# Enhancement of Basophil Chemotaxis In Vitro by Virus-induced Interferon

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A B S T R A C T   It is well established that viral infections may precipitate or worsen attacks of bronchial asthma. Furthermore, in symptomatic atopic subjects, the local accumulation of basophils and the production of a basophil chemotactic factor have been reported. We have investigated the effect of cell-free supernates from viral stimulated cultures of human mononuclear cells on the in vitro migration of human basophils. Our results show the presence of a factor in these culture supernates that enhances the migration of basophils toward two separate chemoattractants, a peptide from C5 and a lymphokine. The enhancing activity, while affecting basophil migration, did not change the response of monocytes.

The enhancing activity resembled viral-induced interferon when (*a*) pH 2 stability, (*b*) heat resistance, (*c*) trypsin sensitivity, and (*d*) species-specificity were compared. Finally, the enhancing activity for basophil chemotaxis and the interferon titer were highly correlated in preparations with a $10^4$-fold difference in interferon specific activity.

Our studies show that viral-induced interferon can augment the in vitro chemotactic response of basophils. Because mediators present in basophils may be involved in the pathogenesis of immediate hypersensitivity, the modulation of basophil movement by interferon suggests a possible mechanism for the association between viral infections and atopic disorders.

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## INTRODUCTION

Viral upper respiratory infections have been shown to trigger recurrent episodes of wheezing in the asthmatic child (1-5). In addition, viral infections can increase bronchial sensitivity to drugs such as methacholine (6-8). Histamine, slow reacting substance of anaphylaxis, and eosinophil chemotactic factors, present in tissue mast cells and peripheral blood basophils, are probable contributors to the pathophysiology of atopic diseases (9). It is not clear at present whether basophils play a causative role in asthmatic attacks. However, their participation is suggested by the findings of Kimura et al. (10, 11) who showed that circulating basophils increase in number during the preattack stage of bronchial asthma and fall during attacks with a concomitant rise in the number of basophils in the sputum of patients.

Recently, Ida et al. (12) have suggested that interferon may be a contributing factor in immediate hypersensitivity reactions. They showed that culture of human leukocytes with virus enhances allergen-mediated release of histamine from basophils. The effect was caused by a soluble factor that had many of the properties of interferon. In the present study, we report the enhancement of in vitro basophil migration following incubation of leukocytes with viral-induced human leukocyte interferon.

## METHODS

*Virus preparation.* Parainfluenza virus type 1 (Sendai) was propagated and assayed by inoculation of the allantoic fluid of embryonating hen's eggs (12). A purified viral pool containing a titer of $10^{9.5}$ egg infectious doses$_{50}$ per ml before ultraviolet inactivation was used throughout the study (12). An influenza subunit vaccine was purchased from Parke-Davis (Morris Plains, N. J.).

*Interferon.* Human leukocyte interferon (G-023-901-527), human fibroblast interferon (G-023-902-527), and mouse in-

terferon (G-002-904-511) were obtained from the Research Resources Branch, National Institute of Allergy and Infectious Diseases. Partially purified human leukocyte interferon was a gift from Dr. K. Paucker, Medical College of Pennsylvania and Hospital. The interferon was induced by Sendai virus according to the method of Cantell, partially purified by antibody affinity chromatography to a specific activity of $2 \times 10^7$ U/mg protein (13) and stabilized in 0.5% bovine serum albumin (BSA,[1] fraction V, Sigma Chemical Co., St. Louis, Mo.).

*Interferon assay.* Interferon was assayed in a microtiter system on human WISH cells using Sindbis virus (14, 15). Interferon activity was expressed in terms of the National Institutes of Health reference interferon. 1 U of interferon is defined as the concentration that resulted in 50% reduction in cytopathogenic effect.

*Preparation and culture of leukocytes.* Peripheral blood from normal donors was anticoagulated with 10 U/ml preservative-free heparin (Gibco Laboratories, Grand Island Biological Co., Grand Island, N. Y.) and diluted 1:3 with Hanks' balanced salt solution (Gibco Laboratories) buffered with 4 mM Hepes. A basophil-enriched cell population containing basophils (1–3%), lymphocytes (70–75%), and monocytes (20–25%) was obtained by centrifugation on a Ficoll-Hypaque layer by the method of Boyum (16). The interface cells were collected, washed twice in Hanks' balanced salt solution buffered with Hepes, and then resuspended in RPMI 1640 medium (Gibco Laboratories) buffered with 25 mM Hepes, and supplemented with penicillin (100 U/ml), streptomycin (100 μg/ml), gentamycin (50 μg/ml), and 2% heat inactivated fetal bovine serum. Cells were cultured in No. 2027 tubes, Falcon Labware, Div. Becton, Dickinson & Co. (Oxnard Calif.), at 5–7 × 10⁶ cells/ml with ultraviolet inactivated Sendai virus, allantoic fluid (control) or influenza vaccine. After 24 h, the leukocytes were sedimented by centrifugation (300 g, 10 min) and the supernatant fluids were stored at −70°C after reconstitution of the control supernate with virus.

