Organic cation transporter 3 modulates murine basophil functions by controlling intracellular histamine levels

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In this study, we identify the bidirectional organic cation transporter 3 (OCT3/Slc22a3) as the molecule responsible for histamine uptake by murine basophils. We demonstrate that OCT3 participates in the control of basophil functions because exogenous histamine can inhibit its own synthesis—and that of interleukin (IL)-4, IL-6, and IL-13—through this means of transport. Furthermore, ligands of H_3/H_4 histamine receptors or OCT3 inhibit histamine uptake, and outward transport of newly synthesized histamine. By doing so, they increase the histamine content of basophils, which explains why they mimic the effect of exogenous histamine. These drugs were no longer effective in histamine-free histidine decarboxylase (HDC)-deficient mice, in contrast with histamine itself. Histamine was not taken up and lost its inhibitory effect in mice deficient for OCT3, which proved its specific involvement. Intracellular histamine levels were increased strongly in IL-3–induced *OCT3*$^{-/-}$ bone marrow basophils, and explained why they generated fewer cytokines than their wild-type counterpart. Their production was enhanced when histamine synthesis was blocked by the specific HDC inhibitor α-fluoro-methyl histidine, and underscored the determinant role of histamine in the inhibitory effect. We postulate that pharmacologic modulation of histamine transport might become instrumental in the control of basophil functions during allergic diseases.

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Because of their difficult identification and isolation, the functions of basophils have remained enigmatic for some time. It is well-established that they play a crucial role during helminth infections and allergic diseases, and are most proficient in producing IL-4 together with histamine, which both facilitate Th2 differentiation (1–4). Even before complete maturation—when the typical granules for histamine storage are few—they constitute an excellent source of pro-Th2 cytokines and histamine, which they synthesize in response to growth factors like IL-3 or other stimuli (5). This newly generated histamine is not stored inside the cells but is released immediately to accumulate in the supernatant (5). We have characterized this low-granule basophil population in murine BM and spleen using in situ hybridization with the *Hdc* riboprobe and ultrastructural criteria (6). Their number and activity increase strikingly in peripheral organs during worm rejection (7), and they are revealed easily by their capacity to respond to hematopoietic growth factors (IL-3 or GM-CSF) or aggregated IgE by concomitant synthesis of histamine, IL-4, and IL-6 (8, 9). These medullary basophils can take up histamine from the environment through a process that does not involve H_1, H_2, or H_3R, although H_3R antagonists compete with histamine for uptake (10, 11). In the present study we addressed two major issues arising from these findings: the functions of histamine transported by medullary basophils, and the identity of the molecule that is responsible for this process.

The online version of this article contains supplemental material.

Here, we provide the first evidence that histamine can modulate the biologic activities of basophils through a transport system that is unrelated to its classical receptors, including the most recently discovered H_4R. We identify the molecule that mediates this process as organic cation transporter (OCT) 3, and show that it is inhibited by available H_3/H_4R ligands. Furthermore, we demonstrate that this negative feedback is triggered by an increase of intracellular histamine, which exerts a transcriptional control of its own synthesis and that of associated pro-Th2 cytokines.

RESULTS AND DISCUSSION

We previously identified a medullary population of basophils with few granules, which produce histamine—together with IL-4 and IL-6—in response to IL-3 (6). Knowing that these cells also can take up histamine from the environment (10), we examined whether this process affected their typical biologic activities. Hence, we stimulated total or basophil-enriched BM cells for 24 h with IL-3 in the presence or absence of histamine (10^{-3} and 10^{-4} M), before measuring cytokine production in supernatants. As shown in Fig. 1 A,

