

Histamine release in intact human skin by monocyte chemoattractant factor-1, RANTES, macrophage inflammatory protein-1 α , stem cell factor, anti-IgE, and codeine as determined by an ex vivo skin microdialysis technique

Lars J. Petersen, MD,^a Klaus Brasso, MD,^b Morten Pryds, MD,^b
and Per S. Skov, PhD^c Copenhagen, Denmark

Background: The chemokines monocyte chemoattractant factor-1, RANTES, and macrophage inflammatory protein-1 α release histamine from human basophils, as well as rat and mouse mast cells. The purpose of this investigation was to determine whether these chemokines release histamine from human skin mast cells in situ.

Methods: A microdialysis technique was used to measure histamine release in skin. First, the model was validated by using anti-IgE, codeine, and stem cell factor (SCF); then the histamine-releasing effects of the chemokines were investigated. A total of 47 skin specimens from 41 donors were investigated. Hollow microdialysis fibers were inserted intradermally, and each fiber was slowly perfused (3 μ l/min). Anti-IgE, codeine, SCF, or chemokines were injected intradermally above individual fibers, and dialysate was collected at 2-minute intervals for 20 minutes. Each series of investigations comprised five to eight single experiments.

Results: Anti-IgE (4 to 4000 U/ml), codeine (0.001 to 1 mg/ml), and SCF ($5.4 \times (10^{-11}$ to 10^{-8} mol/L)) released histamine in a dose-dependent manner; maximum histamine release was 97.4, 116.3, and 9.5 pmol/20 min, respectively. Monocyte chemoattractant factor-1, RANTES, and macrophage inflammatory protein-1 α in concentrations of 10^{-9} to 10^{-6} mol/L did not release histamine; histamine release by 10^{-6} mol/L chemokine was less than 0.2 pmol/20 min. None of the chemokines modulated anti-IgE-induced histamine release. In contrast, SCF significantly potentiated anti-IgE-induced histamine release by 33%. All chemokines, but not SCF, released histamine from human basophils.

Conclusion: We conclude that the chemokines monocyte chemoattractant factor-1, RANTES, and macrophage inflammatory protein-1 α do not release histamine from human skin mast cells. (*J Allergy Clin Immunol* 1996;98:790-6.)

Key words: Histamine release, monocyte chemoattractant factor-1, RANTES, macrophage inflammatory protein-1 α , stem cell factor, anti-IgE, codeine, skin microdialysis

From the Departments of ^aDermatology and ^bSurgical Gastroenterology, Bispebjerg Hospital; and ^cthe Reference Laboratory, National University Hospital, University of Copenhagen.

Supported by the Novo Nordisk Foundation, The Danish Medical Research Council, and the Allergy Foundation of 1983. Dr. L. J. Petersen holds a senior research fellowship from the Weimann Foundation; he is a Pharmacia Research Fellowship 1995 recipient.

Received for publication Oct. 31, 1995; revised Feb. 23, 1996; accepted for publication Mar. 6, 1996.

Reprint requests: Lars J. Petersen, MD, Department of Dermatology, Bispebjerg Hospital, DK-2400 Copenhagen NV, Denmark.

Copyright © 1996 by Mosby-Year Book, Inc.
0091-6749/96 \$5.00 + 0 1/1/73617

During recent years, the role of cytokines and growth factors in allergic diseases has been extensively explored, and great interest has been focused on a number of cytokines related to the intercrine/chemokine family.¹⁻³ Several of these chemokines have been shown to possess potent histamine-releasing capacities in human basophil leukocytes.⁴⁻⁶ The most potent histamine-releasing chemokine thus far characterized is monocyte chemoattractant factor-1 (MCP-1), which releases significant amounts of histamine in nanomolar to micromolar concentrations.⁷⁻¹⁰ Other, but less potent, histamine-releasing chemokines are RANTES^{8, 10, 11} and macrophage inflammatory protein-1 α (MIP-1 α).¹²

Abbreviations used

KRB:	Krebs-Ringer bicarbonate (buffer)
MCP-1:	Monocyte chemoattractant factor-1
MIP-1 α :	Macrophage inflammatory protein-1 α
SCF:	Stem cell factor

