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Histamine-releasing factors and inhibitors: Historical perspectives and possible implications in human illness

J. Andrew Grant, MD, Rafeul Alam, MD, PhD,* and Michael A. Lett-Brown, PhD *Galveston, Texas*

The initiation of allergic reactions with the bridging of surface-bound IgE antibodies on mast cells and basophils by allergens is well recognized. However, it is clear that other factors most likely play a role in regulating these cells. A number of cytokines have been identified that modulate the secretory response of mast cells and basophils. Among the well-characterized cytokines, interleukin-3 and connective tissue–activating peptide III (or its degradation product, neutrophil-activating peptide 2) can increase the secretory response, whereas interleukin-8 specifically inhibits the response to cytokines. Additional factors are currently under investigation. Preliminary studies suggest an important role for these histamine-releasing factors in atopic disorders, as well as in other conditions in which an IgE-dependent mechanism is not demonstrable. Furthermore, these cytokines may modulate the response of basophils and mast cells in physiologic conditions, such as tissue repair and host defense. (J ALLERGY CLIN IMMUNOL 1991;88:683-93.)

Key words: *Histamine-releasing factor, histamine, interleukins, basophils, hypersensitivity*

From the Allergy and Immunology Division, Department of Internal Medicine, The University of Texas Medical Branch at Galveston, Galveston, Texas.

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Reprint requests: J. Andrew Grant, MD, University of Texas Medical Branch, Route G-62, Galveston, TX 77550.

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The cross-linking of adjacent IgE Abs is a necessary feature for initiating basophil and mast cell secretion by allergens; however, this single event may not be sufficient to explain the induction of human atopic illness. This classic theory of allergic hypersensitivity now must be tempered by newer developments. Furthermore, increased numbers of basophils and mast cells are often observed in conditions in which an IgE-dependent mechanism is not apparent.[1, 2] A number of other physiologic triggers for these cells have been identified, including IgG Abs,[3] anaphylatoxins,[4] neuropeptides (such as substance P),[5] serum protein frag-

Abbreviations used

Ag:	Antigen
LPR:	Late-phase response
HR:	Histamine release
HRA:	Histamine-releasing activity
HRIF:	Histamine release inhibitory factor
HRF:	Histamine-releasing factor
MAb:	Monoclonal antibody
IL:	Interleukin
NAP:	Neutrophil-activating peptide
CTAP:	Connective tissue-activating peptide
BH:	Bronchial hyperreactivity
GM-CSF:	Granulocyte-macrophage colony-stimulating factor
Ab:	Antibody
MNC:	Mononuclear cell

ments,[6] and other granulocyte granular constituents (such as eosinophil major basic protein).[7] The role of cytokines has been an active area of recent investigations. Effects of cytokines on basophils and mast cells include cell differentiation, maturation, and trafficking.[8-13] Mast cells themselves may synthesize cytokines.[14-17] This article will focus on modulation of cellular secretion by cytokines.[2, 18, 19]

ALLERGIC LPRs

In 1873, Blackley described upper and lower respiratory reactions to pollen exposure that persisted for hours to days. Prausnitz and Kustner identified a delayed cutaneous component in the response to Ag after serum passive transfer of sensitivity. In 1924, Vaughan discussed the inflammatory nature of this delayed response to skin tests. Jones and Mote described the development of both immediate and delayed cutaneous responses to heterologous proteins. Herxheimer suggested that the late bronchial reaction to Ags might be of considerable importance for patients with more severe asthma.[20]

In the 1970s, delayed cutaneous reactions to Ags and allergens were examined in depth.[1, 21-24] A clear-cut IgE dependence was demonstrated in both the immediate and LPR in allergen skin tests.[25] In many cases, an increase in basophilic infiltration was identified, although this was not consistent. Dvorak et al.[1] coined the term "cutaneous basophil hypersensitivity" and speculated that appropriate Ag stimulation could induce lymphocytes to synthesize and release factors to attract basophils and trigger mediator release.[23] Both lymphocyte-derived chemotactic factors and secretagogues have been identified.[8, 26, 27] There is substantial evidence for lymphocyte activation in allergic disorders, especially bronchial asthma.[28]

The LPR in the respiratory tract, in many ways, resembles the clinical illness induced by natural allergen exposure. Cockcroft[29, 30] reported a correlation between LPR in the lung and BH. An LPR has also been described in the nose.[31] Although the mast cell is the predominant cell source of histamine and other mediators in the immediate allergic response, the pattern of mediators recovered from the LPR more clearly resembles the response of the basophil.[32, 33] Indeed, an increased number of basophils has been detected in the LPR in the skin, nose, and lungs.[31, 33-35]

CYTOKINES AND BASOPHILS

In 1979, Thueson et al.[26, 27] reported that cultured human MNCs release an HRA or HRF. Mitogens, delayed hypersensitivity Ags, allergens, and human tumor cells stimulate increased synthesis of HRF.[26, 36-40] The stimulation of HRF synthesis by delayed hypersensitivity Ags was correlated with the delayed cutaneous response of the cell donor to the same Ag.[26, 38] The generation of HRF was blocked by inhibitors of protein and nucleic acid synthesis. Preliminary characterization of HRF demonstrated that it was a heat-stable protein with an apparent molecular weight of 10 to 20 kd by gel exclusion chromatography. These initial investigations have been confirmed by many investigators who have added to our understanding of the potential importance of HRF.[35, 38, 41-46]

BASOPHIL AND MAST CELL RESPONSE TO HRF

The basophilic response to HRF was clearly distinct from the response to C5a anaphylatoxin, and release of histamine was dependent on the presence of divalent cations.[26] Maximal release of histamine is achieved within 1 to 5 minutes and is optimal at physiologic temperature. Both histamine and leukotriene D are released from leukocytes reacted with HRF.[44] Lung mast cells also degranulate on exposure to HRF.[43, 47]

We have also explored the morphologic changes of basophils induced by HRF. Cells were enriched by Percoll density-gradient centrifugation.[48] By transmission electron microscopy, we observed that HRF induced, in some cells, a noncytotoxic pattern of basophil degranulation very similar to that induced by Ag and C5a.[49] Cytoplasmic granules were extruded singly through multiple fusions between perigranular and plasma membranes. In contrast, other basophils exposed to HRF failed to demonstrate evidence of

