediated through this receptor.[73-75] It has also been claimed that the chemokine (LEC)/CCL16, which is expressed in the liver, targets the H_4R, causing human or mouse eosinophil migration.[76] This finding suggests an intriguing functional similarity between chemokines and H_4R that needs to be confirmed. Using a protein array to evaluate cytokine production by human eosinophils, it has been shown that levoceterizine (H_1R antagonist) inhibits IL-1, IL-7 and SCF production promoted by stimulation with LPS.[77] At relatively high doses (10-100 μM) histamine can also counteract the effect of IL-5 on the survival of human eosinophils by inducing their apoptosis. This effect occurs through an unknown mechanism that does not involve classical receptors,[78] but might be analogous to the cAMP-dependent-apoptotic pathway induced by some H_4R agonists, which inhibit antigen-specific human T-cell responses through an H_4R-independent pathway.[79]

Histamine is also involved in chemotaxis of neutrophils, as shown during their mast cell-dependent recruitment induced by zymosan in vivo[80] and trinitrobenzene sulphonic acid-provoked acute colitis.[81] This effect is mediated through the H_4R, which is likewise responsible for the decrease in bone marrow neutrophils following injection of histamine.[80] In addition to being a target, neutrophils are also a source of histamine, as evidenced in a casein-induced peritonitis model where HDC has been localized on the intracytosolic face of the membrane granules[82] as well as during mycoplasma pneumonia.[83] In this latter model, mycoplasma has been shown to stimulate naive neutrophils directly to synthesize histamine by strongly upregulating HDC mRNA expression. Further investigations will be required to elucidate the nature of signals exchanged between mycoplasma and neutrophils that lead to such an increase in HDC mRNA expression.

Histamine and Autoimmunity

As discussed above, histamine controls accessibility to sites of inflammation by modulating vasopermeability and adhesion molecule expression. In addition, it exerts a chemotactic effect on various cell types, on its own or in synergy with classical chemoattractants. It also targets DCs and Th1/Th2 cells directly, mainly by modulating their cytokine profile, thus establishing



Histamine targets	Cytokines	Receptors	Effect	Ref.
Dendritic cells	IL-12	H1, H2, H4	decrease	12, 14, 16
	IL-10	H2	increase	16,17
	IFNα	H2	decrease	20
	TNFα	H2	decrease	20
TH1 cells	IFNγ	H1	increase	28
TH2 cells	IL-4	H2	decrease	28
CD8+T cells	IL-16	H4	increase	30
iNKT cells	IL-4	H4	increase	44
	IFNγ	H4	increase	44
Monocytes	IL-12	H2	decrease	48,49
	IL-10	H2	increase	48
	TNFα	H2	decrease	51
	CCL2	H2, H4	?	54 ,56
Macrophages	TNFα	H1	increase	52
	IL-8	H1	increase	53
Basophils	IL-4	intra	decrease	70
	IL-6	intra	decrease	70
	IL-13	intra	decrease	70

Figure 2. Histamine-cytokine connection in immune cells.

the histamine/cytokine network illustrated in Figure 2. These multiple biological activities are consistent with a major regulatory function of histamine during the immune response and in the emergence of pathologies resulting from immune disorders such as autoimmunity. In favor of a potential immunointervention, increased production of histamine occurs during diseases such as multiple sclerosis,[84] psoriasis,[85] Crohn's disease and ulcerative colitis[86,87] in which histamine metabolite levels are correlated with disease severity. In the same line of evidence, the increase of mast cell numbers associated with autoimmune diseases argues in favor of the contribution of histamine during onset or effector phase of the pathology, even though it is quite evident that mast cells participate in various other ways in the autoimmune reaction, as summarized in a recent review.[88] For instance, mast cells are found in the brain of patients with multiple sclerosis associated with demyelinated plaques,[89-91] in the synovial fluid of rheumatoid arthritis patients,[93-95] in the salivary gland of individuals suffering from Sjogren's syndrome,[96] in the vicinity of peripheral nerves during experimental neuritis and so on. Basophils, as the second most potent source of histamine, could also participate in these processes, even though there is no reliable evidence for their role in autoimmunity as yet, possibly because these rare cells are difficult to identify. The availability of new specific surface markers and murine models in which basophils have been implicated during the polarization of the immune response,[97] will certainly lead to the reappraisal of their role in the near future. In addition, histamine receptor-bearing cells have been recovered from sites of autoimmune aggression, as exemplified by the presence of infiltrating H_1R and H_2R-positive cells in the brain in experimental autoimmune encephalomyelitis (EAE) models and in synovial fluids of rheumatoid arthritis patients, which contain fibroblasts and macrophages that express H_4R.

