Histamine Downregulates the Th1-Associated Chemokine IP-10 in Monocytes and Myeloid Dendritic Cells

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Abstract
Background: Histamine is an important mediator of allergic diseases. It modulates the cytokine expression of various subtypes of antigen-presenting cells by four known receptors, H₁R–H₄R. The effects of histamine on myeloid dendritic cells (mDC) are unclear. Methods: Monocytes and mDC were isolated from human PBMC. Histamine receptor expression was evaluated by real-time PCR. Cells were stimulated with histamine and histamine receptor ligands, and restimulated with polyinosinic-polycytidylic acid (poly I:C), and supernatants were analyzed by protein array and ELISA. Results: Monocytes and mDC express H₁R and H₂R without significant differences between the two cell types, whereas H₃R mRNA was significantly higher in mDC compared with monocytes and H₄R mRNA was not detected in any cell type. Prestimulation with histamine caused a significant decrease in poly I:C-induced expression of interferon-γ-induced protein (IP-10) in mDC and monocytes. Stimulation with specific H₁R, H₂R and H₄R agonists and antagonists showed that the observed effect was mediated via H₂R and H₄R in monocytes and mDC. Conclusion: Monocytes and mDC have similar histamine receptor repertoires with regard to H₁R, H₂R and H₃R, but H₄R expression is higher on mDC. Histamine stimulation shows similar functional effects on both cell types, i.e., downregulation of TLR3-induced IP-10 production. This might be a new mechanism how histamine fosters a Th2 milieu.

Introduction
Histamine is a major mediator in allergic diseases and inflammatory processes, and it is involved in several physiological functions, e.g. differentiation and proliferation of cells, embryonic development, hematopoiesis and wound healing [1]. It plays an important role in acute inflammatory and immediate-type hypersensitivity responses as well as in chronic inflammation and delayed-type allergic reactions. Histamine concentrations are increased at sites of allergic reactions and inflammation, such as allergic asthma, atopic dermatitis (AD) or allergic contact dermatitis [2]. T helper cells are important for the initiation and regulation of immune responses. They can be divided into Th1 and
subsets are myeloid DC (mDC), characterized by CD11c + and CD123 –, which pick up antigens in the periphery and trigger immunity after migration to lymphoid organs. De-

The main function of these cells is their interaction with T cells: DC trigger the proliferation of specific T cells and they influence the type of T cell responses [11]. Various subtypes of DC are known. One of the main subsets are myeloid DC (mDC), characterized by CD11c+ and CD123+, which pick up antigens in the periphery and trigger immunity after migration to lymphoid organs. Depending on the antigen and other factors, mDC are capable to induce a Th1 or a Th2 cytokine pattern [12].

Whereas effects of histamine on monocytes and monocyte-derived DC (MoDC) have been investigated in previous studies [5, 13], there are no data on the effects of histamine on human mDC. Therefore, we compared histamine receptor expression and function between primary mDC and monocytes. First, we studied the expression of the four histamine receptors at mRNA level and showed that mDC and monocytes express similar repertoires for H1R, H2R and H3R, whereas H4R expression is higher on mDC compared with monocytes. Next, we performed a protein array to evaluate functional effects of histamine on the expression of cytokines and chemokines. Finally, we analyzed the newly observed downregulation of the Th1-associated chemokine IP-10 by histamine in more detail. We observed similar functional effects towards histamine stimulation with regard to IP-10 regulation. Thus, we show our data the similarity of monocytes and mDC with regard to histamine as well as a new mechanism that fosters a Th2 milieu induced by histamine.