*Chemotactic factors.* A C5 peptide(s) with chemotactic activity was partially purified by Sephadex G-75 chromatography of zymosan-activated fresh human serum as previously described (17). Lymphocyte-derived chemotactic factor (LDCF) was prepared by stimulating human leukocytes with streptokinase-streptodornase (SKSD, Varidase, Lederle Laboratories, Pearl River, N. Y.) and partially purified by Ultrogel ACA-44 chromatography as previously reported (18).

*Preincubations.* Fresh basophil-enriched mononuclear cells, prepared as above, were resuspended at 10–15 × 10⁶ cells/ml in RPMI 1640 and incubated for 1 h at 37°C with an equal volume of stimulated supernate. The cells were washed, resuspended at 10–15 × 10⁶ cells/ml in Gey's balanced salt solution (Gibco Laboratories) containing 2% BSA, and assayed for chemotactic response.

*Measurement of migration.* Chemotaxis was measured as previously described (19) in blind well chambers (Neuro Probe, Inc., Bethesda, Md.). The lower compartment, to which 0.2 ml of chemotactic factor solution was added, was separated from the upper compartment by a 10-μm thick polycarbonate filter with 5-μm Diam pores (Neuro Probe, Inc.). A volume of 0.3 ml of cell suspension (10–15 × 10⁶ cells/ml) was added to the upper compartment. Chambers were incubated for 90 min at 37°C. Filters were removed and stained in Wright's stain (20). Slides were coded and migrated basophils were counted blind in 25–50 randomly selected oil immersion fields (1,250×). Results are expressed as the mean number of migrated basophils±SEM of triplicate filters.

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[1] *Abbreviations used in this paper*: BSA, bovine serum albumin; IFN, viral induced interferon; LDCF, lymphocyte-derived chemotactic factor.

## RESULTS

*Effect of supernatant fluids on basophil migration.* Basophil-enriched mononuclear cells were incubated for 1 h in supernates from leukocytes cultured for 24 h in (a) medium alone, (b) medium with allantoic fluid reconstituted with virus at the end of culture (control), and (c) medium with Sendai virus. Basophils from all donors showed an enhanced response to C5 peptide and LDCF following exposure to supernatant fluids from leukocyte cultures stimulated with virus (Fig. 1, $P < 0.01$, paired $t$ test). The enhancement was seen, irrespective of whether the supernates were tested with homologous or autologous basophil-enriched mononuclear cells. Secondly, as shown in Fig. 2, the enhancement was seen over a fourfold concentration range of chemotactic factors ($P < 0.01$, by analysis of variance). The response of basophils to diluent alone (Gey's − 2% BSA) was not affected.

Viral stimulated supernates enhanced the response of basophils, but had no effect on the migration of monocytes (Table I) in the same chemotactic assay.

*Relationship between basophil migration and interferon activity.* Since viral stimulated culture supernatants augmented basophil migration and since viral-induced interferon (IFN) has been shown to enhance IgE-mediated histamine release (12), it was important to consider whether interferon was the active agent in our study. Preliminary results showed that under our conditions of culture all supernates from leukocytes stimulated with virus contained both enhancing activity (1.5 to 2.1 times greater than control) and IFN (1,256±576 U/ml, mean±SD of five supernates). The
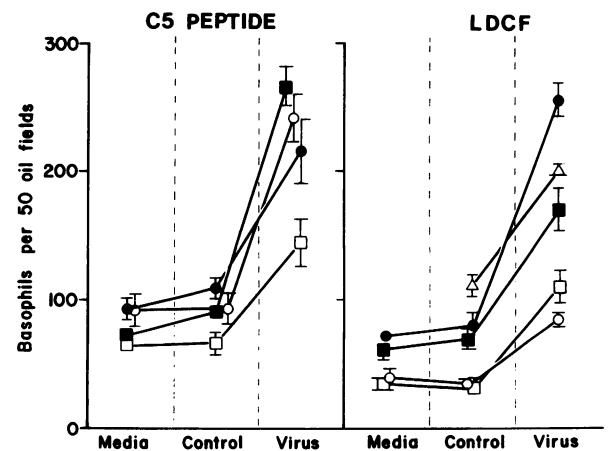


