

Enhancement of basophil histamine release by interleukin-3: reduced effect in atopic subjects

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The inducing and enhancing effects of interleukin-3 (IL-3) on basophil histamine release in patients with respiratory allergy ($n=28$) and in normal subjects ($n=22$) were compared. Leukocyte suspensions, prepared by dextran sedimentation, were stimulated with anti-IgE (1/5000), *N*-formyl-methionyl-leucyl-phenylalanine (FMLP, 1 μ M), and IL-3 (0.1–10 ng/ml), and histamine concentration was measured by an automated fluorometric method. A trend toward higher histamine release after challenge with anti-IgE, FMLP, and IL-3 was found in atopic subjects. Preincubation of basophils with IL-3 resulted in a dose-dependent increase of anti-IgE- and FMLP-induced histamine release, with a more marked effect in nonatopic than in atopic subjects. Mean net enhancement of anti-IgE-induced histamine release by 10 ng/ml IL-3 was $2.5 \pm 5\%$ in atopic subjects and $29.6 \pm 4.2\%$ in nonatopic subjects ($P < 0.001$). The enhancement of FMLP-induced histamine release by IL-3 was $10.3 \pm 3.9\%$ in atopic patients and $29 \pm 2.4\%$ in nonatopic subjects ($P < 0.01$). In atopic subjects, a negative correlation was found between anti-IgE- or FMLP-induced histamine release and net enhancement by IL-3 ($r = -0.45$, $P < 0.02$; $r = -0.48$, $P < 0.01$, respectively). The results of this study indicate that in atopic subjects IgE-mediated histamine release can scarcely be enhanced by a basophil response modifier such as IL-3. It is conceivable that the frequent basophil stimulation in atopic patients leads to a reduced sensitivity to the enhancing effect of IL-3.

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Human basophils play an important role in allergic and inflammatory reactions since they may release potent inflammatory mediators, such as histamine and leukotriene C₄, on challenge by IgE-dependent and IgE-independent stimuli (1–5). One of the major mechanisms of activation of these cells is the allergen–IgE antibody interaction, which is followed by a cascade of biochemical events leading to mediator release. In addition, mediator release can be induced by complement anaphylatoxins, formylmethionine-containing peptides, concanavalin A, and calcium ionophores (6–10). Recently, it has been observed that several histamine-releasing factors (HRFs), generated by activated lymphocytes, monocytes, and neutrophils, may modulate

histamine release (11, 12). Several products of activated T cells regulate the growth and function of human basophils (13).

Among cytokines and histamine-releasing factors, interleukin-3 (IL-3) is a unique molecule, since it induces basophil growth and differentiation from precursors in bone marrow and cord blood (14–16), and modulates their response to various agonists. It has been demonstrated that IL-3 is a potent enhancer of histamine release from human basophils stimulated by anti-IgE (17, 18), *N*-formyl-methionyl-leucyl-phenylalanine (FMLP) (17), C5a (17, 19), C3a (20), and platelet-activating factor (PAF) (21). This cytokine can also change the profile of mediator release, since basophils exposed

to IL-3 generate large amounts of leukotriene C_4 in response to C5a, which by itself causes only histamine release and is unable to promote lipid-mediator formation (19). There is evidence that IL-3 can induce direct histamine release from basophils, predominantly of atopic subjects (18, 22, 23). Furthermore, we have found that IL-3 may directly induce histamine release from the basophils of normal subjects when the inhibitory effect of extracellular sodium has been relieved (24). Therefore, IL-3 is not only a basophil response modifier, but may also be considered a weak agonist, which has the capacity to induce histamine release when basophil releasability is upregulated, as happens in allergic patients, or when the inhibitory effect of sodium has been relieved. It has been demonstrated that basophil releasability is increased in patients with respiratory allergy (25, 26). The increased capacity of basophils from allergic patients to release histamine upon stimulation could depend on intrinsic cellular properties as well as on the presence of extrinsic factors (i.e., cytokines, histamine-releasing factors) enhancing mediator release. Since IL-3 may be the most important cytokine regulating histamine release from human basophils, we decided to compare its inducing and enhancing effects on histamine release from basophils of patients with respiratory allergy and normal subjects.

