

Relationship of Histamine-Releasing Factors and Histamine-Releasing Inhibitory Factors to Chemokine Group of Cytokine

Piotr Kuna, M.D., and Allen P. Kaplan, M.D.*

ABSTRACT

The release of mediators from mast cells and basophils represents the central event in the development of immediate hypersensitivity reactions with release of substances such as histamine, Leukotrienes C₄/D₄, Platelet Activating Factor (PAF), and Prostaglandin D₂. Cytokines such as IL-1, TNF α , and IL-4 may also be secreted. Histamine Releasing Factors (HRF) are cytokine-like molecules that interact with basophils and/or mast cells to cause cell activation and secretion of mediators. Histamine release is the best characterized of these and has been used as the assay for HRFs, but a wide variety of inflammatory mediators can potentially be secreted. We believe this type of cell to cell communication to be important in tissue inflammation, in which infiltrating cells may produce HRFs in proximity to infiltrating basophils and/or mast cells and cause them to degranulate. Such a reaction appears to be independent of IgE antibody, may no longer require the presence of any inciting antigen, and appears to be pertinent to the allergic late phase reaction as it occurs in the nose, lungs, and skin. It is thought that an ongoing antigenic stimulus, as seen in seasonal or perennial allergic rhinitis and asthma, or in certain types of urticaria, or in atopic dermatitis, leads to a perpetuating inflammatory reaction that persists for many weeks or months. A chronic inflammatory reaction of this sort appears to be required

*From the Division of Pneumology and Allergology, the Medical University of Lodz, Poland, and *the Division of Allergy, Rheumatology, and Clinical Immunology, Department of Medicine, SUNY-Stony Brook, NY*

Address correspondence and reprint requests to Dr. Piotr Kuna, Division of Pneumology and Allergology, The Medical University of Lodz, Kopcinskiego 22, 90-153 Lodz, Poland

for an allergic reaction (IgE mediated) to manifest as an allergic disease. The relationship of HRF to the chemokine group of cytokine-like molecules and the importance of HRF in the pathogenesis of bronchial hyperreactivity and asthma has been reviewed in this paper. (Allergy and Asthma Proc 17:5-11, 1996)

Basophils and mast cells are highly specialized effector cells of the immune system and have a significant role in allergic reactions and host defense. Both cells store and synthesize large quantities of the various mediators of inflammation and express high affinity IgE receptors. Basophils and their mediators have been demonstrated in delayed cutaneous hypersensitivity, and in the late phase allergic reaction in the upper airways and skin;¹⁻³ however, the mechanism responsible for protracted histamine release seen during the late phase allergic reaction remains obscure. The late phase appears 4 to 6 hours after an allergen-dependent immediate hypersensitivity reaction, and it seems that factors other than allergen or IgE antibody are responsible for basophil and/or mast cell secretion during that time. In 1979 Thuesen et al. reported that the crude supernatant of mononuclear cell (MNC) cultures contain a factor (Histamine Releasing Factor or HRF) that stimulates basophils to release histamine.⁴ Dvorak et al. later described that HRF is also chemotactic for basophils.⁵ In our efforts to characterize HRF, we demonstrated that a variety of molecules belonging to the chemokine cytokine family stimulate basophils to release histamine and are present in MNC cultures supernatant containing HRF.⁶ Chemokines are small secreted proteins that are structurally related with particular cysteine motifs and are involved in the chemotaxis and activation of leukocytes.⁷ The most potent che-

mokine to release histamine from basophils is Monocyte Chemoattractant and Activating Factor/Monocyte Chemoattractant Protein-1 (MCAF/MCP-1), and it is a major constituent of the activity known as HRF.^{8,9} HRFs are thought to contribute significantly to the protracted histamine release and basophils and/or mast cell degranulation seen in a wide variety of immunologic disorders including chronic urticaria,¹⁰ atopic dermatitis,¹¹ asthma,¹² and rheumatoid arthritis,¹³ although the specific contribution of MCAF/MCP-1 to histamine release in such disorders has not yet been determined. We also reported that IL-8 and Connective Tissue Activating Peptide III (CTAP III) are able to inhibit and activate basophils to release histamine respectively.^{14,15} On the other hand, basophils are "primed" and augment their secretion if preincubated with IL-3, IL-5, or GM-CSF.^{16,17} Thus the array of chemokines present at the site of allergic inflammation may be responsible for either enhanced or diminished responses.

