# T lymphocytes as a target of histamine action

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**Abstract**

Histamine is one of the most important biogenic amines in medicine and biology but its role in allergy, autoimmune and neoplastic diseases has not yet been fully defined. The last few years have brought many discoveries concerning important modulatory effects of histamine and its receptors on basic mechanisms of the immunological processes. The role of histamine H1 and H2 receptors in immunomodulation has been established. The immunomodulatory function of a newly described histamine H4 receptor has been revealed. One of the most important modulatory effects of histamine currently studied is its influence on T lymphocyte differentiation and function. Our present knowledge suggests that histamine may have a wider influence on various immunological processes than is now accepted; therefore, we need further studies to fully clarify the role of histamine and its receptors. This knowledge can bring new therapeutic solutions in allergies, autoimmune diseases and malignancies.

**Key words:** histamine, receptors, inflammation, T lymphocytes, immunomodulation, antihistamines.

## Introduction

Histamine has been widely described throughout the twentieth century. It was synthesized in 1907, 3 years after Dale described its vasodilating effect. Since then, many biological functions of histamine have been characterized, new receptors, beginning with histamine H1 receptors [1], have been described, and intracellular effects of histamine receptors have been explained. The knowledge led to the synthesis of medication used in therapy of allergic and nonallergic diseases. At the end of the twentieth century a number of scientists thought that the role of histamine in allergy was well and nearly completely explained.

The discovery of a novel histamine receptor in 2000 and its characterization [2] was a signal for the need to accelerate studies on histamine functions. Succeeding years brought many discoveries concerning the role of the new histamine receptor. At the same time, new research showed important modulatory effects of histamine and its receptors on basic mechanisms of immunological processes.

## Histamine as immunomodulator of lymphocyte activity

The first evidence indicating histamine's role in modulation of inflammatory processes was the inhibition of T lymphocyte cytolytic activity by

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histamine in mice. This effect, described by Plaut *et al.*, was blocked by the histamine H2/H3 receptor antagonist burimamide, while the histamine H1 receptor agonists diphenhydramine and pyrilamine had no influence on this phenomenon [1]. Further studies confirmed the presence of histamine H2 receptors on T lymphocytes and showed that stimulation of these receptors increases intracellular cyclic adenosine monophosphate (cAMP) [3].

The role of histamine in suppression of peripheral blood mononuclear cell (PBMC) activity was suggested in 1979 by Martinez *et al.*, who also showed differences between histamine effect on PBMC obtained from allergic and healthy people [4]. This study, although in the light of our present knowledge burdened with significant methodological flaws, showed that histamine can play a role in modulation of inflammatory processes; and furthermore, its effects on immunomodulation may differ between allergic and healthy people.

Another early finding, from a study conducted by Rocklin *et al.* in 1980, was revealing the existence of histamine receptors on mononuclear cells appearing during allergen-specific desensitization in ragweed allergic subjects with allergic rhinitis. The presence of histamine receptors on mononuclear cells in peripheral blood, and the suppressive role of these cells in inflammation, were confirmed in animal models. Further studies showed that histamine-binding peripheral blood T lymphocytes are responsible for inhibition of inflammation [5]. In 1992, Shibata *et al.* described an increase of the expression of histamine H2 receptors localized on CD8+ CD25+ T lymphocytes after interleukin 2 (IL-2) stimulation. Treatment of activated CD8+ lymphocytes with the H2 receptor antagonist cimetidine significantly reduced the number of H2 receptors. Suppressor lymphocytes induced by IL-2 were able to suppress both IgG and IgM production, which was reversible with cimetidine [6]. Further studies showed that addition of histamine or histamine H2 receptor agonist to IL-2 significantly enhances the accumulation of CD25+ T lymphocytes in peripheral blood in comparison with IL-2 administered alone. Other studies indicated that histamine can increase secretion of interleukin 5 (IL-5) from Th2 lymphocytes through histamine H2 receptors. Histamine can also inhibit the adhesion of CD4+ T lymphocytes to extracellular matrix proteins, fibronectin and laminin, as histamine induces the increase of intracellular levels of cAMP in these cells. This in turn interferes with calcium influx-associated events that occur during T cell activation. The above mechanism is supported by the finding that T cell adhesion was also inhibited by pharmacological inducers of cAMP. Histamine exerts its suppressive effect on adhesion of T lymphocytes via their H2 receptors, as pre-treat-

ment with H2 antagonists prevented this inhibitory effect [7] (Figure 1).

