



Immune regulation by histamine and histamine-secreting bacteria

Weronika Barcik¹, Marcin Wawrzyniak¹, Cezmi A Akdis^{1,2} and Liam O'Mahony¹

Histamine is a biogenic amine with extensive effects on many immune cell types. Histamine and its four receptors (H1R–H4R) represent a complex system of immunoregulation with distinct effects dependent on receptor subtypes and their differential expression. In addition to mammalian cells, bacteria can also secrete histamine and the influence of microbiota-derived histamine on host immunological processes is only beginning to be described. However, it is clear that histamine-secreting microbes are present within the human gut microbiota and their levels are increased in asthma patients. Additional studies are required to fully understand the complex regulatory interactions between histamine and the host immune response to everyday microbial and environmental challenges.

Addresses

¹Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland

²Christine Kühne – Center for Allergy Research and Education (CK-CARE), Davos, Switzerland

Corresponding author: O'Mahony, Liam (liam.omahony@siaf.uzh.ch)

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Introduction

The microbiota on mucosal surfaces is increasingly being recognised to play an essential role in host development and in particular for inducing immune homeostatic networks. In addition to the taxonomic diversity of the microbiota, its metabolic activity has profound effects on the induction of immune tolerance [1–3]. Accumulating evidence suggests that certain bacterial strains and their associated metabolites may provide disease protective signals while other bacterial strains may stimulate aggressive and tissue damaging immune responses. Thus, the activity of the mammalian immune system seems to be governed by the balance between symbiotic

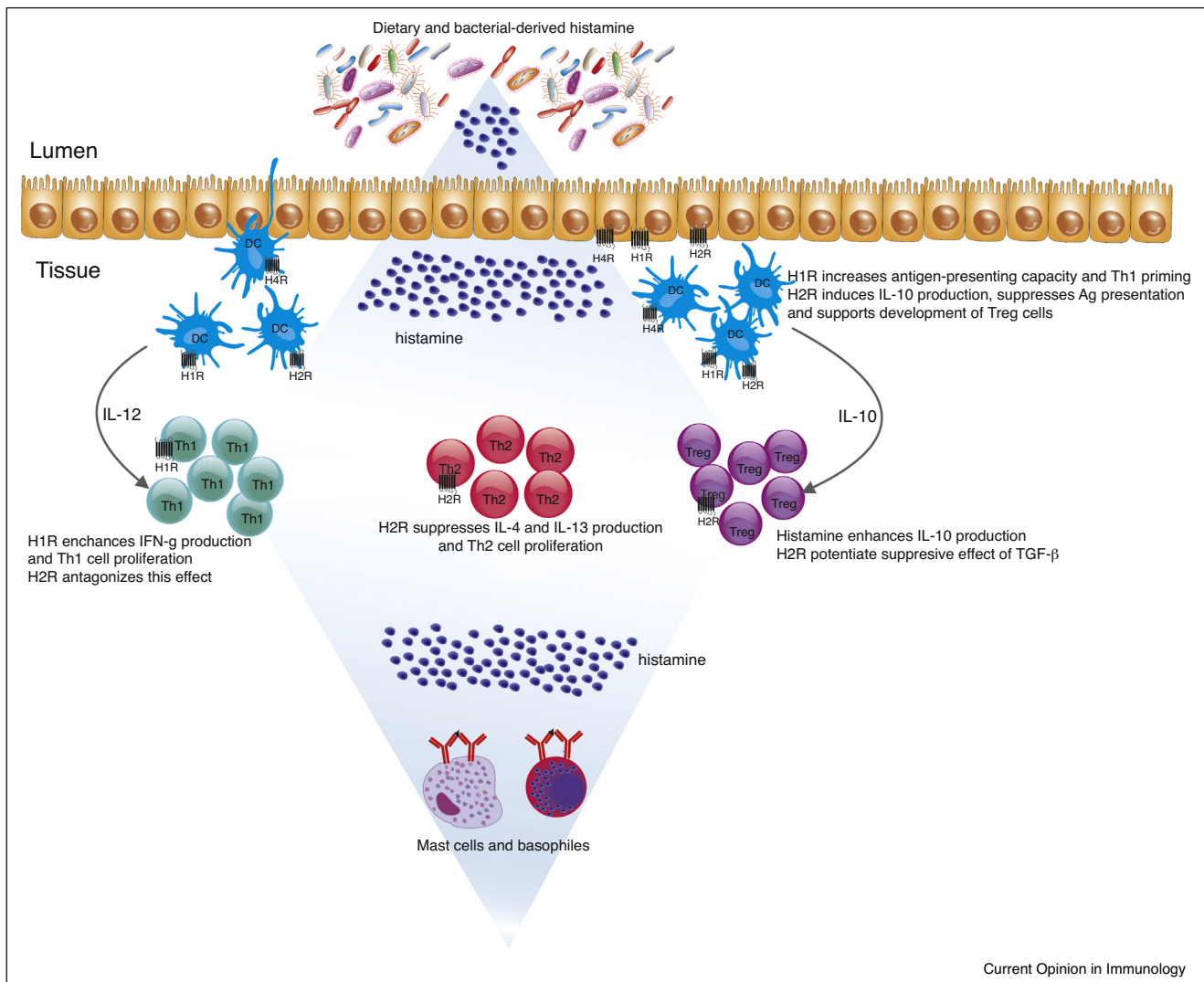
and pathogenic factors derived from our microbial inhabitants [4*].