CHEMOKINES

Interkrines/Chemokines have been divided into two subfamilies (Table I). The first consists of heparin-binding molecules encoded on chromosome 4 that have a free N-terminus, a molecular weight of approximately 8 kD, and a "C-X-C" cysteine structure in which the first two of its four cysteines are separated by one amino acid. The human constituents of this group include platelet factor-4, CTAP III, and its derivatives β -thromboglobulin and NAP-2, melanoma growth-stimulating activity or GRO (GRO/MGSA), IP-10 and IL-8. Platelet factor 4 was previously described as a protein that binds to basophils and induces histamine release at concentrations of 10^{-7} to 10^{-5} M.¹⁸ In the course of HRF purification, we have demonstrated that CTAP III and its derivative NAP-2 also possess HRF-like activity and are similarly active between 10^{-7} to 10^{-5} M.¹⁵ These are all plentiful molecules derived from platelets and may therefore contribute to HRF activity seen in mononuclear cell/platelet supernatants, although they are not very potent on a

molar basis. Interleukin 8 is a chemoattractant for neutrophils that is also active on basophils to induce histamine release at concentrations of 10^{-6} M and above.¹⁹ However, this is a trace cytokine derived from monocytes, endothelial cells, fibroblasts, neutrophils, and epithelial cells, and such activity is unlikely to be within a physiologic range. IL-8 also appears to be chemotactic for basophils, and may contribute to histamine release if the cells are first primed with IL-3.²⁰ IP-10 does not release histamine from human basophils, whereas the remaining member of this subgroup, GRO/MGSA, has not been assessed for HRF activity.

MCAF belongs to the second Interkrine/Chemokine subfamily, the "C-C" subgroup, whose constituent genes are on chromosome 17 and encode proteins having a differing cysteine configuration (Table I). Its other physicochemical properties (size, heparin binding) are similar to the "C-X-C" subgroup. MCAF/MCP-1 is produced by a variety of cells including monocytes, endothelial cells, fibroblasts, epithelial cells, epidermal keratinocytes, and a number of tumor cell lines, and its production is enhanced by IL-1, TNF alpha, platelet derived growth factor, PHA, LPS, and viruses. The primary target cells for MCAF/MCP-1 are monocytes, which are stimulated at concentrations of 10^{-10} M and above, which is similar to the concentrations required for basophil activation. RANTES is a second member of this group and has been shown to be not only chemotactic for monocytes, but also chemotactic for a subpopulation of T lymphocytes (CD4+/CD45+; memory/helper cells).²¹ RANTES is produced by T lymphocytes after stimulation with PHA or anti-CD3, but unlike other members of the Interkrine/Chemokine- β family, its transcription is not rapidly induced in cultured T cells. Specific mRNA for RANTES was isolated from a T cell line 3 days after stimulation. It is a basophil chemoattractant. Alam et al. reported that HuMIP-1 α releases histamine from basophils and mast cells.²² Our studies of other members of this group, MIP-1 β , show that it is a weak agonist for basophils, and I-309 was clearly negative for histamine release.

TABLE I

The Chemokine Cytokine Family	
Subfamily A	Subfamily B
Platelet Factor 4	MCAF/MCP-1
β -thromboglobulin	Rantes
CTAP III	Hu MIP-1 alpha
NAP-2	HU MIP-1 beta
Melanoma Growth Factor (GRO/MGSA)	I-309
Macrophage Inflammatory peptide (MIP-2)	HC-14;MCP-3
IP-10	MCP-2
Chromosome 4	Chromosome 17
8-10 kD	8-10 kD
Bind heparin	Bind heparin
4 cysteines Cys-X-Cys	4 cysteines Cys-Cys

MCAF/MCP-1 AS A POTENT FORM OF HRF

MCAF has been purified as a 15 kD factor from LPS-stimulated myelomonocytic cell line THP-1 and from cultured supernatants of PHA stimulated human PBMC.⁷ The amino acid sequence of MCAF has 20–55% homology with other members of interkrine family, including RANTES, IL-8, GRO/MGSA, PF-4, CTAP III, and its derivatives β -thromboglobulin and NAP-2.

We have investigated the histamine-releasing capability of MCAF and demonstrate that it is the most potent cytokine-like secretagogue hitherto described.^{6,8} It acts as an agonist for basophils of most subjects irrespective of allergic status, and is active at concentrations as low as 10^{-9} M with peak activity at 10^{-7} M (Fig. 1). The magnitude of histamine release by MCAF can be augmented if the cells have been primed by IL-3 or IL-5; however, MCAF does

