Histamine Is a Potent Inducer of IL-18 and IFN-γ in Human Peripheral Blood Mononuclear Cells

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Histamine Is a Potent Inducer of IL-18 and IFN-γ in Human Peripheral Blood Mononuclear Cells

Hideo Kohka,‡ Masahiro Nishibori,† Hiromi Iwagaki, Naoki Nakaya,† Tadashi Yoshino,‡ Kenta Kobashi, Kiyo Miura, Noriaki Tanaka,† and Tadaatsu Akagi‡

Histamine (10⁻⁷ to 10⁻⁴ M) concentration-dependently stimulated the production of IL-18 and IFN-γ and inhibited the production of IL-2 and IL-10 in human PBMCs. Histamine in the same concentration range did not induce the production of IL-12 at all. The stimulatory or inhibitory effects of histamine on cytokine production were all antagonized by H₂ receptor antagonists like ranitidine and famotidine in a concentration-dependent manner, but not by H₁ and H₃ receptor antagonists. Selective H₂ receptor agonists, 4-methylhistamine and dimaprit, mimicked the effects of histamine on five kinds of cytokine production. The EC₅₀ values of histamine, 4-methylhistamine, and dimaprit for the production of IL-18 were 1.5, 1.0, and 3.8 μM, respectively. These findings indicated that histamine caused cytokine responses through the stimulation of H₂ receptors. All effects of histamine on cytokine responses were also abolished by the presence of either anti-IL-18 Ab or IL-1β-converting enzyme/caspase-1 inhibitor, indicating that the histamine action is dependent on mature IL-18 secretion and that IL-18 production is located upstream of the cytokine cascade activated by histamine. The addition of recombinant human IL-18 to the culture concentration-dependently stimulated IL-12 and IFN-γ production and inhibited the IL-2 and IL-10 production. IFN-γ production induced by IL-18 was inhibited by anti-IL-12 Ab, showing the marked contrast of the effect of histamine. Thus histamine is a very important modulator of Th1 cytokine production in PBMCs and is quite unique in triggering IL-18-initiating cytokine cascade without inducing IL-12 production. The Journal of Immunology, 2000, 164: 6640–6646.

Interleukin-18 was originally characterized as an IFN-γ-inducing factor in the blood of mice primed with Propionibacterium acnes and stimulated with LPS (1). IL-18 is secreted from LPS-activated monocytes/macrophages but also from a wide variety of cells (2–5). IL-18 is synthesized as a precursor protein that requires cleavage by the IL-1β-converting enzyme/caspase-1 for activity as in the case of IL-1β (6, 7). After cleavage, the bioactive mature IL-18 is secreted from the cells. In addition to the homology of the primary amino acid sequences (1), IL-18 and IL-1β share a common secondary and tertiary structure, a β-pleated sheet structure. Thus, IL-18 belongs to the IL-1 family. Moreover, it has been shown that they also have similar entity of receptor complex, α binding, and β signaling peptide chains (8, 9).

IL-18 is functionally similar to IL-12 in mediating Th1 response and NK cell activity. IL-18 with IL-12 synergistically produced IFN-γ in T lymphocytes and monocytic cells (10–14) in which IL-12 has been shown to up-regulate IL-18 receptor (12). Kohka et al. (15) demonstrated that IL-18 up-regulated the ICAM-1 expression in a KG-1 monocytic cell line through the IFN-γ-independent pathway.

IL-18 has been suggested to be involved in many pathological conditions including the host defense against fungal and bacterial infection (16, 17), autoimmune diabetes (18), P. acnes-primed LPS-induced hepatitis (19), and autoimmune encephalomyelitis (20). The enhancement of antitumor immunity by IL-18 alone or in combination with IL-12 has also been described recently (21–23). Thus, IL-18 plays an important role in host immune and autoimmune responses.