Histamine and Experimental Autoimmune Encephalomyelitis (EAE)

The large majority of studies looking for a possible implication of histamine during autoimmune diseases has been performed in the murine EAE model, which is most closely related to human multiple sclerosis (MS). Mice are immunized with myelin peptide in the presence of complete Freund adjuvant to generate the autoimmune disease in which Th1[98] and/or Th17 cells are most likely involved. Indeed, IFNγ- or IFNγ receptor-deficient mice express a more severe EAE,[99,100] while IL-23-deficient mice are relatively protected.[101] The etiology of the disease, characterized by myelin destruction in the CNS, is not entirely clear. In MS or EAE, one of the earliest events of disease onset is an increase in blood barrier permeability that allows

inflammatory and immune cells to infiltrate the murine CNS, a step in which the vasoactive properties of histamine could play a major role. In support of this assumption, mice with disrupted H_3R expression develop a more severe disease and neuroinflammation, due to deficient neurogenic control of cerebrovascular tone as well as increased chemokine production.[102] Moreover, histamine can enhance disease progression through the H_1R, as shown by reduced pathological alterations after receptor blockade[98] as well as a significant delay in EAE onset in H_1R-deficient mice, associated with a decrease in the severity of clinical symptoms.[103] By contrast, it has been reported that H_2R activation by the agonist dimaprit has a beneficial effect, alleviating the typical hallmarks of disease.[104] These data, together with the fact that during EAE inflammatory and immune cells bearing H_1R or H_2R infiltrate the CNS, argue strongly in favor of the contribution of histamine to this pathology. This notion is strengthened by the exacerbation of MOG 35-55-induced chronic EAE in histamine-free mice. Indeed, CNS inflammatory infiltrates that develop in brain parenchyma of these mutants are more diffuse and contain more eosinophils and polymorphonuclear leukocytes than their wild-type counterpart. Furthermore, T cells from HDC-deficient mice produce more IFNγ, TNFα and MCP-1 in response to autoantigens, suggesting that the overall effect of histamine might be protective, limiting the CNS immune damage.[105]

Taken together these data are somewhat contradictory. On the one hand, the reduced pathogenicity observed in H_1R KO mice might be explained by decreased inflammatory cell infiltration in the CNS because the vasopermeability at the BBB (Blood-Brain Barrier) is no longer increased via this receptor subtype. In accordance with this finding the disease is exacerbated in H_3R KO mice whose histamine synthesis is no longer regulated by the H_3R, leading to increased vasopermeability, which facilitates the infiltration of immunocompetent cells in the CNS. These data are reminiscent of similar chain of events in cerebral malaria.[106] On the other hand, the question arises why the lack of histamine in HDC KO mice aggravates the disease. To account for this result the control of the vascular tone by histamine might be considered solely as a means of enhancing the pathology by favoring the immune cell infiltration in the CNS, while more pathogenic T_H1 cells are generated and migrate together with other inflammatory cells to the CNS in a histamine-independent fashion. This hypothesis is supported by the observation that IFN-γ production by T cells from HDC KO mice is increased. Moreover, the activity of infiltrating cells could be increased in the absence of histamine, which is known for downregulating leukocyte functions such as production of oxygen radicals, leukotrienes and cytokines.

In agreement with the regulatory functions of histamine in autoimmune diseases, the *Bordetella pertussis* toxin-induced histamine sensitization (Bphs) gene that controls the susceptibility to EAE and experimental allergic orchitis, has been identified as the H_1R.[103] Signaling through this receptor is important during early activation of $CD4^+$ T cells since it is required for their TCR-mediated p38 MAPK activation and optimal IFNγ production.[107] Indeed, structural polymorphism (L263P, M313V and S331P) in the third intracellular loop of the murine H_1R regulates T-cell cytokine production and thereby controls disease susceptibility. The PVP haplotype is associated with increased susceptibility (H_1R^s), while the LMS counterpart develops a less severe disease (H_1R^r). Mechanistically, polymorphism alters H_1R surface expression; the H_1R^r allele being retained within the endoplasmic reticulum of T cells, thus modifying their immune functions and autoimmune disease susceptibility.[108]

Histamine and Autoimmune Chronic Urticaria (CU)