One class of microbial-derived metabolites that have received significant attention are the short-chain fatty acids (SCFA), which include butyrate, acetate and propionate. The production of SCFA occurs in the colon following microbial fermentation of dietary fibers and SCFA can also be consumed in certain foods such as butter [5]. SCFAs are an important energy source for colonocytes and regulate the assembly and organization of tight junctions. Importantly, SCFA promote dendritic cell regulatory activity resulting in the induction of regulatory lymphocytes and IL-10-secreting T cells. Abnormalities in the production of SCFAs (due to dietary factors and/or dysbiosis) have been suggested to play a role in the pathogenesis of type-2 diabetes, obesity, inflammatory bowel disease, colorectal cancer and allergies [6]. The SCFA-induced immunoregulatory activities have largely been attributed to their binding and activation of G protein-coupled receptors (GPCRs) such as GPR41, GPR43 and GPR109a [7]. In addition to SCFAs, the microbiota can secrete a wide range of other metabolites that can also influence mucosal immune responses via activation of GPCRs. One such metabolite is histamine. Histamine (2-[4-imidazolyl]-ethylamine) is a low-molecular-weight biogenic amine and was first chemically synthesized by Windaus and Vogt in 1907. Dale and Laidlaw reported the first biological functions of histamine in 1910, whereby they demonstrated that histamine induced smooth muscle-stimulating and vasodepressor action previously observed during anaphylaxis [8]. Subsequently histamine was isolated from many different tissues, thus its name was based on the Greek word ‘histos’, which means tissue. Histamine binds to four known histamine receptors (HRs) and a range of ‘blockbuster’ drugs have been developed for H1R and H2R, the inventors of which were awarded Nobel prizes in 1957 (Daniel Bovet) and 1988 (James Black). Drugs targeting H3R and H4R are currently being evaluated.

Immune regulation by histamine

Innate and adaptive immune cells throughout the body can produce histamine by decarboxylation of the amino acid L-histidine by the enzyme histidine decarboxylase (HDC) [9]. Mast cells, basophils, gastric enterochromaffin-like cells and histaminergic neurons are the best-described cellular sources of histamine. Other cells such

Figure 1



Influence of histamine on mucosal-associated immune cell subsets. Luminal sources of histamine include the diet and bacteria, while mast cells and basophils are the primary sources of tissue-derived histamine. Epithelial cells and immune cells express histamine receptors. Activation of dendritic cell (DC) H1R supports Th1 lymphocyte polarisation, while H2R inhibits Th1 and Th2 lymphocyte polarisation and supports the expansion of regulatory lymphocytes.