Histamine is a well-known mediator of inflammation and allergic response. In addition to the stable pool of histamine in mast cells and basophilic leukocytes, the presence of histamine with a different dynamic property, called inducible or nascent histamine, was suggested in the earlier works (24, 25). Later, many groups reported the induction of histidine decarboxylase, a histamine-synthesizing enzyme, by LPS, cytokines, and lymphocyte mitogen in macrophages (26), T lymphocytes (27), and in many peripheral tissues (28, 29). The synthesized histamine appeared not to enter the storage pool inside the cells, but rather was spontaneously released from the cells (30). The induction of histidine decarboxylase and this kinetic property of histamine may endow histamine with a mobile nature under the diverse cytokine environment. Although it has long been suggested that histamine may be one of the regulators of immune response (31–34), the estimated functional roles of histamine as immunomodulator were often controversial probably due to the differences in the cell preparations used and the complexity of the involvement of histamine in immunomodulation (35).

In the present study, we investigated the effects of histamine on the production of IL-18, IL-12, IFN-γ, IL-10, and IL-2 in human PBMCs in vitro. We found that histamine was a strong inducer of IL-18 production through the stimulation of H₂ receptors in PBMCs and that histamine in turn regulated IL-18-triggered activation of cytokine cascade without inducing IL-12 production. Therefore, it was concluded that histamine is an important immunomodulator, in addition to being an inflammatory mediator.
FIGURE 1. Effect of IL-18 on IL-12, IL-2, IFN-γ, and IL-10 production in PBMCs. PBMCs (5 × 10^5/ml) were cultured in the presence of increasing concentrations of IL-18 for 24 h. At the end of the culture, the concentrations of IL-12, IL-2, IFN-γ, and IL-10 in the conditioned media were determined using an ELISA kit as described in Materials and Methods. The results are the means ± SEM of three different donors. *, p < 0.05; **, p < 0.01 as compared with the value in the absence of IL-18.

Materials and Methods

Reagents and drugs

Recombinant human IL-18, anti-IL-18 mAb, and caspase-1 inhibitor Z-tyr-Val-Ala-Asp-fluoromethyl ketone (YVAD-FMK) were purchased from Medical & Biological Laboratories (Nagoya, Japan). Anti-IL-12 mAb was purchased from PharMingen (San Diego, CA). Histamine was purchased from Nakalai Tesque (Kyoto, Japan). Dimaprit and 4-methylhistamine were kindly donated from Drs. W. A. M. Duncan and D. J. Durant (The Research Institute, Smith Kline and French Laboratories, Welwyn Garden City, Herts, U.K.). d-Chlorpheniramine maleate, ranitidine, and famotidine were provided by Yoshitomi Pharmaceutical (Tokyo, Japan), Glaxo Japan (Tokyo, Japan), and Yamanouchi Pharmaceutical (Tokyo, Japan), respectively. Thioperamide hydrochloride was provided by Eisai (Tokyo, Japan).

Isolation and culture of PBMCs

Normal human PBMCs were obtained from human volunteers after oral informed consent. Twenty to 50 ml of peripheral blood was withdrawn from the vein of the forearm. PBMCs were isolated from the buffy coat of 10 healthy volunteers by centrifugation on a density gradient of Ficoll-Paque (Pharmacia, Uppsala, Sweden), then washed three times in RPMI 1640 medium (Nissui, Tokyo, Japan) supplemented with 10% (v/v) heat-inactivated FCS and penicillin (Sigma, St. Louis, MO). PBMCs were suspended at a final concentration of 5 × 10^6 cells/ml in RPMI 1640 medium supplemented with 10% (v/v) heat-inactivated FCS.

Cytokine assays

PBMCs (5 × 10^6 cells/ml) were incubated with IL-18, histamine, H₂ receptor agonist, and/or H₁, H₂, H₃ receptor antagonists for 24 h at 37°C in a humidified atmosphere of 5% CO₂ in air. All reagents were added to the media at the start of incubation. After culture, the cell suspensions were transferred into Eppendorf tubes and centrifuged. The cell-free supernatant fractions were assayed for IL-18, IL-12, IL-2, IFN-γ, and IL-10 protein. The cytokines were measured using ELISAs employing the multiple Abs sandwich principle (for IL-18, MBL; for other cytokines, Quantikine, R&D Systems, Minneapolis, MN). The detection limits of the ELISAs for IL-18, IL-12, IL-2, IFN-γ, and IL-10 were 10 pg/ml. When the effect of anti-IL-18 mAb, anti-IL-12 mAb, or caspase-1 inhibitor was examined, these were added to the culture media at the start of incubation with IL-18 (10 ng/ml) or histamine (100 μM). All experiments were done at least in triplicate samples.