Materials and Methods

**Isolation and Culture of Peripheral Blood Mononuclear Cells, Monocytes and mDC**

Peripheral blood mononuclear cells (PBMC) were isolated from buffy coats from anonymous healthy donors obtained from the local blood bank. PBMC were separated by density centrifugation on Lymphoprep (Fresenius Kabi Norge AS, Oslo, Norway) and erythrocytes were removed by Gey’s lysis. Monocytes and mDC [characterized by CD14 (BDCA-1)+ and CD141 (BDCA-3)+; CD11chigh, CD123low, CD32+, CD64+ and FcεR1+] were isolated from PBMC by negative isolation using magnetic cell sorting (MACS, Miltenyi Biotec Inc., Bergisch-Gladbach, Germany). 1 x 10⁶ PBMC were used per isolation and the procedure was executed on ice in the fridge. Cells were washed with MACS buffer and incubated with FcR blocking reagent and mDC antibody-biotin cocktail for 10 min. After centrifugation and two washing steps with MACS buffer, cells were subsequently incubated with anti-biotin MicroBeads for 15 min and separated by magnetic field. The unlabeled cells passing the column contained the desired mDC. Isolated mDC had a purity of at least 90% based on the expression of CD11c and CD141, and a lack of expression of CD3, CD14, CD16 and CD19 (fig 2b). Monocytes and mDC were cultured for the stimulation time in RPMI 1640 medium supplemented with 12 mM HEPES, 2 mM L-glutamine, 100 mg/ml penicillin/streptomycin, 5% v/v fetal calf serum (PAN-Biotech, all other components from Biocrom, Berlin, Germany) at 37 °C in a humidified atmosphere containing 5% CO₂.

**Proteome Analysis**

Isolated mDC (5 x 10⁴) were pretreated with 10⁻⁵M histamine (agonist for all histamine receptors; Alk-Scherax, Wedel, Germany) and stimulated with 10⁻⁵M polyninosinic-polycytidylic acid (poly I:C; Sigma-Aldrich, St. Louis, Mo., USA). Supernatants were collected after 24 h and five different independent experiments were pooled. This supernatant pool was analyzed with the Proteome Profiler™ human cytokine array panel A (R&D Systems, Minneapolis, Minn., USA). The probes were incubated for 1 h with a detection antibody cocktail and then the nitrocellulose membrane, containing 36 different anti-cytokine or anti-chemokine antibodies printed in duplicate, was incubated with 500 μl of the supernatants overnight at 4 °C. Immunoreactivity was detected by chemiluminescence according to the manufacturer’s instructions (Pierce, Thermo Fisher Scientific, Rockford, Ill., USA) and the intensity of the dot plots was evaluated by densitometric analysis with Chemilimager Software (Genetic Technologies, Miami, Fla., USA).

**mRNA Isolation, Reverse Transcription and Quantitative Real-Time PCR**

Monocytes and mDC were pretreated with histamine overnight and subsequently stimulated with 10⁻⁵M poly I:C. Cells were harvested and total RNA was isolated using a Quick-RNA™ MiniPrep kit including additional DNase digestion with DNase I (both ZymoResearch, Orange, Calif., USA). Reverse transcription was performed using a Quantitect reverse transcription kit (Qiagen, Hilden, Germany). Quantification of IP-10, the four histamine receptors and gyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA was performed on a LightCycler (Roche Molecular Biochemicals, Risch, Switzerland) using SYBR Green with QuantiTect primer assays (IP-10: QT01003065; H₄R: QT00199857; DOI: 10.1159/000355960

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H₃R: QT00210861, and GAPDH: QT01192646) according to the manufacturer’s protocol (Qiagen) or for H₂R and H₄R with designed primers (H₂R: 5′-TACCAGCTGTCCGAAATGCTGTCCTGCAAGTG-3′ and 5′-CCCCAGGTGGATAGCAAGAATGCTGTCCTGCAAGTG-3′, and H₄R: 5′-TGCTAGGAAATGCTGTCCTGTC-3′ and 5′-GGTTGAGGGATGTACAAAA-3′) [14] synthesized by Tib Molbiol (Berlin, Germany), under standard cycle conditions (annealing temperature 55°C). Melting curve analysis was performed from 60 to 90°C with a ramp rate of 20°C/s. For visualization of the amplified PCR products, agarose gel electrophoresis (2% agarose; Roth, Karlsruhe, Germany) was used for calculation and using the Relative Quantification Software (Roche Molecular Biochemicals).