as platelets, monocytes/macrophages, dendritic cells, neutrophils and lymphocytes may upon stimulation also express HDC. Activity of HDC is influenced by cytokines including IL-1, IL-3, IL-12, IL-18, GM-CSF, macrophage-colony stimulating factor, TNF- α and calcium ionophore [10]. In the case of mast cells and basophils, histamine is stored in large quantities and released upon cellular activation. All other cells secrete histamine following synthesis and do not store it intracellularly [11]. Before secretion, histamine can be metabolized by ring methylation (HNMT — histamine-N-methyltransferase) to N-methylhistamine, or by oxidative deamination (DAO — diamine oxidase) to imidazole acetic acid. As DAO is secreted extracellularly, this enzyme may be

responsible for scavenging extracellular histamine, while HNMT remains within the cytosol and thereby metabolizes intracellular histamine [12,13].

Histamine receptors

Cells of both the innate and adaptive immune system can be regulated by histamine (Figure 1). Binding of histamine to four subtypes of histamine receptors shape and define the nature of histamine effects in immunological responses. Histamine receptors contain seven transmembrane domains and belong to the rhodopsin-like family of GPCRs. Each HR is associated with specific G α subunits, which result in distinct molecular signalling cascades and diverse modes of action following histamine binding.

Table 1**Overview of histamine receptors.**

	H1R	H2R	H3R	H4R
Chromosomal location	3q25	5q35.2	20q13.33	18q11.2
G protein coupling	Gαq	Gαs	Gαi/0	Gαi/0
Intracellular signal transduction	Activates PLC, PKC and calcium release	Increases cAMP and activates PKA	Inhibits cAMP, activates MAPK, PKB and calcium release	Inhibits cAMP, activates MAPK, PKB and calcium release
Tissue location	Ubiquitous	Ubiquitous	Neurons	Bone marrow, hematopoietic cells, keratinocytes

H1R leads to the activation of Gαq, H2R is coupled to Gαs while H3R and H4R are both activators of Gαi/0 [14]. In humans, H3R and H4R display the highest affinity for histamine binding, followed by H2R and H1R [15]. The different characteristics associated with each of the HRs are summarised in Table 1.

Histamine 1 receptor

A broad range of cell types, including T and B lymphocytes, monocytes, dendritic cells, endothelial cells, airway and vascular smooth muscle cells, hepatocytes, neurons and chondrocytes express H1R [16,17]. Histamine binding to the H1R leads to activation of phospholipase C (PLC), which produces 1,2-diacylglycerol and inositol-1,4,5-trisphosphate, subsequently resulting in activation of protein kinase C (PKC) and release of calcium ions from intracellular stores. Activation of H1R mediates the classical immediate hypersensitivity responses such as airway and vascular smooth muscle cell contraction, increased vascular endothelial cell permeability, synthesis of platelet activating factor and release of von Willbrand factor and nitric oxide. Consequently this results in many pathological processes including allergic rhinitis, atopic dermatitis, urticaria, asthma and anaphylaxis [10,18]. Furthermore, H1R mediates regulation of food and water intake, convulsion, attention and sleep regulation [19].

Histamine 2 receptor

Interestingly many of the H1R-mediated effects can be antagonized by H2R. For example, H2R is responsible for relaxation of blood vessel-associated smooth muscle cells found in the uterus and airways [20]. H2R is an adenylyl cyclase-coupled GPCR, which stimulates cAMP production and downstream effects are mediated by protein kinase A (PKA) and the transcription factor cAMP response element-binding protein. A wide diversity of cells and tissues including cardiac tissue, gastric parietal cells, brain cells, smooth muscle cells, T and B lymphocytes and dendritic cells express H2R which can exhibit constitutive or spontaneous activity [21]. H2R activation regulates both innate and adaptive immune system responses including mast cell degranulation, dendritic cell responses to microbial ligands, T cell proliferation, TH1-derived cytokine production and antibody production by B cells [22,23]. Recently, H2R was shown to