Material and methods

Patients and controls

Twenty-eight adult patients with respiratory allergy (11 with allergic rhinitis and 17 with allergic bronchial asthma) were included in the study. Twelve patients were men and 16 women, and the mean age was 28.8 ± 1.7 years. Respiratory allergy was diagnosed by a detailed clinical history, physical examination, and positive skin prick tests for one or more inhalant allergens. Four patients were allergic to grass pollen, five to house-dust mite, one to *Parietaria*, and one to birch pollen, and 17 were sensitized to two or more of the above allergens. Twenty-two normal donors were used as control: seven men and 16 women whose mean age was 28.5 ± 1.4 years. These subjects were defined as normal and nonatopic on the basis of clinical history, physical examination, and negative skin prick tests. Informed consent was obtained from each subject before blood collection.

Blood sample collection and preparation of leukocyte suspensions

Peripheral venous blood (50–60 ml) was obtained by venipuncture of the antecubital vein. Leukocyte

suspensions were prepared by dextran sedimentation of peripheral venous blood, anticoagulated with 0.01 M EDTA (Sigma Chemical, St Louis, MO, USA) and mixed with 6% dextran in saline solution (Solplex 70, Sifra, Verona, Italy) and 30 mM dextrose (Sigma Chemical). The cells were allowed to sediment for 60–90 min at room temperature, according to Lichtenstein & Osler (3). The leukocyte-rich plasma was centrifuged at 300 g for 15 min at 4°C, and the cell button was washed twice in Tyrode's buffer, pH 7.4, containing (mM): NaCl 140, dextrose 5.5, KCl 2.7, NaH_2PO_4 0.36, and $NaHCO_3$ 12. The cells were then suspended in Tyrode's buffer with 1.8 mM $CaCl_2$ and 0.5 mM $MgCl_2$. Basophil concentration in leukocyte suspensions was evaluated by Alcian blue staining (27) and subsequent counting in a Fuchs-Rosenthal chamber (Walter Schrenk, Hofheim am Taunus, Germany). Basophil concentration ranged between 0.5 and 2%; other cells were polymorphonuclear leukocytes, including eosinophils, lymphocytes, monocytes, and platelets. When cell viability was assessed by trypan blue (Merck, Darmstadt, Germany) exclusion, all leukocyte suspensions were greater than 95% viable.

Histamine release from leukocyte suspensions

Basophil stimulation was performed in 12 by 75 mm polyethylene tubes (LP Italiana, Milan, Italy). Briefly, $2-4 \times 10^4$ basophils, suspended in 0.5 ml Tyrode's buffer with $CaCl_2$ and $MgCl_2$, were added to prewarmed tubes (37°C) containing 0.5 ml of the same solution with the activating agent. Polyclonal goat antihuman IgE (ϵ -chain specific) was purchased from Sigma Chemical and was used at the final dilution of 1/5000, corresponding to a protein concentration of 10 μ g/ml. FMLP (Sigma Chemical) was used at the final concentration of 1 μ M, and recombinant human IL-3 (Amersham, Aylesbury, UK) was used at concentrations ranging from 0.1 to 10 ng/ml. After mixing and incubating for 60 min at 37°C, the reaction was stopped by centrifugation at 1000 g for 20 min at 4°C. For assessment of the priming effect of IL-3, leukocyte suspensions were preincubated for 30 min at 37°C with IL-3 (0.1, 1, and 10 ng/ml) and then stimulated with anti-IgE (1/5000) or FMLP (1 μ M) for 30 min at 37°C. After centrifugation, the supernatants were aspirated, mixed with an equal volume of 6% $HClO_4$, and centrifuged at 2000 g for 15 min at 4°C. Histamine concentration in the supernatants was measured by automated fluorometry (28). Spontaneous histamine release was evaluated by measuring histamine concentration in the supernatant of unstimulated cells; total histamine content was obtained by adding 0.5 ml 6% $HClO_4$ to 0.5 ml cell

suspension. Net histamine release (HR) was calculated as percentage of total histamine content after subtraction of spontaneous release. Net enhancement of anti-IgE- or FMLP-induced histamine release by IL-3 was calculated by the following formula, modified from Hirai et al. (29) and Sugiyama et al. (30):

$$\text{enhancement} = \% \text{ HR induced by stimulus plus IL-3} - \% \text{ HR induced by stimulus} - \% \text{ HR induced by IL-3}$$

In this way, the variability of enhancement was minimized.

Every experiment was carried out in duplicate, and the average difference between replicate determinations was less than 5%. None of the reagents employed in this study interfered with the fluorometric determination of histamine concentration or modified cell viability, as assessed by trypan blue exclusion.

Statistical analysis

The results were expressed as the mean $\pm$ SEM. The two-tailed Student's *t*-test for paired and unpaired data and mixed factorial analysis of variance for repeated measures were used for statistical analysis. The multiple contrasts were performed with Bonferroni's correction of the significance level. Correlation was evaluated by linear regression, calculated according to the least-squares method. *P* values lower than 0.05 were considered significant.

Results

Spontaneous histamine release and basophil response to anti-IgE and FMLP

Mean spontaneous histamine release was $1.6 \pm 0.1\%$ in control subjects and $3.7 \pm 0.8\%$ in allergic patients, with a significant difference between the two populations ($P < 0.03$). Anti-IgE-induced histamine release was $22.5 \pm 4.6\%$ in non-atopic subjects and $30.3 \pm 4.9\%$ in atopic subjects. The corresponding values for FMLP-induced histamine release were $36.3 \pm 3.5\%$ and $41.8 \pm 3.6\%$.

Evaluation of the histamine-releasing activity of IL-3

No differences were found between patients with rhinoconjunctivitis and bronchial asthma, in relation to the response to IL-3, so that the results of the two groups were pooled together. IL-3 caused histamine release above 5% of total histamine content in five allergic patients out of 28 (18%), whereas none of the normal subjects showed histamine release above 5% in response to IL-3. Although there was a trend toward a higher

response to IL-3 in allergic patients, the difference between allergics and nonallergics was not statistically significant. The effect of IL-3 was dose-dependent and more marked at the highest dose employed (10 ng/ml) (Fig. 1). No significant correlation was found between basophil response to IL-3 and spontaneous, anti-IgE- or FMLP-induced histamine release either in normal or in allergic subjects.

Enhancing effect of IL-3 on histamine release induced by anti-IgE and FMLP

In the normal subjects, preincubation of basophils with IL-3 resulted in significant enhancement of the histamine release induced by anti-IgE and FMLP. Histamine release induced by anti-IgE plus IL-3 10 ng/ml was $52.8 \pm 5.4\%$ vs $22.5 \pm 4.6\%$ induced by anti-IgE alone ($P < 0.0002$). Accordingly, preincubation with IL-3 10 ng/ml caused an increase of basophil histamine release induced by FMLP from $36.3 \pm 3.5\%$ to $66.01 \pm 3.6\%$ ($P < 0.0001$). The enhancing effect of IL-3 was much lower in the allergic subjects. Histamine release induced by anti-IgE plus IL-3 10 ng/ml was $38.4 \pm 5.5\%$ vs $30.3 \pm 4.9\%$ induced by anti-IgE alone (NS); FMLP-induced histamine release was $41.8 \pm 3.6\%$ without IL-3 and $57.6 \pm 3.3\%$ in the presence of IL-3 ($P < 0.003$).

The difference between histamine release induced by anti-IgE with IL-3 and histamine release induced by anti-IgE alone was $8.1 \pm 4.5\%$ in allergic patients and $30.3 \pm 4.2\%$ in controls, with a significant difference between the two populations ($P < 0.01$). Furthermore, the difference between histamine release induced by FMLP plus IL-3 and histamine release induced by FMLP alone was $15.8 \pm 4.1\%$ and $29.6 \pm 2.5\%$, respectively ($P < 0.05$).

When net enhancement of histamine release induced by IL-3 was calculated, it was found that IL-3 and anti-IgE or FMLP had clearly supradlative effects on histamine release in normal subjects; conversely, in allergic patients, the effects of IL-3 and anti-IgE were simply additive and the effects of IL-3 and FMLP were slightly supradlative. Furthermore, in some allergic patients, preincubation with IL-3 10 ng/ml resulted in a lower histamine release than that obtained by stimulating basophils with anti-IgE ($n = 6$) or FMLP alone ($n = 8$). As Fig. 2 shows, mean net enhancement of anti-IgE-induced histamine release by 10 ng/ml IL-3 was $2.5 \pm 5\%$ in atopic subjects and $29.6 \pm 4.2\%$ in nonatopic subjects ($P < 0.001$). Similarly, mean net enhancement of FMLP-induced histamine release by IL-3 was $10.3 \pm 3.9\%$ in atopic subjects and $29 \pm 2.4\%$ in nonatopic subjects ($P < 0.01$) (Fig. 3).

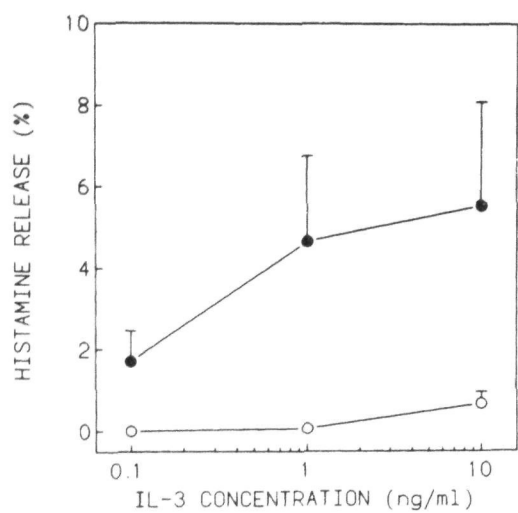


Fig. 1. Histamine release induced by IL-3 (0.1–10 ng/ml) from basophils of normal subjects ($n=22$) (○) and atopic subjects ($n=28$) (●). Results are expressed as mean $\pm$ SEM.

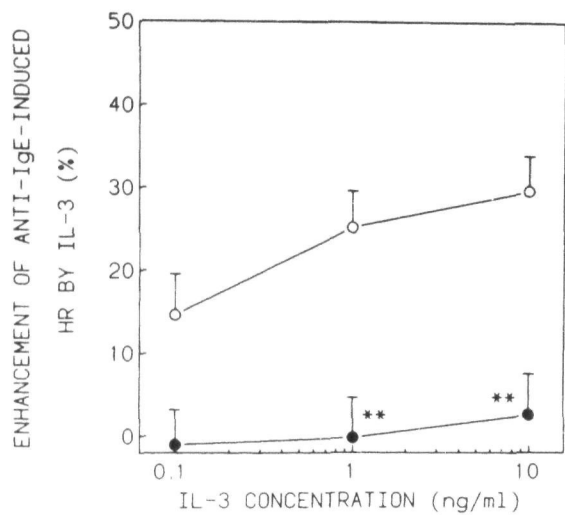


Fig. 2. Enhancing effect of IL-3 (0.1–10 ng/ml) on anti-IgE-induced histamine release (HR) from basophils of normal subjects ($n=22$) (○) and atopic subjects ($n=28$) (●). Net enhancement was calculated by subtracting histamine release induced by single agents (anti-IgE and IL-3) from histamine release induced by both agents together. Results are expressed as mean $\pm$ SEM. ** $P<0.01$ vs release obtained in normal subjects.

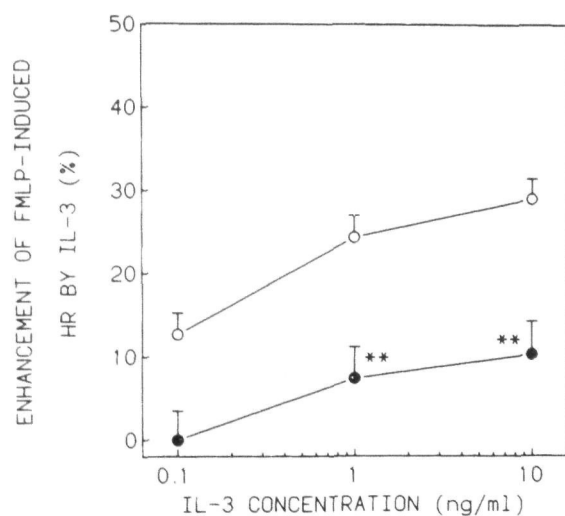


Fig. 3. Enhancing effect of IL-3 (0.1–10 ng/ml) on FMLP-induced histamine release from basophils of normal subjects ($n=22$) (○) and atopic subjects ($n=28$) (●). Results are expressed as mean percentage $\pm$ SEM. ** $P<0.01$ vs release obtained in normal subjects.

In the allergic patients, the enhancement of anti-IgE-induced histamine release by IL-3 was negatively correlated with histamine release induced by anti-IgE alone ($r=-0.45$, $P<0.02$). The enhancement of FMLP-induced histamine release by IL-3 was also negatively correlated with histamine release induced by FMLP alone ($r=-0.48$, $P<0.01$). No correlation was found in the normal subjects between the enhancement of anti-IgE- or FMLP-induced histamine release by IL-3 and histamine release induced by anti-IgE or FMLP alone.

Relation between the priming effect of IL-3 and the magnitude of basophil response to anti-IgE and FMLP

To assess whether the enhancing effect of IL-3 on histamine release is related to the magnitude of basophil response to anti-IgE and FMLP, we divided the subjects included in the study into three groups according to basophil response to anti-IgE and FMLP (Table 1). Basophils releasing 0–20% of total histamine content were classified as low responders; basophils releasing 20–50% were considered intermediate responders, and when histamine release was above 50%, basophils were considered high responders. As Fig. 4 shows, IL-3 exerted a significant enhancing effect on anti-IgE-induced histamine release in the normal subjects whatever the basophil response to anti-IgE, although the effect was more marked in low and intermediate responders than in high responders. In contrast, in allergic patients, IL-3 caused a significant enhancement of anti-IgE-induced histamine release only in low responders ($P<0.05$), whereas no enhancement was found in intermediate and high responders. The picture was similar when the effect of FMLP-induced histamine release was analyzed. IL-3 caused a significant enhancement of FMLP-induced histamine release in the normal subjects, independently of the extent of basophil response. In the allergic patients, IL-3 caused a significant

Table 1. Classification of subjects according to magnitude of basophil response to anti-IgE and FMLP

	Allergic subjects	Normal subjects
	($n=28$)	($n=22$)
Anti-IgE		
Low responders (<20%)	11 (39.3%)	12 (54.5%)
Intermediate responders (20–50%)	11 (39.3%)	6 (27.3%)
High responders (>50%)	6 (21.4%)	4 (18.2%)
FMLP		
Low responders (<20%)	3 (10.8%)	4 (18.2%)
Intermediate responders (20–50%)	16 (57.1%)	14 (63.6%)
High responders (>50%)	9 (32.1%)	4 (18.2%)

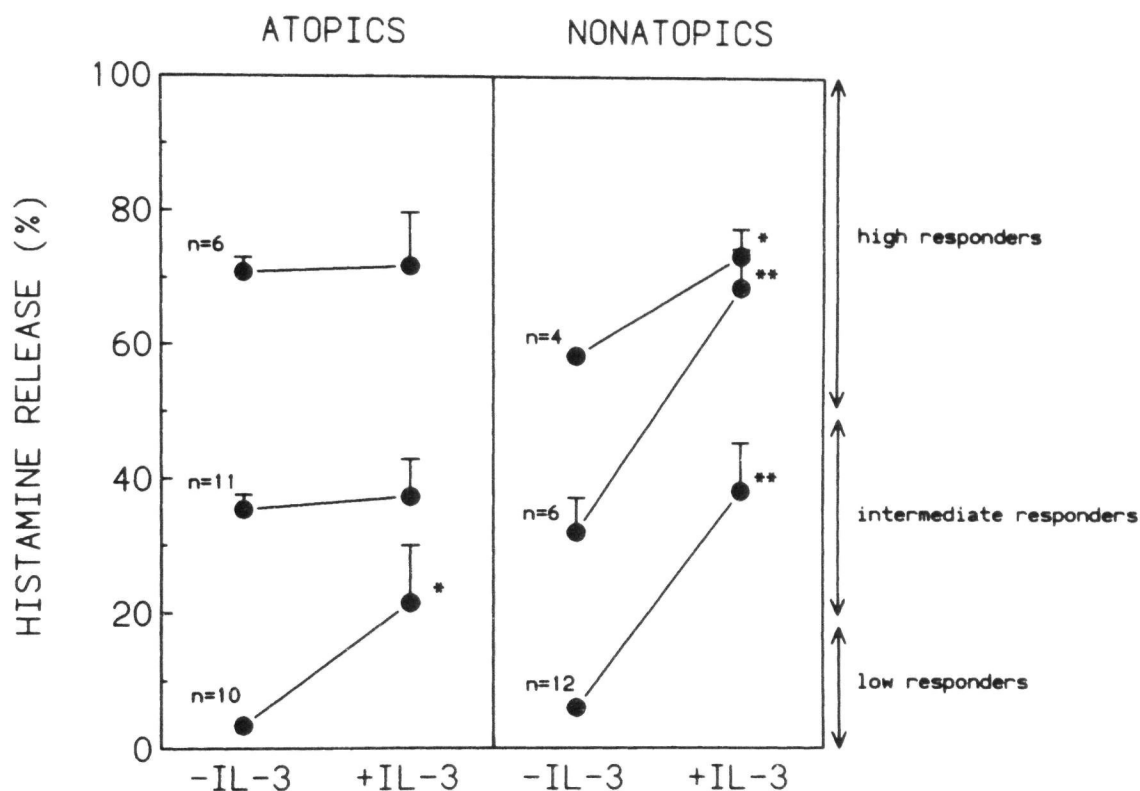


Fig. 4. Effect of IL-3 (10 ng/ml) on basophil histamine release induced by anti-IgE in low, intermediate, and high responders. Atopic and nonatopic subjects were divided into three groups according to basophil response to anti-IgE (Table 1). For each group, we compared histamine release induced by anti-IgE alone and by anti-IgE plus IL-3. Significant enhancement of anti-IgE-induced histamine release was found in normal subjects independently of extent of basophil response to anti-IgE; conversely, in atopic subjects, significant enhancement was found only in low-responding group. Results are expressed as mean $\pm$ SEM. * $P < 0.05$ vs release obtained without IL-3; ** $P < 0.01$ vs release obtained without IL-3.

enhancement of FMLP-induced histamine release in low and intermediate responders, but not in the high responders.

Discussion

The biologic activities of IL-3 are particularly interesting for understanding the mechanisms of allergic disease, since it promotes basophil growth and differentiation, and it can enhance histamine release from stimulated basophils (17–21). Furthermore, IL-3 can provoke a direct histamine release from basophils of selected subjects, predominantly atopic ones (18, 22, 23). To further elucidate this point, which could be important for the study of allergic disease, we compared the inducing and enhancing effects of IL-3 on basophil histamine release in atopic and nonatopic subjects. There was a trend toward a higher spontaneous and stimulated histamine release in atopic than in nonatopic subjects. These results are in line with some previously published data showing higher basophil releasability in allergic patients (25, 26). Our failure to find a statistically significant difference between the two populations may be related to the number of subjects included in the study, which was too limited. In fact, large interindividual variations in basophil releasability have been described both in allergic and in normal subjects; therefore, a large number

of patients have to be examined before drawing any definite conclusion.

The most interesting feature which emerged from our data is that the enhancing effect of IL-3 on stimulated histamine release is reduced in allergic patients. We found that IL-3 is indeed a potent basophil response modifier in normal subjects, since it significantly potentiates basophil histamine release induced by anti-IgE or FMLP. In contrast, IL-3 has little enhancing effect on the basophils of atopic subjects, showing a low response to anti-IgE, whereas no enhancing effect can be observed on intermediate and high responders. When the enhancing effect of IL-3 on FMLP-induced histamine release in atopic subjects was examined, it was found that it could potentiate histamine release in low and intermediate responders, but not in high responders.

Various theories can be advanced to explain the lower enhancing effect of IL-3 on basophils from allergic subjects. It has been shown that basophils from patients with chronic urticaria have reduced releasability, probably because of chronic stimulation (31). It is conceivable that basophils from atopic patients are exposed to cytokines and histamine-releasing factors more often than basophils from normal subjects. This could provoke a kind of “desensitization” to the priming effect of IL-3. The picture observed when examining the enhancing effect of IL-3 resembles that observed when eval-

uating the effect of sodium on basophil histamine release. It has been demonstrated that sodium downregulates histamine release from basophils of normal subjects; that is to say, sodium removal from extracellular medium leads to a significant enhancement of histamine release (24, 32).

Conversely, basophils of allergic patients release similar amounts of histamine after stimulation by anti-IgE, either in the presence or in the absence of extracellular sodium (33). This has been interpreted as a defective inhibitory activity of sodium. The failure to find an enhancement of histamine release from basophils of allergic patients after sodium removal from extracellular medium is in line with the inability of IL-3 to potentiate IgE-mediated histamine release. Therefore, two conditions which are characterized by an increased basophil response do not enhance IgE-mediated histamine release in allergic patients. A possible explanation of this phenomenon is that basophils from each individual have a determined releasability, and the response to IgE-mediated stimulation of basophils from allergic patients is maximal in relation to the individual capacity: therefore, further enhancement of release by IL-3 or sodium removal can hardly be obtained. This is also in line with the negative correlation between anti-IgE-induced histamine release and the enhancement induced by IL-3. Moreover, in atopic patients, IL-3 enhanced anti-IgE-induced histamine release only in low-responding basophils, whereas no potentiation of histamine release from intermediate- and high-responding basophils was observed. Indeed, it seems that basophils from intermediate and high responders in allergic subjects release the maximal amount of histamine in relation to the individual releasability.

Beauvais et al. have demonstrated that the potentiation of anti-IgE-induced histamine release by human basophils involves the activation of a sodium-calcium exchanger (34), since the activity of IL-3 can be antagonized by the amiloride derivative benzamil, a specific inhibitor of the sodium-calcium exchanger. Furthermore, no enhancement of histamine release by IL-3 can take place when basophils are suspended in a sodium-free medium, where sodium-calcium exchanges are markedly reduced. Another hypothetic explanation of our data is that the IL-3-sensitive sodium-calcium exchanger is less efficient in the basophils of allergic patients.

In conclusion, our findings confirm that IL-3 is a potent enhancer of basophil histamine release in normal subjects, but also indicate that this effect is much weaker in allergic patients, particularly when basophils are activated by anti-IgE. Although basophils from allergic patients are more prone to

release histamine after IgE-mediated stimulation, our data indicate that this release is barely enhanced by IL-3.

References

1. Galli SJ, Lichtenstein LM. Biology of mast cells and basophils. In: Middleton E Jr, Reed CE, Ellis EF, et al, editors. *Allergy: principles and practice*. St Louis, MO: Mosby, 1988:106-34.
2. Grant JA, Lett-Brown MA, Warner JA, et al. Activation of basophils. *Fed Proc* 1986;45:2653-8.
3. Lichtenstein LM, Osler AG. Study on the mechanism of hypersensitivity phenomena. IX. Histamine release from human leukocytes by ragweed pollen antigens. *J Exp Med* 1964;120:507-30.
4. Siraganian RP, Hook WA. Complement induced histamine release from human basophils. II. Mechanism of the histamine release reaction. *J Immunol* 1976;116:639-46.
5. Siraganian RP, Hook WA. Mechanism of histamine release by formylmethionine-containing peptides. *J Immunol* 1976;119:2078-83.
6. Grant JA, Dupree E, Goldman AS, Schultz DR, Jackson AL. Complement mediated release of histamine from human leukocytes. *J Immunol* 1975;114:1101-6.
7. Hartman CT, Glovsky H. Complement activation requirements for histamine release from human leukocytes: influence of purified C3a_{hu} and C5a_{hu} on histamine release. *Int Arch Allergy Appl Immunol* 1981;66:274-81.
8. Hook WA, Schiffman E, Aswanikumar S, Siraganian RP. Histamine release by chemotactic, formylmethionine-containing peptides. *J Immunol* 1976;117:594-6.
9. Lichtenstein LM. The mechanism of basophil histamine release induced by antigen and the calcium ionophore A23187. *J Immunol* 1975;114:1692-9.
10. Siraganian PA, Siraganian RP. Basophil activation by concanavalin A. Characteristics of the reaction. *J Immunol* 1974;112:2117-25.
11. Kaplan AP, Reddigari S, Baeza M, Kuna P. Histamine releasing factors and cytokine-dependent activation of basophils and mast cells. *Adv Immunol* 1991;50:237-60.
12. Lett-Brown MA, Alam R, Grant JA. Regulation of basophil and mast cell activation by cytokines. In: Sorg C, editor. *Cytokines regulating the allergic response: cytokines*. Vol 12. Basel: Karger, 1989:90-9.
13. Goetzl EJ, Foster DW, Payan DG. A basophil-activating factor from human T lymphocytes. *Immunology* 1984;53:227-34.
14. Otsuka T, Miyajima A, Brown N, et al. Isolation and characterization of an expressible cDNA encoding human IL-3. *J Immunol* 1988;140:2288-95.
15. Saito H, Hatake K, Dvorak AM, et al. Selective differentiation and proliferation of hematopoietic cells induced by recombinant human interleukins. *Proc Natl Acad Sci U S A* 1988;85:2288-92.
16. Valent P, Schmidt G, Besemer J, et al. Interleukin-3 is a differentiation factor for human basophils. *Blood* 1989;73:1763-9.
17. Kurimoto Y, de Weck AL, Dahinden CA. The effect of interleukin-3 upon IgE-dependent and IgE-independent basophil degranulation and leukotriene generation. *Eur J Immunol* 1991;21:361-8.
18. Macdonald SM, Schleimer RP, Kagey-Sobotka A, Gillis S, Lichtenstein LM. Recombinant IL-3 induces histamine release from human basophils. *J Immunol* 1989;142:3527-32.
19. Kurimoto Y, de Weck AL, Dahinden CA. Interleukin