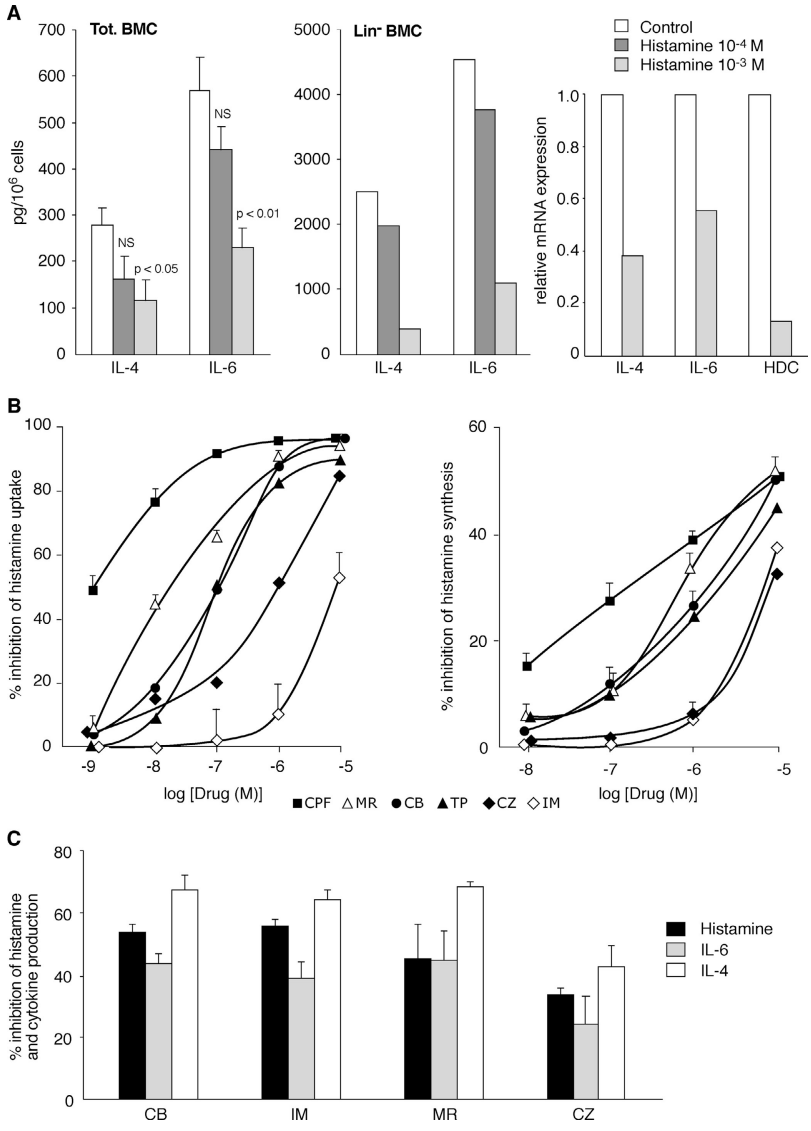

Figure 1. Histamine and H_3/H_4R ligands exert a similar inhibition on histamine and cytokine production by BM basophils. (A) Effect of histamine on IL-3–induced IL-4 and IL-6 production as well as IL-4, IL-6, and HDC mRNA expression. Results are means ± SEM from three separate experiments for BM cells and represent a typical experiment for Lin^- cells. (B) Effect of H_3/H_4R ligands on histamine production and uptake by BM cells stimulated with IL-3. Data, expressed as percentage inhibition relative to controls, are means ± SEM from three to seven separate experiments. CPF, ciproxifan; MR, carboperamide; CB, clobenpropit; TP, thioperamide; CZ, clozapine; IM, imetit. (C) Inhibition of histamine and cytokine production by BMC in the presence of optimal concentrations (10^{-5} M) of H_3/H_4R ligands. Data, expressed as percentage inhibition relative to controls, are means ± SEM from three separate experiments.

histamine inhibited the generation of IL-4 and IL-6 in total and mature cell–depleted Lin$^-$ BM cells. This decrease was preceded by lower mRNA transcription, as measured by real-time PCR in Lin$^-$ BM cells that were incubated for 4 h with histamine (10^{-3} M). Remarkably, transcription of *Hdc*, the gene that encodes the histamine-forming enzyme, also was diminished (Fig. 1 A).

Based on our previous evidence that H_3R antagonists bind to histamine-producing BM cells and compete with histamine for uptake (11), we evaluated the effect of these drugs on histamine and cytokine production measured in culture supernatants after a 24-h exposure to IL-3. They diminished these biologic activities similarly to histamine itself; the degree of inhibition correlated with their potency as inhibitors of histamine uptake (Fig. 1 B). Clobenpropit (CB), classified as an H_3R antagonist and an H_4R agonist (12), inhibited histamine uptake and synthesis, as did thioperamide, although it antagonizes H_3 and H_4 receptor binding. MR 16155 and ciproxifan, two H_3R antagonists were the most potent inhibitors, in contrast with the less effective imetit, an agonist of H_3 and H_4R. None of the drugs impaired cell viability, as assessed by trypan blue exclusion or colorimetric MTT assay (unpublished data).

