

Effects of PBMC-derived histamine-releasing factors on histamine release from human skin and lung mast cells

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Summary

Background A field of study which has attracted much recent interest is the ability of mononuclear cells and neutrophils to interact with histamine releasing cells by production of specific histamine releasing factors (HRFs). However, almost all of these studies have been performed on basophils rather than human mast cells.

Objective We have investigated the effects of lyophilized fractions of HRF preparations on histamine release from human skin and lung mast cells.

Methods Lyophilized fractions of HRF preparations include crude supernatant from mononuclear cell/platelet (crude), void peak from anion exchange chromatography column (void), second peak from anion exchange chromatography (peak 2), neutrophil-activating peptide-2 (NAP-2), which was purified from void peak at molecular weight of 8–12 kDa, and monocyte chemotactic-activating factor (MCAF). Mast cells were enzymatically dispersed.

Results Crude (24.2 µg/mL–2.42 mg/mL), void (5.4 µg/mL–0.54 mg/mL), peak 2 (3.5 µg/mL–0.35 mg/mL), and NAP-2 (1–20 µg/mL) failed to release histamine from lung mast cells. In skin mast cells, only higher concentrations of crude and void caused minimal release of histamine. MCAF up to micromolar concentrations failed to have an effect on mast cells from either source. However, these HRFs induced histamine release from human basophils. We also explored whether HRFs and stem cell factor could act as either priming agents for each other or for anti-IgE. The response of skin mast cells to all these preparations was not enhanced by preincubation in stem cell factor at 1 ng/mL, nor did the HRFs and MCAF enhance the response of skin mast cells to anti-IgE.

Conclusion These results suggest that these HRFs have no significant effect on dispersed human cutaneous and lung mast cells.

Keywords: histamine releasing factor, human mast cells, monocyte chemotactic-activating factor, stem cell factor, anti-IgE

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Introduction

Histamine releasing factor (HRF) was first described by

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Thuesen *et al.* [1,2] as a factor synthesized by human mononuclear cells which induced histamine release from human basophils. Since that time, many HRFs have been reported to be generated from a variety of cell sources including alveolar macrophages [3], platelets [4], B and T lymphocytes [5–7], neutrophils [8], and eosinophils [9]. Furthermore, HRFs have been found in late-phase blister fluids [10] and bronchoalveolar lavage