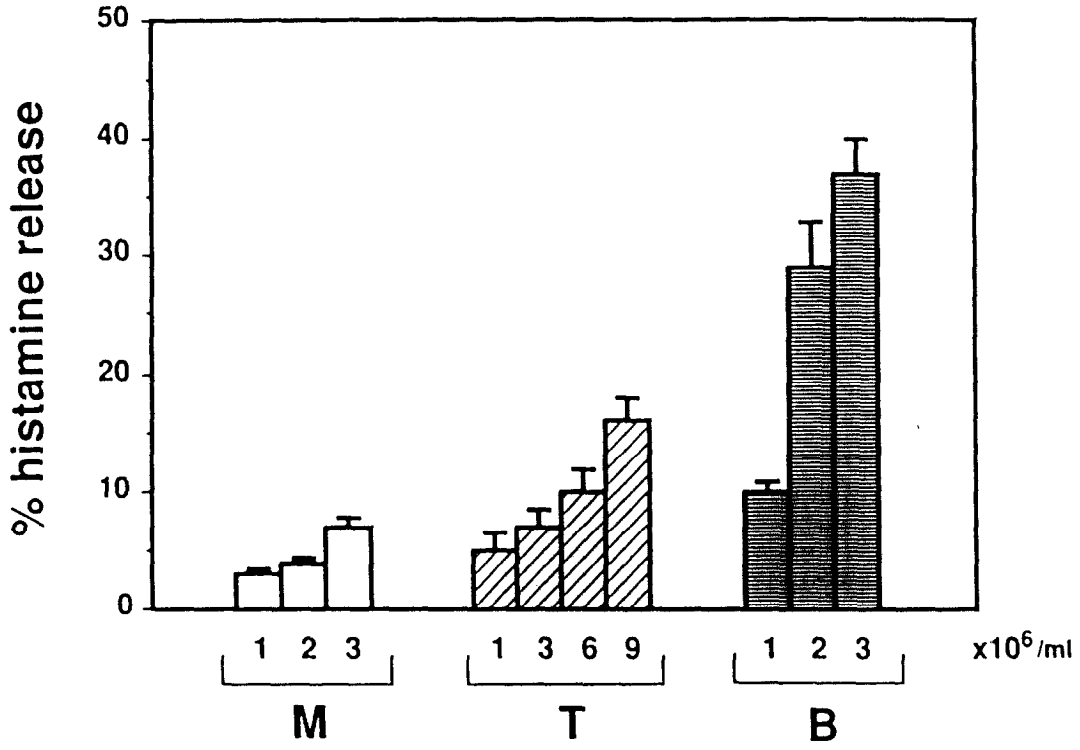

FIG. 1. Synthesis of HRF by human peripheral blood monocytes, T cells, and B cells. Highly enriched subpopulations were cultured without stimulation for 24 hours before harvesting supernatants for measurement of HRF. Data represent the mean and standard error (N = 8 for B cells and N = 4 for monocyte and T cell experiments). (Reprinted with permission from J Immunol 1989;142:3951.)

degranulation but demonstrated a single elongated cellular process. This polarized cellular configuration suggested a chemokinetic or chemotactic effect of the preparation of HRF.

These studies are compatible with the previous study of a lymphocyte-derived chemotactic factor for basophils.[8] When MNC-culture supernatant was subjected to gel filtration and ion exchange chromatography, we were unable to separate basophil chemotactic activity from HRA.[50, 51] We speculate that at low concentrations cytokines direct the chemotaxis of basophils at sites of immune responses, and at higher concentrations, induce cellular secretion.

CELLULAR ORIGIN OF HRF

Early studies suggested that T cells could synthesize HRF.[38, 41] Schulman et al.[52] reported that blood monocytes also release HRF. By plastic adherence, erythrocyte rosetting, and specific MAbs plus complement, we purified different subpopulations from peripheral blood MNCs.[53] On a per cell basis, we found that B-lymphocytes spontaneously release the largest quantity of HRF (Fig. 1). The synthesis by B cells was confirmed by abolishing the release with OKB7 MAb plus complement. Appreciable quantities of HRF also were generated by T cells (both $CD4^-$ and $CD8^-$ cells) and monocytes. The production of HRF, in addition to IgE, places B-lymphocytes at the center of allergic inflammation.

White et al.[54-56] have demonstrated release of HRF by neutrophils, although this species appears biochemically distinct from the factors released by MNCs. HRF has also been recovered from human bronchoalveolar and nasal fluids,[57-61] thoracic duct lymphocytes,[50] platelets,[62] pulmonary monocytes/macrophages,[45, 47, 63] embryonal cells,[64] and endothelial cells. Also, HRF is synthesized by cultured rat, mouse, guinea pig, and dog lymphocytes.[65-70]

BIOCHEMICAL CHARACTERIZATION OF HRF

Since HRF is derived from such a variety of cells, it was anticipated that these factors were heterogeneous. Initially, two species of HRF were identified by ion exchange chromatography.[46, 50, 51, 71] Subsequently, this was confirmed by high-performance liq-

TABLE I. Effect of recombinant cytokines on basophils

Cytokine	Direct HR	Donor specificity	Enhancement of HR by anti-IgE
IL-1	±*	Allergic†	+
IL-2	−	NA	+
IL-3	+	Allergic†	+
IL-8	+	ND	ND
IFN-γ	−	NA	+
GM-CSF	+	Allergic†	+
CTAP III	+	ND	ND
NAP 2	+	ND	ND

NA, Not applicable; *ND*, no data available.
Data derived from references 46, 74, 76-80, 82-85, and 87-89.
The effect of IL-4, 5, 6, and 9, transforming growth factor-β, thromboglobulin-β, tumor necrosis factor-α, soluble CD23, and endothelin were investigated and caused no HR from human basophils (unpublished data and reference 76).
*One study[81] demonstrated direct HR by IL-1, whereas other studies reported a negative result.[84]
†Direct HR from a subgroup of allergic patients at large doses.

uid chromatography.[72, 73] Baeza et al.[72] have isolated three species of HRF with apparent molecular weights of 12, 17, and 41 kd. MAbs have been prepared against the smallest species, permitting recovery of sufficient material by affinity chromatography for sequence analysis.[74] The 12 kd HRF is strongly homologous to CTAP III, a peptide first isolated from platelets, as well as its cleavage product, NAP 2. CTAP III activates fibroblasts, and NAP 2 stimulates neutrophils. Both cytokines may cause HR from basophils. The 17 and 41 kd species of HRF do not react with the MAb specific for the 12 kd moiety and thus might be different gene products.

We have confirmed the existence of at least three species of HRF.[75] With sequential gel filtration and anion exchange high-performance liquid chromatography followed by two-dimensional polyacrylamide gel electrophoresis, we have isolated a species of HRF with an apparent size of 44 kd. This peptide was isolated from MNCs and RPMI 8866 cell-culture fluid.

RELATIONSHIP OF HRF TO OTHER CYTOKINES

IL-1, IL-3, IL-8, NAP 1, and GM-CSF can induce low levels of HR from susceptible basophils, usually cells of highly atopic donors (Table I).[76-82] This phenomenon can be enhanced by previous treatment of basophils with deuterium oxide (Fig. 2). However, the profile of response to these cytokines, as well as other recombinant human cytokines, can clearly be distinguished from the response to MNC HRF.[76] We have examined a variety of other recombinant human cytokines and could not detect HRA over a broad range of concentrations.