In 1997, Lagier *et al.* tried to assess the influence of histamine on various subpopulations of Th lymphocytes (Th1, Th2 and Th0) obtained from bronchial biopsy or peripheral blood in atopic subjects. They found that histamine inhibits IFN-γ production by Th1-like lymphocytes, especially from bronchial biopsy, but has no effect on IL-4 release. Regarding Th0 clones, histamine inhibits IL-4 production in a dose-dependent manner and causes a slight decrease in IFN-γ production, but has no effect on Th2-like lymphocytes. The study showed that histamine has no significant effect on IL-5 production. The H2 receptor antagonist ranitidine completely reverses the inhibition of IL-4 and IFN-γ production, whereas the agonist dimaprit mimics this effect. In contrast, H1 and H3 receptor agonists and antagonists did not influence IL-4 and IFN-γ production. These data demonstrated that histamine via H2 receptors has different effects on IL-4 and IFN-γ release from T helper lymphocytes depending on their phenotype. Histamine H2 receptor stimulation can also lead to proliferation of activated T lymphocytes [8].

In 1998, Elenkov *et al.* observed that histamine suppresses interleukin 12 (IL-12) and stimulates IL-10 secretion via stimulation of H2 receptors on peripheral monocytes, which leads to cAMP elevation. Interleukin-12 stimulates the Th1 immune response, whereas IL-10 is thought to lead to maturation of dendritic cells (DC) into a phenotype which induces Treg and stimulates the Th2 immune response. The observed changes may result in a shift of Th1/Th2 balance toward Th2 dominance [9].

## The role of histamine receptor-bearing T lymphocytes in autoimmune reactions and malignancies

Besides stimulating suppressor T lymphocyte activity, histamine can also partially and reversibly inhibit cytolytic activity of T lymphocytes. This phe-
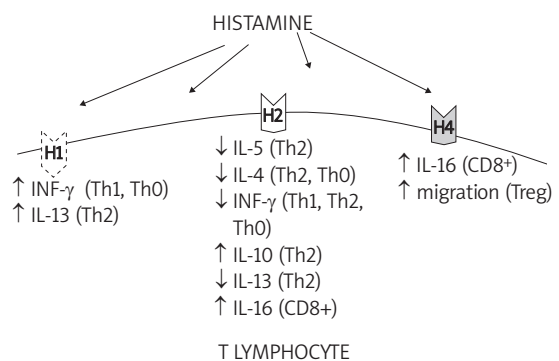


HISTAMINE

H1 ↑ INF-γ (Th1, Th0) ↑ IL-13 (Th2)

H2 ↓ IL-5 (Th2) ↓ IL-4 (Th2, Th0) ↓ INF-γ (Th1, Th2, Th0) ↑ IL-10 (Th2) ↓ IL-13 (Th2) ↑ IL-16 (CD8+)

H4 ↑ IL-16 (CD8+) ↑ migration (Treg)

T LYMPHOCYTE

**Figure 1.** Effects of histamine action on T lymphocytes
↑ – *stimulates secretion*, ↓ – *inhibits secretion*

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nomenon, demonstrated by Khan *et al.*, depends on histamine H2 receptor stimulation [10]. Some data suggest that histamine protects natural killer (NK) cells and T lymphocytes against oxygen radical-induced dysfunction and apoptosis through H2 receptors, and maintains their activation by IL-2 and other lymphocyte activators. Additionally, histamine, again via H2 receptors, binds to monocytes and macrophages, which suppresses the activity of NADPH oxidase, a key enzyme in oxygen radical formation [11].

