

Expression and function of histamine receptors in human monocyte-derived dendritic cells

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Background: Histamine is a well-known mediator eliciting different responses in immune and nonimmune cells, but its role in modulating dendritic cell (DC) functions has been marginally investigated.

Objective: The purpose of this investigation was to analyze whether human monocyte-derived DCs express functional histamine receptors according to their maturation stage.

Methods: DCs were derived from monocytes and used as immature or LPS-differentiated cells. DCs were tested for histamine receptor expression, chemotaxis, cytokine release, and the capacity to induce T-cell differentiation in response to specific histamine receptor agonists.

Results: Immature and mature DCs expressed the mRNA for H₁, H₂, and H₃ histamine receptors. Histamine induced intracellular Ca²⁺ transients, actin polymerization, and chemotaxis in immature DCs. Maturation of DCs resulted in the loss of these responses. In maturing DCs, however, histamine dose-dependently enhanced intracellular cAMP levels and stimulated IL-10 secretion while inhibiting production of IL-12. As a consequence, histamine might contribute to the impairment of generation of allogeneic type 1 responses via maturing DCs. Specific histamine receptor agonists or antagonists revealed that Ca²⁺ transients, actin polymerization, and chemotaxis of immature DCs were due to stimulation of H₁ and H₃ subtypes. Modulation of IL-12 and IL-10 secretion by histamine involved the H₂ and H₃ receptors exclusively.

Conclusions: Our study suggests that histamine has important biological effects on DC activities, opening the possibility that

histamine released during inflammatory or immune responses could regulate DC functions and ultimately favor type 2 lymphocyte-dominated immunity. (*J Allergy Clin Immunol* 2002;109:839-46.)

Key words: Dendritic cells, histamine, T cells, IL-10, IL-12, chemotaxis

Dendritic cells (DCs) are antigen-presenting cells that specialize in the activation of naive T lymphocytes and the initiation of immune responses.^{1,2} Immature DCs reside in most tissues, where they are adapted to capture antigens and are alert for danger signals, such as microorganisms, inflammatory cytokines, and cell necrosis.³ On exposure to these factors, DCs undergo maturation, a process that involves acquisition of high levels of membrane MHC and costimulatory molecules and the production of a broad panel of cytokines, including TNF- α , IL-10, and IL-12.¹ Mature DCs also change the pattern of chemokine receptors⁴ and have a propensity to migrate to secondary lymphoid organs, where they direct the development of immune responses.² A large number of DCs are present in lesional skin of patients with atopic dermatitis.⁵ It is thought that in atopic diseases DCs present efficiently IgE-bound allergens to T lymphocytes, triggering an allergen-specific T_H2 immune response.^{5,6}

Histamine is a preformed mediator that is stored primarily in the cytoplasmic granules of basophils and mast cells.⁷ It is released on activation of IgE receptors or stimulation with degranulating agents, such as complement components, neuropeptides, and cytokines. Histamine plays an essential role in acute allergic reactions and inflammation, but it is also involved in cell-mediated immunity.⁸⁻¹⁰ Three classic G protein-coupled histamine receptor subtypes, designated H₁, H₂, and H₃, have been thoroughly described pharmacologically,¹¹ and a fourth member of the histamine family, the H₄ receptor, has recently been identified.¹² At the moment, the pharmacologic properties of this novel receptor are not fully understood, and reports regarding pharmacologic characterization, binding experiments, and the analysis of signal transduction mechanisms in recombinant systems are at least partially contradictory.¹² The H₁ receptor mediates most of the proinflammatory effects of histamine. Anti-inflammatory and immunosuppressive effects of his-

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Abbreviations used

DC: Dendritic cell
f-actin: Filamentous actin
MIP: Macrophage inflammatory protein
R- α -MeH: (R)- α -methyl-histamine

mine, such as inhibition of polymorphonuclear chemotaxis¹³ and monocyte IL-12 secretion,¹⁴ as well as induction of IL-10 production,¹⁴ are mostly dependent on stimulation of the H₂ receptor, which is coupled to the adenylyl cyclase pathway. The H₃ receptor elicits an increase in intracellular calcium concentration and regulates cytokine release in alveolar macrophages and mast cells.¹⁵ Recently, induction of CD86 expression and chemokine production by histamine in immature DCs as well as polarization of mature DCs in T_H2-promoting effector cells has been shown.¹⁶⁻¹⁸ However, there exists a discrepancy with respect to the mRNA expression of the H₃ receptor between 2 previous publications.^{17,18}

In the present study, we demonstrate that histamine induced intracellular Ca²⁺ concentration transients, actin polymerization, and chemotaxis in immature DCs but not in mature DCs via activation of H₁ and H₃ receptors. In maturing DCs, histamine promoted cAMP increase and IL-10 production, whereas IL-12 secretion was inhibited. Histamine-mediated effects on cAMP and IL-10, as well as inhibition of IL-12 secretion, were mainly mediated by H₂ and H₃ receptors. Finally, histamine depressed the capacity of mature DCs to initiate allogeneic T_H1 responses, suggesting that histamine might represent an important factor influencing the polarization of immune responses.