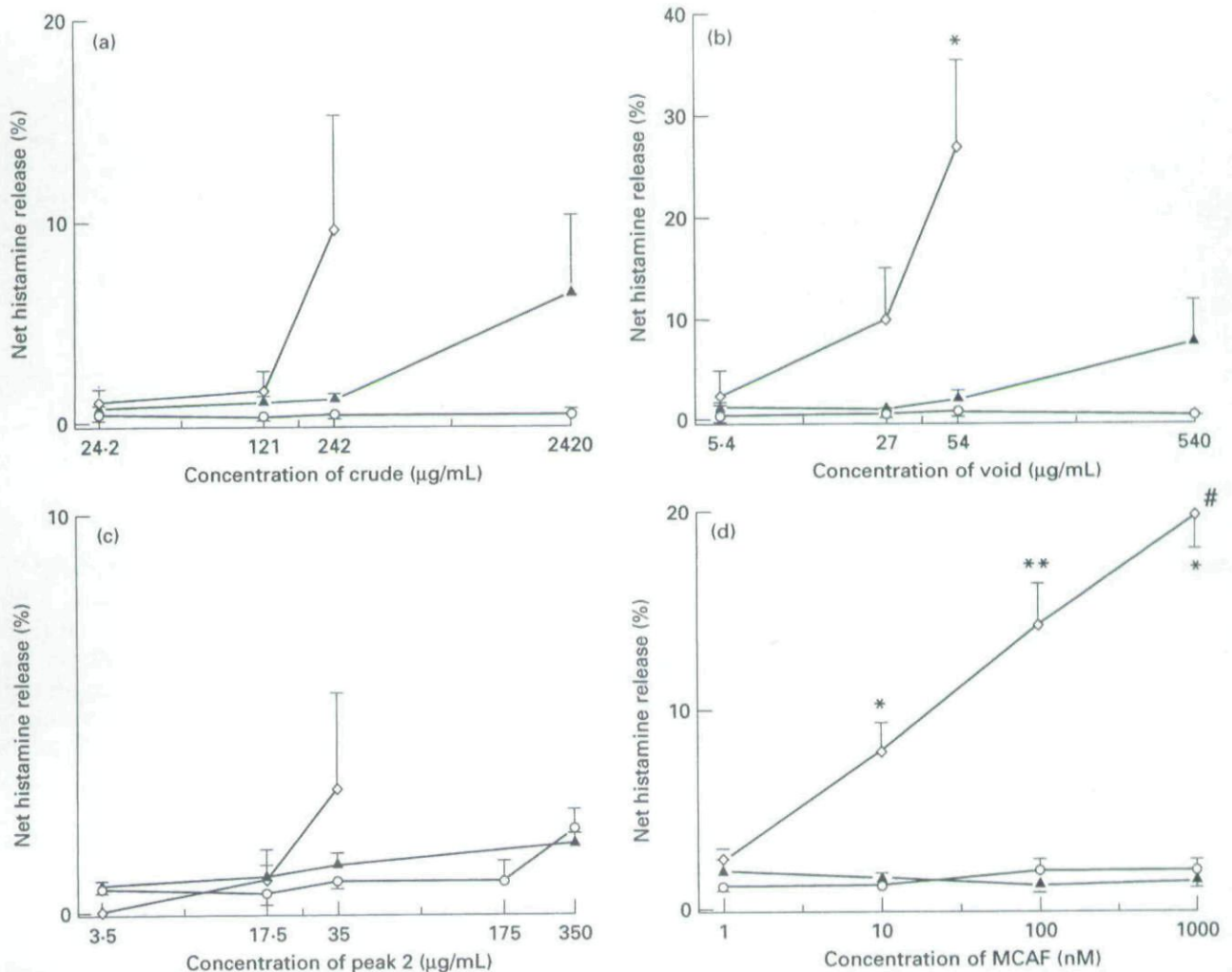


Fig. 1. Effect of PBMC-derived HRFs on histamine release from human skin mast cells (▲), lung mast cells (○) and basophil leukocytes (◇). Panels indicate the activity of (a) crude HRF, (b) the void fraction, (c) peak 2 and (d) MCAF. Human leucocyte and mast cell preparations were incubated with the indicated concentrations of HRFs for 45 and 30 min, respectively. Each result is expressed as a mean net percentage histamine release $\pm$ SEM for seven (skin mast cells), four (lung mast cells), six (crude, the void fraction and peak 2 on leucocytes) and eight experiments (MCAF on leucocytes), in which spontaneous histamine releases were $5.5 \pm 0.9\%$, $2.8 \pm 0.6\%$, $4.6 \pm 1.3\%$ and $4.5 \pm 2.3\%$ respectively. As positive controls, net histamine release induced by the optimal concentrations of anti-IgE (3% for mast cells and 0.3% for leucocytes) were $11.5 \pm 2.2\%$, $15.8 \pm 2.6\%$, $21.6 \pm 6.4\%$ and $22.6 \pm 4.8\%$ for skin mast cells, lung mast cells, the crude, the void fraction and peak 2 experiments on leucocytes, and MCAF experiments on leucocytes, respectively. * $P < 0.05$, ** $P < 0.01$ vs histamine release induced by the lowest concentration of each HRF. # indicates the results from four experiments.

fluids [11]. Initial purification of supernatants from stimulated peripheral blood mononuclear cells (PBMC) and platelets revealed three separate peaks of activity of 8–10, 15–17, and 35–41 kDa [12–14]. Further characterization of the 8–10 kDa material showed it to comprise of two platelet basic protein-derived substances, connective tissue-activating peptide III (CTAP III) and its derivative, neutrophil-activating peptide 2 (NAP-2). A further

PBMC-derived HRF is monocyte chemotactic-activating factor (MCAF), which is a member of the proinflammatory 'intercrine' cytokine family [15]. This is the most potent of the various molecular forms of HRF on a molar basis. All of these agents have been shown to release histamine from human basophils [12,14,15]. We now investigate their effects on histamine release from dispersed skin and lung mast cells.