Mast cell–derived histamine plays a pivotal role in the immediate phase of allergic reactions, but only a few studies have investigated the effect of chemokines on histamine release from mast cells. Partly purified histamine-releasing factors from human macrophages and lymphocytes are known to release histamine from human lung and synovial mast cells,^{13,14} whereas those from peripheral blood mononuclear cells are without effect on dispersed human lung and skin mast cells.¹⁵ Recombinant MIP-1 α releases histamine from mouse peritoneal mast cells¹²; and MIP-1 α , and to a lesser degree MCP-1, histologically cause degranulation of mouse skin mast cells.¹⁶ Multiple recombinant chemokines including MCP-1, RANTES, and MIP-1 α do not release histamine in dispersed human lung mast cells^{12,15,17,18} or in skin mast cells according to recent studies.^{15,18} So far, the only cytokine/growth factor known to trigger human mast cells is stem cell factor (SCF).^{19,20} SCF induces histamine release from dispersed human mast cells from the skin,^{21,22} uterus,²³ and heart^{23,24}; and it potentiates histamine release by anti-IgE antibodies in lung and skin mast cells.^{21,23,25,26} SCF does not release histamine from human basophils.^{21,25}

In this study we have applied a microdialysis technique to study the histamine-releasing properties of MCP-1, RANTES, and MIP-1 α from mast cells in intact human skin *ex vivo*. The microdialysis technique has previously been used for measurement of histamine release in human skin *in vivo* after intradermal injection of substance P, codeine, and allergen.²⁷⁻²⁹ As an initial part of this study, we measured histamine release *ex vivo* by using classical skin mast cell secretagogues and SCF.

METHODS

Materials

Codeine was purchased by the institutional pharmacy; anti-IgE was from Behring Werke (Marburg, Germany); human recombinant SCF, MCP-1, RANTES, and MIP-1 α were purchased from PeproTech Inc. (Rocky Hill, N.J.). A stock solution of the lyophilized chemokine or SCF was made at a concentration of 10^{-6} mol/L in Krebs-Ringer bicarbonate (KRB). Human serum albumin (0.2%; Statens Serum Institut, Copenhagen, Den-

mark) was added to the KRB. All substances were diluted with KRB. The final concentrations of the substances were as follows: codeine, 0.001 to 1 mg/ml; anti-IgE, 4 to 4000 U/ml; SCF, $5.4 \times (10^{-11}$ to 10^{-8} mol/L) (corresponding to 1 to 1000 ng/ml); and MCP-1, RANTES, and MIP-1 α , 10^{-9} to 10^{-6} mol/L. KRB with 0.2% human serum albumin served as the vehicle control.

Skin specimens

The study included 47 skin specimens from 41 women (mean age, 68.9 ± 12.4 years (SD); range, 49 to 91 years) undergoing surgery for treatment of breast cancer. The allergic status of the donors was not known. Skin specimens (10 to 15 cm²) were taken in areas remote from sites of suspected tumors, placed immediately in ice-cold KRB, dissected into appropriate pieces, and kept at 5° C until use within 1 to 2 hours. Informed consent was obtained from each subject before surgery, and the study was approved by the local ethics committee.

Microdialysis instrumentation and skin challenge

Dialysis probes with an outer diameter of 216 μ m, a molecular weight cutoff of 2000 d, a length of 15 mm available for diffusion, and an outlet of 30 mm were constructed from dialysis fibers as previously described.^{27,29} A 100 μ m stainless steel wire was inserted into the lumen of the dialysis fiber to stabilize the dialysis probe. The skin specimens were cut into pieces to allow insertion of up to six dialysis fibers arranged in parallel in each piece. The dialysis probes were inserted intradermally with 23-gauge guide cannulas. The distance between each cannula was 10 to 15 mm. Previous studies *in vivo* have shown that histamine release occurs exactly at the site of stimulus and that histamine diffusion within the skin is minimal.³⁰

Each skin specimen was fixed on a temperature-regulated plate. The skin temperature was kept within 32° to 34° C, controlled by a precision thermometer (DM 852; Ellab, Copenhagen, Denmark) with a needle-type sensor.