The most potent cytokine in terms of HRA is IL-3; however, HRF can be distinguished from IL-3 by an anti-IL-3 MAb.[76] IL-1, IL-2, IL-3, GM-CSF, and interferon-γ act to enhance the basophilic response to a number of secretagogues, including Ag, C5a, anti-IgE, and IL-8.[82-89]

We conclude that a number of known cytokines may induce mediator release from basophils. The most important might be IL-3 and CTAP III/NAP 2. However, there remain other factors in MNC-culture supernatant that are responsible for the predominant HRA, and their purification and characterization are anticipated shortly.

HRIF

Given the plethora of histamine-releasing cytokines and ubiquitous nature of these substances, it should be assumed that there must exist a precise mechanism for regulation of basophil/mast cell activation. Alam et al.[67] demonstrated the synthesis of an HRIF by guinea pig spleen cells. This factor nonspecifically inhibited mediator release from guinea pig lung mast cells. Subsequently, Alam et al.[90] demonstrated the synthesis of HRIF by human MNCs. The generation of human HRIF is increased by physiologic concentrations of histamine, suggesting a mechanism for feedback inhibition of histamine secretion. Synthesis of HRIF is also increased by culture with mitogens, allergens, and phorbol myristate acetate. HRIF is a trypsin- and chymotrypsin-sensitive protein, with a predominant species recovered at 6 to 10 and 35 to 45 kd by gel filtration. When basophils or lung mast cells are preincubated with HRIF for a period of 5 minutes, the response to HRF is blocked. HRIF specifically antagonizes HRF but does not affect release initiated by other secretagogues, such as allergens, anti-IgE, C5a, Concanavalin A, and phorbol myristate acetate. Like HRF, HRIF is synthesized in greater quantity by B cells, followed by T cells and monocytes.[91]

Because of its similar apparent molecular weight (8 kd), we have investigated the inhibitory properties of IL-8 on HR. We observed that IL-8 inhibited mediator release from basophils when it reacted with HRF. This action was also specific for HRF; IL-8 had no effect on release initiated by C5a and *N*-formylmethionyl peptides. Thus, IL-8 resembles the lower molecular weight species of HRIF in terms of apparent size and specificity.

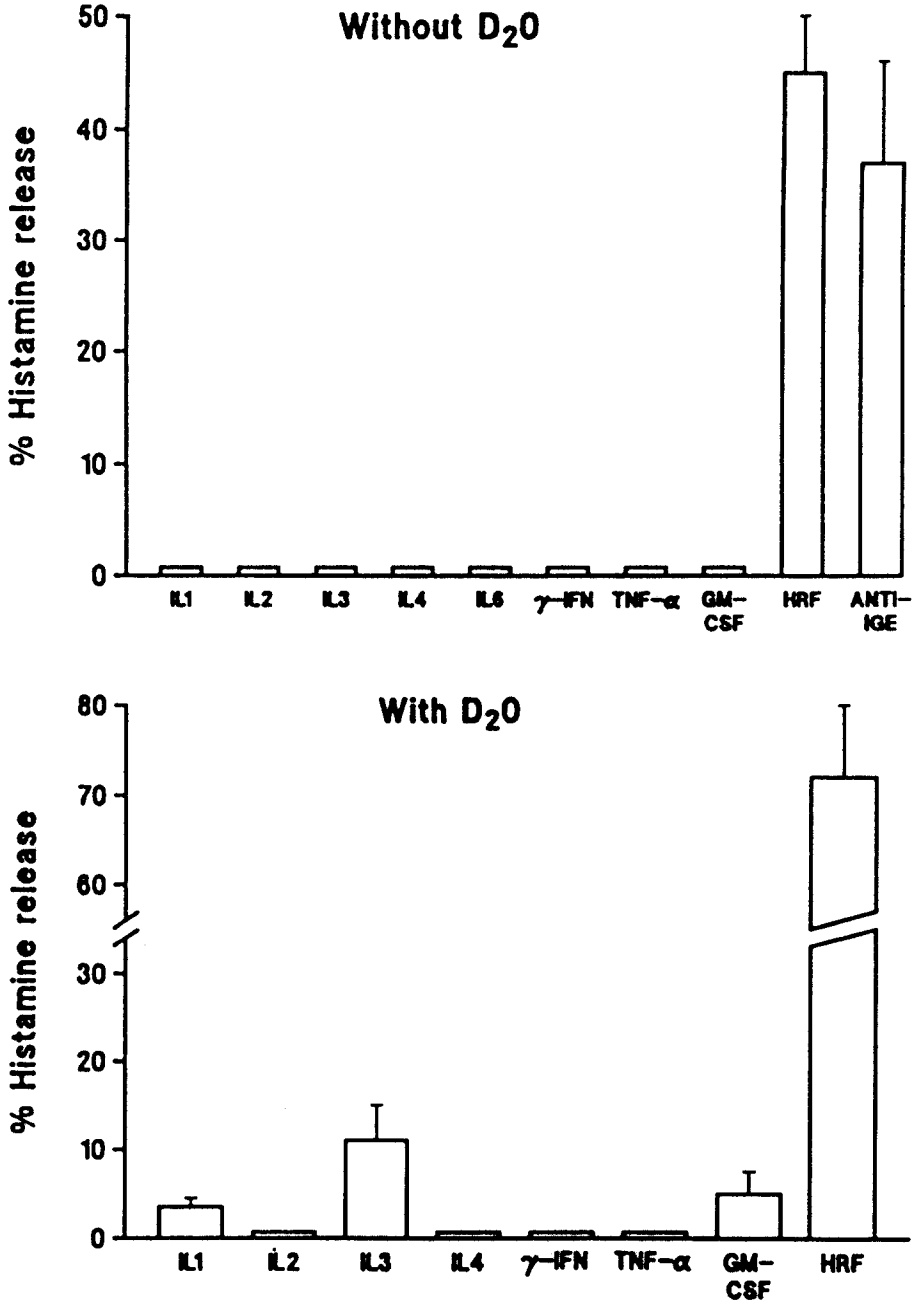

FIG. 2. Human basophil HR, when basophils are reacted with recombinant cytokines, partially purified HRF and anti-IgE. Cells were suspended with or without deuterium oxide (D_2O) (40% final concentration) shortly before challenge with graded concentrations of each cytokine (5×10^{-13} to 5×10^{-9} gm/ml), anti-IgE (10^{-5} to 10^{-3}), or HRF (1/12, 1/6 and 1/3). Results with the highest concentration are illustrated, N = 8 to 13. (Reprinted with permission from J Immunol 1989;142:3431.)