Table 1. Effect of priming skin mast cells with SCF or HRFs upon histamine release induced by anti-IgE or HRFs

	Histamine release (%)					MCAF
	Buffer	Anti-IgE	Crude	Void	Peak 2	
Buffer	—	9.2 ± 1.1	1.9 ± 0.4	1.5 ± 0.1	1.0 ± 0.1	0.4 ± 0.3
SCF	0.1 ± 0.2	14.4 ± 1.7*	1.2 ± 0.2	1.5 ± 0.1	1.4 ± 0.3	1.0 ± 0.6
crude		9.9 ± 0.3				
void		9.2 ± 0.4				
peak 2		10.7 ± 1.0				
MCAF		10.2 ± 0.2				

Human skin mast cells from four separate donors were preincubated in buffer or with SCF (1 ng/mL) or HRFs: crude HRF (242 µg/mL), void fraction (54 µg/mL), peak 2 (35 µg/mL) or MCAF (100 nM) for 30 min at 37°C and then challenged with anti-IgE (3%), crude HRF (242 µg/mL), void fraction (54 µg/mL), peak 2 (35 µg/mL) or MCAF (100 nM) for 30 min. The mean ± SEM of net histamine release is shown. * $P < 0.05$: statistically significant augmentation of release.

Materials and methods

Purification of histamine releasing factors

Crude HRF derived from human PBMC and platelets (crude HRF) plus two anion exchange chromatographic fractions, 8–10 kDa (void fraction, which contains NAP-2, CTAP III and MCAF) and 15–17 kDa (peak 2) were prepared as previously described [12–14]. Recombinant MCAF was obtained from Pepro Tech Inc., Rocky Hill, NJ, USA [15].

Cell preparation

Human foreskin and lung mast cells were enzymatically dispersed as previously described (approximately 5% purity) [16]. Dispersed cells were cultured for 12–16 h at 37°C in DMEM (HyClone Europe Ltd, Cramlington, UK) supplemented with 2 mM L-glutamine, 200 U/mL penicillin and 200 µg/mL streptomycin and 10% fetal calf serum (FCS) (GIBCO BRL, Paisley, UK) [17]. Mixed leucocytes, containing approximately 1% basophils, were prepared as previously described [14,15].

Histamine release and assay

Duplicate suspensions of 2×10^4 mast cells or basophils in 90 µL N-2-hydroxyethyl-N-2-ethanesulphonic acid (HEPES)-buffered salt solution (HBSS), pH 7.2, containing 137 mM NaCl, 20 mM HEPES, 5 mM D-glucose, 2.7 mM KCl, 0.4 mM NaH₂PO₄, 1.8 mM CaCl₂, 0.5 mM MgCl₂ and 1% FCS were stimulated with 10 µL of HRF at 37°C for 45 min (leucocytes) or for 30 min (mast cells). In priming experiments, human skin mast cells were preincubated with 1 ng/mL of stem cell factor (SCF) (a

gift from Cytomed Inc., MA, USA) for 30 min and then challenged with crude HRF (242 µg/mL), the void fraction (54 µg/mL), peak 2 (35 µg/mL), MCAF (100 nM) or anti-IgE (3%) (Serotec, Oxford, UK) for 30 min. Skin mast cells were preincubated with these concentrations of HRFs for 30 min and then activated with anti-IgE (3%) for 30 min. Histamine was measured spectrofluorimetrically and results expressed as net percentage release corrected for spontaneous release.

Statistical analyses

Results are expressed as the mean ± SEM. Differences between means were tested for significance with Student's *t*-test for paired data. Differences were considered significant when the probability (*P*) was <0.05.