Some of the evidence for the role of histamine H2 receptors in suppressing inflammatory processes was obtained by revealing the lack of H2 receptor-bearing T lymphocytes in patients with histiocytosis X. The lymphocyte abnormalities were reversed in vitro after incubation in a crude extract of calf thymus gland, and therefore all patients were treated with daily intramuscular injections of this extract. A positive clinical response was associated with an increase in the number of H2 receptor-bearing T lymphocytes to normal levels and with correction of other immunological abnormalities. At the same time, Mavligit *et al.* showed that histamine H2 receptor stimulation inhibits T lymphocyte induced graft versus host disease (GVHD). In this study, addition of the histamine H2 receptor inhibitor cimetidine caused a relapse of GVHD because of defective suppressive T cell function [11].

Further studies on the role of histamine stimulation via H2 receptors localized on suppressor T lymphocytes showed its positive function of extinguishing autoimmune inflammatory reactions in Graves disease, as well as possible unfavourable effects of accelerating the growth of lethal tumours, studied in a murine model. Gorczynski *et al.* confirmed that H2 receptor-bearing T lymphocytes participate in stimulating malignant tumour growth in mice. They also showed that addition of a selective H2 receptor antagonist prevents this effect because of suppressor T lymphocyte activity inhibition [12]. Histamine also reduces ICAM-1 expression and cytokine production in human mixed lymphocyte reaction stimulated with IL-18 through histamine H2 receptors, whereas histamine alone did not show any effects on these responses in the absence of IL-18 [13, 14]. Histamine was also found to enhance the immune suppressive effects of transforming growth factor-β on T lymphocytes, acting by the same receptor [13]. In some autoimmune diseases, such as minimal change nephrotic syndrome, the number of suppressor T lymphocytes bearing histamine H2 receptors is reduced, but treatment with glucocorticosteroids elevates it to a level observed in healthy individuals [15]. The important contribution of histamine in extinguishing autoimmune inflammation was recently confirmed in a murine model by Musio *et al.* [16].

## Functional antagonism between histamine H1 and H2 receptors localized on T lymphocytes

In 1981, Rocklin and Haberek-Davidson reported the presence of H2 receptor and absence of histamine H1 receptors on PBMC responsible for histamine-dependent inhibition of inflammation [17]. The same year, Lima and Rocklin revealed the modulatory role of PBMC histamine stimulation on immunoglobulin IgG production [18]. However, the non-specific experimental model of inflammation selected by the authors was unable to answer the following important questions: which of the PBMC suppressive cells contain histamine H2 receptors in their membrane, and what is their role in *in vivo* processes?

A study on the regulation of allergic inflammation conducted by Beer *et al.* revealed essential differences in the activities of T lymphocyte subpopulations between atopic and healthy subjects. In that study, the authors showed that PBMC from atopic subjects generate less histamine-induced suppressor activity than from non-atopic, healthy subjects. The percentage of T lymphocytes bearing histamine H2 receptors was lower in the atopic group than in the control group, but the percentage of cells with H1 receptors was the same in both groups. In the atopic subjects, the functional suppressor-cell abnormality positively correlated with the decreased phenotypic expression of histamine H2 receptors. Non-atopic control subjects with systemic mastocytosis had normal functional and phenotypic data, suggesting that chronic activation of atopic T lymphocytes *in vivo* by circulating histamine does not explain the abnormal histamine-induced suppressor response observed in atopics [19]. This phenomenon was confirmed by Zak-Nejmark *et al.* in 1991. They found that lymphocytes from atopic subjects showed a statistically significant decrease in the binding of the H2 receptor antagonist ranitidine. In addition, lymphocytes from atopic and control subjects had similar capacity of H1 receptor antagonist promethazine binding. The ratio of the amount of H1 and H2 antagonists, bound to lymphocytes from atopic and healthy subjects, was calculated by the authors, and the difference between the values in the group of atopic (2.55) and control subjects (1.55) was statistically significant [20]. In the same year, Chinese authors published results of a study in which identification and quantitative analysis of specific histamine H1 and H2 receptors on lymphocytes were performed and histamine-induced suppressor cell activity was examined using 3H-histamine radioligand-binding assay. Peripheral lymphocytes from asthmatic subjects generated less histamine-induced suppressor activity than those from healthy individuals. In asthmatics, the functional suppressor cell abnormality positively correlated with the decreased quantity of H2 receptors on the lymphocytes [21].