CLINICAL SIGNIFICANCE OF HRF AND HRIF

In vitro synthesis of HRF

The first notion that HRF had relevance to human atopic illness came from the observation of Alam and Rozniecki[37] and Alam et al.[40] that MNCs obtained from subjects with asthma spontaneously synthesized greater amounts of HRF. This was true for MNCs from subjects with extrinsic or intrinsic asthma. Subsequently, they observed a correlation between the quantity of HRF synthesized and the BH of the donor with asthma (assessed by histamine bronchoprovocation) (Fig. 3).[92] The quantity of HRF released by

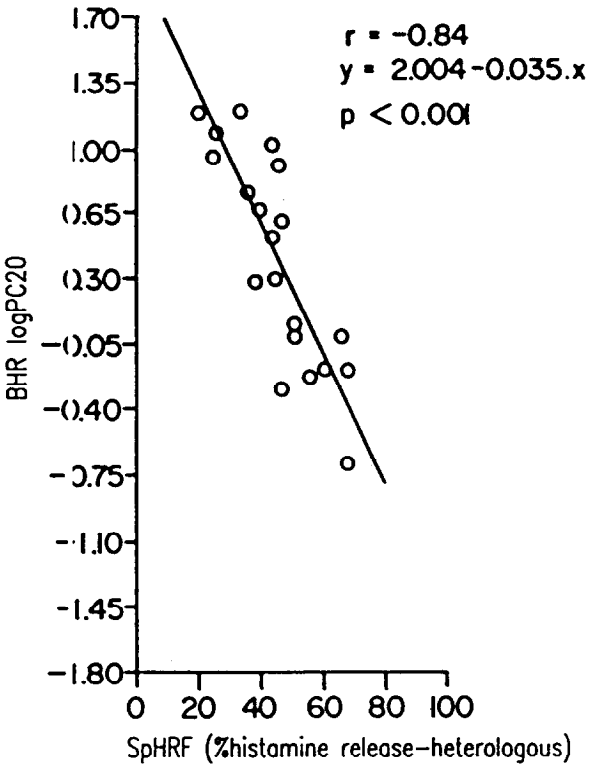

FIG. 3. Relationship between BH (provocative concentration of histamine causing a 20% fall in FEV_1) and the spontaneous production of HRF by MNCs in culture. (Reprinted with permission from J ALLERGY CLIN IMMUNOL 1987;79: 103.)

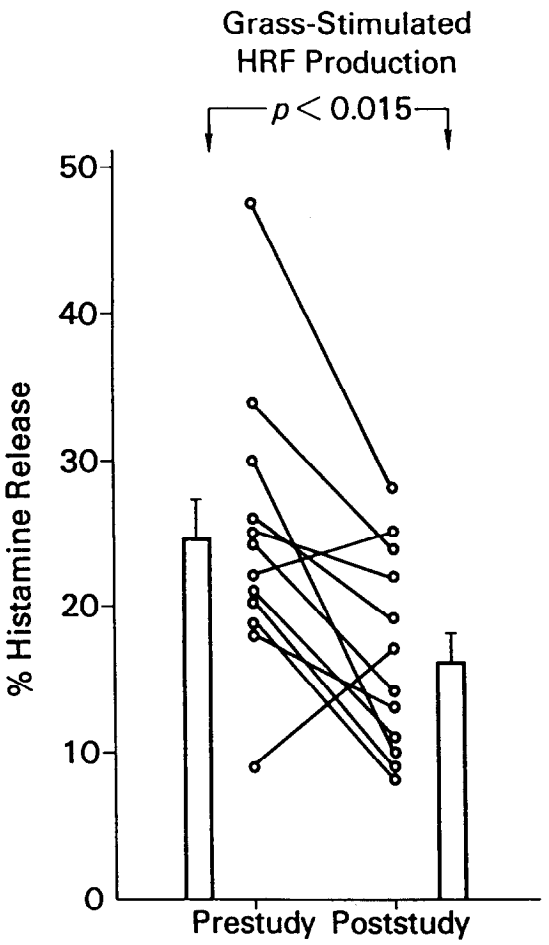

FIG. 4. Production of HRF by grass-stimulated MNCs. Subjects receiving active immunotherapy were studied before onset of the study and after 2 years of preseasonal immunotherapy. (Reprinted with permission from J ALLERGY CLIN IMMUNOL 1989;83:816.)

MNCs is increased when it is cultured with relevant allergens, especially during the pollen season.[39] Otte et al.[91] reported that MNCs from patients with scleroderma synthesized increased quantities of HRF. Leukocytes from dogs with asthma have been observed to release large quantities of HRF when these leukocytes are challenged with ragweed-pollen Ag (Frick OL. Personal communication). The same Ag produces intense and protracted hyperreactivity after bronchial challenge. These observations support the hypothesis that HRF is involved in the genesis of BH.

Kuna et al.[94] evaluated the effect of allergen immunotherapy on the synthesis of HRF with a double-blind, placebo-controlled trial. They observed that effective grass-pollen immunotherapy in patients with seasonal asthma was correlated with abrogation in the seasonal rise in HRF synthesis (Fig. 4). This observation was recently confirmed by Hsieh and Liao.[95]

Effects of HRF in vivo

The response to partially purified HRF has been studied in humans and other animals. Alam and Rozniecki[37] observed that MNC-derived HRF induced bronchospasm as well as a positive cutaneous response in allergic patients. Both human MNC-derived HRF[66] and neutrophil-derived HRF[56] cause an immediate and late-phase cutaneous reaction in guinea pigs. Recently, Fisher et al.[96] performed bronchial challenge with human platelet-derived HRF on rabbits. They reported that allergic animals with asthma, but not normal animals, developed changes in pulmonary compliance, hyperreactivity, and an eosinophilic infiltration.

HRF and cutaneous disorders

Elias et al.[97] demonstrated an increase in the number of activated T-lymphocytes and monocytes in skin biopsy specimens of patients with chronic urticaria. Since the skin mast cells in patients with this condition are hyperreleasable, the authors speculated that HRF might be responsible. HRF has been recovered from skin blisters during the LPR induced by allergen chal-