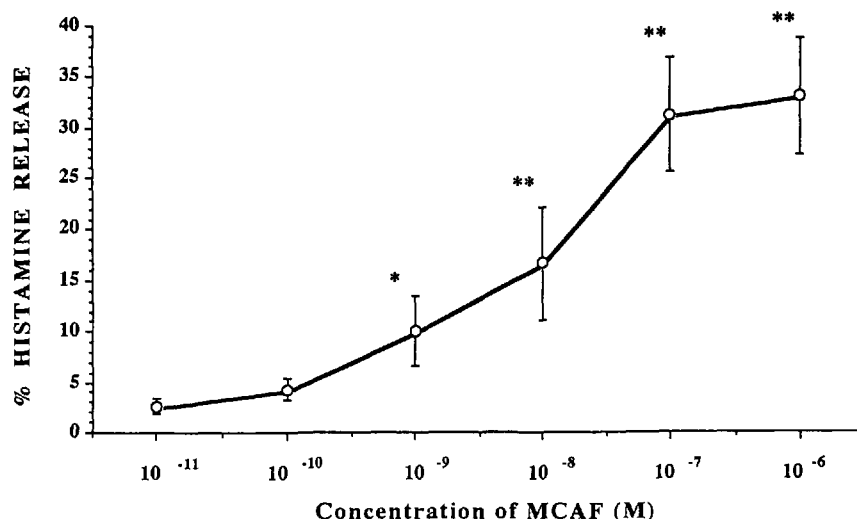


Figure 1. Dose dependent histamine release by MCAF. Basophils of six individuals were challenged with MCAF from 10^{-11} M to 10^{-6} M and the percentage histamine release determined. Results are expressed as a mean percentage of histamine release $\pm$ SEM. (*) indicates $P \leq 0.022$. (**) indicates $P \leq 0.014$ versus histamine release induced by 10^{-11} M MCAF (Wilcoxon's rank sum test).

not act as a primer for other agonists. MCAF releases no significant amount of peptido-leukotriene compared to anti-IgE, and as such, appears to be an "incomplete" releaser, similar perhaps to C5a (Fig. 2). MCAF-caused histamine release in 85% of donors studied, anti-IgE also released histamine in 85% of donors, and FMLP released histamine in all subjects tested (Fig. 3). Thus, MCAF appeared to cause histamine release in the vast majority of individuals tested; the nonresponders to MCAF were not the same subjects who did not respond to anti-IgE. The mean histamine release for each group is shown in Figure 3 (upper panel) by the horizontal lines. The mean percent histamine release by MCAF of 29.3 ± 3.3 was significantly less than that obtained with anti-IgE, which were $44.9 \pm$

4.6 and 44.5 ± 2.8 percent, respectively. The percentage of histamine release upon stimulation with MCAF in atopics versus nonatopics was 35 ± 5.7 and 27 ± 4.3 , respectively, and this difference was not statistically significant ($P > 0.05$ Student's *t* test). When the response to MCAF was compared to the response to anti-IgE and FMLP in atopic subjects only, there was no statistically significant difference among the three. However, MCAF caused less histamine release in the nonatopic group (27 ± 4.3 percent release) versus anti-IgE at $41.8 \pm 5.9\%$ or FMLP at $43.6 \pm 3.3\%$. Thus, the difference seen in all 31 subjects was reflected by the lesser response to MCAF in the nonatopic group. Histamine release from human basophils is most likely caused by direct interaction of MCAF with the sur-

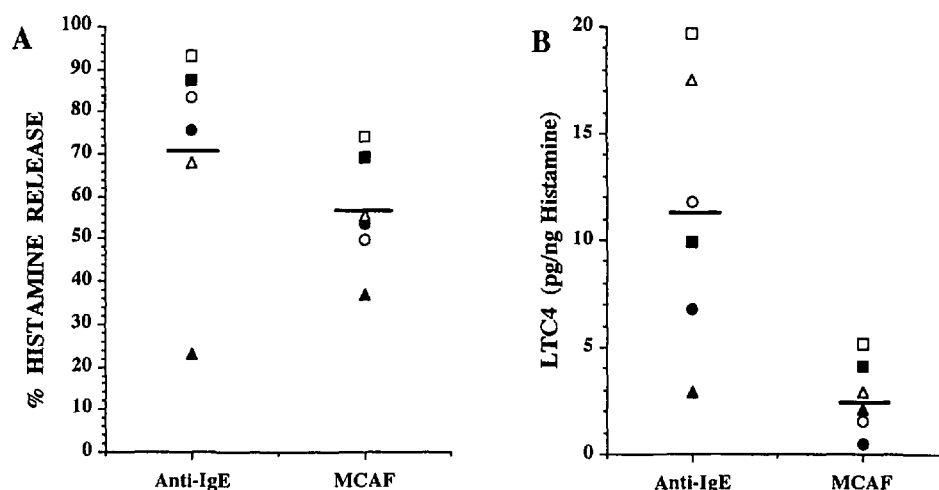


Figure 2. Comparison of histamine and $\text{LTC}_4/\text{D}_4/\text{E}_4$ release by anti-IgE and MCAF. Purified basophils were incubated with $1 \mu\text{g/ml}$ anti-IgE and 10^{-7} M MCAF for 45 min. at 37°C and the supernatant assayed for histamine and peptido-leukotrienes. Histamine release (percent) shown in Panel A averaged $71.7 \pm 10.3\%$ for anti-IgE and $56.5 \pm 5.4\%$ for MCAF. In Panel B, we express leukotrienes release as pg per ng of total histamine content in a given sample for anti-IgE and MCAF. The mean $\pm$ SEM values are 11.4 ± 2.6 pg and 2.7 ± 0.7 pg, respectively.