Results

To confirm their effects on basophils, the histamine releasing capacity of crude HRF (24.2–242 µg/mL), the void fraction (5.4–54 µg/mL), peak 2 (3.5–35 µg/mL) and MCAF (1–1000 nM) was examined on leucocyte preparations from six to eight donors. Although sensitivity differed, release with HRFs was seen in all preparations (Fig. 1). The void fraction (54 µg/mL) and MCAF (10–1000 nM) induced significant histamine release from leucocytes ($P < 0.05$ or $P < 0.01$). Human skin and lung mast cells were then examined in seven and four experiments respectively. Crude HRF (24.2–2420 µg/mL), the void fraction (5.4–540 µg/mL), peak 2 (3.5–350 µg/mL) and MCAF (1–1000 nM) all failed to show significant histamine release, although some indication of potential activity was seen with the highest

concentrations of 2420 $\mu\text{g/mL}$ of crude HRF and 540 $\mu\text{g/mL}$ of the void fraction, net histamine releases of $6.6 \pm 3.8\%$ and $7.8 \pm 4.2\%$ being observed in skin mast cells (Fig. 1).

Prior studies have indicated that stem cell factor (SCF) is capable of priming human mast cells for histamine release due to anti-IgE [18–20]. In this study we wished to corroborate the data and investigate whether HRFs and SCF could act as a priming agent for each other or for anti-IgE. To investigate whether SCF could enhance HRF-induced histamine release or whether HRFs could enhance that induced by anti-IgE, four experiments were performed in human skin mast cells. As can be seen in Table 1, preincubation for 30 min with SCF (1 ng/mL) failed to increase histamine release induced by crude HRF (242 $\mu\text{g/mL}$), the void fraction (54 $\mu\text{g/mL}$), peak 2 (35 $\mu\text{g/mL}$) or MCAF (100 nM), while that induced by anti-IgE (3%) was increased from $9.2 \pm 1.1\%$ to $14.4 \pm 1.7\%$ ($P < 0.05$). Furthermore, these concentrations of HRFs failed to enhance histamine release induced by anti-IgE (3%) (Table 1).

Discussion

Histamine releasing factors are a heterogeneous family of molecules varying in molecular size, stability when heated and in their requirement for interactions with surface-bound IgE leading to histamine release [21]. Most of HRFs are members of the chemokine group of cytokine-like molecules, which consists of two subgroups of chemokines termed α and β [22]. All chemokines have four critical cysteine residues positioned similarly. The first two cysteines may have a single amino acid between them (C-X-C) characteristic of the α subgroup, or these two cysteines may be adjacent (C-C), as seen in β subgroup. Relatively few studies have reported on the effect of HRFs on mast cell mediator release.

HRFs generated by PBMC and platelets have been suggested to contribute to the protracted histamine release observed in allergic inflammation by their effects on basophils [12,14,15]. Our data would support this hypothesis. It has been reported that human lung mast cells degranulate when exposed to a macrophage-derived HRF [3] and also that synovial mast cells are activated by a mononuclear cell-derived HRF [23]. Crude and partially purified HRF from activated lymphocytes was previously reported to degranulate human lung mast cells [24]. However, our experiments show that crude HRF, the void fraction, peak 2 and MCAF caused neither significant histamine release nor primed human mast cells for anti-IgE-induced histamine release, although some indication of potential activity was seen with the highest concentrations of crude HRF and the

void fraction in skin mast cells. At least part of this discrepancy between our results and those cited above may be accounted for by variability in the cellular source of HRFs and mast cell heterogeneity as well as the stage of the disease. Our results also suggest an important biological control concept; activation of PBMC does not induce inflammatory mediator release from mast cells normally resident within a tissue but requires the secondary influx of basophils which occurs only in severe inflammatory conditions.

The α subfamily includes platelet factor-4 (PF-4), CTAP III and its derivatives β -thromboglobulin and NAP-2, myeloma growth stimulating activity or GRO (GRO/MGSA), IP-10 and IL-8 [22]. Platelet factor-4, CTAP III and its derivative NAP-2 were previously described to induce histamine release from basophils at concentrations of 10^{-7} to 10^{-5} M [14,25]. IL-8 induces histamine release from basophils at concentrations of 10^{-6} M and above [26] and inhibits HRF-induced histamine release at 10^{-10} to 10^{-8} M [27]. IP-10 was reported to fail to release histamine from basophils [28].