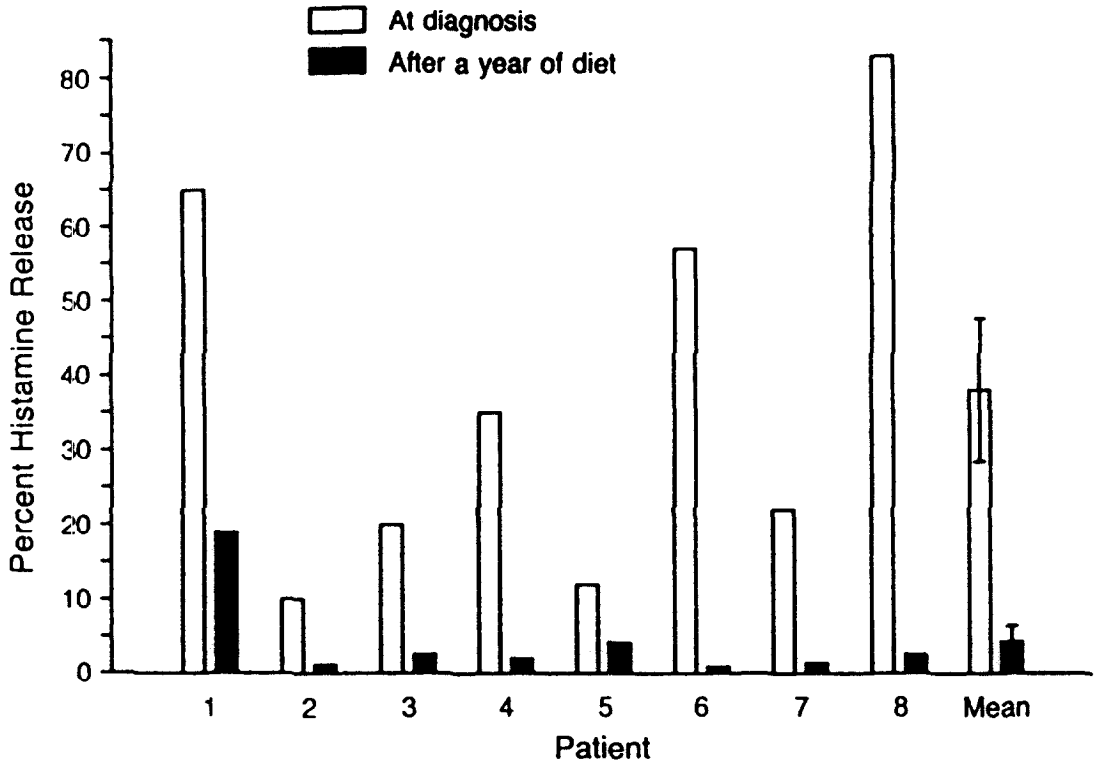

FIG. 5. Rates of spontaneous HR in eight patients with atopic dermatitis. Assays were performed at the time of diagnosis and after a year receiving an appropriate allergen-avoidance diet. The decrease in HR in vitro paralleled clinical improvement in the patient's dermatitis. (Reprinted with permission from N Engl J Med 1989;321:228.)

lenge.[98] However, HRF was not observed in the immediate phase samples. Sampson et al.[99] have evaluated children with atopic dermatitis associated with food hypersensitivity. Basophils from these subjects had high spontaneous HR that returned to normal as their skin condition improved on an allergen-avoidance diet (Fig. 5). MNCs from these patients demonstrated a heightened synthesis of HRF that declined after a year of diet (57.1% ± 9.3% HR versus 2.0% ± 0.9% after diet; $N = 10$; $p < 0.01$). The authors concluded that exposure to food allergen provokes synthesis of HRF that enhances basophil mediator release. Coupled with the observation of increased basophils recovered during the LPR in the skin, nose, and lung,[31, 33-35] this finding provides indirect evidence for a fundamental role for HRF in chronic allergic reactions.

Cytokines in respiratory fluids

HRF and HRIF have also been recovered from respiratory secretions.[57-61] The quantity of HRF in bronchial and nasal washings demonstrate considerable variation in both allergic and nonatopic individuals; differences are not correlated with atopic status of the patient. Broide et al.[100] observed that lavage fluid from patients with idiopathic pulmonary fibrosis contained elevated quantities of HRF. They distinguished the HRF from other known cytokines causing HR and demonstrated that it had an apparent size of 30 to 50 kd.

Basophil response to HRF

The basophils of allergic donors, especially donors with asthma, release a greater percentage of cellular histamine in response to MNC HRF than cells from normal volunteers.[57, 61, 101] However, the response of cells from allergic patients with asthma does not correlate with the severity of disease.[61] HRF obtained from nasal and bronchial lavage and lung macrophages more selectively activates the cells of atopic donors.[45, 58, 61, 63] The response to HRF was substantially blocked when cells were treated with lactic acid under conditions that strip surface-bound IgE.[57, 61] Reactivity to HRF was restored by incubating the cells in serum from certain atopic donors, but not by IgE myeloma or by serum from nonatopic subjects. There was no correlation between the concentration of IgE and the ability of a serum to reactivate basophils to HRF. The factor in serum responsible for reestablishing the basophilic response to HRF was sensitive to

heat treatment and could be removed by matrix-bound anti-IgE.[57] These findings suggest a profound IgE dependence for certain species of HRF recovered from platelets and respiratory secretions. However, in other disorders, the major species of HRF detected in bronchoalveolar lavage fluid may not be IgE dependent, as demonstrated by Broide et al.[100] in pulmonary fibrosis.

IgE heterogeneity

The observations regarding IgE dependence of certain HRFs provided the basis for the concept of IgE heterogeneity in terms of its ability to bind HRF. Lichtenstein[63] postulated that subjects with IgE reaginic Abs incapable of binding HRF would elicit positive skin tests but only mild atopic symptoms. Individuals with IgE+ Ab capable of binding HRF would have more severe allergic disorders. Recently (MacDonaldSM. Personal communication), the IgE-dependent HRF moiety has been partially purified and has been demonstrated to have an approximate size of 32 kd. Furthermore, it was found that the IgE+ moiety is formed by postsynthetic glycosylation of the immunoglobulin.

CONCLUDING HYPOTHESIS

The synthesis of IgE specific for allergens is a necessary condition for development of atopic illnesses. However, the intrinsic reactivity of basophils and mast cells may be determined by a variety of substances that increase (HRF and IL-3) or decrease (HRIF and IL-8) cellular response. MNCs and other cells release factors (including HRF) that attract and activate additional inflammatory cells, especially eosinophils and basophils, during the LPR. The cycle continues, even in the absence of allergens, and ultimately leads to the development of nasal hyperreactivity and BH.[92] Histamine, a major mediator of allergic injury, may have an additional effect by increasing synthesis of HRIF, a specific inhibitor of HRF, which may restore local homeostasis. The clinical relevance of cytokine-dependent mediator release from mast cells/basophils extends beyond the boundary of the atopic diseases. Increases in the total number of tissue mast cells and/or basophils is observed in many chronic inflammatory disorders. These include rheumatoid arthritis, ulcerative colitis, sarcoidosis, hypersensitivity pneumonitis, atopic dermatitis, parasitic infestations, and the rejection process of some tumors.[2] In addition, the degranulation of mast cells has been reported in chronic urticaria, pulmonary fibrosis, systemic sclerosis, neurofibromatosis, and graft-versus-host disease. However, an IgE-dependent mechanism in most of these conditions is unlikely. We speculate that HRF is the missing link between the activated lymphocytes and degranulated mast cells frequently observed in these disorders.