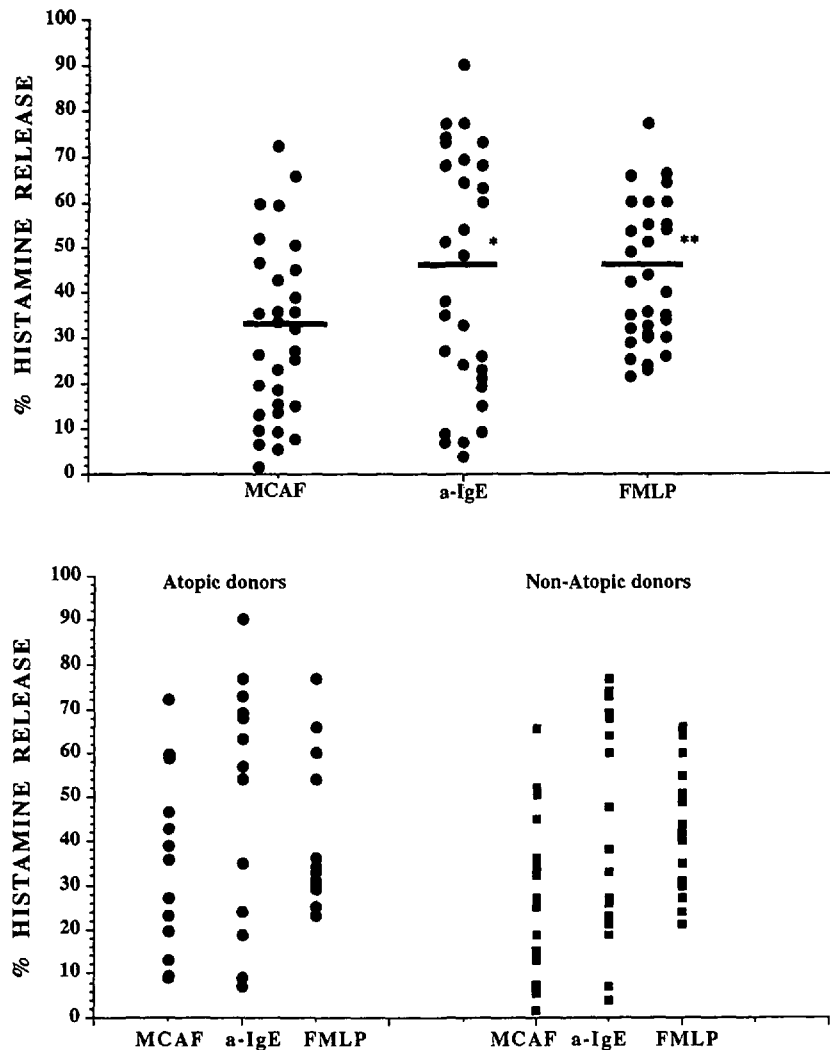


Figure 3. Histamine release from basophils of 31 donors upon stimulation with MCAF (10^{-7} M), anti-IgE (1.0 μ g/ml) and FMLP (10^{-5} M). Individual results are shown. The horizontal lines indicate mean histamine release for each agonist (upper panel). (*) indicates $P \leq 0.006$, (**) indicates $P < 0.001$ when compared with histamine release induced by MCAF (Student's *t* paired test). In the lower panel, individual results for atopic and nonatopic donors are shown.

face of basophils rather than *via* another cell intermediate. We infer the presence of a receptor because the release is extremely rapid and is augmented when highly purified basophils are compared with mixed leukocytes.

RANTES AS A FORM OF HRF

We demonstrate that RANTES is active as a histamine-releasing agonist in approximately 80 percent of basophil donors with a dose response similar to that of MCAF/MCP-1 and present evidence that they may use a common receptor or signaling pathway since they appeared to cross-desensitize suggesting a common receptor mechanism.²³ Two general types of HRF have been described, one whose activity appears to be dependent upon cell surface IgE and another that is IgE independent.^{24,25} Our results indicate that there is considerable variation in response to the different cytokine-like agonists among donors. Basophils obtained from atopic persons appear to be more responsive to

RANTES than basophils of nonatopics, because the percentage histamine release in the allergic group was almost twice as much as release in the nonallergic group. However, we do not know whether this is due to a special kind of IgE molecule present on the cell surface, or priming of basophils *in vivo* in atopic subjects, or other unknown factors leading to hyperresponsiveness. The activation of basophils by RANTES is clearly associated with a pertussis-toxin sensitive GTP-binding protein.