Consecutive studies brought data suggesting antagonism between histamine H1 and H2 receptors localized on T lymphocytes. Stimulation of histamine H1 receptors led to a decrease of T lymphocyte suppressor activity. Stimulation of histamine H2 receptors localized on these cells led to an increase of inflammation suppression. These phenomena were described in many publications based on *in vitro* studies in human and rodent blood cells [22]. Data obtained from *in vivo* studies are much more difficult to interpret. For example, histamine causes inhibition of immunoglobulin synthesis through stimulation of histamine H1 receptors. This effect is independent of histamine H2 receptor stimulation and probably caused by indirect induction of glucocorticosteroid excretion from suprarenal glands. Histamine interacts with H1 receptors and causes the release of adrenocorticotropic hormone (ACTH) from pituitary glands. An increased serum level of glucocorticosteroids leads to inhibition of the synthesis of antibodies [23]. In another study, histamine via H2 receptors caused a decrease in antibody production after immunization in mice [24].

In 1983, Weinstock *et al.* proved that histamine H2 receptors suppress and H1 receptors stimulate the granulomatous response of *Schistosoma mansoni*-infected mice. They also showed that suppression of the response depends on stimulation of histamine H2 receptors on suppressor T lymphocytes, and stimulation of the response is associated with activation of histamine H1 receptors, localized on numerous cells of the granulomas, including T helper lymphocytes [25]. At the same time, other researchers revealed that histamine, by interaction with histamine H2 receptors on T lymphocytes, induces the production of a cytokine called histamine-induced suppressor factor (HSF). The HSF inhibits lymphocyte proliferation and the production of lymphokine and a cytokine called lymphotactic factor (LCF), while cells that bear histamine H1 receptors produce lymphocyte migration inhibition factor (LMIF) [26]. In 1987, Schnaper *et al.* described that secretion of a cytokine called soluble immune response suppressor (SIRS) from human T lymphocytes was stimulated by histamine H2, but not H1 receptors [27].

Further studies have shown more differences in cytokine secretion after stimulation of H1 or H2 receptors. In the study of Plaut *et al.*, histamine, acting on cytotoxic T lymphocytes, inhibited activity of these cells through increase of intracellular cAMP in mice [28]. According to our current knowledge, this effect was associated with stimulation of histamine H2 and H4 receptors, which causes increase of adenyl cyclase activity. Increase of intracellular cAMP after histamine H2 receptor stimulation can be enhanced by activation of T lymphocytes by

interleukin 2 (IL-2) [29]. The studies also showed differences in localization of histamine H1 receptors between various subpopulations of T lymphocytes, as twice as many histamine H1 receptors were expressed by CD8+ T lymphocytes as compared to CD4+ T lymphocytes. The Th1 lymphocytes show predominant expression of H1 receptors, while Th2 lymphocytes show increased expression of H2 receptors. Histamine enhances Th1-type responses by triggering the H1 receptors, whereas both Th1 and Th2-type responses are negatively regulated by H2 receptors, because of the activation of different biochemical intracellular signals [30]. In mice, deletion of H1 receptors results in suppression of IFN-γ and dominant secretion of Th2 cytokines (IL-4 and IL-13). The H2 receptor-deleted mice showed up-regulation of both Th1 and Th2 cytokines. In addition, histamine stimulation induced IL-10 secretion through H2 receptors. Increased IL-10 production in both DC and T lymphocytes may account for an important regulatory mechanism in the control of inflammatory functions through histamine. In accordance with this phenomenon, it was demonstrated that histamine supports the suppressive effect of transforming growth factor β (TGF-β) on T lymphocytes via H2 receptors [13]. The Th2 lymphocytes are more affected by histamine-enhanced TGF-β suppression, which is important for the regulation of allergen-specific T lymphocytes in allergic immune responses. Then, stimulation of the T lymphocyte function engaged in suppression of inflammation by selective stimulation of histamine H2 receptor on rat T lymphocytes was questioned by Binderup. However, the results of his study are also questionable, as the selective H2 receptor antagonist did not reverse the effects of selective stimulation [26]. Most studies show that histamine H2 receptor localized on T lymphocytes has an inhibitory effect on inflammation and an enhancing effect on suppressive processes leading to reduction of inflammation (Figure 1).