METHODS**Reagents**

Histamine, betahistine, and recombinant human complement fragment 5a (C5a) were obtained from Sigma (Deisenhofen, Germany); RANTES (CCL5) and macrophage inflammatory protein-3 β (MIP-3 β /CCL19) were obtained from PeproTech (London, United Kingdom); and dimaprit, (R)- α -methyl-histamine (R- α -MeH), diphenhydramine, cimetidine, and thioperamide were purchased from ICN Biomedicals (Costa Mesa, Calif).

Preparation of human DCs

PBMCs were separated from buffy coats through use of Ficoll-Paque gradients (Amersham-Pharmacia Biotech AB, Uppsala, Sweden). Cells were further separated with anti-CD14 mAb-coated MicroBeads through use of Macs single-use separation columns from Miltenyi Biotec (Bergisch Gladbach, Germany). The CD14⁺ cells were resuspended in RPMI 1640 medium containing 10% FCS, 1% glutamine, 50 IU/mL penicillin, 50 μ g/mL streptomycin (all from Life Technologies GmbH, Karlsruhe, Germany), 1000 U/mL IL-4, and 200 ng/mL GM-CSF (Natutec, Frankfurt, Germany). After 6 days of culture, cells were >95% CD1a⁺ and CD14⁻. Further maturation was obtained by incubating DCs with 3 μ g/mL LPS (Sigma Chemicals, St Louis, Mo) for 24 hours. Mature DCs expressed CD83 and upregulated expression of HLA-DR, CD54, CD80, and CD86 molecules, as assessed by means of flow cytometry analysis. All mAbs and the respective isotype-matched controls were from Coulter-Immunotech (Krefeld, Germany).

Detection of mRNA by RT-PCR analysis

mRNA was isolated through use of QIAshredder and RNeasy kits (Qiagen, Hilden, Germany). mRNA, M-MLV reverse transcriptase, and pd(N)₆ primers (GIBCO BRL, Gaithersburg, Md) were used to obtain cDNA. Primer sequences were as follows:

H₁ receptor (403 bp product): sense, 5'-CATTCTGGGGGC-CTGGTTCTCT-3'; antisense, 5'-CTTGGGGGTTTGGGATG-GTGACT-3'

H₂ receptor (497 bp product): sense, 5'-CCCGGCTCCGCAAC-CTGA-3'; antisense, 5'-CTGATCCCGGGCGACCTTGA-3'

H₃ receptor (589 bp product): sense, 5'-CAGCTACGAC-CGCTTCTTGTC-3'; antisense, 5'-GGAGCCCTTCTTGAGT-GAGC-3'

β_2 -microglobulin (259 bp product): sense, 5'-CCTTGAGGC-TATCCAGCGTA-3'; antisense, 5'-GTTCACACGGCAGGCAT-ACT-3'.

Thirty-five PCR cycles were run at 94°C (denaturation, 1 minute), 62°C (annealing, 1 minute), and 72°C (extension, 1 minute). PCR products were subjected to electrophoresis on a 2% agarose gel and visualized by means of ethidium bromide staining. Identity of the PCR products was confirmed by sequencing after cloning. A control run without reverse transcriptase yield no PCR products.

Intracellular Ca²⁺ ([Ca²⁺]_i) changes measurement

Ca²⁺ transients were measured in DCs loaded with the Ca²⁺ indicator Fura-2/AM (Calbiochem, La Jolla, Calif), as described previously.¹⁹

Actin polymerization

The content of filamentous actin (f-actin) was analyzed by means of flow cytometry with NBD-phalloidin staining, as described previously.¹⁹ The relative f-actin content in comparison with medium is given.

Migration assay

Experiments were performed in a 48-well chamber through use of a 10- μ m-thick polycarbonate membrane with 5- μ m pores. Migrated DCs on the lower side of the membrane were quantified.¹⁹

Measurement of intracellular cAMP

Intracellular cAMP levels were determined by means of enzyme immunoassay (Amersham Pharmacia Biotech AB), as described previously.¹⁹

Cytokine assays

IL-10 was measured in DC supernatants by means of ELISA through use of a matched pair of mAbs from BD PharMingen (San Diego, Calif). IL-12 (p70) was measured through use of an OptiEIA kit from BD PharMingen. Samples were assayed in triplicate for each condition.