CYTOKINES AND HISTAMINE RELEASE

In the latest study, we have tested the histamine-releasing properties and priming abilities of a wide range of recombinant or purified cytokines and growth factors on the basophils of 20 subjects (10 atopic and 10 nonatopic). We confirm that members of the intercrine/chemokine family MCAF/MCP-1, RANTES, Human Macrophage Inflammatory Proteins HuMIP-1 α and HuMIP-1 β , Connective Tissue

Activating Peptide III (CTAP III) cause histamine release from basophils (Table II).⁶ All other cytokines and growth factors tested were negative, with the exception of IL-3, which caused histamine release in a subpopulation of subjects and also primed basophils for release by anti-IgE. Other basophil primers for anti-IgE-dependent histamine release were IL-5, mast cell growth factor (MGF)(c-kit ligand), and insulin-like growth factor II (IGF-II). Using specific neutralizing antibodies, we have shown that MCAF/MCP-1, RANTES, and IL-3 contribute significantly to the activity found in MNC culture supernatants. Granulocyte Macrophage-CSF (GM-CSF), IP-10, I-309, IL-7, IL-8, IL-9, IL-10, IL-11, IgE-binding factor (IgE-BF), TNF α , TGF- β 1, Fibroblast Growth Factor (FGF), Epidermal Growth Factor (EGF), and Endothelial Cell Growth Factor (ECGF) were negative for direct histamine release and as primers of basophils.

CHEMOKINES AS HISTAMINE RELEASE INHIBITORY FACTORS

Soon after the concept of HRF was reported, mononuclear cell supernatants were found to contain an inhibitor of HRF-dependent histamine release, and the activity was designated Histamine Release Inhibitory Factor (HRIF).²⁶ IL-8 has been shown to fulfill the function attributed to HRIF, as preincubation of basophils with concentrations ranging from 10^{-11} to 10^{-8} M inhibit HRF-induced histamine release as well as histamine release due to purified (or recombinant) MCAF/MCP-1.^{14,27} The observation that preincubation of basophils with low concentrations (10^{-10} to 10^{-9} M) of MCAF/MCP-1 can inhibit a subsequent challenge by 10^{-7} M MCAF/MCP-1 suggests that either receptor blockade or an active process of cell inhibition (desensitization) is possible, and RANTES can similarly desensitize itself. On the other hand, preincubation of basophils with low concentration of chemokines has no effect upon IgE-dependent histamine release. Thus the inhibition demonstrated specificity for the chemokines. More recently, low concentrations of RANTES have been shown also to inhibit HRF or MCAF/MCP-1 induced histamine release.^{19,28} Recently, we

tested other members of the α and β chemokines families for HRIF-like activity and attempted to shed light upon the mechanism of inhibition. Our studies suggested that most, if not all, members of the α or β chemokine family can inhibit basophil histamine release by MCAF/MCP-1 (10^{-7} M) and that receptor blockade is the likely mechanism.²⁸ We found that inhibition of MCAF/MCP-1 induced histamine release is dose dependent, has an optimal concentration of 5×10^{-10} to 5×10^{-8} M, which is 2–200 fold lower than the optimal MCAF/MCP-1 dose required for histamine release, and that inhibition is reversed by washing the cells before challenge with 10^{-7} M MCAF/MCP-1. The cells have to be exposed for at least 5 minutes for the inhibitory effect to be seen, and comparable inhibition is seen with purified basophils (80–90%) as is seen with mixed leukocytes (0.5–2% basophils) suggesting a time-dependent, direct interaction with the cell surface. The effect is opposite that of basophil primers such as IL-3 (10), IL-5, and GM-CSF, which augment MCAF/MCP-1 induced histamine release. Our data suggest that a balance between molecules with HRF or HRIF activities exists that may determine the level of inflammation seen in allergic diseases. We demonstrated that HRIF is not a specific molecular species, but is due to receptor blockade by α and β chemokines in general; but a specific mechanism of desensitization by MCAF/MCP-1 and perhaps RANTES is possible.

CYTOKINES AS PRIMERS OF BASOPHILS

Priming of basophils is demonstrated by augmenting the release of histamine and/or LTC₄ to suboptimal concentrations of secretagogues such as C5a or anti-IgE after preincubation with cytokines, interleukins, or growth factors. Priming factors may include cytokines that do not directly cause histamine release, or cytokines with HRF activity that prime basophils at concentrations below those effective for histamine release. IL-3, IL-5, GM-CSF, and to a lesser degree IL-1 have been shown to prime basophils for histamine release by anti-IgE.^{8,16,17} We confirm the observations with IL-3 and IL-5. MGF has been reported to prime mast cells but not basophils, although a recent paper sug-