In 2001, Jutel *et al.* revealed that histamine H1 and H2 receptor densities significantly differ between Th1 and Th2 lymphocytes. They also affirmed that Th1-type responses are enhanced by histamine, whereas Th2-type responses are negatively regulated, due to different intracellular signals generated by histamine stimulation. They showed that deletion of H1 receptors results in suppression of INF-γ and dominant secretion of the Th2 cytokines interleukin 4 (IL-4) and interleukin 13 (IL-13) in mice. Mutant mice lacking H2 receptors showed upregulation of both Th1 and Th2 cytokines. Relevant to T cell cytokine profiles, mice lacking H1 receptors displayed an increased specific antibody response with increased immunoglobulin E (IgE) and IgG1, IgG2b and IgG3 compared with

mice lacking H2 receptors. According to the authors, these findings account for an important regulatory mechanism in the control of inflammatory functions through effector-cell-derived histamine [31]. The same year, Osna *et al.* showed that histamine stimulates secretion of interleukin 10 (IL-10) from Th2 lymphocytes through histamine H2 receptors. Further results of the Osna group were different from Jutel's, suggesting that histamine enhanced IL-13 secretion and mRNA levels in Th2 lymphocytes via histamine H1 and H2 receptors in a dose-dependent manner. They also revealed that pre-treatment of Th2 lymphocytes with IL-12 reverses histamine's effects on IL-13 secretion in mice from stimulatory to inhibitory [32].

Further important information about the function of histamine receptors were brought about by the studies of Mazzoni *et al.*, who showed that histamine, coupled by a maturation signal, acts directly upon immature dendritic cells (iDCs), profoundly altering their T cell polarizing capacity. They demonstrated that iDCs express two active histamine receptors, H1 and H2. Histamine did not significantly affect the lipopolysaccharide (LPS) driven maturation of iDCs with regard to phenotypic changes or capacity to prime native T lymphocytes, but it dramatically altered the repertoire of cytokines and chemokines secreted by mature DCs. In particular, histamine, acting upon the H2 receptor for a short period of time, increased IL-10 production and reduced IL-12 secretion. As a result, histamine-matured DCs polarized native CD4+ T lymphocytes toward Th2 phenotype, contrary to DCs that had matured in the absence of histamine [33]. In a further study, Mazzoni's group proved that histamine acts on plasmacytoid DCs leading to a marked down-regulation of IFN-$\alpha$ and TNF-$\alpha$ and a moderate switch in their capacity to polarize native T lymphocytes [34]. In the differentiation process of type 1 DC from monocytes, H1 and probably H4 receptors can act as positive stimulants that increase antigen-presentation capacity and proinflammatory cytokine production as well as Th1 priming activity. The important role of DC in regulation of the activity and cytokine profile of Th lymphocytes was confirmed by Teusher and colleagues. They observed that DC activity and cytokine production are altered in mice lacking histamine H2 receptors, resulting in a decrease of IL-12 and IL-6 secretion and increase of MCP-1 secretion. These phenomena *in vivo* can considerably modify cytokine secretion from Th1 and Th2 lymphocytes in mice, observed *in vitro* by Jutel *et al.* [35].