Enzyme-Linked Immunosorbent Assay

Protein expression of IP-10 was analyzed after 24 h by ELISA. 0.5 to 1 × 10⁵ mDC and 3 × 10⁵ monocytes were seeded per well in 96-well plates and were preincubated overnight with histamine (Alk-Scherax) or one of the histamine receptor agonists (H₁R antagonist levocetirizine; UCB, Anderlecht/Brüssel, Belgium; H₂R antagonist ranitidine; Biomol, Hamburg, Germany, and H₄R antagonist JNJ7777120; Sigma Aldrich).

Statistical Analysis

Data are expressed as means ± SEM. A Wilcoxon matched pair test (fig. 1 and 3a mDC) or paired t test (fig. 3–6) was applied to determine statistically significant differences; a value of p < 0.05 was considered statistically significant. GraphPad Prism® (version 5; GraphPad Software, San Diego, Calif., USA) was used for statistical analysis.

Results

H₁R, H₂R and H₄R Expression on mDC and Monocytes

First we analyzed the expression of the four different HR in monocytes and mDC. Real-time PCR was performed and the amplified products were analyzed by LightCycler melting curves and agarose gel electrophoresis, where sharp bands at the expected sizes could be demonstrated (fig. 1a). The majority of monocytes expressed more H₁R receptor compared with mDC, but the experiments were inconsistent and the difference not statistically significant (fig. 1b). H₂R mRNA was detected at similar amounts and no mRNA for H₄R was detected in both cell types. With respect to H₄R, we observed a significantly higher expression pattern on mDC compared with monocytes (fig. 1b).

Effects of Histamine on Chemokine and Cytokine Expression on mDC

To assess the effects of histamine on mDC, we performed a proteome array. We stimulated mDC with poly I:C or with poly I:C and histamine. We pooled the cell-free supernatants from five different cell preparations. Proteome analysis revealed the regulation of different cytokines and chemokines and we observed upregulation of the poly I:C-induced CXCL1 expression (poly I:C + histamine results in 120% densitometry compared to stimulation with poly I:C only) and a downregulation of poly I:C-induced expression of TNF-α (76%), CCL1 (78%), IL-6 (46%) and IP-10 (63%) following preincubation with histamine by densitometry (fig. 2a).

Inhibitory Effect of Histamine on Poly I:C-Induced Expression of IP-10

To confirm our observations from the protein array and to gain a deeper insight, we analyzed the effect of different histamine concentrations (10⁻⁵–10⁻⁸ M). As shown in figure 3a in mDC, histamine concentrations from 10⁻⁶ to 10⁻⁸ M led to a significant downregulation of IP-10. Also, in monocytes, it was possible to inhibit the production of IP-10 by histamine concentrations from 10⁻⁵ to 10⁻⁷ M (fig. 3a).

To analyze the time dependence of the poly I:C-induced IP-10 expression, monocytes were preincubated with histamine and incubated for different time periods with poly I:C. IP-10 mRNA was detected after 2, 4, 6 and 8 h and maximal mRNA expression was reached after 4 h. Subsequently, we analyzed the IP-10 protein in supernatants between 2 and 24 h. Protein expression peaked at 24 h. At all measured time points, we could observe a significant downregulation of IP-10 by histamine at the protein level, while at the mRNA level a difference was only detected for the first three time points between 2 and 6 h (fig. 3b).

Effect of H₂R and H₄R on Poly I:C-Induced Expression of IP-10 on Monocytes and mDC