REFERENCES

1. Dvorak HF, Dvorak AM, Simpson BA, Richerson HB, Leskowitz S, Karnovsky MJ. Cutaneous basophil hypersensitivity. II. A light and electron microscopic description. J Exp Med 1970;132:558.
2. Alam R. Role of mast cells and basophils in human diseases. Insights in Allergy 1987;2(6):1-8.
3. Grant JA, Lichtenstein LM. Reversed in vitro anaphylaxis induced by anti-IgG: specificity of the reaction and comparison with antigen-induced histamine release. J Immunol 1972;109:20-5.
4. Findlay SR, Lichtenstein LM, Grant JA. Generation of slow-reacting substance by human leukocytes. II. Comparison of stimulation by antigen, anti-IgE, calcium ionophore, and C5-peptide. J Immunol 1980;124:238-42.
5. Church MK, Lowman MA, Rees PH, Benyon RC. Mast cells, neuropeptides, and inflammation. Agents Actions 1989;27:8-16.
6. Carraway RE, Cochrane DE, Boucher W, Mitra SP. Structures of histamine-releasing peptides formed by the action of acid proteases on mammalian albumin(s). J Immunol 1989;143:1680-4.
7. Thomas LL, Zheutlin LM, Gleich GJ. Pharmacological control of human basophil histamine release stimulated by eosinophil granule major basic protein. Immunology 1989;66:611-5.
8. Lett-Brown MA, Boetcher DA, Leonard EJ. Chemotactic responses of normal human basophils to C5a and to lymphocyte-derived chemotactic factor. J Immunol 1976;117:246-54.
9. Iikura Y, Nagakura T, Nakamura N, Shichijo K, Saito N. Mediator release from basophilic cells derived from cultured cord blood cells. Int Arch Allergy Appl Immunol 1987;82:341-3.
10. Tanno Y, Bienenstock J, Richardson M, Lee TD, Befus AD, Denburg JA. Reciprocal regulation of human basophil and eosinophil differentiation by separate T-cell-derived factors. Exp Hematol 1987;15:24-33.
11. Razin E, Ihle JN, Seldin D, et al. Interleukin-3: a differentiation and growth factor for the mouse mast cell that contains chondroitin sulfate E proteoglycan. J Immunol 1984;132:1479-86.
12. Lett-Brown MA, Aelvoet M, Hooks JJ, Georgiades JA, Thueson DO, Grant JA. Enhancement of basophil chemotaxis in vitro by virus-induced interferon. J Clin Invest 1981;67:547-52.
13. Valent P, Schmidt G, Besemer J, et al. Interleukin-3 is a differentiation factor for human basophils. Blood 1989;73:1763-9.
14. Plaut M, Pierce JH, Watson CJ, Hanley Hyde J, Nordan RP, Paul WE. Mast cell lines produce lymphokines in response to cross-linkage of Fc epsilon R I or to calcium ionophores. Nature 1989;339:64-7.
15. Wodnar Filipowicz A, Heusser CH, Moroni C. Production of the haemopoietic growth factors GM-CSF and interleukin-3 by mast cells in response to IgE receptor-mediated activation. Nature 1989;339:150-2.
16. Burd PR, Rogers HW, Gordon JR, et al. Interleukin-3 dependent and independent mast cells stimulated with IgE and antigen express multiple cytokines. J Exp Med 1989;170:245-57.

17. Costa JJ. Mast cells and cytokines: new insights into the pathogenesis of allergic diseases. Insights in Allergy 1990; 5(6):1-8.
18. Grant JA, Lett-Brown MA, Warner JA, et al. Activation of basophils. Fed Proc 1986;45:2653-8.
19. Lett-Brown MA, Alam R, Grant JA. Regulation of human basophils and mast cells: activation by cytokines. Year Immunol 1989;5:195-204.
20. Lemanske RF, Kaliner MA. Late-phase allergic reactions. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, eds. Allergy: principles and practice. St. Louis: CV Mosby, 1988:224-46.
21. Askenase PW, Haynes JD, DeBernardo R. Specific basophil hypersensitivity induced by skin testing and transferred using immune serum. Nature 1975;256:52.
22. Askenase PW. Effector and regulatory mechanisms in delayed-type hypersensitivity. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, eds. Allergy: principles and practice. St. Louis: CV Mosby, 1988:247-74.
23. Dvorak HF, Mihm MC, Dvorak AM, et al. Morphology of delayed-type hypersensitivity reactions in man. I. Quantitative description of the inflammatory response. Lab Invest 1974;31:111-30.
24. Dvorak AM, Mihm MC, Dvorak HF. Degranulation of basophilic leukocytes in allergic contact dermatitis reactions in man. J Immunol 1976;116:687.
25. Solley GD, Gleich GJ, Jordan RE. The late phase of the immediate wheal and flare reaction: its dependence on IgE antibodies. J Clin Invest 1976;58:408-18.
26. Thueson DO, Speck LS, Lett-Brown MA, Grant JA. Histamine-releasing activity (HRA). I. Production by mitogen- or antigen-stimulated human mononuclear cells. J Immunol 1979;123:626-32.
27. Thueson DO, Speck LS, Lett-Brown MA, Grant JA. Histamine-releasing activity (HRA). II. Interaction with basophils and physicochemical characterization. J Immunol 1979;123: 633-9.
28. Corrigan CJ, Hartnell A, Kay AB. T-lymphocyte activation in acute severe asthma. Lancet 1988;1:1129-32.
29. Cockcroft DW. Airway hyperresponsiveness and late asthmatic responses. Chest 1988;94:178-80.
30. Cockcroft DW. The bronchial late response in the pathogenesis of asthma and its modulation by therapy. Ann Allergy 1985;55:857-62.
31. Walden SM, Proud D, Bascom R, et al. Experimentally induced nasal allergic responses. J ALLERGY CLIN IMMUNOL 1988;81:940-9.
32. Naclerio RM, Kagey-Sobotka A, Lichtenstein LM, et al. Observations on nasal late-phase reactions. Immunol Invest 1987;16:649-85.
33. Charlesworth EN, Hood AF, Soter NA, Kagey-Sobotka A, Norman PS, Lichtenstein LM. Cutaneous late-phase response to allergen: mediator release and inflammatory cell infiltration. J Clin Invest 1989;83:1519-26.
34. Guo CB, Liu MC, Galli SJ, Kagey-Sobotka A, Lichtenstein LM. The histamine containing cells in the late-phase response in the lung are basophils [Abstract]. J ALLERGY CLIN IMMUNOL 1990;85:172.
35. Bascom R, Wachs M, Naclerio RM, Pipkorn U, Galli SJ, Lichtenstein LM. Basophil influx occurs after nasal antigen challenge: effects of topical corticosteroid pretreatment. J ALLERGY CLIN IMMUNOL 1988;81:580-9.
36. Langford MP, Lett-Brown MA, Stanton GJ, Grant JA. Histamine-releasing activity (HRA) produced by leukocytes cocultured with tumor cells. Immunol Invest 1987;16:129-38.
37. Alam R, Rozniecki J. A mononuclear cell-derived histamine releasing factor in asthmatic patients. II. Activity in vivo. Allergy 1985;40:124-9.
38. Sedgwick J, Holt PG, Turner KJ. Production of a histamine-releasing lymphokine by antigen- and mitogen-stimulated human peripheral T cells. Clin Exp Immunol 1981;45:409-18.
39. Alam R, Rozniecki J, Kuzminska B. A lymphocyte-derived histamine-releasing factor in asthmatic patients. III. Further studies. Ann Allergy 1985;55:825-9.
40. Alam R, Rozniecki J, Salmaj K. A mononuclear cell-derived histamine-releasing factor (HRF) in asthmatic patients: histamine release from basophils in vitro. Ann Allergy 1984;53:66-9.
41. Goetzl EJ, Foster DW, Payan PG. A basophil activating factor from human T cells. Immunology 1984;53:227-34.
42. Ezeamuzie IC, Assem ES. Histamine-releasing lymphokine—characteristics of its production. Agents Actions 1985;17:21-6.
43. Ezeamuzie IC, Assem ES. A study of histamine release from basophils by products of lymphocyte stimulation. Agents Actions 1983;13:222-30.
44. Ezeamuzie IC, Assem ES. Release of slow-reacting substance (SRS) from human leucocytes by lymphokine. Int J Immunopharmacol 1985;7:533-42.
45. Liu MC, Proud D, Lichtenstein LM, et al. Human lung macrophage-derived histamine-releasing activity is due to IgE-dependent factors. J Immunol 1986;136:2588-95.
46. Kaplan AP, Haak-Frendscho M, Fauci A, Dinarello C, Halbert E. A histamine-releasing factor from activated human mononuclear cells. J Immunol 1985;135:2027-32.
47. Schulman ES, Liu MC, Proud D, MacGlashan DW Jr, Lichtenstein LM, Plaut M. Human lung macrophages induce histamine release from basophils and mast cells. Am Rev Respir Dis 1985;131:230-5.
48. Dvorak AM, Lett-Brown MA, Thueson DO, et al. Histamine-releasing activity (HRA). III. HRA induces human basophil histamine release by provoking noncytotoxic granule exocytosis. Clin Immunol Immunopathol 1984;32:142-50.
49. Dvorak AM, Lett-Brown MA, Thueson DO, Grant JA. Complement-induced degranulation of human basophils. J Immunol 1981;126:523-8.
50. Lett-Brown MA, Thueson DO, Plank DE, Langford MP, Grant JA. Histamine-releasing activity. IV. Molecular heterogeneity of the activity from stimulated human thoracic duct lymphocytes. Cell Immunol 1984;87:434-44.
51. Thueson DO, Plank DE, Lett-Brown MA, Grant JA. Lymphokine-induced release of basophilic histamine: separation of the activity into two factors. In: Khan A, ed. Human lymphokines: biological immune response modifiers. New York: Academic Press, 1982:229-39.
52. Schulman ES, McGettigan MC, Post TJ, Vigderman RJ, Shapiro SS. Human monocytes generate basophil histamine-releasing activities. J Immunol 1988;7:2369-75.
53. Alam R, Forsythe PA, Lett-Brown MA, Grant JA. Cellular origin of histamine-releasing factor produced by peripheral blood mononuclear cells. J Immunol 1989;142:3951-6.
54. White MV, Kaplan AP, Haak-Frendscho M, Kaliner MA. Neutrophils and mast cells: comparison of neutrophil-derived histamine-releasing activity with other histamine-releasing factors. J Immunol 1988;141:3575-83.
55. White MV, Kaliner MA. Neutrophils and mast cells. I. Human neutrophil-derived histamine-releasing activity. J Immunol 1987;139:1624-30.
56. White MV, Baer H, Kubota Y, Kaliner M. Neutrophils and mast cells: characterization of cells responsive to neutrophil-