Preparation of T cell/monocyte-rich, and B cell-rich fractions

To obtain T cell/monocyte-enriched preparations, total PBMCs were depleted of B lymphocytes using magnetic beads (Dynal, Lake Success, NY) coated with mAb specific for the CD19 (Pan-B cells) surface Ag. Total PBMCs at 1 × 10^6 cells/ml were incubated and gently mixed with the magnetic beads at 4°C for 30 min. Bead-cell complexes were eliminated by magnetic separation. The T/monocyte cell-enriched preparations contained 75%/80% T/monocyte cells, and B cell-enriched preparations contained 70% B cells as determined by flow cytometry (FACScan, Cell Quest, Becton Dickinson, Mountain View, CA) with FITC-conjugated anti-CD3 Ab, anti-CD14 Ab, and anti-CD19 Ab.

Determination of histamine and tele-methylhistamine

The histamine and tele-methylhistamine levels in the cell-free supernatant of conditioned media after the incubation with IL-18 (0.1–10 ng/ml) for 2, 12, and 24 h were determined as described previously (36).

Statistical examination

Statistical significance was evaluated using ANOVA followed by the Student’s two-tailed t test. Values of p < 0.05 were considered to be statistically significant.

Results

Effect of IL-18 on IL-12, IL-2, IFN-γ, and IL-10 production in PBMCs

IL-18 (0.1–100 ng/ml) concentration-dependently stimulated the release of IL-12 and IFN-γ from human PBMCs when these cytokines were determined 24 h after the start of culture with IL-18 (Fig. 1). In contrast, the productions of IL-2 and IL-10 during the same culture period were inhibited by IL-18 in a concentration-dependent manner (Fig. 1). The effects of IL-18 on the production of IFN-γ and IL-10 were especially marked for IL-18 concentrations of 1 ng/ml and above.

Effect of histamine on IL-18, IL-12, IL-2, IFN-γ, and IL-10 production in PBMCs

Histamine alone concentration-dependently stimulated the release of IL-18 from PBMC when IL-18 was determined 24 h after the start of culture with histamine (Fig. 2). The EC₅₀ value for the histamine effect on IL-18 production was estimated to be 1.5 μM. Histamine in the same concentration range stimulated IFN-γ production, whereas IL-2 and IL-10 production was inversely
inhibited by histamine (Fig. 2). The levels of IL-12 were below the detection limit (10 pg/ml) for all of the histamine concentrations examined (Fig. 2).

**Effects of histamine antagonists on the modulatory effects of histamine on cytokine production in PBMCs**

To examine the involvement of subtypes of histamine receptors in the effects of histamine, d-chlorpheniramine (H1 receptor antagonist), famotidine (H2 receptor antagonist), or thioperamide (H3 receptor antagonist) was added to the culture medium at the concentration of 1 or 100 μM with histamine (100 μM). These antagonists alone did not affect on the basal levels of cytokine production examined, except for the slight increase in IFN-γ by 100 μM famotidine. Famotidine at 1 and 100 μM concentration-dependently antagonized the stimulatory or inhibitory effects of histamine on IL-18, IL-2, IFN-γ, and IL-10 production (Fig. 3). In contrast, the same concentrations of d-chlorpheniramine and thioperamide did not exert any antagonizing action on the histamine effect. Another H2 receptor antagonist, ranitidine, showed substantially similar effects to famotidine (data not shown).