T-cell differentiation assay

T lymphocytes were separated by Percoll gradients and immunomagnetic depletion through use of a mixture of anti-HLA-DR and anti-CD19 mAb-conjugated beads (Dynal, Oslo, Norway). Allogeneic naive T cells were generated through use of anti-CD45RO mAb and goat antimouse immunoglobulin-coupled immunomagnetic beads and then cocultured with DCs in 1640 RPMI medium supplemented with 5% human serum and 30 U/mL IL-2 for 10 days. Thereafter, T cells were restimulated with 1 μ g/mL anti-CD3

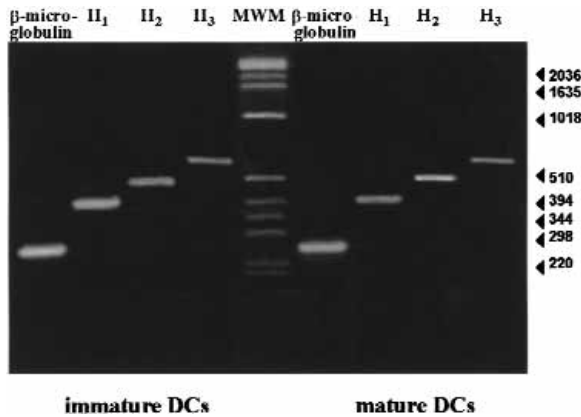


FIG 1. Human DCs express the mRNA for histamine receptors. DCs were prepared and matured as detailed in the Methods section. Experiments were repeated 5 times with identical results.

or 1 μ g/mL anti-CD28 mAb (BD PharMingen) and examined by means of flow cytometry for intracellular INF- γ and IL-4 after 6 hours through use of FITC- and PE-conjugated antibodies.²⁰

Statistical analysis

Unless otherwise stated, data are expressed as means $\pm$ SEMs. ANOVA was used to compare experimental groups with controls. When the global test of differences was significant at the 5% level, pairwise tests of differences between groups were applied (Tukey's multiple comparison test).

RESULTS

Histamine induces intracellular Ca^{2+} mobilization and actin polymerization in immature DCs but not in mature DCs

Expression of mRNA for the different histamine receptor subtypes was analyzed in immature and mature DCs by RT-PCR. Fig 1 shows no major changes in the amounts of mRNA for the H_1 , H_2 , and H_3 histamine receptor subtypes in immature and LPS-matured DCs.

Stimulation of immature DCs with histamine induced a rapid and dose-dependent $[Ca^{2+}]_i$ increase, with maximal and half-maximal responses at 10^{-6} mol/L and 10^{-10} mol/L histamine concentrations, respectively (Fig 2, A). To identify the histamine receptor subtypes, DCs were stimulated with selective histamine receptor agonists. Fig 2, B shows that the H_1 agonist betahistine induced a spiking Ca^{2+} rise that was followed by a slow declining phase. In addition, the H_3 agonist R- α -MeH was able to increase $[Ca^{2+}]_i$ levels in a dose-dependent manner (Fig 2, C). In contrast, the H_2 agonist dimaprit triggered a small Ca^{2+} increase only at high concentrations (10^{-2} mol/L); this could be completely abrogated by the H_3 antagonist thioperamide (data not shown), indicating that dimaprit activated at high concentrations the H_3 receptor subtype. The activity of the other receptor subtype agonist could be blocked only by the specific-receptor antagonists (data not shown). Stimulation of DCs with histamine, betahistine, or R- α -MeH in a Ca^{2+} -free ethyleneglycol-bis-(β -aminoethylether)-N,N,N',N'-tetraacetic acid (EGTA)-

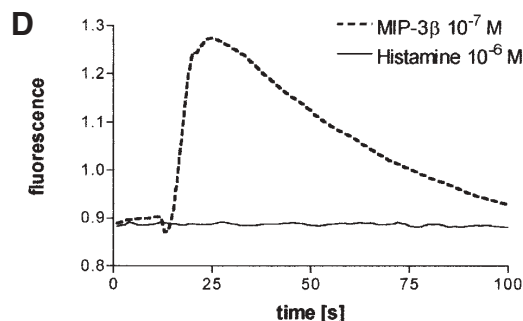
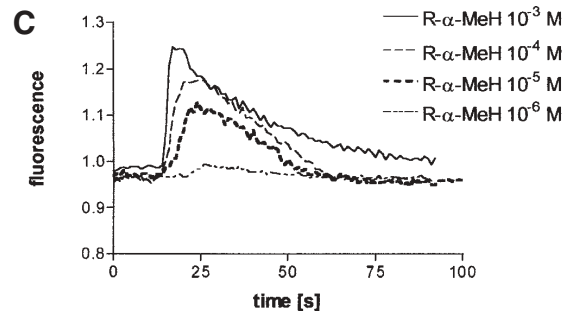
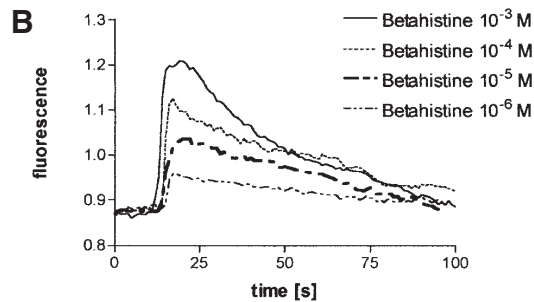
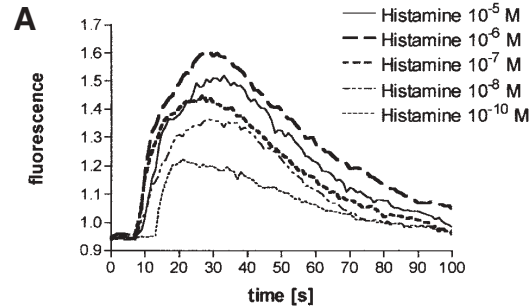