regulate invariant natural killer T cell (iNKT cell) activity and loss of H2R signalling on iNKT cells resulted in exaggerated inflammatory responses within the lung [24]. Similarly, the transfer of H2R-deficient T cells to SCID mice was associated with more severe colitis and TH17 responses within the gut, compared to mice that received wild-type T cells [25]. Interestingly, mucosal histamine levels are increased in patients with irritable bowel syndrome and inflammatory bowel disease, but the cellular sources of histamine in these patients is not well described [26]. However, it was recently shown that inflammatory bowel disease patients do display dysregulated expression of histamine receptors, with diminished anti-inflammatory effects associated with H2R signalling [25]. Collectively, these studies suggest that H2R is an important immunoregulatory receptor.

Histamine 3 receptor

The next histamine receptor, H3R was formerly identified as a neurotransmitter release controlling pre-synaptic receptor and is characterized by a high degree of constitutive activity *in vitro* and a large number of splice variants with similar pharmacological properties [27]. Histamine binding to H3R results in the activation of mitogen-activated protein kinase (MAPK) pathways, protein kinase B (PKB) and an increase in calcium ion concentration. Most of the knowledge about H3R activity comes from studies using H3R-deficient mice. H3R deficient animals are characterized by the enhanced expression of MIP-3 (macrophage inflammatory protein 3), IP-10 (IFN-inducible protein 10) and CXCR3 expression by peripheral T cells which leads to increased severity of neuro-inflammatory disease. Furthermore these animals display increased insulin and leptin levels, associated with late-onset obesity partially mediated by an abnormally increased appetite [28,29].

Histamine 4 receptor

The most recently described histamine receptor, H4R, shares some molecular, pharmacological and signal transduction features with H3R but the expression pattern is different to H3R as it is found on keratinocytes, Langerhans cells, dendritic cells, neutrophils, mast cells, basophils and lymphocytes [30]. Histamine receptor 4 is involved in cytokine production and chemoattraction of eosinophils, mast cells and basophils as well as T

lymphocytes and dendritic cells [31,32]. Data from animal models suggest that treatment with H4R antagonists supports the importance of this receptor in regulation of immunological processes in colitis, arthritis and asthma [33,34].

Histamine-secreting bacteria

In addition to mammalian cells, a number of different bacterial strains have been identified as being able to secrete histamine following decarboxylation of histidine via HDC activity. The best described are those bacteria that are able to secrete histamine in food products. Their presence is monitored and controlled in cheese, meat, vegetables, dairy products and also during beer and wine fermentation [35,36]. However the most notorious examples of histamine secreting bacteria are those associated with spoiled fish and sea food products. Histamine fish poisoning (HFP), or scombroid food poisoning, is an illness associated with consumption of high levels of histamine in fish, following the metabolism of histidine in the fish by bacteria during inappropriate handling during storage or processing [37,38]. The earliest record of the disease was in 1799. Symptoms of HFP resemble those of food allergy and can include facial itching, torso or body rash, nausea, vomiting, diarrhoea, tachycardia, hypotension, respiratory distress and in rare severe cases may result in death [39]. HFP is often misdiagnosed as a food allergic response. The bacterial species with histidine decarboxylase activity and which have been implicated in HFP include *Morganella morganii*, *Escherichia coli*, *Hafnia alvei*, *Proteus vulgaris*, *Proteus mirabilis*, *Enterobacter aerogenes*, *Raoultella planticola*, *Raoultella ornithinolytica*, *Citrobacter freundii*, *Pseudomonas fluorescens* and *Photobacterium damsela* [40].