Each dialysis probe was connected to individual syringes mounted in a microinjection pump (CMA/100; CMA/Microdialysis, Stockholm, Sweden), and each fiber was perfused with KRB in parallel at a rate of 3.0 μ l/min. Collection of dialysate began 10 minutes after removal of the guide cannulas; the dialysates were collected directly from the efferent tube into microtiter wells coated with glass fiber matrix used for analysis of histamine. Dialysate was collected at 2-minute intervals (6 μ l fractions). Before skin challenge, two baseline values of 6 μ l were collected over 4 minutes. After skin challenge, dialysate was collected at 2-minute intervals (6 μ l) for 20 minutes.

All substances were administered as 25 μ l aliquots to the skin by intradermal injections. Each injection was placed 1 mm from the fiber at the midpoint of the 15 mm dialysis fiber.

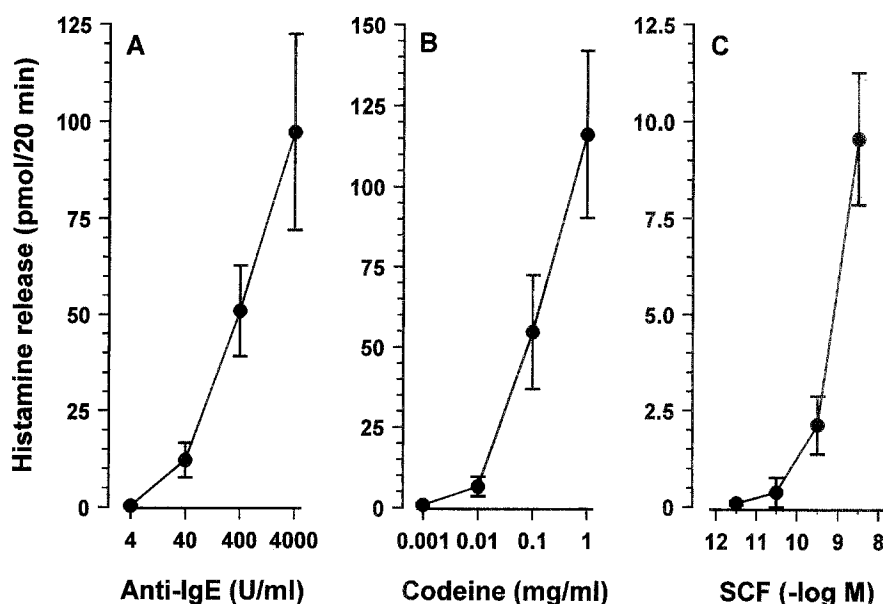


FIG. 1. Histamine release by serial dilutions of anti-IgE (A), codeine (B), and SCF (C). Increasing concentrations of each compound produced a concentration-dependent release of histamine. Histamine is expressed as net total histamine release (picomoles in 20 minutes). Values are means $\pm$ SEM of eight (anti-IgE), seven (codeine), and five (SCF) experiments.

Basophil histamine release

Histamine release from washed whole blood was performed as previously described.³¹ In brief, 3 ml of venous blood from four healthy donors (4 women aged 55 to 58 years) was drawn into heparinized glass, mixed with 7 ml of piperazine-N-N'-bis[2-ethanesulfonic acid] buffer, and centrifuged at 400 g for 6 minutes at room temperature. Thereafter, the supernatant was discharged, and the blood cells were resuspended in piperazine-N-N'-bis[2-ethanesulfonic acid] buffer to a final volume of 3 ml.

Aliquots of 25 μ l of anti-IgE (0.4 to 400 U/ml), 10^{-6} mol/L MCP-1, RANTES, MIP-1 α , or 5.4×10^{-8} mol/L SCF were incubated with 25 μ l of washed blood in glass fiber-prepared microtiter plates for 60 minutes at 37°C. Each experiment was done in duplicate. The plates were then washed twice with 0.4% sodium dodecylsulfate, and the histamine content was analyzed. The total histamine content of the cells was measured after the samples were boiled. Histamine release was expressed as percent of total histamine content.

Histamine analysis

Histamine was analyzed spectrofluorometrically in a glass fiber-based assay.³² The specificity of this assay for measuring histamine in skin dialysate has been confirmed,²⁷ and the limit of detection is 25 nmol/L histamine.