FIG 2. Histamine induces $[Ca^{2+}]_i$ transients in immature DCs but not in mature DCs. Immature (A-C) and LPS-matured DCs (D) were loaded with Fura-2/AM and stimulated with different concentrations of histaminergic agonists. **A**, Histamine. **B**, Betahistine (H_1 receptor agonist). **C**, R- α -MeH (H_3 agonist). **D**, MIP-3 β , but not histamine, induces Ca^{2+} transients in mature DCs. One representative of 7 similar experiments is shown.

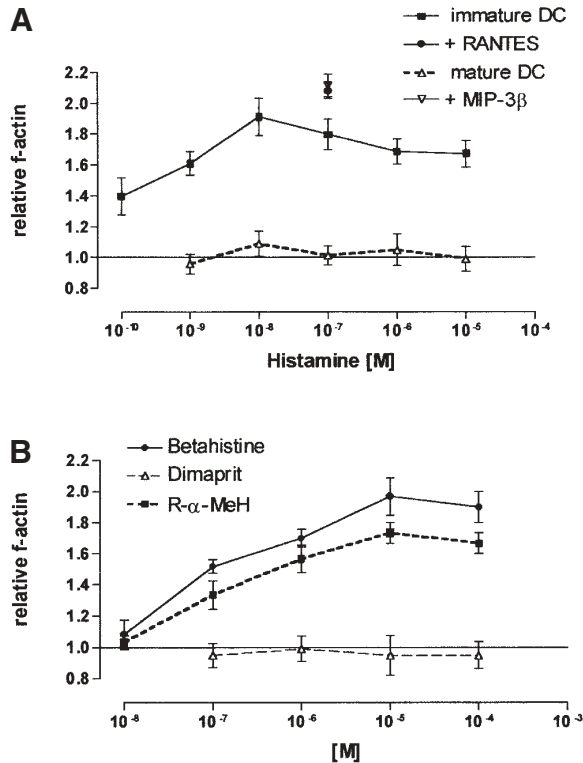


FIG 3. Histamine induces actin polymerization in immature DCs but not in mature DCs. **A**, Cells were stimulated with grading doses of histamine. **B**, Betahistine and R-α-MeH, but not dimaprit (H_2 receptor agonist), induce actin polymerization in immature DCs. The relative f-actin content was analyzed by means of flow cytometry after 25 seconds, as reported in the Methods section. Control experiments with RANTES (100 ng/mL) in immature DCs and with MIP-3β (100 ng/mL) in mature DCs showed relative f-actin content values of 2.12 ± 0.07 and 2.16 ± 0.08 , respectively. Data are expressed as means $\pm$ SEMs ($n = 5$).

containing saline solution (4 mmol/L EGTA) did not abrogate the histamine-induced $[Ca^{2+}]_i$ increase, suggesting that the Ca^{2+} rise was due to Ca^{2+} mobilization from the intracellular stores (data not shown). Strikingly, histamine did not elicit Ca^{2+} transients in mature DCs (Fig 2, *D*), whereas MIP-3β was effective in inducing this response. A dose-dependent effect of histamine on actin polymerization is shown in Fig 3, *A*. Histamine caused a rapid actin polymerization in immature DCs but not in mature DCs, with a 50% increase in the f-actin content within 25 seconds after stimulation (data not shown). Maximal and half-maximal effects were observed at 10^{-8} mol/L and 10^{-9} mol/L histamine, respectively. An increase in f-actin was also induced by betahistine and R-α-MeH but not by dimaprit, in agreement with the lack of intracellular Ca^{2+} mobilization by this agonist (Fig 3, *B*). In contrast, no actin reorganization was seen in mature DCs on stimulation with histamine, though the chemokine MIP-3β induced actin polymerization in these cells (data not shown).