Although the presence of histamine-secreting bacteria has been well documented in foods, their presence within the human gut microbiota has not been investigated in detail. We recently performed an analysis of fecal samples from 161 volunteers to quantify the presence of bacterial HDC, using primers that do not amplify human HDC. Microbial-specific HDC was detected in all fecal samples, however a wide inter-individual range was evident [41^{••}]. Interestingly, bacterial HDC gene levels were significantly elevated in adult patients with asthma compared to healthy controls. In addition, non-obese patients with asthma had the highest level of the bacterial HDC gene compared with obese patients with asthma. The difference in HDC positive bacteria between obese and non-obese asthma patients suggests that factors other than histamine secretion by microbes in the gut may be more important for the development of asthma in obese patients. The bacteria isolated from these fecal samples, which were able to secrete the highest levels of histamine, belong to *E. coli*, *M. morganii* and *L. vaginalis* species [41^{••}]. The level of histamine secretion depended on the strain and *in vitro* culture conditions that were used (e.g.

pH and culture media composition). Of note, *E. coli* and *M. morganii* were commonly reported to be the causative isolates associated with cases of HFP. Intriguingly, increased levels of *M. morganii* were positively associated with more severe asthma symptoms. Based on these observations, one might speculate that increased levels of bacterial-derived histamine in certain adult asthma patients may contribute to histamine-mediated pathologies due to a higher systemic level of histamine, which then reduces the level required for host-derived histamine to drive allergic responses following allergen exposure. However, this hypothesis remains unproven. In addition, certain bacterial strains can degrade histamine and it is currently unknown if the levels of these bacteria are altered in inflammatory disorders such as asthma [42].

Immune regulation by histamine-secreting bacteria

Given the potent immunological effects associated with histamine signalling, it is not surprising that histamine from the microbiota may also influence immune responses. *In vitro*, culture supernatants from histamine-secreting bacteria were able to stimulate CHO cells, which possessed a H1R reporter. Specific activation of the H1R by bacterial-derived histamine was confirmed as activity was blocked using the H1R antagonist diphenhydramine [41^{••}]. In addition, *Lactobacillus reuteri*-derived histamine was shown to inhibit TLR-induced TNF- α production by human monocytoic cells via signalling through the H2R and downstream cAMP and PKA activity [43].

In murine models, it was recently shown that gut microbiota-derived histamine influences host-microbiome homeostasis via epithelial IL-18 secretion, co-modulating NLRP6 inflammasome signalling and downstream antimicrobial peptide secretion [44[•]]. Administration of the histamine-secreting *Lactobacillus* strain 30A to mice resulted in rapid weight loss and reduced Peyer's patch cytokine secretion [45]. However, weight loss was exaggerated in H2R-deficient mice and IL-4, IL-6, and IL-17 secretion by Peyer's patches was increased, an opposite result to that observed for wild-type animals. This data suggests that histamine-derived from gut microbes can have immunological effects within the mucosa, but the nature of these effects is determined by the histamine receptor that is triggered. In a separate study, the suppression of intestinal inflammation by a *Lactobacillus reuteri* strain was shown to be dependent on histamine secretion by the bacterium and its activation of H2R [46[•]].

Conclusions

Histamine and its four receptors represent a complex system of immunoregulation with distinct effects dependent on receptor subtype expression and activity. The role for differential expression or activation of histamine receptors on immune competent cells in chronic

inflammatory diseases is still poorly described to date and further examination of this potent immunoregulatory network will likely lead to a better understanding of these disorders. Recent developments in histamine research suggest that we need to re-evaluate the role that histamine plays in innate and adaptive immune responses. In addition, no longer can we assume that mast cells and basophils are the principal cellular sources of histamine in the human body as clearly many resident bacterial strains produce histamine and their levels are increased in the gut of adult non-obese asthma patients. More accurate endotyping of asthma patients (and other chronic inflammatory disorders) may be assisted by further analysis of the composition and metabolic activity of an individual's microbiome and future clinical studies of new therapeutic agents should consider performing microbiome and metabolite analysis to determine if specific microbiome features correlate with responses to treatment. In addition, therapeutics directly targeting microbiome activities, such as histamine secretion, may be considered as complementary to existing drugs.

Conflict of interest

Liam O'Mahony has received research support from GSK and consulted for Alimentary Health Ltd. Cezmi Akdis has received research support from Novartis and Stallergenes and consulted for Actellion, Aventis and Allergopharma. Weronika Barcik and Marcin Wawrzyniak have no potential conflicts of interest.

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