Depletion of mature cells markedly increased IL-3–induced histamine production (391.0 ± 15.3 ng/10^6 Lin$^-$ versus 65.7 ± 3.9 ng/10^6 total BM cells), whereas CB maintained a similar inhibition (159.0 ± 9.5 ng/10^6 Lin$^-$ versus 30.0 ± 2.4 ng/10^6 total BM cells; means ± SEM from three separate experiments). The reduced histamine levels in BM cell supernatants after exposure to CB were due to lower histidine decarboxylase (HDC) activity as measured by the transformation of radiolabeled histidine into histamine (49,102 ± 6,598 dpm/h/mg protein in controls incubated for 24 h with IL-3 alone versus 25,923 ± 5,360 dpm/h/mg protein in the presence of CB; means ± SEM from five separate experiments; $P < 0.05$). This was preceded by decreased *Hdc* transcription, quantified by real-time PCR after a 4-h exposure to CB (81.0 ± 12.53% decrease relative to controls; mean ± SEM from three separate experiments). As shown in Fig. 1 C, H_3/H_4R ligands reduced the production of IL-4 and IL-6 similarly to histamine (Fig. 1 A), and CB decreased their mRNA expression after a 4-h incubation of IL-3-induced Lin$^-$ BMC (34.7 ± 13.3% for IL-6 and 67.0 ± 11.4% for IL-4 transcripts; means ± SEM from three separate experiments). In further support of the basophilic identity of histamine-producing cells, IL-3–induced Lin$^-$ BM cells produced IL-13, a typical basophil-associated cytokine (1), which was inhibited similarly by CB (212 ± 40 and 58 ± 3 pg/10^6 cells, respectively; means ± SD from two separate experiments).

The preferential expression of H_4R in the BM (13), together with its pharmacologic characteristics, suggested its implication in histamine uptake (14). Yet, although H_4R mRNA was expressed in basophil-enriched BM cells (Fig. S1, available at http://www.jem.org/cgi/content/full/jem.20050195/DC1), the inhibition exerted by H_3/H_4R ligands was not impaired in mice in which the gene encoding either receptor had been disrupted (Fig. S1; references 15 and 16), nor was it diminished in the presence of the highly specific H_4R antagonist JNJ7777120 (not depicted; reference 17). Furthermore, blocking H_1, H_2, and H_4 receptors on BM cells from $H_3R^{-/-}$ mice did not prevent histamine uptake or inhibition of histamine and cytokine synthesis by the drugs (unpublished data); this ruled out the participation of any classical histamine receptor alone or in combination.