TABLE II
The Effect of Various Factors on Histamine Release from Basophils

Stimulus	No. of Donors	% Responders	% Histamine Release
Anti-IgE 1 μ g/mL	33	82.0	40.5 $\pm$ 4.6
FMLP 10–5 M	33	100.0	44.0 $\pm$ 3.1
HRF crude 300 μ g/mL	24	100.0	48.7 $\pm$ 5.0
MCAF 10–7 M	33	100.0	41.1 $\pm$ 2.9
HRF void 50 μ g/mL	24	80.0	25.9 $\pm$ 3.6
RANTES 10–7 M	33	78.8	21.8 $\pm$ 3.1
CTAP III 5 μ g/mL	24	58.3	12.8 $\pm$ 2.5
IL-3 5000 U/mL	24	33.3	11.0 $\pm$ 1.7
MIP-1 alpha 10–7 M	16	37.5	8.1 $\pm$ 1.3
MIP-1 beta 10–7 M	16	31.3	4.7 $\pm$ 1.3

gests the occurrence of basophil priming as well.^{6,29} Our data indicated that MGF can prime basophils, but the concentration required was high (1 $\mu\text{g/mL}$). IGF-1 has been reported to prime basophils for histamine release, and we have demonstrated that IGF-II can do so also.

CLINICAL CONSIDERATIONS

The involvement of HRF in asthma has been the subject of a number of investigations. The following observations suggest that HRF may play an important role in the pathogenesis of asthma. Mononuclear cells from asthmatic patients spontaneously produce relatively high amounts of HRF.^{12,30} This production is enhanced upon incubation of lymphocytes with specific allergens.³¹ The magnitude of spontaneous production of HRF highly correlates with the severity of asthma as assessed by symptom score and bronchial hyperreactivity in asthmatic patients.^{12,30} Synthesis of HRF by mononuclear cells increases significantly after allergen inhalation challenge only in patients who develop a late phase asthmatic reaction.³² The increase in HRF synthesis occurred at 6 hours, and it tended to correlate with the fall in FEV₁ in the late phase reaction. A later study of immunotherapy as a treatment for seasonal allergen rhinitis was performed to determine whether HRF production was affected. Using grass pollen-sensitive patients, specific immunotherapy was shown to diminish spontaneously produced HRF when the patient's mononuclear cells were cultured overnight, and the increase in HRF production seen upon incubation with grass pollen was blunted. The spontaneous HRF production correlated with those whose asthma improved, and all treated patients had a diminution in antigen-induced HRF production.¹² An analogous study of subjects with food-dependent atopic dermatitis likewise revealed increased spontaneous HRF production associated with cutaneous symptoms that reversed when compulsive avoidance of skin test positive food was introduced.¹¹ Although much is known about etiologic factors and mechanism of allergic asthma, the pathogenesis of intrinsic asthma remains a major challenge to date. Since HRF represents a novel mechanism of mediator release, it was tempting to speculate that this mechanism is involved in intrinsic asthma. We have reported that mononuclear cells from intrinsic asthmatic patients spontaneously produce high amounts of HRF.³³ The production was stimulated by culture of mononuclear cells with bacterial antigens in some patients. Because infectious agents have been implicated in the pathogenesis of this form of asthma, it is possible that the stimulation of HRF production by these and other unidentified agents contributes to the development of intrinsic asthma. Recently similar observation was made with viruses. Another recent finding is that the allergic late phase reaction in the nose and skin is characterized by basophils infiltration and protracted histamine release, and that the latter apparently occurs independently of IgE.³⁴⁻³⁶ HRF has been shown to be present in skin blisters placed over sites of

cutaneous late phase reactions, but the specific form of HRF involved has not been identified.³⁷ Asthma also appears to be characterized by activated T cells and eosinophils, but few basophils if any have been seen. Rather, there are abundant mast cells. It should be pointed out that mast cell degranulation is prominent in a disease such as scleroderma, where they are adjacent to activated mononuclear cells.³⁸ HRF was also demonstrated in rheumatoid synovial fluid.¹³ Thus, it is possible that HRFs are active in a wide variety of inflammatory conditions. Future studies are needed to determine which particular form of HRF participates in a pathogenesis of specific disorders such as bronchial asthma, chronic urticaria, atopic dermatitis, scleroderma, and rheumatoid arthritis.