Statistics

Results are expressed as means $\pm$ SEM (n = number of observations). Statistical analyses were performed by using Friedman nonparametric analysis of variance and

Wilcoxon's signed rank test. Two-sided p values of less than 0.05 were considered statistically significant.

RESULTS

In each single experiment, peak histamine concentration (in nanomoles per liter) and total histamine release in 20 minutes (picomoles per 20 minutes) were calculated, and the results were corrected for spontaneous histamine release before skin challenge. Spontaneous histamine release in 41 subjects was 47 ± 3 nmol/L.

Histamine release by anti-IgE, codeine, and SCF

Fig. 1 shows total histamine release in 20 minutes after skin challenge with serial dilutions of anti-IgE, codeine, and SCF. Statistically significant dose-response relationships were seen for anti-IgE ($p < 0.001$, $n = 8$), codeine ($p < 0.001$, $n = 7$), and SCF ($p < 0.01$, $n = 5$). When individual concentrations of mast cell secretagogues were examined, a significant histamine release was seen, with codeine concentrations greater than 0.001 mg/ml and anti-IgE concentrations greater than 4 U/ml. The number of observations in the SCF experiments did not allow such calculations.

The kinetics of histamine release after skin challenge with anti-IgE, codeine, and SCF are shown in Fig. 2. The peak histamine release concentration in

each separate experiment was identified; thereafter, the histamine concentrations in the other samples in that experiment were expressed relatively to that sample. To ensure a valid representation of histamine kinetics, only experiments showing a net peak histamine release of 50 nmol/L or more were included in the analysis (25 of 28 codeine experiments, 21 of 36 anti-IgE experiments, and 6 of 20 SCF experiments fulfilled this criterion). Because the kinetics of histamine release by each secretagogue were independent of the magnitude of histamine release, data from all experiments were pooled. Peak histamine release was observed within 4 to 6 minutes after intradermal injection of codeine and SCF. In comparison, histamine release by anti-IgE was more protracted; a peak plateau was reached 8 to 16 minutes after skin challenge.

Histamine release by chemokines

MCP-1, RANTES, and MIP-1 α did not release significant amounts of histamine from skin mast cells. Total histamine release by 10^{-9} to 10^{-6} mol/L concentrations of chemokine, vehicle and the positive control, anti-IgE (400 U/ml), was as follows: MCP-1 (0.19 ± 0.14 , 0.28 ± 0.17 , 0.14 ± 0.09 , 0.00 ± 0.00 , 0.04 ± 0.04 , and 60.38 ± 14.14 pmol/20 min [$n = 7$]), RANTES (0.00 ± 0.00 , 0.16 ± 0.16 , 0.00 ± 0.00 , 0.00 ± 0.00 , 0.00 ± 0.00 , and 60.18 ± 15.84 pmol/20 min [$n = 6$]), and MIP-1 α (0.15 ± 0.08 , 0.11 ± 0.11 , 0.14 ± 0.09 , 0.08 ± 0.08 , 0.12 ± 0.09 , and 47.16 ± 4.65 pmol/20 min [$n = 6$]). Because the data in Fig. 2 showed a decline in histamine concentrations after reaching peak histamine levels, it might be that the chemokines released small amounts of histamine, which became negligible in the total histamine release calculations. Fig. 3 shows net peak histamine release by serial dilutions of MCP-1, RANTES, MIP-1 α , vehicle, and anti-IgE (400 U/ml). All chemokines showed no significant histamine release, and peak histamine release by the chemokines was comparable with vehicle responses. Anti-IgE (400 U/ml) showed peak histamine release of 776, 999, and 1035 nmol/L in the three series of experiments (in the first series of experiments, shown in Fig. 1, A, peak histamine release by anti-IgE [400 U/ml] was 824 nmol/L).