Chronic urticaria is a common disease characterized by recurrent, transitory and itchy wheals for more than six weeks that may severely worsen the quality of life. No precise pathogenesis has been established so far for all cases of CU, although a serologic component has been identified in many cases of autoimmune origin.[109] Indeed, in around 50% of CU patients circulating antibodies directed against the high affinity receptor for IgE (FcεRI) and more rarely against IgE have been detected.[110] These autoantibodies are responsible for in vitro histamine release from basophils or mast cells and explain the in vivo wheal-and-flare response observed following intradermal injection of autologous serum (autologous serum skin test, ASST). In addition, the binding of these

autoantibodies to receptors triggers the activation of the complement cascade and production of anaphylatoxins such as C5a that synergizes in turn with FcεRI autoantibodies to enhance histamine release from mast cells.[111] The autoimmune origin of CU is also supported by its association with thyroid autoimmune disease in some patients.[112] In a limited number of cases, skin biopsies with infiltrating $CD4^+$ T cells contained some $CD4^+C25^+$ Treg cells characterized by an uncommon decrease in their ability to inhibit $CD4^+CD25^-$ proliferation in response to mitogen.[113]

Circulating autoantibodies directed against high-affinity IgE receptors were also found in some patients suffering from asthma, suggesting that autoimmunity may contribute to intrinsic asthma pathogenesis.[114]

Histamine and Rheumatoid Arthritis (RA)

Rheumatoid arthritis is defined as an autoimmune disease with chronic inflammation of the synovium that leads to the destruction of bone and articular cartilage. Histamine is found both in diseased synovium and joint fluid[115-118] and originates either from an increased number of activated and degranulated mast cells at the inflammatory sites or from neosynthesis by chondrocytes of osteoarthritic cartilage.[119,120] Based on these data and the fact that histamine receptor-bearing cells are present in the synovium,[121,122] it has been suggested that histamine could increase inflammation during RA.[120,123] However, histamine injected in mouse knee joints does not induce any signs of synovitis on its own. In addition, even in combination with HMGB1 or peptidoglycans, histamine injection does not modify the inflammatory effect of these molecules. The fact that mast cell membrane stabilization does not alter in vivo inflammatory responses supports the idea that histamine is not responsible for this process. Lastly, a recent study shows that histamine levels both in synovial fluids and in sera of patients suffering from RA are significantly lower than in healthy individuals and anti-TNFα treatment of RA patients restores normal histamine levels.[124] Taken together, these data does not fit with previous data and argue in favor an anti-inflammatory rather than a pro-inflammatory role of histamine during RA.

Histamine and Experimental Autoimmune Myocarditis

Experimental autoimmune myocarditis represents another model in which a possible implication of histamine has been evaluated. The development of this pathology is associated with H_1R expression in the myocardium, which does not occur in healthy individuals.[125-127] It might be hypothesized that histamine provided by infiltrating cardiac mast cells impairs cardiomyocyte functions via H_1R activation, as suggested by the improvement of viral myocarditis following treatment with H_1R antagonists.[128]

Conclusion

The regulatory functions of histamine during the immune response are widely documented. However, the complexity of interactions between immune cells through a variety of receptors and other binding sites has engendered some conflicting data. They are probably explained by the relative selectivity of histamine receptor agonists and antagonists used in these studies, depending on their concentrations and the identity of target cells. Moreover, the contribution of other sites of interaction, such as membrane transporters like OCT3 or intracellular receptors has certainly been underestimated in the overall effect of histamine. The most recent discovery of the H_4R and its predominant expression in hematopoietic and immunocompetent cells has led to a reappraisal of the role of histamine during the immune response and provided a new pharmacological target with potential therapeutic applications. Although interesting data have already been obtained in some models of autoimmune diseases, the appreciation of the influence of histamine on the equilibrium between immunity and tolerance and its complex network of interactions is far from complete. Differences between species, routes of administration of histamine response modifiers and the like, are probably responsible for the confusing picture obtained so far. This needs to be put into better focus in order to evaluate the impact of future therapeutic strategies. Furthermore the involvement of histamine during self-recognition has yet to be addressed, although recent data implicate histamine during T-cell tolerance to high

dose bee venom exposure in beekeepers that is caused by an in vivo switch from venom-specific Th2 to IL-10-secreting Treg cells via H_2R activation.[129]

Finally, the peculiar interaction between histamine and cytokines raises hope for new pharmaceutical developments of histamine-related molecules acting on the inflammatory axis of autoimmune diseases. For example, the demonstration that H_4R antagonists affect TNFα production in a model of colitis could lead to new treatments of autoimmune diseases that are so far based mainly on anti-TNFα therapies.

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