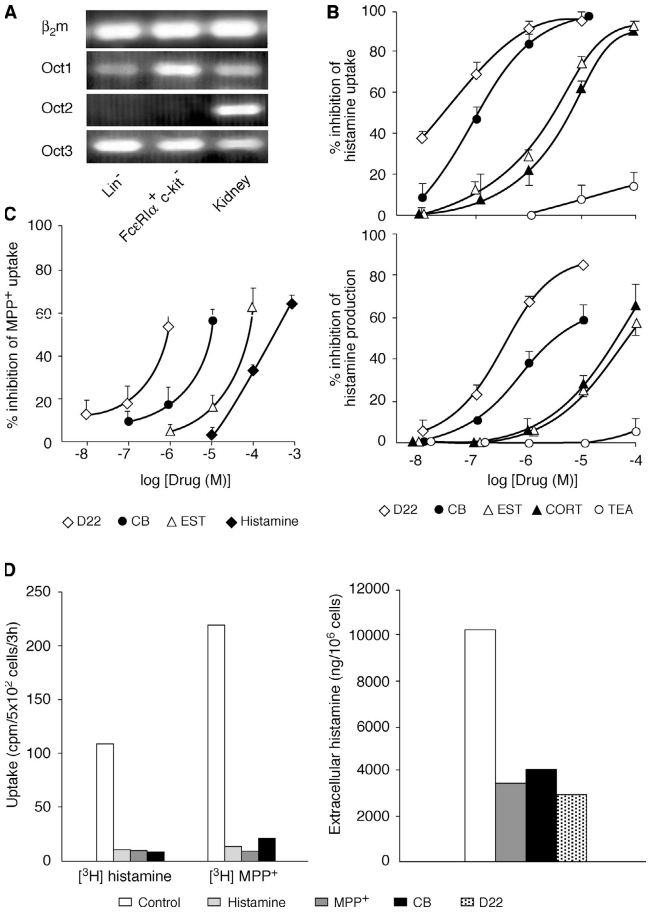

Figure 2. OCT3 is expressed and functional in BM-derived basophils. (A) *Oct3* and *Oct1* mRNAs are detected in basophil-enriched Lin$^-$ BM cells and sorted FcεRIα$^+$c-kit$^-$ cells, in contrast with *Oct2* transcripts. (B) OCT3 substrates inhibit uptake and IL-3–induced synthesis of histamine. Data are means ± SEM from three separate experiments. (C) The prototypical substrate of OCTs, MPP$^+$, is taken up by BM basophils and inhibited by D22, CB, β-estradiol, and histamine (data are means ± SEM from three separate experiments). (D) Electronically sorted FcεRIα$^+$c-kit$^-$ basophils derived from BM cells cultured for 8 d in IL-3 take up radiolabeled histamine and MPP$^+$ and respond to CB, MPP$^+$, and D22 by decreasing their IL-3–induced histamine synthesis (data represent a typical experiment out of three).

Recent progress in the characterization of transmembrane transporters, which enable small electrically charged molecules to cross the cell membrane, prompted us to address their potential role in histamine uptake by basophils.

One member of the organic cation transporter family (18–20), OCT3, was particularly interesting in our model because of its relatively broad tissue distribution and usage of histamine as substrate (18). *Oct3* mRNA was detected easily in basophil-enriched Lin^- BM cells and $Fc\varepsilon RI\alpha^+c\text{-}kit^-$ basophils sorted after 8 d of culture in IL-3 (Fig. 2 A). Transcripts for *Oct1*, which cannot transport histamine (18), also were detected, whereas *Oct2* mRNA was not (Fig. 2 A). We examined the effect of several substrates or inhibitors of OCT3 in our experimental set up, namely decynium 22 (D22), β-estradiol, and corticosterone. As shown in Fig. 2 B, they reduced uptake and synthesis of histamine by BM cells that were exposed to IL-3, in accordance with their reported potencies for OCT3 (18–20). In contrast, tetraethylammonium, which recognizes human OCT1 and OCT2, but not human OCT3, had no such effect (Fig. 2 B). Using radiolabeled 1-methyl-4-phenylpyridinium (MPP^+), the prototypical substrate of OCTs, we found that it was effectively taken up by BM cells and inhibited by OCT3 substrates, CB, and unlabeled histamine (Fig. 2 C). The low efficiency of histamine in inhibiting MPP^+ uptake probably is explained by its exclusive transport by OCT3 because it fails to label $OCT3^{-/-}$ BM cells (see Fig. 4 A), whereas MPP^+ also can interact with OCT1 (18), as confirmed by its residual labeling of $OCT3^{-/-}$ BM cells (not depicted). As shown in Fig. 2 D, [^{3}H]histamine and [^{3}H]MPP^+ uptake was enhanced greatly among sorted $Fc\varepsilon RI\alpha^+c\text{-}kit^-$ basophils (50 times on average), and inhibited by CB, MPP^+, and D22; this proved that OCT3 is associated effectively with the basophil lineage. The transporter was clearly functional in these purified basophils because the large amounts of histamine generated in response to IL-3 were decreased markedly in the presence of the drugs.

The bidirectional mode of action of OCT3 (19, 20), which is shared by the histamine transporter we reported previously (21), provides an explanation for the paradox that H_3/H_4R ligands and inhibitors of OCT3 exert the same effect on basophils as histamine itself. As shown in Fig. 3 A, a 24-h incubation with CB significantly increased intracellular histamine levels in BM cells, whereas overall production and extracellular concentrations diminished. This intracellular increase was observed in response to all inhibitory drugs (Fig. 3 B). It is most likely due to a partial blockade of the outward transport after neosynthesis. Commonly, cellular secretion occurs through a regulated or a constitutive process. It is plausible that the latter mechanism, which takes place continuously in many cells and does not involve granules, can be controlled by OCT3. The localization of intracellular histamine is likely to be important for the efficiency of the negative feedback because exogenous histamine at inhibitory doses induced 10-fold greater intracellular levels than those generated endogenously in response to IL-3 and trapped inside the cells by the blockade of OCT3 (117 ± 12% increase after a 24-h exposure to IL-3 + CB, versus 1,623 ± 234% after uptake of exogenous histamine; means ± SEM from five different experiments). It is possible that histamine distributes differently inside the cells, depending on its origin. In its newly synthesized form it may remain in the cytosol preferentially, ready to exert its negative feedback, whereas exogenous histamine could be taken up and stored immediately in vesicles or granules, and thus, prevent most of its inhibitory action. This immediate storage of exogenous histamine was demonstrated for mast cells (22). Although the intracellular localization of histamine is important, it remains possible that OCT3 ligands enter the cells and synergize with histamine to enhance the susceptibility of basophils to the negative feedback. Whatever the mechanism, the inhibition of cytokine production by CB depends on newly synthesized histamine, because it was diminished strikingly in *Hdc*-deficient mice (23), whereas exogenous