Modulation of anti-IgE-induced histamine release by chemokines and SCF

To determine whether the chemokines or SCF altered the responsiveness of skin mast cells for anti-IgE-induced histamine release, another series of experiments was performed. Fifty microliters of

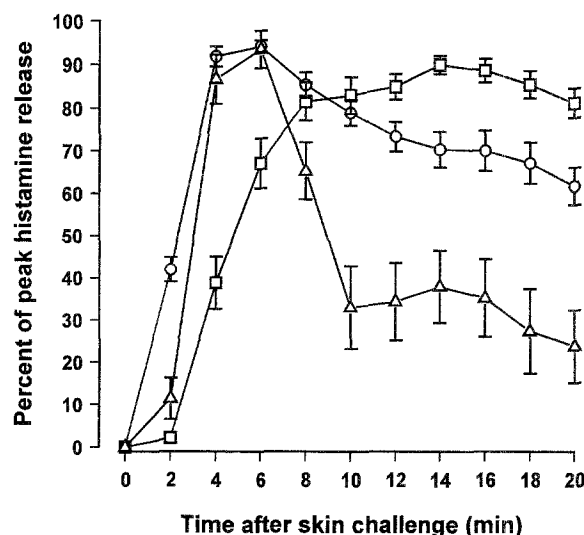


FIG. 2. Kinetics of histamine release by anti-IgE (squares), codeine (circles), and SCF (triangles). For each experiment, peak histamine release in 10 consecutive samples, after intradermal injection of the secretagogue, was found. This value was set as 100%, and histamine concentrations in the remainder samples in that experiment were expressed relatively to that sample. Values are means $\pm$ SEM of 21 (anti-IgE), 25 (codeine), and 6 (SCF) experiments (see Methods section).

each chemokine, SCF, or vehicle was injected intradermally above individual dialysis fibers, followed 10 minutes later by 25 μ l of anti-IgE (400 U/ml). The concentrations of MCP-1, RANTES, and MIP-1 α were 10^{-6} mol/L, whereas the concentration of SCF was 5.4×10^{-10} mol/L. These concentrations of substances showed no significant histamine release alone. The results are shown in Fig. 4. The short period of incubation by the chemokines did not affect the histamine release in response to a suboptimal concentration of anti-IgE, whereas SCF increased anti-IgE-induced histamine release by 33% ($p < 0.05$).

Basophil histamine release

In all four donors, 0.5×10^{-6} mol/L concentrations of MCP-1, RANTES, and MIP-1 α but not SCF 10^{-8} mol/L released notable amounts of histamine (defined as greater than 10% of total histamine content). Histamine release was $46.1\% \pm 5.8\%$, $33.7\% \pm 4.3\%$, $14.8\% \pm 2.0\%$, and $4.4\% \pm 1.4\%$ of total histamine content with MCP-1, RANTES, MIP-1 α , and SCF, respectively.

DISCUSSION

In this study the microdialysis technique was introduced for the first time for the measurement of histamine release from intact human skin mast