**Effects of selective H2 receptor agonists on IL-18, IL-12, IL-2, IFN-γ, and IL-10 in PBMCs**

Selective H2 receptor agonists, dimaprit (37) and 4-methylhistamine (38), concentration-dependently caused responses of IL-18, IFN-γ, IL-2, and IL-10 identical with those of histamine (Fig. 4). The EC50 values for the production of IL-18 were 3.8 μM for dimaprit and 1.0 μM for 4-methylhistamine, respectively. The effective antagonist profile against histamine action, mimicry of histamine actions by two selective H2 receptor agonists, and the relative potencies of the three agonists as a whole indicated that the effects of histamine on IL-18, IL-2, IFN-γ, and IL-10 were all mediated by the stimulation of H2 receptors.
Effect of anti-IL-18 mAb, caspase-1 inhibitor, and anti-IL-12 mAb on cytokine responses to IL-18 and histamine in PBMCs

The addition of anti-IL-18 mAb (10 ng/ml) to the culture medium, which abolished the effect of 2500 pg/ml IL-18, completely inhibited the effects of histamine (100 μM) on IL-2, IFN-γ, and IL-10 production (Table I). The same concentration of histamine (100 μM) caused the increase in IL-18 levels, and the final concentration of IL-18 induced by histamine was 2486 pg/ml, which was comparable to the IL-18 concentration exogenously added in these experiments. Treatment of PBMCs with a caspase-1 inhibitor YVAD-FMK (100 nmol/ml) decreased the histamine (100 μM)-induced IL-18 production to levels below the detection limit (Table I). Under this condition, the remaining cytokine responses to histamine (100 μM) disappeared as in the case of the addition of anti-IL-18 mAb. The complete inhibition of histamine effects by either anti-IL-18 Ab or caspase-1 inhibitor strongly suggested that the stimulation of IL-18 production by histamine was present in most upstream of the cytokine cascade response to histamine in PBMCs and that subsequent responses were dependent on the secretion of mature IL-18 from PBMCs.

On the other hand, the addition of anti-IL-12 mAb concentration-dependently inhibited the IL-18-induced IFN-γ production by up to 77%, suggesting a cooperative effect of IL-18 with endogenously produced IL-12 on IFN-γ production (Fig. 5). Higher concentrations of anti-IL-12 mAb slightly increased the production of IL-10, which suggested the minor involvement of IL-12 in IL-18-induced inhibition of IL-10 production.

### Table I. Effects of anti-IL-18 mAb and caspase-1 inhibitor on cytokine responses induced by histamine and IL-18

<table>
<thead>
<tr>
<th>Additions</th>
<th>Cytokines (pg/ml)</th>
<th>IL-18</th>
<th>IL-12</th>
<th>IL-2</th>
<th>IFN-γ</th>
<th>IL-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>ND</td>
<td>ND</td>
<td>124 ± 15</td>
<td>32 ± 8</td>
<td>286 ± 35</td>
<td></td>
</tr>
<tr>
<td>Histamine (100 μM)</td>
<td>2486 ± 175</td>
<td>ND</td>
<td>24 ± 5</td>
<td>165 ± 23</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>IL-18 (2500 pg/ml)</td>
<td>–</td>
<td>15 ± 6</td>
<td>53 ± 11</td>
<td>186 ± 31</td>
<td>19 ± 5</td>
<td></td>
</tr>
<tr>
<td>IL-18 + anti-IL-18 mAb (10 ng/ml)</td>
<td>–</td>
<td>132 ± 23*</td>
<td>28 ± 12*</td>
<td>301 ± 19*</td>
<td>19 ± 5</td>
<td></td>
</tr>
<tr>
<td>Histamine + anti-IL-18 mAb (10 ng/ml)</td>
<td>ND</td>
<td>141 ± 17*</td>
<td>51 ± 16†</td>
<td>274 ± 18†</td>
<td>236 ± 27†</td>
<td></td>
</tr>
</tbody>
</table>

* The results are the means ± SEM of three different donors. 
†, p < 0.01 as compared with the corresponding value in the presence of histamine alone.
Effect of histamine on IL-18, IL-12, IL-2, IFN-γ, and IL-10 production in T cell/monocyte-rich and B cell-rich populations

We fractionated PBMCs into T cell/monocyte-rich and B cell-rich populations. Using these two cellular preparations, we examined the cellular predominance of histamine-induced cytokine response. Table II summarizes the results. The IL-18 response to histamine in the B cell-rich fraction was about one-tenth of that in the T cell/monocyte-rich fraction. Moreover, no IFN-γ response to histamine was observed in the B cell-rich fraction. Therefore, it was concluded that the cytokine response to histamine mainly occurred in the T cell/monocyte-rich fraction.