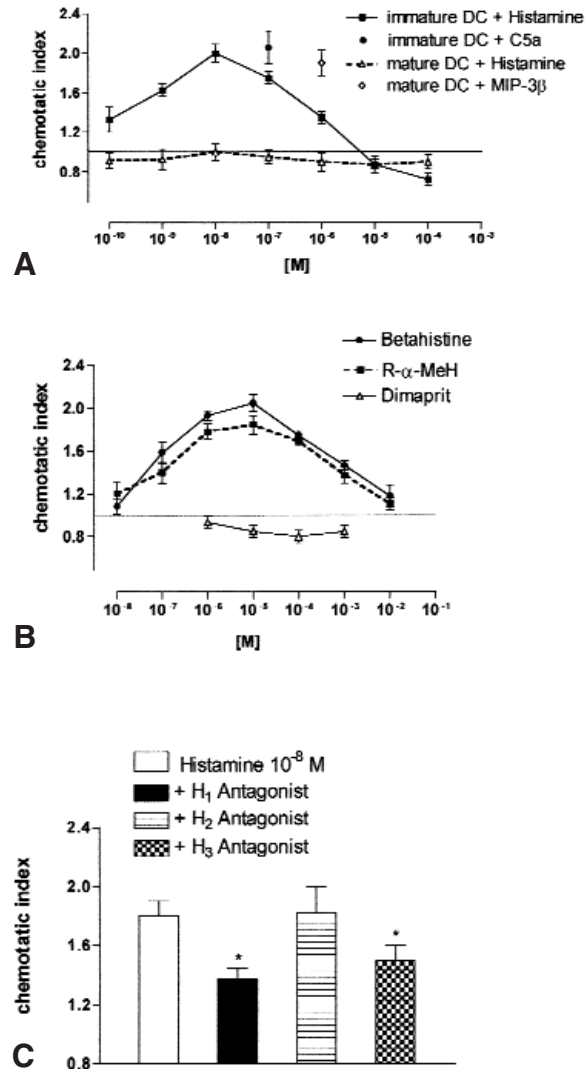


FIG 4. Histamine is chemotactic for immature DCs but not for mature DCs. Cells were exposed to the indicated histaminergic drugs at 37°C for 90 minutes in a Boyden chamber. The chemotactic index was calculated as reported in the Methods section. **A**, Histamine promotes the migration of immature DCs but not mature DCs. Control experiments with C5a in immature DCs and MIP-3β in mature DCs showed that both types of cells are able to migrate toward appropriate stimuli. **B**, The H_1 and H_3 receptor agonists, but not the H_2 agonist, are chemotactic for immature DCs. **C**, The H_1 and H_3 receptor antagonists, diphenhydramine and thioperamide, reduce the chemotactic activity of histamine. Data are expressed as means $\pm$ SEMs ($n = 5$). ** $P < .001$ and * $P < .01$ vs DCs treated with histamine alone.

Histamine is chemotactic for immature DCs but not for mature DCs

Recruitment of DCs into peripheral tissues and secondary lymphoid organs is driven by chemokine receptors expressed on the DC membrane.⁴ Immature DCs express CCR1, CCR5, and CCR6, whereas CCR7 (the

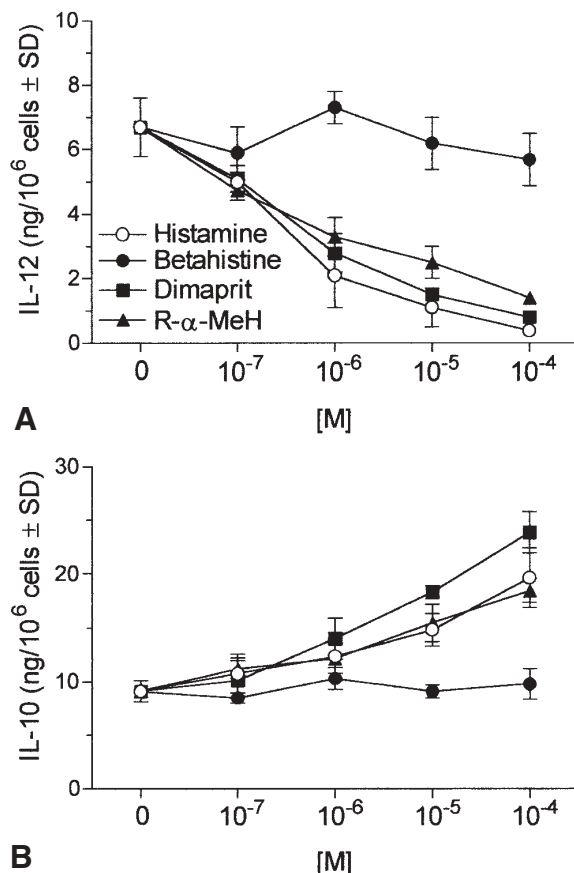


FIG 5. Histamine, dimaprit, and R- α -MeH inhibit IL-12 release (A) and stimulate IL-10 secretion (B) from maturing DCs. Cells were incubated with LPS in the presence or absence of the indicated agonists. Supernatants were collected after 24 hours, and cytokines were measured by ELISA. One representative of 3 or 4 similar experiments is shown.