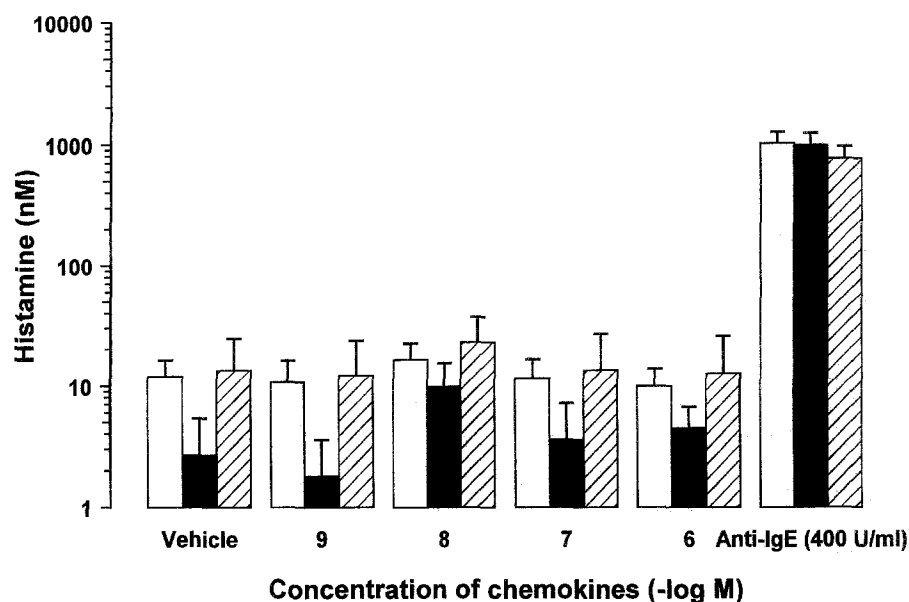


FIG. 3. A semi-logarithmic diagram showing peak histamine release in three series of experiments after serial dilutions of MCP-1 (open bars), RANTES (filled bars), and MIP-1 α (hatched bars), all compared with vehicle responses and the positive control, anti-IgE (400 U/ml), in that particular series of experiments. Neither MCP-1, nor RANTES, nor MIP-1 α released significant amounts of histamine; peak histamine release by chemokines was similar to vehicle responses. In comparison, anti-IgE (400 U/ml) showed a significant peak release of 800 to 1000 nmol/L. Values are means $\pm$ SEM of seven (MCP-1) and six (RANTES and MIP-1 α) investigations.

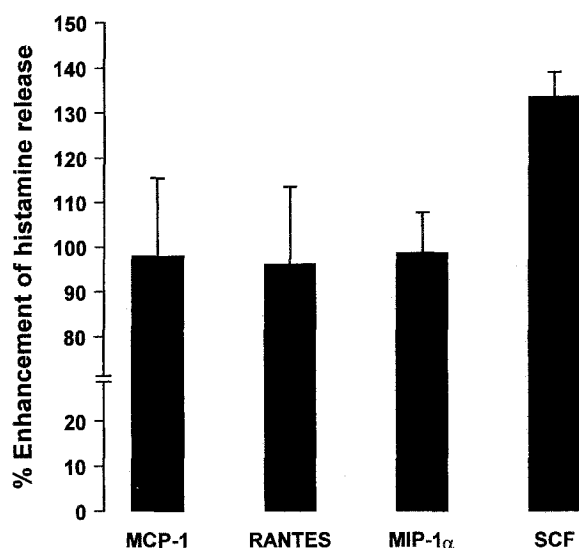


FIG. 4. Effect of a brief incubation (10 minutes) with 50 μ l of MCP-1 (10^{-6} mol/L), RANTES (10^{-6} mol/L), MIP-1 α (10^{-6} mol/L), and SCF (5.4×10^{-10} mol/L) versus incubation with vehicle on total histamine release induced by intradermal injection of 25 μ l of anti-IgE (400 U/ml) in human skin. Histamine release after preincubation with vehicle is set as 100%. SCF significantly ($p < 0.05$) potentiated anti-IgE-induced histamine release by 33%, whereas none of the chemokines modulated anti-IgE-induced histamine release. Values are means $\pm$ SEM of eight (MCP-1) and seven (RANTES, MIP-1 α , and SCF) experiments.

cells ex vivo. As an initial part of these studies, the microdialysis method was validated with respect to dose-response relations and kinetics of histamine release induced by anti-IgE and codeine. SCF was also used because SCF has previously been shown to potentiate anti-IgE-induced histamine release in skin mast cells. After the ex vivo microdialysis setup was validated, the histamine-releasing properties of the chemokines MCP-1, RANTES, and MIP-1 α were studied.

Intradermal injection of anti-IgE, codeine, and SCF induced a statistically significant dose-related histamine release. Further, the kinetics of histamine release were described. The kinetics of histamine release in the skin ex vivo by anti-IgE and codeine, expressed as the time to reach peak histamine heights, are comparable with previous results in dispersed human skin mast cells in vitro^{33, 34} and histamine release by allergens and codeine in vivo.^{28, 29} The kinetics of histamine release by SCF were rapid; peak histamine was observed within 2 to 6 minutes. To our knowledge, this is the first study showing the kinetics of histamine release by SCF in skin human mast cells. A similar rapid histamine release has been demonstrated in rat peritoneal mast cells.³⁵ After peak levels were reached by 2 to 6 minutes (codeine and

SCF) or by 8 to 16 minutes (anti-IgE), the histamine concentrations declined as previously demonstrated *in vivo*.^{28, 29} Because the experimental situation *ex vivo* is different from studies *in vivo*, it is not possible to determine which parameters influence elimination of histamine in the skin. In the *ex vivo* situation there is no blood flow, implying that the washout of histamine and the washout and extracellular redistribution of the injected compounds are different from the *in vivo* situation. Further changes taking place in the composition of the extracellular water compartment, occurring *in vivo* as a consequence of the wheal formation, are not seen *ex vivo*. Additional studies are required to examine in detail the histamine elimination and degradation pathways in human skin.