Determination of histamine and tele-methylhistamine levels in the conditioned media after the incubation of PBMCs with IL-18

Histamine levels in the conditioned medium in the presence of IL-18 (0.1–10 ng/ml) were determined at 2, 12, and 24 h after the start of culture. There were no increases in the histamine and tele-methylhistamine concentrations in the conditioned media at any time intervals.

Discussion

In the present study, we revealed that histamine exerted profound effects on the cytokine production in human PBMCs. Histamine-induced responses of IL-18, IL-2, IFN-γ, and IL-10 were all concentration-dependently antagonized by H₂ receptor antagonists, famotidine and ranitidine, but not by H₁ and H₃ receptor antagonists, and the effects of histamine were mimicked by selective H₂ receptor agonists dimaprit and 4-methylhistamine. The relative potencies of three agonists were similar to those previously reported on H₂ receptors in different tissues (39, 40). All these findings as a whole indicated that the effects of histamine on the plural cytokine responses were solely mediated by the stimulation of H₂ receptors.

Originally, IL-18 was identified as an IFN-γ-inducing factor in the mouse liver that augmented NK activity in the spleen cells (1). The synergistic action of IL-18 with IL-12 has been reported for the production of IFN-γ (10, 12, 13, 41, 42). Yoshimoto et al. (12) demonstrated that IL-12 up-regulated the expression of IL-18 receptors in T cells, Th1 cells, and B cells, which enabled the synergistic production of IFN-γ. In contrast, IL-18 can stimulate IFN-γ production in an IL-12-independent manner in KG-1, a monocytic cell line (15). In the present study, the dose-response curve of IL-18 for the production of IFN-γ was steep between 0.1 and 1 ng/ml, suggesting the amplification of the effect of IL-18 in this concentration range. In fact, IL-12 production was detected at 1 ng/ml of IL-18 or above. Moreover, the IFN-γ production induced by IL-18 was inhibited by 80% by the addition of anti-IL-12 Ab, confirming the synergistic action of IL-18 and IL-12 in IFN-γ production in human PBMCs.

In contrast to the IL-18-induced IFN-γ production, histamine induced IFN-γ production without inducing IL-12 production.

Table II. Cytokine responses to histamine in T cell/monocyte and B cell fractions

<table>
<thead>
<tr>
<th>Cytokines (pg/ml)</th>
<th>IL-18</th>
<th>IL-12</th>
<th>IL-2</th>
<th>IFN-γ</th>
<th>IL-10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T cell + Monocytes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histamine (M)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>ND</td>
<td>ND</td>
<td>32 ± 11</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>10⁻⁷</td>
<td>16 ± 7</td>
<td>ND</td>
<td>13 ± 3*</td>
<td>12 ± 2*</td>
<td>ND</td>
</tr>
<tr>
<td>10⁻⁶</td>
<td>126 ± 16*</td>
<td>ND</td>
<td>ND</td>
<td>25 ± 12*</td>
<td>ND</td>
</tr>
<tr>
<td>10⁻⁵</td>
<td>356 ± 54*</td>
<td>ND</td>
<td>ND</td>
<td>63 ± 8*</td>
<td>ND</td>
</tr>
<tr>
<td>10⁻⁴</td>
<td>1018 ± 19*</td>
<td>ND</td>
<td>ND</td>
<td>89 ± 5*</td>
<td>ND</td>
</tr>
<tr>
<td><strong>B cell</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histamine (M)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>32 ± 8</td>
<td>ND</td>
</tr>
<tr>
<td>10⁻⁷</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>11 ± 3*</td>
<td>ND</td>
</tr>
<tr>
<td>10⁻⁶</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>10⁻⁵</td>
<td>34 ± 4*</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>10⁻⁴</td>
<td>121 ± 47*</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

* The T cell/monocyte-rich and B cell-rich fractions were prepared as described in Materials and Methods. The results are the means ± SEM of three different donors.

* p < 0.05 as compared with the value in the presence of IL-18 alone.