ligand of MIP-3 β) is found only on mature DCs. However, several other molecules can also regulate DC migration, including platelet-activating factor, leukotrienes, complement fragments, sympathetic neurotransmitters, and sensory neuropeptides.²¹⁻²⁴ As shown in Fig 4, A, histamine was a strong chemotaxin for immature DCs, with a bell-shaped dose-dependent response curve (10⁻¹⁰ to 10⁻⁶ mol/L) and a potency comparable to that of C5a and RANTES. In contrast, mature DCs did not migrate in response to C5a and histamine, whereas they did so when stimulated with MIP-3 β . Incubation of immature DCs with the H₁ receptor agonist betahistine or the H₃ receptor agonist R- α -MeH induced migration of DCs, whereas the H₂ agonist dimaprit had no effect (Fig 4, B). Moreover, preincubation with diphenhydramine or thioperamide, which are H₁ and H₃ receptor antagonists, reduced the chemotactic activity of histamine (Fig 4, C); in contrast, the H₂ antagonist cimetidine was ineffective. Histamine receptor antagonists alone did not induce any DC migratory response (data not shown).

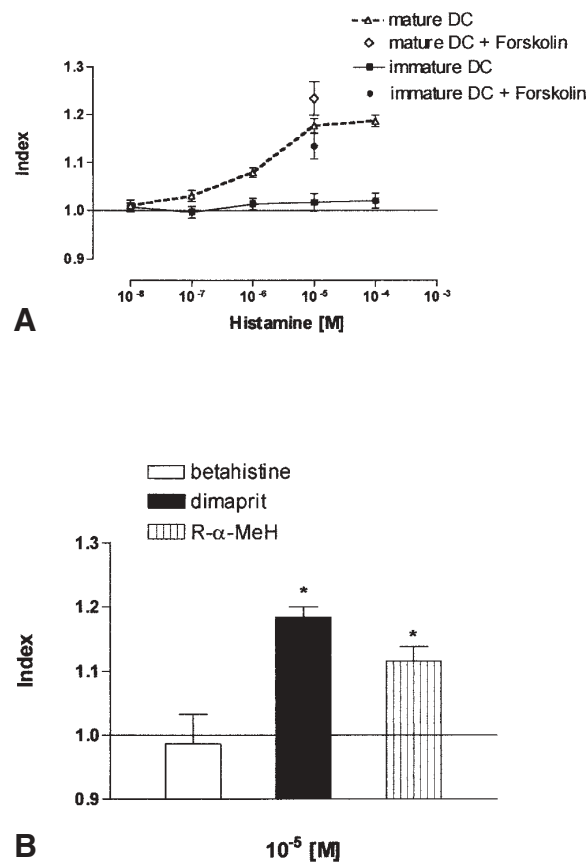


FIG 6. Histamine increases cAMP levels in mature DCs. **A**, Immature and mature DCs were treated with the indicated histamine concentrations. Forskolin (10⁻⁵ mol/L) was used as a positive control. **B**, Stimulation of mature DCs with dimaprit or R- α -MeH, but not with betahistine, also resulted in cAMP increase. The index was calculated as the ratio between stimulated cells and control medium. Data are means $\pm$ SEMs (n = 4). **P* < .05 vs untreated DCs.

Histamine reduces IL-12 production, augments IL-10 release from maturing DCs, and inhibits the capacity of mature DCs to induce type 1 responses

Recent evidence suggests that histamine modulates the production of cytokines in different cell types, including T cells, monocytes, endothelial cells, and fibroblasts.²⁵⁻²⁷ Fig 5, A shows that histamine added to LPS dose-dependently inhibited the production of IL-12 in maturing DCs. This effect was mimicked by the H₂ and H₃ receptor agonists dimaprit and R- α -MeH but not by the H₁ receptor agonist betahistine. In contrast, histamine, dimaprit, and R- α -MeH increased the release of IL-10 in maturing DCs, whereas betahistine was ineffective (Fig 5, B). Histamine did not affect basal cytokine production in immature DCs.