Neither MCP-1, nor RANTES, nor MIP-1 α showed direct histamine release from human skin mast cells in our experiments. In addition, a brief incubation with the chemokines did not modulate anti-IgE-induced histamine release as observed with SCF. Studies of chemokine-induced histamine release in human basophils have previously shown that the exocytosis process is fast, and maximum histamine release by chemokines is observed within 0.5 to 2 minutes compared with 5 to 15 minutes by anti-IgE.^{7, 9} No chemokine-induced histamine release was observed within an observation period of 20 minutes after stimulation. Further, the nanomolar to micromolar range concentrations of chemokines were ineffective in skin mast cells, whereas these concentrations of chemokines have been shown to be relevant in basophils. In comparison with the general atopic population, the age, sex, and atopic status of the donors might have influenced histamine releasability to chemokines in our experiments. However, because histamine release by anti-IgE, codeine, and SCF in these subjects was pronounced, these covariates seemed to be of minor importance. The histamine release by 10^{-6} to 10^{-7} mol/L concentration of chemokines demonstrated in our four donors is similar to results previously published.⁷⁻¹⁰

Studies have shown MIP-1 α to release histamine from mouse peritoneal and skin mast cells,^{12, 16} but contradictory results have been reported.³⁶ In this study MCP-1, RANTES, and MIP-1 α did not demonstrate histamine release in human skin mast cells. Our findings are in agreement with recent studies showing that human recombinant chemokines, including MCP-1 and RANTES, do not release histamine in human dispersed skin mast cells.^{15, 18, 37} Because similar findings have been demonstrated in hu-

man lung mast cells,^{12, 15, 17, 18} these data suggest that recombinant chemokines, up to micromolar concentrations, do not release histamine from human mast cell lines.

During recent years, it has been established that SCF produced by endothelial and other stromal cells plays a pivotal role in the development and maturation of mast cells.^{19, 20} SCF is the only cytokine/growth factor known to possess functional activity regarding mediator release from human mast cell lines. Previous studies have shown that SCF releases histamine from dispersed human skin mast cells.^{21, 22} In this study we showed that SCF significantly released histamine in intact human skin at nanomolar concentrations and potentiated anti-IgE-induced histamine release at even lower concentrations. Whether SCF exerts a pathogenic role in allergic and inflammatory skin diseases has yet to be determined. It has recently been shown that SCF can be synthesized and released in a soluble form into the extracellular water space in human skin.³⁸

In conclusion, by using an *ex vivo* microdialysis technique, we demonstrated that MCP-1, RANTES, and MIP-1 α did not release histamine from human skin mast cells and did not potentiate histamine release by anti-IgE after a brief period of incubation. Our data suggest that these chemokines are not involved in the acute phase of immediate-type allergic skin reactions.

We thank Mrs. Inge Aakilde and the staff at the Reference Laboratory for skillful technical assistance.