Research on the role of histamine in modulation of T lymphocyte function is complicated by histamine autosecretion observed in both CD4+ and CD8+ Th lymphocyte populations. In the study of Sonobe *et al.*, the authors assessed the role of his-

tamine autosecretion on cytokine profile in CD4+ and CD8+ lymphocytes [36], but their results are different from observations on histamine from an external source added to a suspension of cells. Recently, Jelinek *et al.* showed that histidine decarboxylase knockout (HDC–/–) mice, which are genetically histamine-free, exhibit predominantly a DC cytokine pattern leading to Th1 lymphocyte polarization [31].

New data obtained by McIlroy *et al.* show that histamine causes an increase of chemokine CCL 17 and CCL 22 secretion and decrease of CXCL10 secretion from iDC via H2 receptors [37]. Chemokines CCL 17 and CCL 22 are chemoattractants of Th2 lymphocytes and CXCL10 is a chemoattractant of Th1 lymphocytes, so the phenomenon described above leads to accumulation of Th2 lymphocytes and a change in Th1/Th2 balance to the advantage of Th2. The role of this phenomenon remains unclear, because the main role in promoting the migration of Th2 lymphocytes into sites of allergen exposure falls to histamine H1 receptors. Therefore, T lymphocytes obtained from mice lacking these receptors failed to confer airway inflammation or airway hyperresponsiveness after allergen stimulation [38].

Despite one century of studies on the role of histamine in physiology and pathogenesis of diseases, our knowledge about histamine is still far from complete. New questions about its participation in immunological processes await answers. Its role in regulation of lymphocyte function is most fascinating. We are looking forward to an explanation of the role of histamine H1 and H2 receptors located on Th1 and Th2 lymphocytes in the pathogenesis of allergies and autoimmune diseases. So far, data from different studies vary and do not authorize us to make final conclusions. Additional problems are caused by the heterogeneity of immunomodulatory effects of known histamine receptor ligands acting on the same histamine receptors, observed by Ashenager *et al.* [39]. Other issues awaiting explanation are the role of histamine in macrophages, monocytes and dendritic cells, in differentiation and maturation of various subpopulations of T lymphocytes, as well as the role of histamine in regulatory T lymphocyte (Treg) maturation and function.

## The role of histamine H4 receptor in modulation of lymphocyte function

Described in 2000 by Oda *et al.*, the new histamine H4 receptor was also found on T lymphocytes [40]. The role of this receptor remains poorly understood. The first evidence concerning its role in modulation of T lymphocyte function was delivered by Gantner *et al.* in 2002. They observed that histamine stimulation of human CD8+ T lymphocytes purified from peripheral blood led to an increase in

the release of IL-16. This increase was significantly blocked by a histamine H2 receptor selective antagonist, or by a histamine H4 receptor antagonist. They also showed that selective agonists of H2 and H4 receptors were capable of inducing the release of bioactive IL-16 from CD 8+ T lymphocytes [41]. Localization of H4 and other histamine receptors is presented in Table I.

In 2006, Dunford *et al.* showed that H4 receptor-deficient mice and mice treated with H4 receptor antagonists exhibited decreased allergic lung inflammation. In mutant mice lacking H4 receptors the number of infiltrating lung eosinophils and lymphocytes was decreased and Th2 responses were also reduced. *Ex vivo* restimulation of T lymphocytes showed decreases in IL-4, IL-5, IL-13, IL-6, and IL-17 levels, suggesting that T cell functions were disrupted. *In vitro* studies indicated that blockade of H4 receptor on dendritic cells leads to reduction in cytokine and chemokine production and limits their ability to induce Th2 responses in T lymphocytes [42].

## Clinical experience

In 1988, Italian authors described a randomized trial, carried out in perennial atopic rhinitis. The patients were divided into two homogeneous groups and treated with histamine H2 antagonists of different chemical structure: cimetidine and ranitidine. Identity of clinical and humoral results was noted in the two groups. The results led the authors to believe that the effects induced by these two drugs are linked to the properties of H2 receptor antagonists and not to other potential action. The improvement in all subjective and objective parameters, decrease in total serum IgE, as well as the delayed onset of clinical improvement, suggested, according to the authors, that H2 receptor antagonists in fact induce a modulatory effect on the T lymphocyte subpopulations with a variation in the CD4+/CD8+ ratio towards the latter subpopulation that identifies the suppressor lymphocytes [43]. This study was questioned during the following years.