To gain insight into the mechanisms responsible for altered cytokine production by DCs exposed to histamine, we tested its capacity to modify cAMP levels. Fig

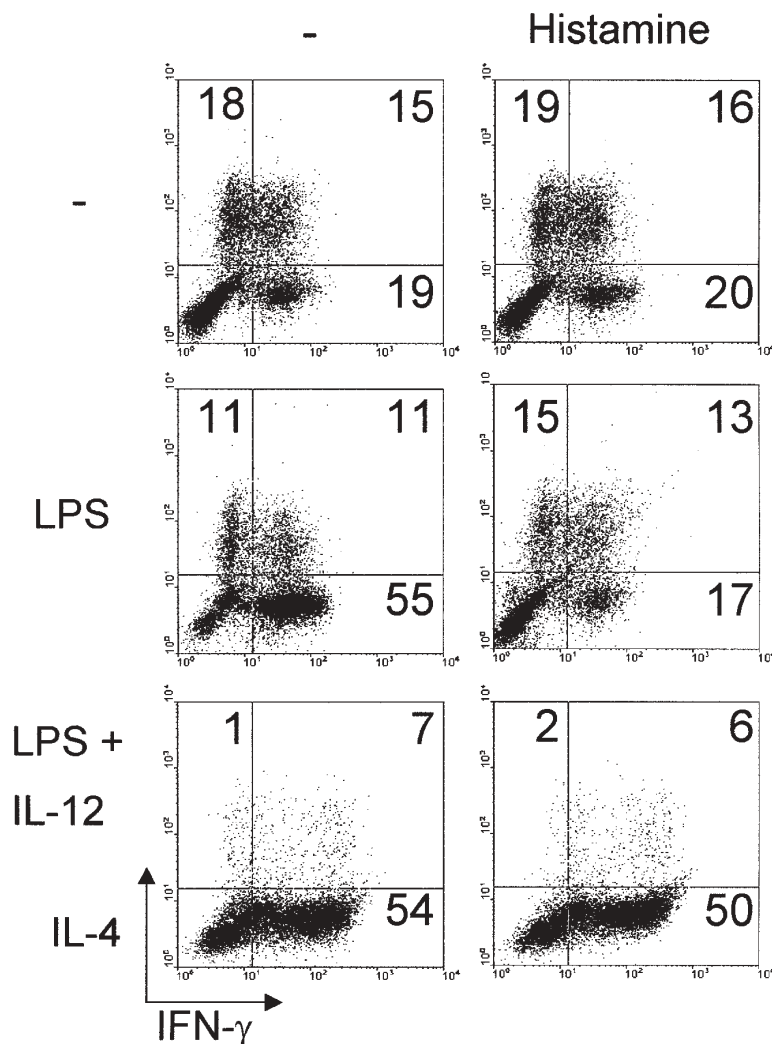


FIG 7. DCs matured in the presence of histamine are impaired in their capacity to initiate type 1 responses in vitro. Immature DCs were stimulated with and without 10^{-5} mol/L histamine in the presence or absence of LPS. After 24 hours, purified allogeneic CD45RA⁺ naive T lymphocytes were primed with generated DCs, and intracellular IFN- γ and IL-4 in T cells were analyzed by means of flow cytometry after 6 hours. Numbers indicate the percentages of positive cells in each quadrant. Data for 1 representative experiment are shown. Experiments were repeated 4 times with identical results, and the percentages of IFN- γ - and IL-4-producing T cells stimulated by mature DCs were $60\% \pm 12\%$ and $8\% \pm 5\%$, respectively (means $\pm$ SDs), whereas T cells activated by histamine-maturing DCs were $18\% \pm 5\%$ IL-4⁺ and $20\% \pm 6\%$ IFN- γ ⁺ (mean $\pm$ SD).

6, A reveals that activation of maturing DCs with histamine induced an increase in intracellular cAMP levels. In contrast, immature DCs did not show a cAMP rise when exposed to histamine (Fig 6, B), though they did respond when activated with 10^{-5} mol/L forskolin. In mature DCs, stimulation with dimaprit or R- α -MeH, but not stimulation with betahistidine, also resulted in cAMP increase (Fig 6, B), showing that H₂ and H₃ receptor subtypes were involved in this response.

IL-12 released by maturing DCs is the most important factor driving the differentiation of IFN- γ -producing type 1 cells.² Given the inhibitory effect of histamine on

IL-12 production by DCs, we examined the quality of the primary T-cell response induced by histamine-maturing DCs. Naive CD45RA⁺ allogeneic T cells primed with immature DCs differentiated to a similar extent into T_H2, T_H1, and T_H0 cells, whereas those stimulated with maturing DCs differentiated mainly into T_H1 lymphocytes, producing large amounts of IFN- γ and low levels of IL-4 (Fig 7). Histamine did not change the capacity of immature DCs to drive T-cell polarization. In contrast, T cells primed with histamine-maturing DCs displayed an impaired T_H1 polarization, similar to that obtained with immature DCs. Addition of recombinant IL-12 at the