To analyze which receptor is at the functional level responsible for the observed effects of histamine, we performed experiments with specific agonists and antagonists. We demonstrated that amthamine (H₂R agonist) and ST1006 (H₄R agonist) mimic the histamine effect on IP-10 expression in both monocytes and mDC (fig. 4). To verify these observations, we incubated the cells for
Fig. 1. mDC and monocytes express the histamine receptors H1R, H2R and H4R at mRNA level. a Representative real-time LightCycler PCR melting peaks and agarose gel bands with the correct size of the amplified PCR products (H1R = 116 bp, H2R = 239 bp, H3R = 150 bp, H4R = 130 bp and GAPDH = 119 bp) of histamine receptors and GAPDH of 7 independent experiments are presented. As positive control for H3R amplification H3R-transfected HEK cells were used. b Both cell types were isolated from PBMC and mRNA expression for H1R, H2R, H3R and GAPDH was analyzed by LightCycler PCR. The relative amounts of the different receptors in monocytes and mDC were determined to a calibrator and normalized to GAPDH. mDC expressed less H1R mRNA, equal amounts of H2R mRNA and significantly more H4R mRNA compared to monocytes. Results of 9 (H1R and H4R) or 12 (H2R) independent experiments are shown. *p < 0.05 (Wilcoxon matched pair test).
30 min with specific receptor antagonists before they were stimulated with histamine. In monocytes, blockade of H$_2$R with ranitidine as well as of H$_4$R with JNJ7777120 abolished the histamine effect. However, in mDC the histamine effect could be reversed only by blocking H$_4$R with JNJ7777120 (fig. 5). As both cell types also express H$_1$R, we performed experiments with a specific H$_1$R agonist and antagonist. With these ligands, no effects were observed in both monocytes and mDC (fig. 6). Taken together, the results with agonists and antagonists showed that IP-10 expression is regulated via H$_2$R and H$_4$R stimulation in these two cell types.

**Discussion**

In the immune system, histamine plays a role as an important mediator of inflammation and allergic diseases, and the development of some infections and allergic reactions is associated with a substantial production of histamine. It is also known that histamine modulates the function and activity of different cells of the immune system, including T lymphocytes and APC. Therefore, we focused our study on the expression pattern of histamine receptors and histamine effects on mDC, a major subpopulation of APC. Monocytes and mDC are human blood cell subpopulations and have the same myeloid descent from bone marrow stem cells, so they are related with each other [16]. Since mDC represent a rather small fraction of around 0.5% of PBMC [17], most previous investigations used in vitro generated MoDC as a model to determine the effects of histamine on the expression and function on mDC [5, 18–20]. MoDC have differentiated from monocytes in vitro using a cytokine cocktail, most commonly IL-4 and granulocyte/macrophage colony-stimulating factor, and incubation results in so-called immature DC with high antigen-processing capacity and poor capability for T cell activation [21, 22]. To eliminate possible effects of this in vitro generation and to get a more realistic view of the natural conditions, we isolated mDC directly from human blood by negative magnetic separation from PBMC. These cells represent the natural mDC population and were compared in our experiments to monocytes from the same donors. In earlier studies, other subtypes of DC and monocytes expressed the histamine receptors H$_1$R, H$_2$R and H$_4$R [23]. The results of our present study demonstrated that mDC and monocytes also expressed three different histamine receptors at mRNA level (H$_1$R, H$_2$R and H$_4$R). Comparing monocytes and...
**Fig. 3.** The expression of IP-10 occurs in a concentration- and time-dependent manner. ns = Nonstimulated. **a** Monocytes and mDC were pretreated overnight with different concentrations of histamine (Hista; 10⁻⁵–10⁻⁸ M) and then stimulated for 24 h with 10⁻⁵ M poly I:C. The content of IP-10 in supernatants was detected by ELISA (means and SEM of 6 independent experiments). Histamine significantly and dose-dependently decreased IP-10 release from human monocytes (mean ± SEM at 24 h of poly I:C = 2,119 ± 570 pg/ml, range 606–4,211 pg/ml) and mDC (mean ± SEM at 24 h of poly I:C = 4,302 ± 1,127 pg/ml, range 1,509–9,142 pg/ml) in response to poly I:C. **b** Monocytes were pretreated with 10⁻⁵ M histamine overnight and then stimulated for different time points with 10⁻⁵ M poly I:C. mRNA expression was detected by RT-PCR and peaked after 4 h (mean ± SEM at 4 h of poly I:C = 257 ± 120 relative mRNA expression, range 6–714; mean ± SEM at 4 h of poly I:C + 10⁻³ M histamine = 122 ± 89 relative mRNA expression, range 3–552). Expression of IP-10 at protein level was detected in supernatants by ELISA (means and SEM of 6 independent experiments) and peaked after 24 h (mean ± SEM at 24 h of poly I:C = 2,119 ± 570 pg/ml, range 606–4,211 pg/ml). * p < 0.05, ** p < 0.01 poly I:C vs. poly I:C + histamine.