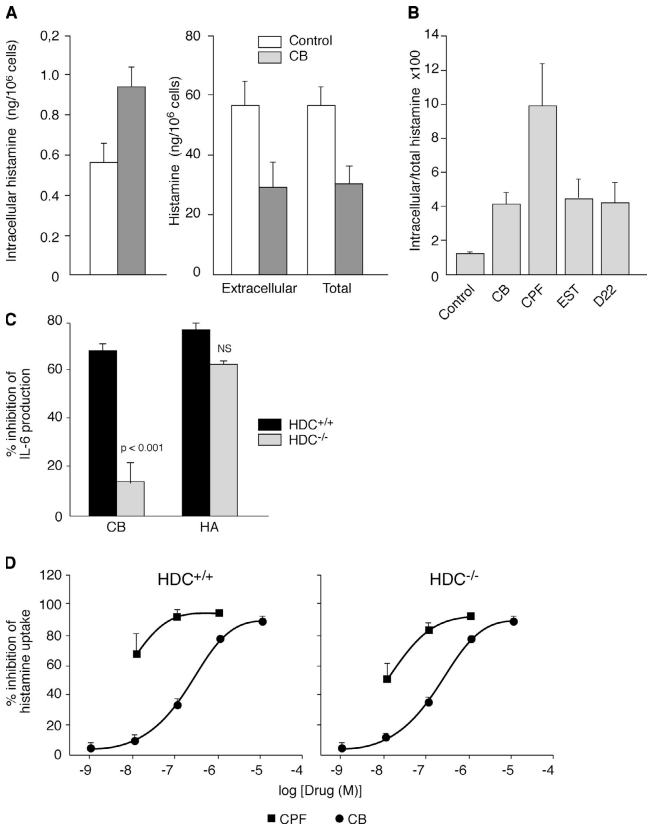

Figure 3. Clobenpropit requires intracellular histamine for its inhibitory effect. (A) CB increases the intracellular histamine content of BM cells stimulated for 24 h with IL-3, whereas extracellular and total histamine decrease (means ± SEM from three separate experiments). (B) All inhibitory drugs tested increased the proportion of intracellular histamine in BM cells, relative to its overall IL-3–induced production (means ± SEM from three separate experiments). (C) The inhibition of IL-6 production by CB (10^{-5} M) is diminished strikingly in BM cells from histamine-deficient $HDC^{-/-}$ mice, whereas exogenous histamine (HA, 10^{-3} M) remains effective. Data are means ± SEM from three separate experiments. (D) Histamine deficiency does not affect histamine uptake, and its inhibition by ciproxifan (CPF) and CB (data are means ± SEM from three separate experiments).