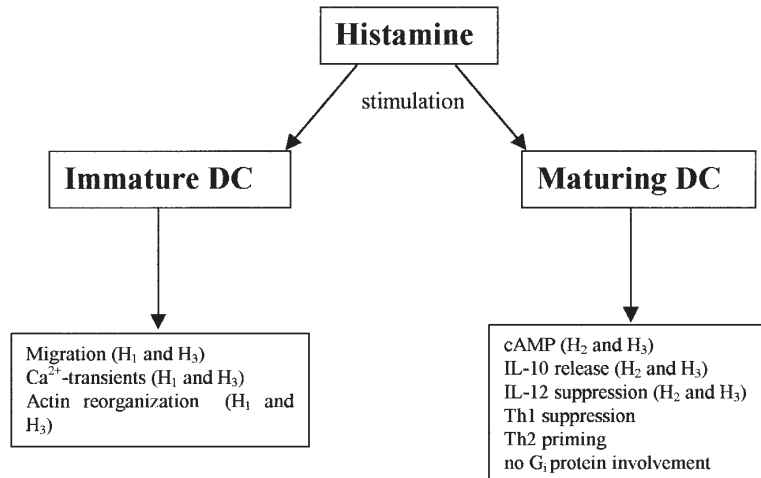


FIG 8. Biological function and signal transduction mechanisms of histamine in DCs.

beginning of the T-cell culture restored IFN- γ production and inhibited IL-4, suggesting that most of the histamine effects on the T cell–differentiating properties of DCs were consequent to the depressed IL-12 release.

DISCUSSION

Histamine is a well-established mediator of type I hypersensitivity, whereupon release from mast cells and basophils causes vasodilatation, increased capillary permeability, and bronchoconstriction. However, it is now evident that histamine can be synthesized by many different cell types, including platelets, enterochromaffin-like cells, endothelial cells, and neurons, and can exert a variety of other biological functions. In addition to its action in immediate allergic reactions, histamine can effect inflammatory responses through the induction of adhesion molecule expression and cytokine synthesis. Moreover, histamine can influence cell-mediated immune responses by regulating the synthesis of IL-10 and IL-12 and by suppressing T-cell proliferation.¹³

The present study reveals that DCs express functional histamine receptors, which are differently coupled to second messenger generation, chemotaxis, and cytokine secretion in immature and maturing DCs. In immature DCs, activation of H₁ and H₃ receptor subtypes trigger intracellular Ca²⁺ transients and a chemotactic response (Fig 8). The increase in [Ca²⁺]_i is due to mobilization from intracellular stores, inasmuch as it is insensitive to chelation of extracellular Ca²⁺. In contrast to what is seen in immature DCs, all of these intracellular signaling events are fully abrogated in mature DCs, and histamine fails to induce cell migration. On exposure to maturation signals, DCs migrate to secondary lymphoid organs to prime T cells.^{1,2} This trafficking is thought to be directed primarily by chemokines and their receptors. Like MCP-

3, RANTES, and platelet-activating factor, histamine might be responsible for the retention and accumulation of DCs at inflammatory sites. Loss of the histamine chemotactic activity during the DC maturation process could clear the way for migration to secondary lymphoid organs along a gradient of chemokines such as MIP-3 β . Loss of chemotactic activity of RANTES, MCP-3, and platelet-activating factor during maturation of DCs is caused by downregulation of their receptors.⁴ In contrast, RT-PCR revealed no major change in the mRNA levels for the H₁, H₂, and H₃ subtypes in immature and mature DCs, suggesting that the oppositeness of the responses in immature and mature DCs is due to a differential coupling to intracellular second messenger pathways. Indeed, H₂ and H₃ receptor subtypes are functional in maturing and mature DCs, because exposure to histamine during maturation stimulates adenylyl cyclase activity and cytokine production (Fig 8). In contrast to what is seen in immature DCs, in which H₁ and H₃ receptor stimulation is coupled to IP₃ production, H₂ and H₃ receptor activation in maturing and mature DCs is mainly coupled to adenylyl cyclase activation. This phenomenon might also explain the observation that in maturing DCs histamine inhibits IL-12 and stimulates IL-10 secretion, as previously described for peripheral monocytes.¹⁴ Although histamine regulates the outcome of cell-mediated immunity by direct effects on T cells,¹⁰ the data presented here suggest that histamine, by suppressing IL-12 release from DCs, could also indirectly favor T_H2 versus T_H1 differentiation.^{17,18} Therefore, histamine might not only regulate the circulatory pathway of DC but also influence the quality of effector T-cell responses via DCs in allergic diseases—for example, atopic disorders are characterized by an increased number of mast cells in the target tissues (the skin and respiratory mucosae), enhanced mast cell releasability, and augmented levels of

histamine in the blood and tissues. Moreover, affected organs harbor an increased number of DCs, a portion of which closely resemble monocyte-derived DCs. Such DCs can efficiently present IgE-bound allergens to T lymphocytes because they display an upregulated expression of the high-affinity IgE receptor (FcεRI) and can thus be very important for amplifying the allergen-specific immune response. Therefore, in the context of atopic disorders, the abundant release of histamine might effectively change DC functions and should create a microenvironment that favors the emergence and the perpetuation of T_H2 immune reactions.

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