**Fig. 4.** Different histamine (Hista) receptor agonists mimic the histamine effect of downregulating IP-10 protein production in monocytes (**a**) and mDC (**b**). Monocytes and mDC were pretreated overnight with 10⁻⁵ M histamine or a specific histamine receptor agonist and then stimulated for 24 h with 10⁻⁵ M poly I:C. The content of IP-10 in supernatants was detected by ELISA (means and SEM of 8 (mDC) or 10 (monocyte) independent experiments are shown). **a** In monocytes, both the H₂R agonist amthamine (Amtha) and the H₄R agonist ST1006 mimics the histamine effect on the IP-10 expression (mean ± SEM at 24 h of poly I:C = 2,273 ± 449 pg/ml, range 738–5,038 pg/ml). **b** In mDC, H₂R (Amtha) and H₄R (ST1006) agonists imitate the histamine effect of reduced IP-10 protein expression (mean ± SEM at 24 h of poly I:C = 2,710 ± 715 pg/ml, range 682–6,376 pg/ml). * p < 0.05, ** p < 0.01. ns = Nonstimulated.
mDC, in most donors, monocytes expressed more H₁R than mDC. The amounts of H₂R were not different between the two cell types. This is consistent with our previous finding that compared to monocytes MoDC downregulate H₁R mRNA but not H₂R mRNA [13]. In contrast, we were unable to detect H₃R mRNA in both cell types, although other studies reported H₃R expression on monocytes and MoDC [5, 18]. However, H₃R is a presynaptic autoreceptor which is mainly present in the peripheral and central nervous system. The expression of H₄R mRNA was significantly higher in mDC than monocytes. This is consistent with our previous observation that compared to monocytes in vitro MoDC upregulate H₄R during their differentiation [5].

Histamine can modulate T helper cell responses, influence antigen presentation capacity and enhance proinflammatory cytokine production [6]. Histamine is a factor for DC polarization but not for DC maturation [20, 24], and mediates its influence on the Th1/Th2 balance through several effects on different cell types and through involvement of different histamine receptors. DC are of-

**Fig. 5.** Different histamine receptor antagonists blocked the downregulation of IP-10 protein by histamine (Hista) in monocytes (a) and mDC (b). Monocytes and mDC were pretreated for 30 min with 10⁻⁵ M of the specific antagonist and subsequently incubated overnight with 10⁻⁵ M histamine. The next day, cells were stimulated for 24 h with 10⁻⁵ M poly I:C. The content of IP-10 in supernatants was detected by ELISA (mean and SEM of 7 independent experiments are shown). ns = Nonstimulated. a In monocytes, both antagonists for H₂R (ranitidine) and for H₄R (JNJ7777120) reverse the histamine effect of reduced IP-10 protein expression (mean ± SEM at 24 h of poly I:C = 2,565 ± 613 pg/ml, range 738–5,038 pg/ml). b In mDC, only the H₄R antagonist JNJ7777120 can reverse the effect of histamine (mean ± SEM at 24 h of poly I:C = 2,180 ± 746 pg/ml, range 599–6,144 pg/ml). * p < 0.05, ** p < 0.01.

