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 H3/H4 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+/HDC−/− 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.

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 H1, H2, or H3R, although H3R 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.
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 H₄R. We identify the molecule that mediates this process as organic cation transporter (OCT) 3, and show that it is inhibited by available H₃/H₄R 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,
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 H3R 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 H3R antagonist and an H2R agonist (12),
hindered histamine uptake and synthesis, as did thioperamide,
although it antagonizes H3 and H2 receptor binding. MR
16155 and ciproxifan, two H2R antagonists were the most
potent inhibitors, in contrast with the less effective imetit, an
agonist of H3 and H2R. None of the drugs impaired cell vi-
ability, as assessed by trypan blue exclusion or colorimetric
MTT assay (unpublished data).

Depletion of mature cells markedly increased IL-3–
duced histamine production (391.0 ± 15.3 ng/106 Lin−
versus 65.7 ± 3.9 ng/106 total BM cells), whereas CB main-
tained a similar inhibition (159.0 ± 9.5 ng/106 Lin− versus
30.0 ± 2.4 ng/106 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/μg protein in controls incubated
for 24 h with IL-3 alone versus 25,923 ± 5,360 dpm/h/μg protein in the presence of CB; means ± SEM from five separate experiments; P < 0.05). This was preceded by de-
creased \( Hdc \) 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, H2/H3R 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 cyto-
kine (1), which was inhibited similarly by CB (212 ± 40
and 58 ± 3 pg/106 cells, respectively; means ± SD from
two separate experiments).

The preferential expression of H3R in the BM (13),
together with its pharmacologic characteristics, suggested
its implication in histamine uptake (14). Yet, although
H3R 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 H3/

Figure 2. OCT3 is expressed and functional in BM-derived baso-
philis. (A) Oct3 and Oct1 mRNAs are detected in basophil-enriched Lin−
BM cells and sorted FcεRα+“c-kit+” cells, in contrast with Oct2 tran-
scripts. (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 baso-
philis and inhibited by D22, CB, β-estradiol, and histamine (data are
means ± SEM from three separate experiments). (D) Electronically
sorted FcεRα+“c-kit+” basophilis 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).

H3R ligands was not impaired in mice in which the gene
encoding either receptor had been disrupted (Fig. S1; ref-
ences 15 and 16), nor was it diminished in the presence
of the highly specific H3R antagonist JNJ7777120 (not de-
picted; reference 17). Furthermore, blocking H1, H2, and
H3 receptors on BM cells from H3R−/− mice did not pre-
vent histamine uptake or inhibition of histamine and cy-
tokine synthesis by the drugs (unpublished data); this ruled
out the participation of any classical histamine receptor
alone or in combination.

Recent progress in the characterization of transmem-
brane transporters, which enable small electrically charged
molecules to cross the cell membrane, prompted us to ad-
dress 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 FcεRIα+ c-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, tetrathylammonium, 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, [3H]histamine and [3H]MPP+ uptake was enhanced greatly among sorted FcεRIα+ c-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 H3/H4 R 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).
histamine conserved its effect (Fig. 3 C). It also was decreased when histamine synthesis was blocked by \(\alpha\)-fluoromethyl histidine (\(\alpha\)-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 \(Oct3^{-/-}\) 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 their wild-type counterparts, both spontaneously and in response to a 24-h exposure to IL-3 (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 (Fig. 4 E).

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). \(H_{\alpha}\)R- and \(H_{\beta}\)R-deficient mice were provided by Johnson & Johnson Pharmaceutical Research Department and Development, L.L.C., whereas \(Oct3^{-/-}\) mice were generated by Ohtsu et al. (23).
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 (carnitopramine) and ciproxifan were from Bioproject, and CB dihydrobro- 
mide was from Tocris. The specific H4R antagonist, [N]77777120, was de-
veloped and provided by Johnson & Johnson (17). [H]methyl-4-phenyl-
pyridinium was purchased from Boehrnd Chemikalien. All other histamine
receptor ligands and OCTR substrates, as well as the irreversible HDC in-
hibitor, 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 me-
dium (MEM) supplemented with 10% horse serum (all from GIBCO BRL).
Various doses (10^{-7}–10^{-5} M) of the drugs were added shortly before the ad-
dition of IL-3 (1 ng/ml), followed by a 24-h incubation at 37°C, 5% CO2.
In some experiments, BM cells were enriched for histamine-producing cells
using the SpinSep depletion kit (StemCell Technologies Inc.), which elimi-
nates cells bearing lineage-specific antigens (Lin-), according to the manu-
ufacturer’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 FcεRα^+ c-kit
phenotype. In some experiments, these cells were sorted using a FACSVan-
tage (Becton Dickinson). They were 98% pure upon reanalysis, and con-
tained a majority of cells with basophil morphology as assessed by MGG.

**Cytokine assays, measurement of histamine production, and up-
take.** IL-6 and IL-4 production was measured in cell supernatants recov-
ered after a 24-h incubation. Histamine was quantified by an automated
continuous flow spectrophotometric technique (5). For binding experi-
ments, 10^6 total BM cells, 10^5 Lin^- , and 50,000 FcεRα^+ c-kit^- cells were
plated in round-bottomed 96-well polypropylene plates (Costar). Unless
stated otherwise, the cells were incubated (37°C, 5% CO2) for 3 h with 3 µCi/ml of [H]histamine dihydrochloride (2.5 × 10^{-3} M; 12 Ci/mmol) or
2 µCi/ml of MPP^+ (2.5 × 10^{-3} M; 80 Ci/mmol) 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 calcu-
lated from total cpm after subtraction of nonspecific binding to filters. mRNA
assays in cell lysates were performed as previously described (5).

**mRNA expression.** RNAs were extracted from 2 × 10^6 cells by TRizol
(Livtrogen), according to the supplier’s recommendations. Primers and
probes for mouse IL-4, IL-6, HDC, and GAPDH real-time PCR were de-
cigned using the Computer Primer Express software (Applied Biosystems),
except for H3 receptors 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 MgCl2,
200 μM deoxynucleoside triphosphate, 100 nM of each primer, 200 nM of
the specific probe, 60 nM passive reference (Rox), and 0.5 U hot gold star
enzyme (Applied Biosystems). 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 normal-
ized to an internal standard—the GAPDH expression in each sample—and
expressed as relative expression using the ΔΔC_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
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 neg-
ative feedback on histamine and cytokine production by basophils is not me-
diated through H3/H4R. The primers and probes for qualitative and quanti-
tative 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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