derived histamine-releasing activity (HRA-N). J ALLERGY CLIN IMMUNOL 1989;84:773-80.
57. MacDonald SM, Lichtenstein LM, Proud D, et al. Studies of IgE-dependent histamine-releasing factors: heterogeneity of IgE. J Immunol 1987;139:506-12.
58. Sim TC, Forsythe PA, Alam R, Welter JB, Lett-Brown MA, Grant JA. Evaluation of histamine releasing factor (HRF) in nasal washings from individual subjects [Abstract]. J ALLERGY CLIN IMMUNOL 1990;85:156.
59. McClean SP, Forsythe PA, Alam R, Lett-Brown MA, Welter JB, Boyars M, Grant JA. Synthesis of histamine-releasing factors and histamine-release inhibitory factors by bronchoalveolar cells [Abstract]. J ALLERGY CLIN IMMUNOL 1989; 83:236.
60. Alam R, Welter JB, Forsythe PA, et al. Detection of histamine-release inhibitory factor and histamine-releasing factor-like activities in bronchoalveolar lavage fluids. Am Rev Respir Dis 1990;141:666-71.
61. Alam R, Forsythe PA, Rankin JA, Boyars MC, Lett-Brown MA, Grant JA. Sensitivity of basophils to histamine releasing factor(s) of various origin: dependency on allergic phenotype of the donor and surface-bound IgE. J ALLERGY CLIN IMMUNOL 1990;86:73-81.
62. Orchard MA, Kagey-Sobotka A, Proud D, Lichtenstein LM. Basophil histamine release induced by a substance from stimulated human platelets. J Immunol 1986;136:2240-4.
63. Lichtenstein LM. Histamine-releasing factors and IgE heterogeneity. J ALLERGY CLIN IMMUNOL 1988;81:814-20.
64. Cocchiara R, di Trapani G, Azzolina A, Albeggiani G, Geraci D. Isolation of a histamine-releasing factor from two-cell human embryo. Int Arch Allergy Appl Immunol 1987;84:321-3.
65. Alam R, Lewis DM, Olenchock SA. Activation of guinea pig lymphocytes and mast cells by grain-dust extract. J ALLERGY CLIN IMMUNOL 1988;81:598-604.
66. Alam R, Lewis DM, Olenchock SA. Production and properties of histamine-releasing factor of guinea pigs. J Immunol 1988;140:1946-52.
67. Alam R, Lewis DM, Olenchock SA. Identification of a histamine-release inhibitory factor (HRIF) and an inhibitor of histamine-releasing factor synthesis (IHS) produced by guinea pig lymphoid cells. Cell Immunol 1988;115:447-59.
68. Alam R, Wyczokowska J, Suowska Z. Studies on histamine-releasing factor (HRF) of human, murine, and guinea pig origin. Agents Actions 1986;18:163-6.
69. Alam R, Wyczolkowska J. Action of the human lymphokine histamine-releasing factor on mouse peritoneal mast cells. Immunol Lett 1985;11:111-5.
70. Cochrane DE, Boucher W, Carraway RE. Mast cell histamine-releasing activity from stimulated rat neutrophils. Int Arch Allergy Appl Immunol 1988;87:269-74.
71. Kaplan AP, Sheikh I, Frendscho MH. Assessment of histamine release and kinin formation in man: identification of kinin degradation products and characterization of a lymphocyte-dependent histamine-releasing factor. Int Arch Allergy Appl Immunol 1985;77:64-8.
72. Baeza ML, Reddigari S, Haak-Frendscho M, Kaplan AP. Purification and further characterization of human mononuclear cell histamine-releasing factor. J Clin Invest 1989;83: 1204-10.
73. Lett-Brown MA, Thueson DO, Plank DE, Duffy L, Grant JA. Histamine-releasing activity. V. Characterization and purification using high-performance liquid chromatography. Cell Immunol 1984;87:445-51.
74. Baeza ML, Reddigari SR, Kornfeld D, et al. Relationship of one form of human histamine releasing factor (HRF) to connective tissue activating peptide-III (CTAP-III). J Clin Invest 1990;85:1516-21.
75. Alam R, Forsythe PA, Welter JB, Lett-Brown MA, Grant JA. Purification of histamine-releasing factor produced by mononuclear cells and cell lines [Abstract]. J ALLERGY CLIN IMMUNOL 1990;85:257.
76. Alam R, Welter JB, Forsythe PA, Lett-Brown MA, Grant JA. Comparative effect of recombinant IL-1, 2, 3, 4, and 6, IFN-gamma, granulocyte-macrophage-colony-stimulating factor, tumor necrosis factor-alpha, and histamine-releasing factors on the secretion of histamine from basophils. J Immunol 1989;142:3431-5.
77. White MV, Yoshimura T, Hook W, Kaliner MA, Leonard EJ. Neutrophil attractant/activation protein-1 (NAP-1) causes human basophil histamine release. Immunol Lett 1989;22: 151-4.
78. Haak-Frendscho M, Dinarello C, Kaplan AP. Recombinant human interleukin-1 beta causes histamine release from human basophils. J ALLERGY CLIN IMMUNOL 1988;82:218-23.
79. Haak-Frendscho M, Arai N, Arai K, Baeza ML, Finn A, Kaplan AP. Human recombinant granulocyte-macrophage colony-stimulating factor and interleukin-3 cause basophil histamine release. J Clin Invest 1988;82:17-20.
80. 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.
81. Subramanian N, Bray MA. Interleukin-1 releases histamine from human basophils and mast cells in vitro. J Immunol 1987;138:271-5.
82. Morita Y, Goto M, Miyamoto T. Effect of interleukin-2 on basophil histamine release. Allergy 1987;42:104-8.
83. Ida S, Hooks JJ, Siraganian RP, Notkins AL. Enhancement of IgE-mediated histamine release from human basophils by viruses: role of interferon. J Exp Med 1977;145:892-6.
84. Massey WA, Randall TC, Kagey-Sobotka A, et al. Recombinant human IL-1 alpha and 1 beta potentiate IgE-mediated histamine release from human basophils. J Immunol 1989;143:1875-80.
85. Kurimoto Y, de Weck AL, Dahinden CA. Interleukin-3-dependent mediator release in basophils triggered by C5a. J Exp Med 1989;170:467-79.
86. Valent P, Besemer J, Muhm M, Majdic O, Lechner K, Bettelheim P. Interleukin-3 activates humana blood basophils via high-affinity binding sites. Proc Natl Acad Sci USA 1989;86:5542-6.
87. Dahinden CA, Kurimoto J, Baggiolini M, Dewald B, Walz A. Histamine and sulfidoleukotriene release from human basophils: different effects of antigen, anti-IgE, C5a, f-Met-Leu-Phe and the novel neutrophil-activating peptide NAF. Int Arch Allergy Appl Immunol 1989;90:113-8.
88. Dahinden CA, Kurimoto Y, de Weck AL, Lindley I, Dewald B, Baggiolini M. The neutrophil-activating peptide NAF/NAP-1 induces histamine and leukotriene release by interleukin-3-primed basophils. J Exp Med 1989;170:1787-92.
89. Hirai K, Morita Y, Misaki Y, et al. Modulation of human basophil histamine release by hemopoietic growth factors. J Immunol 1988;141:3958-64.
90. Alam R, Grant JA, Lett-Brown MA. Identification of a histamine release inhibitory factor produced by human mononuclear cells in vitro. J Clin Invest 1988;82:2056-62.