**Fig. 6.** H₁R is not involved in the regulation of poly I:C-induced IP-10 expression. Monocytes (a) and mDC (b) were treated in the presence or absence of the H₁R antagonist levocetirizine (Levo) with histamine (Hista) or the H₁R-specific agonist 2-pyridylethylamine (2-Pyr) overnight. Then cells were stimulated for 24 h with 10⁻⁵ M poly I:C. The content of IP-10 in supernatants was detected by ELISA (mean and SEM of 8–13 independent experiments are shown). The results show no significant involvement of H₁R in monocytes (mean ± SEM at 24 h of poly I:C = 2,893 ± 573 pg/ml, range 283–5,594 pg/ml) and mDC (mean ± SEM at 24 h of poly I:C = 1,789 ± 549 pg/ml, range 305–4,508 pg/ml; * p < 0.05, ** p < 0.01). ns = Nonstimulated.
found predominantly on Th1 lymphocytes and neutrophils, and CXC receptors are involved in the Th1/Th2 balance by an upregulation of the Th2 attractants CCL17 and CCL22 and the downregulation of IFN-γ-induced IP-10 in immature human MoDC through involvement of H2R. In other cell types, we were able to show that H2R and H4R stimulation led to downregulation of cytokine and chemokine production, e.g. of TNF-α, CXCL8 and IFN-α in plasmacytoid DC and of IL-27 in monocytes [28, 29]. van der Pouw Kraan et al. [30] demonstrated that histamine inhibits the production of IL-12 via stimulation of H2R in monocytes. Also, in whole blood cultures, histamine dose-dependently increases IL-10 expression and significantly decreases IL-12 after lipopolysaccharide treatment via H2R stimulation [31]. Another mechanism for the influence of Th1/Th2 polarization is the DC type. Subtypes of DC (DC1 and DC2) have been characterized that stimulate either a Th1 or Th2 response, respectively [32]. DC1 have a high expression of H1R and histamine acts as a stimulus for increased antigen presentation capacity, enhanced production of pro-inflammatory cytokines and Th1 priming activity. In DC2, histamine plays a suppressive role on antigen-presenting ability, increases IL-10 production and induces Th2 cells via H2R [6]. Taken together, histamine is a potent mediator that primes DC to induce Th2 polarization [24, 32].

To evaluate the functional role of histamine on mDC, we used a protein array to study the effects of histamine on cytokine and chemokine expression on mDC. We observed a regulation of the expression of CXCL1, TNF-α, CCL1, IL-6 and IP-10 through histamine. The expression of the C-X-C motif chemokine 10 (CXCL10), also called IP-10, is associated with inflammation. This chemokine is released from different cell types, e.g. monocytes, DC, endothelial and epithelial cells and keratinocytes, in response to IFN-γ [33]. CXCL chemokines primarily attract Th1 lymphocytes and neutrophils, and CXC receptors are found predominantly on Th1 lymphocytes [34]. Twenty to 40% of circulating Th1 lymphocytes express CXC receptors, whereas Th2 lymphocytes express predominantly CC chemokine receptors [35]. Due to the important role of IP-10 in inflammation and as a key chemokine for the recruitment of Th1 lymphocytes into tissue and the association of IP-10 with inflammatory and allergic diseases, including allergic contact dermatitis, allergic pulmonary inflammation and AD [36–39], we chose IP-10 as a target for further investigations. For the first time, we describe an influence of histamine on poly I:C-induced expression of IP-10 in natural untouched mDC. Our results fit well in the picture that histamine exerts anti-inflammatory effects and promotes a Th2 milieu via H2R and H4R.

H2R and H4R might be new therapeutic targets also in allergic diseases such as AD. Potential antagonists of H2R and H4R mediate their therapeutic potential through alleviation of Th1 responses by targeting the expression of relevant cytokines such as IP-10 or IL-12. Thus, H2R and H4R antagonists might be useful for the treatment of allergic and inflammatory disorders with Th2 predominance, such as AD.

Since IP-10 is a Th1 chemokine and plays an important role in numerous diseases, first studies evaluating IP-10 as a therapeutic target are in progress. Fife et al. [40] showed that the application of an anti-IP-10 antibody resulted in a decreased clinical and histological manifestation of experimental autoimmune encephalomyelitis. Blocking of IP-10 and CXCR3 reduced inflammatory colitis in mice [41].

In summary, our study demonstrates that mDC as another APC subpopulation express H1R, H2R and H4R. In addition, the histamine-induced downregulation of IP-10 via H2R and H4R might affect the regulation of the Th1/Th2 balance. These results improve the understanding of immunological functions of histamine and suggest that specific receptor antagonists might be candidates for pharmacological treatment to inhibit the Th2 shift in inflammatory and allergic disorders.

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Histamine Downregulates IP-10 in APC