FIGURE 1  Enhancement of basophil chemotaxis by supernatants from viral stimulated cell cultures. Basophil-enriched mononuclear cells from nine donors were incubated with supernatant fluids from leukocyte cultures exposed for 24 h to (a) media alone; (b) allantoic fluid (control), or (c) UV-inactivated Sendai virus. After 1 h of incubation, the basophil chemotactic response to C5 peptide or LDCF was assayed.
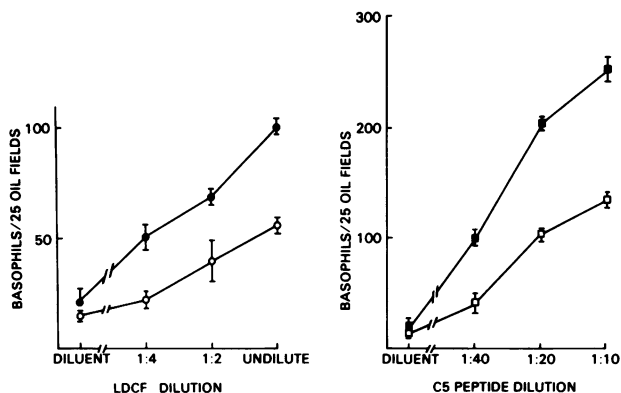
FIGURE 2 Effect of concentration of chemotactic factor on enhanced migration. Basophil-enriched mononuclear cells were incubated 1 h with supernates from leukocytes stimulated with either (a) UV-inactivated virus (●, ■), or (b) allantoic fluid (○, □).

control supernates contained neither IFN nor enhancing activity. Furthermore, Fig. 3 illustrates the effect of reference leukocyte IFN. In all cases, the IFN preparation enhanced the migration of basophils to C5 peptide ($P < 0.01$, paired $t$ test).

*Physicochemical properties.* To see if the IFN titer could be dissociated from the enhancing activity, viral-stimulated culture fluids were exposed to: (a) pH 2, (b) heat, or (c) trypsin. Table II shows that trypsin essentially destroyed both activities, heat caused a small reduction in both activities, and treatment at pH 2 failed to affect either activity.
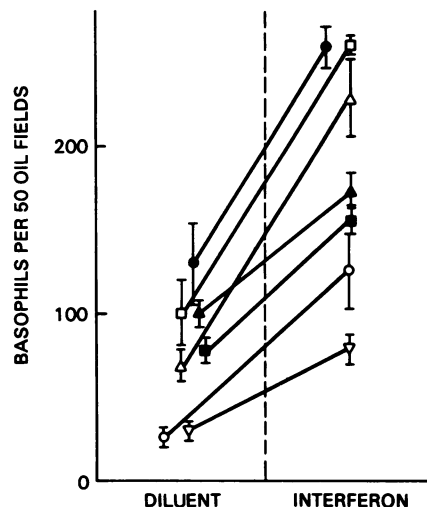


FIGURE 3 Enhancement of chemotaxis by leukocyte interferon. Basophil-enriched mononuclear cells from seven donors were incubated with reference leukocyte interferon (2,000 U/ml) or diluent (Gey's-BSA) for 1 h. Chemoattractant = C5 peptide.

*Effect of mouse interferon.* Since the response to viral IFN is usually species specific (13, 21, 22), the effect of mouse IFN on human basophil migration was examined. Mouse IFN had no enhancing activity at a titer of 2,000 U/ml while human leukocyte IFN increased basophil migration at a titer of 250 U/ml (Table III). Furthermore, human fibroblast IFN was as effective as viral-induced leukocyte IFN.

*Partially purified interferon.* Since the reference leukocyte IFN preparations may contain other soluble products of biological significance, we tested the enhancing activity of an enriched IFN preparation. Fig. 4 compares the enhancing activity and IFN titer of (a)

TABLE I
*Specificity of Enhancing Activity**

| Exp. | Supernate | Chemotactic factor | Basophils per 50 oil fields | Monocytes per 20 oil fields |
|---|---|---|---|---|
| A | Virus | LDCF | 109±17 | 198±32 |
| | Control | | 31±6 | 228±21 |
| | Media | | 35±4 | 204±21 |
| | Virus | Diluent | 4±1 | 77±18 |
| | Control | | 5±2 | 80±8 |
| B | Interferon | C5 peptide | 252±30 | 250±20 |
| | Media | | 106±24 | 308±28 |
| | Interferon | Diluent | 15±3 | 55±8 |
| | Media | | 12±5 | 50±7 |

* Mononuclear cells from two donors (A and B) were incubated for 24 h in media, media + allantoic fluid (Control), media + UV-inactivated Sendai virus or media + 2,000 U/ml human leukocyte interferon. The supernates were harvested and stored at −70°C. Fresh basophil enriched mononuclear cells from the same donors were incubated for 1 h in the supernates, washed, resuspended in Gey's-BSA, and the chemotactic response of the basophils and monocytes to either C5 peptide or LDCF assayed.