REFERENCES

1. Miller MD, Krangel MS. Biology and biochemistry of the chemokines: a family of chemotactic and inflammatory cytokines. *Crit Rev Immunol* 1992;12:17-46.
2. Oppenheim JJ, Zachariae CO, Mukaida N, Matsushima K. Properties of the novel proinflammatory supergene "inter-crine" cytokine family. *Annu Rev Immunol* 1991;9:617-48.
3. Schall TJ. Biology of the RANTES/SIS cytokine family. *Cytokine* 1991;3:165-83.
4. Dahinden CA, Krieger M, Brunner T, Bischoff SC. Basophil activation by members of the chemokine superfamily. *Adv Exp Med Biol* 1993;351:99-110.
5. Kaplan AP, Kuna P, Reddigari SR. Chemokines as allergic mediators: relationship to histamine-releasing factors. *Allergy* 1994;49:495-501.
6. Baggiolini M, Dahinden CA. CC chemokines in allergic inflammation. *Immunol Today* 1994;15:127-33.
7. Kuna P, Reddigari SR, Rucinski D, Oppenheim JJ, Kaplan AP. Monocyte chemotactic and activating factor is a potent histamine-releasing factor for human basophils. *J Exp Med* 1992;175:489-93.
8. 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* 1992;7:427-33.
9. Alam R, Lett Brown MA, Forsythe PA, Anderson Walters D, Kenamore C, Grant JA. Monocyte chemotactic and activating factor is a potent histamine-releasing factor for basophils. *J Clin Invest* 1992;89:723-8.
 10. Kuna P, Reddigari SR, Schall T, Rucinski D, Sadick M, Kaplan AP. Characterization of the human basophil response to cytokines, growth factors, and histamine releasing factors of the intercrine/chemokine family. *J Immunol* 1993;150:1932-43.
 11. Kuna P, Reddigari SR, Schall TJ, Rucinski D, Viksman MY, Kaplan AP. RANTES, a monocyte and T lymphocyte chemotactic cytokine releases histamine from human basophils. *J Immunol* 1992;149:636-42.
 12. Alam R, Forsythe PA, Stafford S, Lett Brown MA, Grant JA. Macrophage inflammatory protein-1 alpha activates basophils and mast cells. *J Exp Med* 1992;176:781-6.
 13. Gruber B, Poznansky M, Boss E, Partin J, Gorevic P, Kaplan AP. Characterization and functional studies of rheumatoid synovial mast cells. Activation by secretagogues, anti-IgE, and a histamine-releasing lymphokine. *Arthritis Rheum* 1986;29:944-55.
 14. 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.
 15. Okayama Y, Brzezinska-Blaszczek E, Kuna P, Kaplan AP, Church MK. Effects of PBMC-derived histamine-releasing factors on histamine release from human skin and lung mast cells. *Clin Exp Allergy* 1995;25:890-5.
 16. Alam R, Kumar D, Anderson Walters D, Forsythe PA. Macrophage inflammatory protein-1 alpha and monocyte chemoattractant peptide-1 elicit immediate and late cutaneous reactions and activate murine mast cells in vivo. *J Immunol* 1994;152:1298-303.
 17. Takaishi T, Morita Y, Hirai K, Yamaguchi M, Ohta K, Noda E, et al. Effect of cytokines on mediator release from human dispersed lung mast cells. *Allergy* 1994;49:837-42.
 18. Füreder W, Agis H, Semper H, Keil F, Maier U, Müller MR, et al. Differential response of human basophils and mast cells to recombinant chemokines. *Ann Hematol* 1995;70:251-8.
 19. Valent P. The riddle of the mast cell: kit(CD117)-ligand as the missing link? *Immunol Today* 1994;15:111-4.
 20. Galli SJ, Zsebo KM, Geissler EN. The kit ligand, stem cell factor. *Adv Immunol* 1994;55:1-96.
 21. Columbo M, Horowitz EM, Botana LM, MacGlashan DW Jr, Bochner BS, Gillis S, 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* 1992;149:599-608.
 22. Columbo M, Botana LM, Horowitz EM, Lichtenstein LM, MacGlashan DW. Studies of the intracellular Ca²⁺ levels in human adult skin mast cells activated by the ligand for the human c-kit receptor and anti-IgE. *Biochem Pharmacol* 1994;47:2137-45.
 23. Sperr WR, Czerwenka K, Mundigler G, Müller MR, Semper H, Klappacher G, et al. Specific activation of human mast cells by the ligand for c-kit: comparison between lung, uterus and heart mast cells. *Int Arch Allergy Immunol* 1993;102:170-5.
 24. Sperr WR, Bankl HC, Mundigler G, Klappacher G, Grossschmidt K, Agis H, et al. The human cardiac mast cell: localization, isolation, phenotype, and functional characterization. *Blood* 1994;84:3876-84.
 25. Bischoff SC, Dahinden CA. c-kit Ligand: a unique potentiator of mediator release by human lung mast cells. *J Exp Med* 1992;175:237-44.
 26. Louis R, Dowlati A, Weber T, Bury T, Corhay JL, Radermecker MF. Modulation of immunological histamine release from human lung fragments by stem cell factor, IL-3, IL-5 and GM-CSF: comparison with human leukocytes. *Int Arch Allergy Immunol* 1994;105:18-25.
 27. Petersen LJ, Poulsen LK, Søndergaard J, Skov PS. The use of cutaneous microdialysis to measure substance P-induced histamine release in intact human skin in vivo. *J Allergy Clin Immunol* 1994;94:773-83.
 28. