

SPONTANEOUS RELEASE OF HISTAMINE FROM BASOPHILS AND HISTAMINE-RELEASING FACTOR IN PATIENTS WITH ATOPIC DERMATITIS AND FOOD HYPERSENSITIVITY

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Abstract Patients with hypersensitivity to food documented by a double-blind, placebo-controlled oral food challenge have been reported to have a high rate of release of histamine from basophils in vitro. To determine whether patients with atopic dermatitis and food hypersensitivity had similar high rates of spontaneous histamine release in vitro, whether dietary elimination of relevant food antigens affected this release, and whether a cytokine, histamine-releasing factor, could account for it, we evaluated 63 patients with atopic dermatitis and food hypersensitivity (38 of whom had eliminated the offending foods from their diets), 20 patients with atopic dermatitis without food hypersensitivity, and 18 normal volunteers.

Patients with atopic dermatitis and food hypersensitivity were found to have higher rates of spontaneous release of histamine from basophils than controls (mean $\pm$ SE, 35.1 ± 3.9 percent vs. 2.3 ± 0.2 percent; $P < 0.001$). Those who had eliminated the offending food allergen from the

diet for an extended period had a significantly lower rate of histamine release (3.7 ± 0.5 percent; $P < 0.001$). In patients with atopic dermatitis without food hypersensitivity, the rate (1.8 ± 0.2 percent) did not differ from that in normal controls. Mononuclear cells from persons with food allergies spontaneously produced a histamine-releasing factor in vitro that provoked the release of histamine from the basophils of other food-sensitive persons, but not from those of normal controls. Patients who adhered to a restricted diet had a decline in the rate of spontaneous generation of the factor by their mononuclear cells. The histamine-releasing factor was found to activate basophils through surface-bound IgE.

We conclude that in patients with food hypersensitivity, exposure to the relevant antigens produces a cytokine (histamine-releasing factor) that interacts with IgE bound to the surface of basophils, causing them to release histamine. (N Engl J Med 1989; 321:228-32.)

WHILE evaluating the in vitro release of histamine by basophils in response to food antigens, May observed high rates of "spontaneous" histamine release in the basophils of 85 percent of children with food hypersensitivity as proved in a double-blind, placebo-controlled oral food challenge, but in only 5 percent of persons without food allergies.^{1,2} More than 25 percent of the total basophil histamine was released when leukocyte preparations from the cells of food-sensitive persons were incubated at 37°C without the addition of antigen or other inducers of histamine release. However, these findings were not confirmed by other investigators.^{3,4}

Our purpose in this study was to confirm May's findings, to determine whether the spontaneous release of histamine from basophils was mediated by a cytokine histamine-releasing factor, and to determine whether eliminating the relevant food antigens from the diet would affect spontaneous histamine release.

METHODS

Subjects

Eighty-three patients were evaluated who fulfilled the criteria of Hanifin and Rajka⁵ for the diagnosis of atopic dermatitis. The patients ranged in age from 2 to 23 years; approximately two thirds also had asthma and allergic rhinitis. Food hypersensitivity was diagnosed by double-blind, placebo-controlled oral food challenges, as described elsewhere.^{6,7} The selection of foods for oral challenge was based on a history of suspected adverse food reactions, plus the

results of prick skin testing and radioallergosorbent testing. Challenges were considered positive only when any of several objective symptoms developed. Cutaneous symptoms included an erythematous morbilliform rash involving more than 5 percent of the body-surface area, or urticaria; gastrointestinal symptoms included vomiting, diarrhea, or both; upper respiratory symptoms included conjunctival erythema and tearing, nasal pruritus, rhinorrhea, and sneezing; and lower respiratory symptoms included wheezing audible on auscultation or a decrease of 20 percent in the forced expiratory volume in one second. Twenty children with atopic dermatitis and no food hypersensitivity demonstrable by double-blind, placebo-controlled oral food challenge and 18 adult volunteers not allergic to foods served as controls. Informed consent was obtained for each subject, and all studies were approved by the Johns Hopkins University Joint Committee on Clinical Investigation.

Preparation of Peripheral-Blood Basophils

After we obtained informed consent, venous blood was collected in sterile plastic syringes containing EDTA (pH 7.2) at a final concentration of 25 mM. The syringes were inverted several times for proper mixing, and then the anticoagulated samples were added to detergent-free polycarbonate tubes containing 6 percent Dextran 70 (Pharmacia, Uppsala, Sweden). The erythrocytes were sedimented at room temperature for 90 minutes, and the leukocyte-containing plasma was removed. After centrifugation at $300 \times g$ for 12 minutes at 4°C, the cell pellet was washed three times in cold HEPES-buffered saline (0.01M, pH 7.4) containing 0.3 mg of human serum albumin per milliliter. The final cell pellet was resuspended and adjusted to 10 to 15×10^9 cells per milliliter in HEPES-buffered saline containing albumin, 2 mM calcium, and 1 mM magnesium (HEPES-ACM) for use in the histamine-release assay.

Preparation of Peripheral-Blood Mononuclear Cells

Venous blood from patients and controls was drawn into preservative-free heparin (7 units per milliliter) and separated over Ficoll-Hypaque solution with a modification of the method of Boyum, as described elsewhere.⁸ The final mononuclear-cell pellet was resuspended in RPMI 1640 buffered with 25 mM HEPES and containing penicillin and streptomycin (5×10^9 cells per milliliter), and cultured at 37°C in a humidified 5 percent carbon dioxide environment for 24 hours, as described initially by Thuesen et al.^{9,10} All supernatants containing histamine-releasing factor that were used in the leukocyte histamine-release assays were derived from mononuclear cells not cultured with the addition of mitogens or antigens — i.e.,

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the histamine-releasing factor was generated spontaneously. After centrifugation at $300\times g$ for 10 minutes, the cell-free supernatant was removed, dialyzed for 36 to 48 hours against HEPES-ACM to remove residual histamine, and stored at -20°C until analyzed for activity. The residual histamine concentration was consistently less than 50 pg per milliliter.

Leukocyte Histamine-Release Assay

Duplicate 50- μl aliquots of the leukocyte suspension (approximately 1.5 to 2×10^6 basophils) were incubated in polystyrene tubes containing 50 μl of prewarmed HEPES-ACM for 15 minutes at 37°C to determine the rate of spontaneous release of histamine by basophils. Similar duplicate samples were heated at 100°C for 10 minutes to measure the total histamine content. To determine the rate of histamine-releasing activity by basophils that was induced by histamine-releasing factor, we added 50 μl of supernatant from the mononuclear-cell culture to 50 μl of the leukocyte preparation (1.5 to 2×10^6 basophils) and incubated the result for 15 minutes at 37°C . The cell suspensions were centrifuged, the supernatants were removed, and the histamine content was determined with use of a sensitive radioenzymic assay, as described by Verburg et al.¹¹ This assay used purified histamine methyltransferase and gave results that were highly reproducible within the range of 30 pg to 10 ng per milliliter. The release of histamine, either spontaneously or as induced by histamine-releasing factor, was recorded as a percentage of the total leukocyte histamine content. The basophils were counted by means of toluidine blue¹² and alcian blue¹³ staining.

Lactic Acid Stripping of Basophil IgE

Surface-bound IgE was dissociated from the basophils with use of the lactic acid elution method of Pruzansky et al.¹⁴ The leukocytes were washed once in buffer and once in normal saline, resuspended in 5 ml of 0.01 M lactic acid (pH 3.0) containing 140 mM sodium chloride and 5 mM potassium chloride, and incubated for 3.5 minutes at 23°C . Cells were then diluted in 30 ml of PIPES buffer containing 25 mM PIPES, 110 mM sodium chloride, 5 mM potassium chloride, 0.003 percent human serum albumin, and 0.1 percent D-glucose and adjusted to pH 7.4 (PIPES-AG). After two washes in PIPES-AG, cells were resuspended in PIPES-AG containing 4 mM EDTA and 10 μg of heparin per milliliter.

Passive Sensitization of Lactic Acid-Treated Basophils

The method of Levy and Osler¹⁵ was used to sensitize the stripped basophils passively. Acid-treated leukocytes from three donors were incubated with serum diluted in PIPES-AG containing EDTA and heparin for 90 minutes at 37°C . Unless indicated, serum samples high in IgE from patients with myeloma or patients' serum samples were diluted to contain 417 IU of IgE per milliliter, or 250 ng per leukocyte-cell pellet. The leukocytes were then washed twice before use in the leukocyte histamine-release assays.

Statistical Analysis

The data were analyzed with the nonparametric Wilcoxon signed-ranks test for paired data or the Wilcoxon nonpaired rank-sum test for nonpaired data. The *in vitro* basophil-stripping experiments were analyzed with the paired *t*-test, after normality was confirmed by the Wilk-Shapiro test.

RESULTS

Figure 1 shows the results of the spontaneous release of histamine from basophils in 25 patients with atopic dermatitis and food hypersensitivity who had not yet begun an appropriate allergen-elimination diet (group 1; median age, 5.7; range, 0.8 to 21.2), 38 patients with atopic dermatitis and food hypersensitivity who had followed an allergen-elimination diet for at least one year (group 2; median age, 5.8; range, 0.8 to 19.3), 20 children with atopic dermatitis who were not

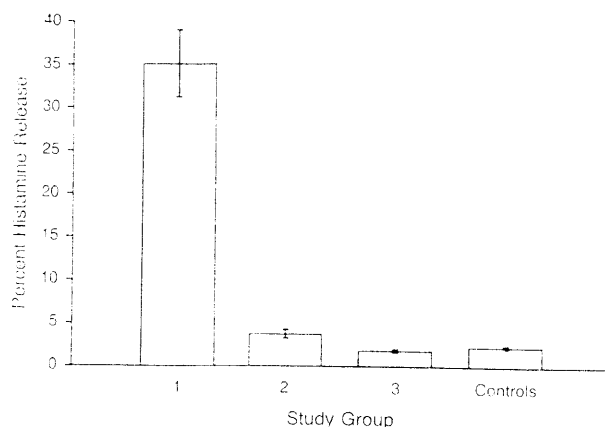


Figure 1. Mean ($\pm$ SE) Rates of Spontaneous Release of Histamine from Basophils in Three Groups of Patients with Atopic Dermatitis and a Group of Control Subjects.

Group 1 included 25 patients with recent diagnoses of food hypersensitivity who had not started an allergen-avoidance diet; group 2 included 38 patients with food hypersensitivity who had followed such a diet for one year; group 3 included 20 patients with atopic dermatitis but no food hypersensitivity. The controls were 18 volunteers with no food hypersensitivity.

sensitive to food (group 3; median age, 7.6; range, 0.3 to 25), and 18 normal volunteers (all adults) who were not allergic to food. Group 1 had significantly higher rates of spontaneous histamine release (mean $\pm$ SE, 35.1 ± 3.9 percent; range 10 to 83 percent) than normal controls (2.3 ± 0.2 percent; range, 0 to 4.6 percent; $P<0.001$), group 2 (3.7 ± 0.5 percent; range, 1 to 15 percent; $P<0.001$), and group 3 (1.8 ± 0.2 percent; range, 0.4 to 3.1 percent; $P<0.001$). No patient in group 1 had a rate of spontaneous release of histamine of less than 10 percent. Rates of histamine release above 5.5 percent (corresponding to the mean of the control values plus 3 SD) were considered elevated. As a group, the patients with food sensitivity who eliminated appropriate allergens from their diet (group 2) had significantly higher rates of spontaneous histamine release than patients with atopic dermatitis without food allergy (group 3) ($P=0.002$), but considerable overlap was seen. The rates of histamine release in patients with atopic dermatitis without food allergy (group 3) were not different from those in normal controls ($P>0.1$).

To ascertain whether the ingestion of allergens affected the activation of basophils in the short term, we undertook studies to determine whether the rate of spontaneous histamine release was altered after the ingestion of a food allergen. Twenty-two of the study patients underwent double-blind, placebo-controlled food challenges; of these patients, 14 from group 1 had not been evaluated previously and were therefore not following a restricted diet, and 8 from group 2 had documented food sensitivity and had maintained a restricted diet for approximately one year. Blood samples were obtained for leukocyte preparations before the food challenge, when the first objective symptom appeared, and 30 minutes later. In the 14 patients not

on diets, high rates of spontaneous histamine release from basophils were found before challenge (36.0 ± 5.0 percent). The rates were not altered significantly by challenge with the relevant food allergen, either at the time of the development of symptoms or 30 minutes afterward (36.9 ± 7.6 percent and 42.6 ± 7.5 percent, respectively; $P > 0.1$). In the eight patients with food sensitivity who were on restricted diets, the rates of histamine release before the food challenge were low (3.6 ± 1.2 percent), rising moderately but not significantly 30 minutes after the appearance of objective clinical symptoms (19.7 ± 4.5 percent; $0.05 < P < 0.1$). There was no difference in the number of circulating basophils in either group, before or after symptoms developed; in the 8 patients from group 1, the counts were $3.4 \pm 0.7 \times 10^6$ cells per liter before the challenge and $3.0 \pm 0.5 \times 10^6$ afterward, whereas in the 14 patients from group 2 the counts were $3.4 \pm 1.5 \times 10^6$ cells per liter before the challenge and $2.9 \pm 1.4 \times 10^6$ afterward. In addition, there was no significant difference in the total histamine content of the various leukocyte preparations obtained at different times. This would suggest that circulating basophils may have the capacity to release more histamine in response to a given signal, but are unlikely to contribute significantly to the rise in the plasma histamine level after a positive food challenge that was seen in a previous study.¹⁰

The effect of the elimination of allergens on rates of spontaneous histamine release from basophils was examined in another subset of eight patients from group 1. Rates of histamine release at diagnosis were compared with those after one year of an appropriate elimination diet in seven patients, and after four months of the diet in one patient (Patient 1), as shown in Figure 2. All the patients had a significant decrease in the rate of histamine release, with a mean decline from 38.0 ± 9.6 percent to 4.3 ± 2.1 percent ($P < 0.01$).

Since persistent circulating food antigens seemed an

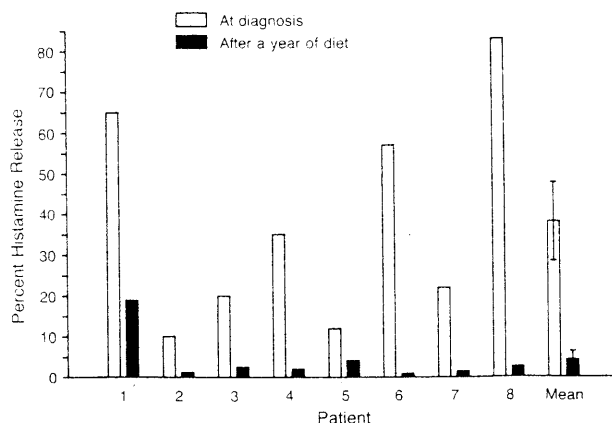


Figure 2. Rates of Spontaneous Histamine Release in Eight Patients.

The rates shown were determined at diagnosis and after one year of an appropriate allergen-avoidance diet (four months in the case of Patient 1).

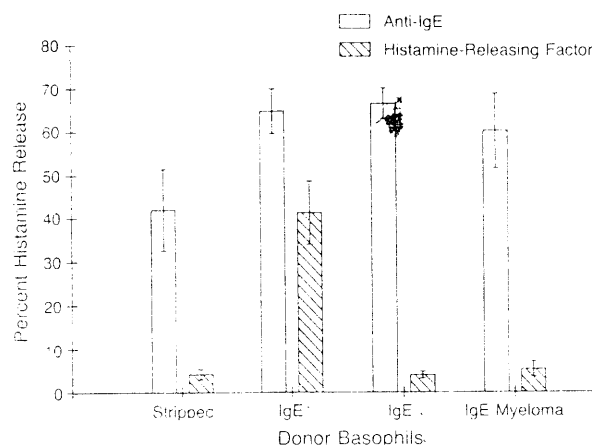


Figure 3. Mean Rates of Histamine Release from Basophils Induced by Anti-IgE Histamine-Releasing Factor after Passive Sensitization.

Basophils not responsive to histamine-releasing factor were passively sensitized with serum samples from five patients with atopic dermatitis and food allergies (containing IgE⁺), serum samples from six subjects without food allergies (containing IgE⁻), and three IgE myeloma proteins.

unlikely cause of the release of histamine noted, the possibility of a histamine-releasing factor that could activate basophils was entertained. The mononuclear-cell supernatants from 13 patients with food sensitivity and atopic dermatitis not yet following an appropriate elimination diet were added to basophils from a food-sensitive control, who was allergic to a different food. With the supernatants added, there was a significant increase in each case in the rate of histamine release as compared with the values for spontaneous release, with a mean rise of 26.9 ± 8.6 percent from 3.0 ± 1.2 percent ($P = 0.006$). Supernatants generated from the mononuclear cells of 10 subjects without food allergies produced no increase in histamine release over the rate of spontaneous release of the basophil donor. This would suggest that a histamine-releasing factor was secreted spontaneously from the mononuclear cells of patients with food allergies into the culture supernatant, probably as a result of an in vivo signal.

The spontaneous release of histamine and generation of histamine-releasing factor by mononuclear cells in vitro were examined in 10 patients with food allergies before their diagnosis of food hypersensitivity and approximately one year after they were placed on an appropriate diet for the elimination of food allergens. Aliquots of mononuclear-cell supernatants obtained at the time of diagnosis were stored frozen, to be analyzed together with samples obtained at follow-up. All the supernatants were added to basophils from the leukocytes of a single donor with food allergies for comparisons. The supernatants were also added to leukocytes from other food-sensitive basophil donors, and the results were similar. Since the rate of histamine releasability varies among basophil donors, the results of the single-donor experiment are reported. In

the 10 patients examined, the rate of spontaneous release of histamine decreased from 32.1 ± 10.0 percent (range, 2 to 83 percent) at diagnosis to 2.6 ± 0.6 percent (range, 0 to 6 percent; $0.01 < P < 0.05$) approximately one year later. The mean rate of release of histamine induced by the histamine-releasing factor generated spontaneously decreased significantly from 57.1 ± 9.3 percent (range, 3 to 87 percent) at diagnosis to 2.0 ± 0.8 percent (range, 0 to 5 percent) approximately one year later ($P < 0.01$). The institution of the elimination diet resulted in the loss of production of spontaneously generated histamine-releasing factor as well as the normalization of spontaneous histamine release from basophils.

In assaying the activity of histamine-releasing factor in different basophil donors, a variable response to the factor was found. Mononuclear-cell supernatants from patients with food sensitivity added to basophils from six donors without food allergies failed to produce an increase in the rate of histamine release over the spontaneous-release rate. Basophils from these donors had responded well to histamine-releasing factor generated by concanavalin A.

To determine whether this variability of response was intrinsic to the basophil or to the surface-bound IgE, experiments involving lactic acid stripping and passive sensitization were carried out. In accordance with the recent designation of MacDonald and co-workers,¹⁷ the IgE of patients with food allergies was termed IgE⁺, and the IgE of patients without food allergies was termed IgE⁻. Figure 3 shows how basophils obtained from three donors who did not respond to histamine-releasing factor were affected by passive sensitization with serum samples from five patients with food hypersensitivity (containing IgE⁺), serum samples from six persons without food hypersensitivity (containing IgE⁻), and three different IgE myeloma proteins. Both kinds of serum and the myeloma proteins restored the response of the stripped cells to anti-IgE, with a significantly higher rate of histamine release in the passively sensitized cells than in the stripped cells (65 percent vs. 42 percent; $P < 0.05$), but only the addition of serum samples containing IgE⁺ from patients with food allergies resulted in a significant response to histamine-releasing factor in basophils that had been unresponsive to the factor (IgE⁻, 41.2 ± 7.3 percent; IgE⁺, 4.4 ± 0.8 percent; IgE myeloma, 5.3 ± 1.8 percent; $P < 0.05$). As with the findings reported recently by MacDonald et al.¹⁷ with respect to a histamine-releasing factor derived from nasal fluid, these studies demonstrate a functional heterogeneity of IgE molecules.

DISCUSSION

These studies confirm the findings of high rates of spontaneous histamine release from basophils in patients with food hypersensitivity documented by a blinded oral food challenge, as reported by May.¹² The finding of high rates of histamine release in vitro appears to depend on the continued ingestion of the

offending food allergen. Once a patient is placed on an appropriate allergen-elimination diet for a sufficient period, histamine release returns to normal levels. On the basis of preliminary observations, it appears that patients in whom food allergy is newly diagnosed require four to six months of an allergen-avoidance diet for the rate of histamine release to decline into the normal range. On the other hand, when patients following such diets ingest a small quantity of a food allergen (as in a blinded oral food challenge), they have a brief, mild rise in the rate of spontaneous histamine release, which returns to normal after 24 hours. Therefore, in a patient with a diagnosis of food hypersensitivity, the rate of histamine release may be monitored to assess compliance with avoidance diets, to indicate a failure to detect and eliminate all relevant food allergens from the diet, or both.

The mononuclear cells of patients with newly diagnosed food hypersensitivity produced histamine-releasing factor spontaneously, as evidenced by the ability of the cell supernatants to promote the release of histamine from donor basophils. The production of this factor is probably due to the activation of mononuclear cells by an intermittent circulating food allergen in vivo, since prolonged avoidance of the food allergen results in the loss of spontaneous production of the factor. Although we have not proved that high rates of spontaneous histamine release in subjects with food allergies are due to histamine-releasing factor, there is a direct correlation between the presence of such rates and the spontaneous production of histamine-releasing factor in vitro by the mononuclear cells of patients. All patients tested who had high rates of spontaneous histamine release were found to produce histamine-releasing factor spontaneously. Conversely, no patients with normal rates of histamine release were found to generate this factor spontaneously.

It is postulated that the production of histamine-releasing factor in vivo may also lead to the increased "releasability" of histamine by basophils reported in some patients with atopic dermatitis¹⁸ and to the "cutaneous hyperreactivity" (increased pruritus due to a variety of minor stimuli, such as heat, stress, or irritants) seen in many such patients. Specific studies to test this hypothesis are under way. Patients with food allergies and atopic dermatitis who follow an appropriate elimination diet have substantial clinical improvement⁷ and decreased cutaneous responsiveness to noxious stimuli. Furthermore, bronchial hyperreactivity has recently been reported to be associated with the spontaneous generation of histamine-releasing factor by the mononuclear cells of patients with asthma.¹⁹

In examining the effects of histamine-releasing factor on basophil donors, we found that the ability of the factor to induce the release of histamine depended on the type of IgE that was bound to the cell surface. All patients with food allergies who were tested had basophils with IgE⁺, which release histamine when ex-

posed to the histamine-releasing factor derived from mononuclear cells. In addition, the passive sensitization of lactic acid-stripped basophils unresponsive to histamine-releasing factor with the IgE of patients with food allergies converts these cells into basophils responsive to the factor. Conversely, the sensitization of basophils from patients with IgE results in unresponsiveness to the histamine-releasing factor. Similar IgE heterogeneity has been reported recently by MacDonald et al.¹⁷ with respect to a histamine-releasing factor derived from nasal fluid. Several investigators have reported the production of the factor in a variety of cell types.^{9,10,19,23} How these cytokines compare in structure, mode of action, and physiologic effect remains to be determined.

From these studies it is apparent that IgE-mediated hypersensitivity is much more complex than was thought in the classic formulation of Gell and Coombs.²⁴ The production of cytokines capable of interacting with the IgE that is bound to the surface of basophils and mast cells may play an important part in the prolonged reactivity of target organs (such as the skin in atopic dermatitis, or the lung in asthma) and provide a better explanation of the characteristic clinical manifestations of atopic disorders.

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