TABLE II
*Physicochemical Characterization of Enhancing Activity**

| Cells preincubated for 1 h in: | Basophils per 50 oil fields | Interferon |
|---|---|---|
| | | *U/ml* |
| Media | 43±7 | <10 |
| Control supernate | 38±2 | <10 |
| Viral stimulated supernate | | |
| Untreated | 128±3 | 1,000 |
| 18 h at pH2 | 135±10 | 1,000 |
| 57°C for 1 h | 100±8 | 600 |
| 1 h with trypsin | 51±6 | 50 |

* The interferon titers of untreated or treated supernates from stimulated cells were measured. The enhancing activity in the supernates was assayed by preincubation of mononuclear cells for 1 h in the supernatants followed by assaying the chemotactic response of the basophils to C5 peptide.

## Table III
### Species Specificity of Interferon*

| Cells preincubated for 1 h in | Basophils per 50 oil fields |
|---|---|
| Media alone | 18±2 |
| Human leukocyte interferon, 2,000 U/ml | 66±10 |
| Human leukocyte interferon, 250 U/ml | 66±12 |
| Human fibroblast interferon, 2,000 U/ml | 80±12 |
| Human fibroblast interferon, 250 U/ml | 64±6 |
| Mouse interferon, 2,000 U/ml | 18±2 |

* Following incubation of the mononuclear cells with the reference interferons, cells were washed, resuspended in Gey's-BSA and the chemotactic response of the basophils to C5 peptide assayed.

partially purified IFN, (b) a supernate from leukocytes stimulated with Sendai virus, and (c) a supernate from leukocytes stimulated with influenza vaccine. As can be seen, plots of the enhancing activity vs. IFN titer were superimposable for all three preparations. The specific activity of the IFN in the two supernates was ~10³ U/mg protein, whereas the partially purified
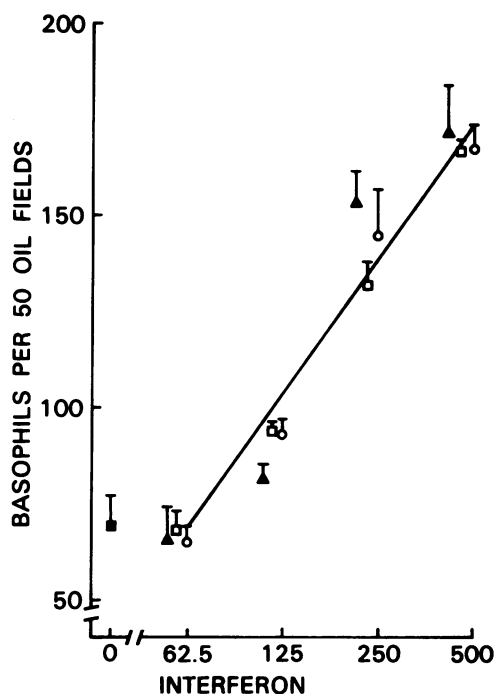


FIGURE 4 Correlation between interferon titer (units per milliliter) and enhancement of chemotaxis towards C5 peptide. Basophil-enriched mononuclear cells were exposed for 1 h to different dilutions of: (O) Supernate from cells stimulated with UV-inactivated Sendai virus. Specific activity of interferon ≃10³ U/mg protein. (□) Supernate from cells stimulated with influenza vaccine. Specific activity of interferon ≃10³ U/mg protein. (▲) Partially purified interferon. Specific activity ≃ 2 × 10⁷ U/mg protein. (■) Control supernate (no interferon).

preparation had a specific activity of 2 × 10⁷ U/mg protein (13). Since the specific activity of the interferon preparations varied by a factor of 10⁴, these results clearly support the notion that the enhancing activity is mediated by interferon.

## DISCUSSION

The present study shows that preincubation of human basophil-enriched mononuclear cells with supernates from leukocytes cultured with virus enhanced the migration of basophils toward chemotaxins (LDCF and C5-peptide). This effect is specific in that the chemotactic response of basophils was affected while that of monocytes remained unchanged. Moreover, random migration of basophils was not increased.