- 3-dependent mediator release in basophils triggered by C5a. *J Exp Med* 1989;170:467-79.
20. Bischoff SC, de Weck AL, Dahinden CA. Interleukin 3 and granulocyte/macrophage-colony-stimulating factor render human basophils responsive to low concentrations of complement C3a. *Proc Natl Acad Sci USA* 1990;87:6813-17.
21. Brunner T, de Weck AL, Dahinden CA. Platelet-activating factor induces mediator release by human basophils primed with IL-3, granulocyte-macrophage colony-stimulating factor, or IL-5. *J Immunol* 1991;147:237-42.
22. Miadonna A, Roncarolo MG, Lorini M, Tedeschi A. Inducing and enhancing effects of IL-3, -5, and -6 and GM-CSF on histamine release from human basophils. *Clin Immunol Immunopathol* 1993;67:210-15.
23. Okayama Y, Begishvili B, Church MK. Comparison of mechanisms of IL-3 induced histamine release and IL-3 priming effect on human basophils. *Clin Exp Allergy* 1993;23:901-10.
24. Tedeschi A, Palella M, Milazzo N, Lorini M, Miadonna A. IL-3-induced histamine release from human basophils. Dissociation from cationic dye binding and down-regulation by Na⁺ and K⁺. *J Immunol* 1995;155:2652-60.
25. Assem ESK, Attallah NA. Increased release of histamine by anti-IgE from leukocytes of asthmatic patients and possible heterogeneity of IgE. *Clin Allergy* 1981;11:367-74.
26. Gaddy NK, Busse WW. Enhanced IgE-dependent basophil histamine release and airway reactivity in asthma. *Am Rev Respir Dis* 1984;134:969-74.
27. Gilbert HS, Ornstein L. Basophil counting with a new staining method using Alcian blue. *Blood* 1975;46:279-86.
28. Siraganian RP. An automated continuous-flow system for extraction and fluorometric analysis of histamine. *Anal Biochem* 1974;57:383-94.
29. Hirai K, Morita Y, Misaki Y, et al. Modulation of human basophil histamine release by hemopoietic growth factors. *J Immunol* 1988;141:3958-64.
30. Sugiyama H, Eda R, Hopp RJ, Bewtra AK, Townley RG. Importance of interleukin-3 in histamine release from human basophils. *Ann Allergy* 1993;71:391-5.
31. Kern F, Lichtenstein LM. Defective histamine release in chronic urticaria. *J Clin Invest* 1976;57:1369-76.
32. Beauvais F, Shimahara T, Inoue I, Hieblot C, Burtin C, Benveniste J. Regulation of human basophil activation. II. Histamine release is potentiated by K⁺ efflux and inhibited by Na⁺ influx. *J Immunol* 1992;48:149-54.
33. Tedeschi A, Palella M, Cottini M, Milazzo N, Miadonna A. Impairment of the inhibitory effect of sodium on basophil histamine release in allergic patients [Abstract]. *Allergy* 1995;50:15.
34. Beauvais F, Echasserieau K, Burtin C, Benveniste J. Regulation of human basophil activation; the role of Na⁺ and Ca²⁺ in IL-3-induced potentiation of IgE-mediated histamine release from human basophils. *Clin Exp Immunol* 1994;95:191-4.

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