91. Alam R, Forsythe PA, Lett-Brown MA, Grant JA. Study of the cellular origin of histamine release inhibitory factor using highly purified subsets of mononuclear cells. J Immunol 1989;143:2280-4.
92. Alam R, Kuna P, Rozniecki J, Kuzminska B. The magnitude of the spontaneous production of histamine-releasing factor (HRF) by lymphocytes in vitro correlates with the state of bronchial hyperreactivity in patients with asthma. J ALLERGY CLIN IMMUNOL 1987;79:103-8.
93. Otte RW, Tharp M, Fireman P. Histamine releasing factor (HRF) by stimulated mononuclear cells in scleroderma [Abstract]. Ann Allergy 1990;64:55.
94. Kuna P, Alam R, Kuzminska B, Rozniecki J. The effect of preseasonal immunotherapy on the production of histamine-releasing factor (HRF) by mononuclear cells from patients with seasonal asthma: results of a double-blind, placebo-controlled, randomized study. J ALLERGY CLIN IMMUNOL 1989;83:816-24.
95. Hsieh KH, Liao TN. Altered production of and responsiveness to histamine releasing factor(s) after immunotherapy [Abstract]. J ALLERGY CLIN IMMUNOL 1990;85:258.
96. Fisher RH, Henriksen RA, Wirfel-Svet KL, Atkinson LB, Metzger WJ. Bronchial challenge with platelet-derived histamine-releasing factor (PD-HRF) supernatant induces prolonged changes in dynamic compliance (Cdyn) and hyperreactivity in the allergic asthmatic rabbit model [Abstract]. J ALLERGY CLIN IMMUNOL 1990;85:261.
97. Elias J, Boss E, Kaplan AP. Studies of the cellular infiltrate of chronic idiopathic urticaria: prominance of T-lymphocytes, monocytes, and mast cells. J ALLERGY CLIN IMMUNOL 1986;78:914-8.
98. Warner JA, Pienkowski MM, Plaut M, Norman PS, Lichtenstein LM. Identification of histamine releasing factor(s) in the late phase of cutaneous IgE-mediated reactions. J Immunol 1986;136:2583-7.
99. Sampson HA, Broadbent KR, Bernhisel Broadbent J. Spontaneous release of histamine from basophils and histamine-releasing factor in patients with atopic dermatitis and food hypersensitivity. N Engl J Med 1989;321:228-32.
100. Broide DH, Smith CM, Wasserman SI. Mast cells and pulmonary fibrosis: identification of a histamine releasing factor in bronchoalveolar lavage fluid. J Immunol 1990;145:1838-44.
101. Baeza ML, Haak-Frendscho M, Satnick S, Kaplan AP. Responsiveness to human mononuclear cell-derived histamine-releasing factor: studies of allergic status and the role of IgE. J Immunol 1988;141:2688-92.