* p < 0.01 compared with the corresponding value in the absence of histamine.
concentrations of IL-18 detected in the presence of histamine at 1 μM was above 1 ng/ml, and this concentration was sufficient to induce IL-12 production as shown in Fig. 1. However, histamine did not induce any IL-12 production at all even at 100 μM. This strongly suggested that, independent of the IL-18-inducing effect, histamine had strong inhibitory effects on IL-12 production. Thus, it is quite likely that the IFN-γ production induced by histamine was not dependent on IL-12. Recently, two groups have reported that IL-12 production was inhibited by histamine through the interaction of H3 receptors using human whole blood (44) and human monocyte cultures (44), respectively. Thus it is possible that histamine through the stimulation of H3 receptors inhibited IL-18 receptor-mediated production of IL-12 in PBMCs.

The pattern of IL-18-induced effects on cytokine production was the same as that of histamine except for IL-12 production, strongly suggesting that the activation cascade after IFN-γ production was common to both stimulations. Because it was already reported that IFN-γ strongly inhibited IL-10 production in PBMCs (45), it is likely that the response of IL-10 was considered to be present in the downstream IFN-γ response. Inhibition of IL-2 production by histamine and IL-18 was antagonized with anti-IL-18 mAb, suggesting that IL-18 directly inhibited the production of IL-2. Monocyte/macrophage was identified as an IL-18-producing cell (1). Consistent with this finding, histamine-induced IL-18 production was observed in the T cell/monocyte-rich fraction but not in the B cell-rich fraction. The responses of IFN-γ and IL-2 to histamine were also present in the T cell/monocyte-rich fraction. Thus, cytokine responses to histamine as well as IL-18 occurred in the T subset. Further research is necessary to clarify this topic.

It has been suggested that histamine functions as an immune-modulator (32, 35). However, the effects of histamine on immune cells have proved controversial (35). We showed here that histamine can trigger the IL-18-initiating Th1 cytokine cascade in PBMC. Because IL-18 up-regulates perforin-mediated NK activity (46) and histamine was reported to enhance NK cell activity (47), it is possible that the effect of histamine on NK activity may be mediated by IL-18 secretion. Dohlsht et al. (48) observed that histamine inhibited the production of IFN-γ in activated PBMCs, while Asea et al. reported that histamine enhanced the production of IFN-γ in NK cells cocultured with monocytes by reducing monocyte production of reactive oxygen species (49). Both effects were reported to be mediated by H3 receptors (48, 49), suggesting that H3 receptors are present on many subsets of lymphocytes and that the stimulation of these receptors differentially regulates the production of IFN-γ depending on the activation state of each subset. Further research is necessary to clarify this topic.

While we could not detect any increase in histamine or its major metabolite tele-methylhistamine in the conditioned media of PBMCs in the presence of IL-18, the induction of histidine decarboxylase was reported in monocyte/macrophage (26) and T lymphocytes (27) by LPS, IL-1, and TNF-α (50). Such inducible histamine appeared to be released after the synthesis without entering into the stable storage pool (26, 27, 50). Therefore, it is speculated that inducible histamine may regulate the host immune response by modulating cytokine production in PBMCs. In the same context, it is noteworthy that the elevation of histidine decarboxylase activity was observed in the spleen and lung in tumor-bearing animal models (29). It would be interesting to characterize the relationship between inducible histamine and the regulation of cytokine production.

In conclusion, we demonstrated that histamine alone is a potent inducer of IL-18 and IFN-γ production. Histamine is a storage amine of mast cells and basophils. The proliferation of the progenitor of both cells and the production of Ig E Abs are stimulated by Th2 cytokines such as IL-4, which are secreted by stimulated mast cells and basophils (51, 52). Therefore, the effects of histamine on Th1 cytokine production may function as a negative feedback on excessive Th2 response. A recent report (53) also showed that IL-18 with IL-3 can stimulate histamine release from cultured basophils, suggesting the presence of a positive feedback system between histamine release and IL-18 secretion under certain conditions. Histamine appears to play much more diverse effects on immune cells than expected by modulating the cytokine production and to be a factor enabling the cross-talk between Th1 and Th2 cells.

Acknowledgments

We thank Drs. W. A. M. Duncan and D. J. Durant (The Research Institute, Smith Kline and French Laboratories) for generously donating dimaprit and 4-methylhistamine.

References