REFERENCES

1. Dvorak HF, Mihm MC. Basophilic leukocytes in allergic contact dermatitis. *J Exp Med* 135:235-254, 1972.
2. Naclerio RM, Proud D, Togias AG Jr, et al. Inflammatory mediators in late antigen-induced rhinitis. *N Engl J Med* 313:65-70, 1985.
3. Elias J, Boss E, Kaplan AP. Studies of the cellular infiltrate of chronic idiopathic urticaria: Prominence of T-lymphocytes, monocytes, and mast cells. *J Allergy Clin Immunol* 78:914-918, 1986.
4. Thuesen DO, Speck LS, Lett-Brown MA, Grant JA. Histamine-releasing activity (HRA). I. Production by mitogen or antigen stimulated human mononuclear cells. *J Immunol* 122:623-632, 1979.
5. Dvorak AM, Lett-Brown MA, Thuesen DO, et al. Histamine releasing activity (HRA). III. HRA induces human basophil histamine release by provoking noncytotoxic granule exocytosis. *Clin Immunol Immunopathol* 32:142-150, 1984.
6. Kuna P, Reddigari SR, Schall TJ, et al. Characterization of the human basophil response to cytokines, growth factors, and histamine releasing factors of the intercrine/chemokine family. *J Immunol* 150:1932-1943, 1993.
7. Oppenheim JJ, Zacharie COC, Mukaida N, Matsushima K. Properties of the novel proinflammatory supergene "Intercrine" cytokine family. *Ann Rev Immunol* 9:617-648, 1991.
8. Kuna P, Reddigari SR, Rucinski D, et al. Monocyte chemotactic and activating factor is a potent histamine-releasing factor for human basophils. *J Exp Med* 175:489-493, 1992.
9. Alam R, Lett-Brown MA, Forsythe PA, et al. Monocyte chemotactic and activating factor is a potent histamine releasing factor for basophils. *J Clin Invest* 89:723-728, 1992.
10. Kaplan AP, Reddigari S, Baeza M, Kuna P. Histamine releasing factors and cytokine-dependent activation of basophils and mast cells. *Adv Immunol* 50:237-260, 1991.
11. 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* 321:228-232, 1989.
12. Kuna P, Alam R, Kuzminska B, Rozniecki J. The effect of pre-seasonal 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* 83:816-824, 1989.
13. Gruber B, Poznansky M, Boss E, et al. Characterization and functional studies of rheumatoid synovial mast cells: Activation by secretagogues, anti-IgE, and histamine-releasing lymphokine. *Arthritis Rheum* 29:944-955, 1986.
14. Kuna P, Reddigari SR, Kornfeld D, Kaplan AP. IL-8 inhibits histamine release from human basophils induced by histamine releasing factors, connective tissue activating peptide III, and IL-3. *J Immunol* 147:1920-1924, 1991.