In 1992, Bury *et al.* showed that administration of histamine (inhaled and intravenous) causes inhibition of T cell proliferation. This effect occurred also after administration of H2 receptor agonists and was blocked by H2 receptor antagonists, while histamine H1 receptor ligands had no effect on T lymphocyte proliferation [44].

The long-term protection from honeybee stings by terfenadine premedication during rush immunotherapy with honeybee venom was analysed in a double-blind, placebo-controlled trial. After an average of 3 years, 41 patients were re-exposed to honeybee stings. None of the 20 patients who had been given H1 receptor antihistamine premedication, as compared to 6 of 21 given placebo, had

**Table I.** Histamine receptors localization

| Receptor | Localization |
| --- | --- |
| H1 | Vessels, smooth muscles, heart, central nervous system, macrophages, mastocytes, eosinophils, and Th lymphocytes |
| H2 | Heart, stomach, uterus, central nervous system, dendritic cells, neutrophils, macrophages, mastocytes, eosinophils, and Th lymphocytes |
| H3 | Respiratory tract, gastrointestinal tract and central nervous system |
| H4 | Bone marrow, spleen, thymus, colon, mastocytes, CD8+ lymphocytes, and neutrophils |

a systemic allergic reaction to the re-exposure by either a field sting or a sting challenge. This highly significant difference suggests that antihistamine premedication during the initial dose-increase phase may have enhanced the long-term efficacy of immunotherapy. Expression of H1 receptor on T lymphocytes is strongly reduced during ultra-rush immunotherapy, which may lead to the dominant expression and function of the tolerance-inducing H2 receptor. This indicates a positive role of histamine in immune regulation during systemic immunotherapy [45]. However, since publishing these data, no clinically significant effects of histamine receptor modulation in allergen-specific immunotherapy have been confirmed. The lack of evident proof of the clinical effectiveness of histamine receptor modulation leads to a conclusion that the results of *in vitro* studies cannot be transferred directly into a clinical setting.

## Histamine H1 and H2 receptors during pregnancy

Histamine receptors localized on T lymphocytes are also believed to participate in maintenance of pregnancy. Significantly reduced amounts of histamine H1 receptors were noted during the second trimester of pregnancy and this was associated with a decreased H1/H2 receptor ratio [46]. Women in the first and second trimester of pregnancy had greater histamine-induced suppression of phytohaemagglutinin (PHA)-stimulated proliferation at high concentrations of histamine, but less suppression at the lower concentrations in comparison to non-pregnant controls. In contrast, pregnant women studied in the third trimester failed to respond to any concentration of histamine. Recently, Pap *et al.* have shown that in the absence of local histamine the cytokine balance is shifted toward Th1 lymphocytes at the maternal-placental interface, threatening pregnancy, because successful pregnancy is closely related to polarization toward a Th2 type immune response in mice [46].

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Until now, the phenomena mentioned above remain poorly understood and need further research. Their clarification can bring progress in comprehending spontaneous abortion and lead to development of its prophylaxis or treatment.

## Conclusions

Histamine is one of the best-known and one of the most important biogenic amines in medicine and biology. Histamine, released during inflammation, interacts with histamine receptors and triggers vasodilatation, increases vascular permeability, and interacts with inflammatory cells, thus resulting in acute inflammatory and allergic responses as well as the chronic phase of inflammation. Its immunomodulatory effect, which depends mostly on the influence of histamine on T lymphocytes, is still not fully understood. Understanding histamine and histamine receptors as well as their role in modulation of T cell activity is very important for scientists and medical practitioners and can bring some clues for further investigation and for new therapeutic solutions in some illnesses such as allergies, autoimmune diseases and malignancies.

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