Several lines of evidence indicate that the enhancing activity is mediated by interferon. All preparations of human IFN, whether leukocyte or fibroblast derived, cause enhancement. The soluble factor causing enhancement cannot be dissociated from IFN by standard physicochemical means (13, 22) and is species specific (21). Anti-interferon globulin neutralized the antiviral effect of interferon and blocked the enhancing activity (data not shown). The strongest evidence, illustrated in Fig. 4, is the correlation between enhancing activity and IFN titer when a partially purified preparation of IFN (specific activity ≃ 2 × 10⁷ U/mg protein) was compared to two leukocyte culture supernates (stimulated by either Sendai virus or influenza vaccine, specific activity ≃10³ U/mg protein). Thus, although the degree of purity varied by a factor of 10⁴, plots of IFN titer vs. enhancing activity were superimposable for the three preparations.

Our interest in the effect of IFN on basophil migration was stimulated by the report of Ida et al. (12) that IFN enhances the degranulation of human basophils and the subsequent release of histamine. While the enhancement of IgE-mediated release of histamine by IFN requires an induction period of 6–9 h and RNA synthesis (23), in our assay the effect of IFN was rapid. Preincubation with IFN for only 1 h was sufficient to increase the chemotactic response of basophils; moreover, preliminary results show that enhancement can be achieved by adding high concentrations of IFN (2,000 U/ml) to basophils and measuring the chemotactic response immediately afterwards (data not shown). Several other non-antiviral activities have been attributed to interferon, which also occur rapidly. Blalock and Stanton (24) showed maximal stimulation of myocardial cells by IFN in 2 min.

The mechanism of enhancement by IFN is not clear. A number of studies have shown that changes in intracellular concentration of cyclic nucleotides can modulate the movement of cells and thus, their chemotactic responsiveness (25, 26). Recently it has been shown

that IFN can alter the intracellular cyclic nucleotide levels (27–29). However, the effect of IFN on basophil nucleotide levels is unknown. Microfilaments and microtubules are probably involved in both cellular movement (30) and IFN action (31). Cytochalasin B (a drug reported to inhibit microfilament action) and colchicine (an antimicrotubule agent) inhibit both the chemotaxis of cells (32) and the induction of the antiviral effect by IFN (31). Interferon has been shown to enhance the expression of receptors on cells (33); an increased number of chemotactic receptors on basophils would likely lead to enhanced migration in our system. Since basophils represent only 1–3% of the cells in suspension, we cannot exclude the possibility that IFN acts on another cell type (e.g. lymphocytes), which in turn releases a factor (e.g. prostaglandins) affecting basophils.

A variety of additional factors, including histamine, regulate basophil function in vitro. The effect of IFN on both the secretory and migratory responses of basophils is the opposite of the effects of histamine. We have shown that histamine inhibits the chemotaxis of basophils (34) and Bourne et al. (35) have reported that histamine augments leukocyte adenosine 3,5-monophosphate and blocks histamine release from basophils.

The accumulation of basophils during immediate and delayed hypersensitivity reactions is probably determined by the relative concentrations of chemotactic factors, and the presence of modulating factors such as histamine and interferon. Interferon is found in nasal secretions from infants with viral respiratory tract infections (36, 37). Since interferon does not have chemotactic activity or affect random migration of basophils, we would not expect basophils to accumulate in nasal passages during viral respiratory infections. Indeed, Hastie et al. (38) observed basophils in the nasal secretions of patients with allergic rhinitis, but not of subjects with viral respiratory infections. Recently, Hirsch and Kalbfleisch (39) found that serum from persons with symptomatic allergic rhinitis contained a basophil chemotactic factor.

Asthma is another clinical problem that involves (at least in some patients) the release of mediators by allergic stimuli. Viral infections are known to precipitate and aggravate asthmatic attacks (4, 5). Studies in vitro show that IFN will enhance both basophil chemotaxis and the IgE-mediated release of histamine (12, 23, 40). Moreover, IFN has been shown to modulate various immune responses both in vitro and in vivo (41). While the exact role of IFN in allergic reactions in man is not known, IFN has been demonstrated in the circulation of patients with autoimmune and allergic diseases (42, 43). It is reasonable to suggest that any stimulus which would normally induce accumulation and/or degranulation of basophils and mast cells may result in a more severe reaction when interferon is present. In addition, a normally sub-threshold stimulus may induce a reaction during a viral infection. The possibility that IFN may augment chemotaxis of basophils and enhance mediator release in vivo during allergic diseases in man merits further study.

## ACKNOWLEDGMENTS

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