The β subfamily includes MCAF/monocyte chemoattractant peptide (MCP)-1, MCP-2, MCP-3, RANTES, macrophage inflammatory protein (MIP)-1 α , MIP-1 β , and fibroblast-induced cytokine (FIC) [22]. MCAF is a potent basophil HRF and accounts for 50–60% of the total histamine-releasing capability of mononuclear cell supernatants in basophils, and about 90% of the activity of the void fraction, which also contains CTAP III/NAP-2 and IL-8 [15,29]. However, MCAF had no ability to cause induction of histamine release from human skin and lung mast cells. This is in agreement with Alam *et al.*'s findings [30] which reported that MCAF had no effect on human lung mast cells. Histamine release by MCAF is G-protein dependent [31] and is exceedingly rapid with a $t_{1/2}$ of approximately 30 s [15]. The effect of RANTES is also rapid with the peak histamine release observed within the first minutes and no further increment between one minute and 1 h [28]. Preincubation of basophils with a wide variety of α and β chemokines including RANTES, MIP-1 α , MIP-1 β , PF4, IL-8, CTAP-III and IP10, inhibits subsequent secretion by MCAF, suggesting that this may reflect 'receptor class desensitization' in which the agonists act on different receptors which couple to the same or very similar G proteins [32]. Other β chemokines including MIP-1 α , MCP-2, MCP-3 and FIC also have histamine releasing activity on some donors' basophils [30,33,34]. The previous reports [13,35] suggest that PBMC-derived HRFs do not function via IgE and they include CTAP-III/NAP-2. In our study, anti-IgE induced histamine release from dispersed lung and skin mast cells, and so the lack of activity of PBMC-derived HRFs and MCAF

on human mast cells may not be due to the lack of cell membrane IgE or shortness of incubation time of mast cells with HRFs.

With regard to other chemokines which have been thought relevant to the secretion of basophils, murine MIP-1 α caused degranulation of mouse peritoneal mast cells from DBA/2 mice but MCAF did not [30]. MIP-1 α and MCAF/MCP-1 elicit an immediate and late phase reaction, and degranulate murine cutaneous mast cells *in vivo* [36]. MCP-2, MCP-3 and FIC did not cause degranulation of mouse peritoneal mast cells [34]. In human mast cells, Bischoff and Dahinden [18] surveyed a large variety of cytokines, including many of the chemokines such as NIP-1/IL-8, using human lung mast cells, and reported that SCF was the only one with significant histamine-releasing activity. MIP-1 α does not release histamine from human lung mast cells when stimulated either in the presence or absence of SCF (Dr C. Dahinden, personal communication). Similarly, RANTES does not release histamine from human lung mast cells [37]. Although sensitivity differed, NAP-2 has been reported to be capable of releasing histamine from human basophils [14]. We investigated the activity of NAP-2 on human skin and lung mast cells, and found that NAP-2, 1–20 μ g/mL, failed to induce histamine release from mast cells ($n = 4$, control net histamine release by 3% anti-IgE = $18.5 \pm 1.2\%$ and $9.0 \pm 0.5\%$ from lung and skin mast cells, respectively). Similarly NAP-2 had no effect on priming anti-IgE-induced histamine release from skin mast cells (data not shown).

In human basophils, both IL-1 and IL-3 have been shown to be weak histamine releasing agents and to enhance release induced by immunological and non-immunological stimuli [7,38–41]. Of the other cytokines examined on basophils, both granulocyte-macrophage colony-stimulating factor (GM-CSF) [40,42,43] and IL-5 [44] enhance histamine release. Experiments on human mast cells have reported that only SCF enhances the IgE-dependent release of mediators from human lung [18,20] and skin mast cells [19] and that in high concentrations, it directly induces histamine release [19,20]. However, SCF has no effect on histamine release and priming of anti-IgE-induced histamine from basophils [18]. We recently reported that major basic protein, which induces histamine release from basophils [9], has little or no histamine releasing activity on human skin mast cells [45]. Our observations and those cited above revealed a major functional difference between mast cells and basophils in relation to stimulation for mediator release. Further experiments in which the effect of HRFs are investigated on human mast cells in allergic disorders would be needed to explore the possibility that HRFs are relevant to mast cell degranulation.

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