15. Reddigari SR, Kuna P, Miragliotta GF, et al. Connective Tissue Activating Peptide-III and its derivative, Neutrophil Activating Peptide-2 Release Histamine From Human Basophils. *J Allergy Clin Immunol* 89:666–672, 1992.
16. Hirai K, Morita Y, Misaki Y, et al. Modulation of human basophil histamine release by hemopoietic growth factors. *J Immunol* 141: 3958–3964, 1988.
17. Hirai K, Yamaguchi M, Misaki Y, et al. Enhancement of human basophil histamine release by interleukin-5. *J Exp Med* 172:1525–1528, 1990.
18. Brindley LL, Sweet JM, Goetzel EJ. Stimulation of histamine release from human basophils by human platelet factor 4. *J Clin Invest* 72:1218–1223, 1983.
19. Alam R, Forsythe PA, Lett-Brown MA, Grant JA. Interleukin-8 and RANTES inhibit basophil histamine release induced with monocyte chemotactic and activating factor/monocyte chemoattractant peptide-1 and histamine releasing factor. *Am J Respir Cell Mol Biol* 7:427–433, 1992.
20. Dahinden CA, Kurimoto Y, De Weck AL, et al. The neutrophil-activating peptide NAF/NAP-1 induces histamine release and leukotriene release by interleukin 3-primed basophils. *J Exp Med* 170: 1787–1792, 1989.
21. Schall TJ, Bacon K, Toy KJ, Goeddel DV. Selective attraction of monocytes and T lymphocytes of the memory phenotype by cytokine RANTES. *Nature* 347:669–671, 1990.
22. Alam R, Forsythe PA, Stafford S, et al. Macrophage inflammatory protein-1 α activates basophils and mast cells. *J Exp Med* 176:781–786, 1992.
23. Kuna P, Reddigari SR, Schall TJ, et al. RANTES a monocyte and T lymphocyte chemotactic cytokine releases histamine from human basophils. *J Immunol* 149:636–642, 1992.
24. Lichtenstein LM. Histamine-releasing factors and IgE heterogeneity. *J Allergy Clin Immunol* 81:814–820, 1988.
25. Kaplan AP, Haak-Frendscho M, Fauci A, et al. A histamine-releasing factor from activated human mononuclear cells. *J. Immunol* 135: 2027–2032, 1985.
26. Alam R, Grant JA, Lett-Brown MA. Identification of a histamine releasing inhibitory factor produced by human mononuclear cells *in vitro*. *J Clin Invest* 82:2056–2062, 1988.
27. Kuna P, Rucinski D, Kaplan AP. Inhibition of MCAF-induced histamine release from human basophils by RANTES, MIP-1 α , MIP-1 β , PF4, CTAP-III, IL-8, and IP-10. *J Allergy Clin Immunol* 91:314, 1993.
28. Kuna P, Reddigari SR, Rucinski D, Kaplan AP. MCAF/MCP-1, RANTES, MIP-1 α , MIP-1 β , and CTAP III/NAP-2 participate in the activity known as histamine releasing factor (HRF). *Allergy* 48:109, 1993.
29. Columbo SM, Horowitz EM, Botana LM, et al. The human recombinant c-kit receptor ligand, rhSCF, induces mediator release from human cutaneous mast cells and enhances IgE-dependent mediator release from both skin mast cells and peripheral blood basophils. *J Immunol* 149:599–608, 1992.
30. Alam R, Kuna P, Rozniecki J, Kuzminska B. The magnitude of spontaneous production of histamine releasing factor (HRF) by lymphocytes *in vitro* correlates with the state of bronchial hyperactivity in patients with asthma. *J Allergy Clin Immunol* 79:103–107, 1987.
31. Alam R, Rozniecki J, Selmaj K. A mononuclear cell-derived histamine releasing factor (HRF) in asthmatic patients. Histamine release from basophils *in vitro*. *Ann Allergy* 53:66–69, 1984.
32. Kuna P, Alam R, Marciniak M, Rozniecki J. Early and late asthmatic reactions following an allergen bronchoprovocation are associated with an increase in histamine releasing factor (HRF) synthesis by mononuclear cells (MNC). *J Allergy Clin Immunol* 85:268, 1990.
33. Alam R, Kuna P, Rozniecki J, Kuzminska B. Bacterial antigens stimulate the production of histamine releasing factors (HRF) by lymphocytes from intrinsic asthmatic patients. *Clin Exp Immunol* 63:241–248, 1986.
34. Charlesworth EN, Hood AF, Soter NA, et al. Cutaneous late-phase response to allergen. Mediator release and inflammatory cell infiltration. *J Clin Invest* 83:1519–1526, 1989.
35. Bascom R, Wachs M, Naclerio RM, et al. Basophil influx occurs after nasal antigen challenge: Effects of topical corticosteroid pretreatment. *J Allergy Clin Immunol* 81:580–589, 1988.
36. Reshef A, Kagey-Sobotka A, Adkinson NF, et al. The pattern and kinetics in human skin of erythema and mediators during the acute and late-phase response (LPR) *J Allergy Clin Immunol* 84:678–687, 1989.
37. Warner JA, Pienkowski MM, Plaut M, et al. Identification of histamine releasing factors in the late phase of cutaneous IgE-mediated reactions. *J Immunol* 136:2583–2587, 1986.
38. Seibold JR, Giorno RC, Claman HN. Dermal mast cell degranulation in systemic sclerosis. *Arthritis Rheum* 33:1702–1709, 1990. □

9TH YEAR OF PUBLICATION

American Journal of Rhinology

95 Pitman Street, Providence, RI 02906 Telephone: (401)331-2510 Fax (401)331-5138

Official Journal of the American Rhinologic Society

An Invitation

to subscribe to the only MEDICAL JOURNAL in
the USA that concentrates scientific knowledge
exclusively on the nose.

Featuring: nasal physiology, immunology/allergy,
bio-chemistry, pathology and treatment.

The American Journal of Rhinology is directed mainly to specialties that deal with disorders of the nose: Otolaryngology, Allergy/Immunology, and Plastic Surgery. It publishes peer reviewed, original articles, review manuscripts and abstracts of important world-wide research publications on the nose. The innovative goal of this publication is to concentrate new knowledge on the nose in one Journal which is of special interest to the above three specialties.

This multi-specialty approach is exciting and unique. It translates into better patient care and into more meaningful research. The AMERICAN JOURNAL OF RHINOLOGY is widely read and presents a new concept of seeking a common ground that crosses intradisciplinary lines.

Editor-in-Chief for the Otolaryngologic section is David W. Kennedy, MD, Professor of Otolaryngology, University of Pennsylvania Medical Center. Editor-in-Chief for the Allergy/Immunological section is Philip Fireman, MD, Professor of Pediatrics, University of Pittsburgh.

TO ORDER:

Name _____

ISSN 1050-6586

Address _____

ANNUAL SUBSCRIPTION:

Individual \$ 75.00 (U.S.A.)

Institution \$105.00 (U.S.A.)

Outside U.S.A. please add \$30.00

Visa/MasterCard accepted

Payment must be made in advance in U.S. dollars drawn upon a U.S. bank to:
American Journal of Rhinology, 95 Pitman Street, Providence, RI 02906 (USA)

Published Bimonthly by OceanSide Publications, Inc.

95 Pitman Street, Providence, RI 02906

401-331-2510

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.