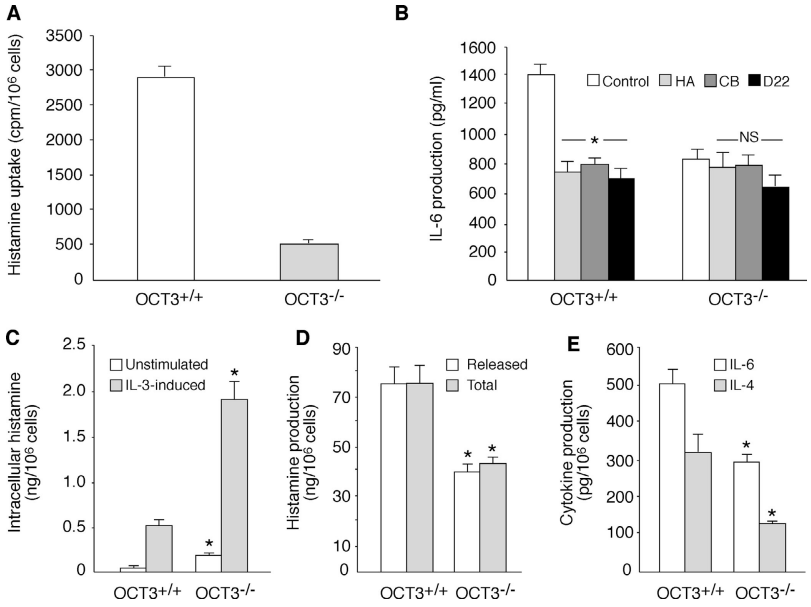

Figure 4. OCT3 and the transport system of histamine are identical. (A) *Oct3* deficiency abolishes histamine uptake, as compared with wild-type FVB/N BM cells (data are means ± SEM from five separate experiments). (B) *Oct3* deficiency prevents the inhibitory effect of histamine, CB, and D22 on IL-3–induced IL-6 production by BM cells (data are means ± SEM from four separate experiments). (C) Intracellular histamine is increased in BM cells from $Oct3^{-/-}$ mice, whether they were stimulated for 24 h with IL-3 or not. (D) In contrast, histamine levels in supernatants as well as total histamine production are decreased. (E) IL-3–induced IL-6 and IL-4 production by BM cells from $Oct3^{-/-}$ mice is significantly lower than in wild-type controls. (Data are means ± SEM from four separate experiments; $^*P < 0.01$).

histamine conserved its effect (Fig. 3 C). It also was decreased when histamine synthesis was blocked by α-fluoromethyl histidine (α-FMH), the suicide substrate of HDC (unpublished data). The disruption of the *Hdc* gene had no effect on histamine uptake and its inhibition by CB and ciproxyfan, as shown in Fig. 3 D.

Ultimate proof of the implication of OCT3 in histamine uptake and the ensuing diminution of the biologic activities of basophils was provided by the use of BM cells from mice in which the corresponding gene had been disrupted (24). These cells neither took up [^{3}H]histamine (Fig. 4 A), nor was their cytokine production affected by histamine, CB, or D22 (Fig. 4 B). In accordance with the notion that OCT3 behaves like a release valve for newly synthesized histamine, its intracellular levels were higher in BM cells from *Oct3*-deficient mice than in their wild-type counterparts, both spontaneously and in response to a 24-h exposure to IL-3 (Fig. 4 C). In contrast, extracellular histamine levels were significantly lower in BM cells from mice that lacked OCT3 than in controls (Fig. 4 D), as was total histamine production. Exocytosis of the few granules present in BM basophils (6) or vesicular secretion (piecemeal degranulation), reported for basophils cultured in IL-3 (25), could account for the residual release in *Oct3*-deficient mice (Fig. 4 D). IL-6 and IL-4, generated during a 24-h incubation with IL-3, were decreased in BM cell supernatants from OCT3-deficient mice, relative to wild-type controls (Fig. 4 E). This result indicates that in the absence of the transporter, when release of newly synthesized histamine is hampered, its intracellular levels increase sufficiently to trigger the negative feedback signal. In support of this notion, we found that IL-3–induced IL-4 and IL-6 synthesis in $Oct3^{-/-}$ BM cells was enhanced significantly when histamine synthesis was abrogated by α-FMH, the specific inhibitor of HDC (74 ± 21% and 51 ± 12% increase in IL-3–induced IL-4 and IL-6 production, respectively; means ± SEM from three separate experiments).

The mechanism by which intracellular histamine decreases the transcription of cytokine and HDC genes remains unknown. Involvement of molecules of the cytochrome P450 (CYP450) family is most likely because it was shown that they bind histamine (26). Furthermore, their heme moiety recognizes various histamine receptor antagonists, particularly H_3 receptor antagonists, such as thioperamide, CB, and ciproxifan (27), which were effective in our experimental set up.

In conclusion, we postulate that OCT3 participates in the control of histamine and pro-Th2 cytokine synthesis by modulating intracellular histamine levels. Once it has attained a critical concentration in the cytosol, histamine is ready to exert its negative feedback control; this alleviates its deleterious effect during allergic reactions, and hampers the development of Th2 immune response (28).

MATERIALS AND METHODS

Mice and reagents. 6–8-wk-old C57BL/6 mice, bred in our own facility, were used. $Hdc^{-/-}$ mice were generated by Ohtsu et al. (23). H_4R- and H_3R-deficient mice were provided by Johnson & Johnson Pharmaceutical Research Department and Development, L.L.C., whereas $Oct3^{-/-}$ mice

were produced by Zwart et al. (24). Recombinant murine IL-3 and DuoSet ELISA IL-4 and IL-6 kits were purchased from R&D Systems. MR16155 (carboperamide) and ciproxifan were from Bioproject, and CB dihydrobromide was from Tocris. The specific H_4R antagonist, JNJ7777120, was developed and provided by Johnson & Johnson (17). [^{3}H]methyl-4-phenylpyridinium was purchased from Biotrend Chemikalien. All other histamine receptor ligands and OCT3 substrates, as well as the irreversible HDC inhibitor, α-FMH, were from Sigma-Aldrich.

Cell cultures and flow cytometry. BM cells were prepared as reported (5) and adjusted to a final concentration of 2.5×10^6 per ml in culture medium (MEM) supplemented with 10% horse serum (all from GIBCO BRL). Various doses (10^{-5}–10^{-9} M) of the drugs were added shortly before the addition of IL-3 (1 ng/ml), followed by a 24-h incubation at 37°C, 5% CO_2. In some experiments, BM cells were enriched for histamine-producing cells using the SpinSep depletion kit (StemCell Technologies Inc.), which eliminates cells bearing lineage-specific antigens (Lin^+), according to the manufacturer's instructions. Basophil-enriched populations also were derived from total BM cells according to Yoshimoto et al. (29). After 8–9 d of culture with IL-3, the proportion of basophils was identified by their $Fc\varepsilon R\alpha^+$c-kit^- phenotype. In some experiments, these cells were sorted using a FACSVantage (Becton Dickinson). They were 98% pure upon reanalysis, and contained a majority of cells with basophil morphology as assessed by MGG.

Cytokine assays, measurement of histamine production, and uptake. IL-6 and IL-4 production was measured in cell supernatants recovered after a 24-h incubation. Histamine was quantified by an automated continuous flow spectrofluorometric technique (5). For binding experiments, 10^6 total BM cells, 10^5 Lin^-, and 50,000 $Fc\varepsilon RI\alpha^+$c-kit^- cells were plated in round-bottomed 96-well polypropylene plates (Costar). Unless stated otherwise, the cells were incubated (37°C, 5% CO_2) for 3 h with 3 μCi/ml of [^{3}H]histamine dihydrochloride (2.5×10^{-7} M; 12 Ci/mmol) or 2 μCi/ml of MPP^+ (2.5×10^{-8} M; 80 Ci/mol) in a final volume of 100 μl. Competition assays were performed as previously described (10,11). Each experiment was performed in triplicate, and histamine binding was calculated from total cpm after subtraction of nonspecific binding to filters. HDC assays in cell lysates were performed as previously described (5).

mRNA expression. RNAs were extracted from 2×10^6 cells by TRIzol (Invitrogen), according to the supplier's recommendations. Primers and probes for mouse IL-4, IL-6, HDC, and GAPDH real-time PCR were designed using the Computer Primer Express software (Applied Biosystems), except for H_4R primers that were provided by F. Cogé (Servier Laboratory, Servier, France). All other oligonucleotides were purchased as HPLC-purified molecules from Eurogentech. PCR reactions contained 1 μl cDNA samples at different dilutions, 10 mM Tris-HCl, pH 8.3, 50 mM KCl, 5 mM $MgCl_2$, 200 μM deoxyribonucleoside triphosphate, 100 nM of each primer, 200 nM of the specific probe, 60 nM passive reference (Rox), and 0.5 U hot gold star Taq DNA polymerase (Eurogentech). Each amplification was performed in triplicate using the following conditions: 2 min at 50°C and 10 min at 94°C, followed by 45 cycles of 15 s at 94°C and 30 s at 60°C. All data were normalized to an internal standard—the GAPDH expression in each sample—and expressed as relative expression using the $\Delta\Delta C_T$ method as described in the User Bulletin #2 from Applied Biosystems.

The probes carried a 5′ FAM reporter label and a 3′ dark quencher group and were synthesized by Eurogentech.

Statistics. The standard Student's *t* test was used to establish statistical significance.

Online supplemental material. Fig. S1 shows histamine uptake and negative feedback on histamine and cytokine production by basophils is not mediated through H_3/H_4R. The primers and probes for qualitative and quantitative PCR analyses are described online. Online supplemental material is available at http://www.jem.org/cgi/content/full/jem.20050195/DC1.

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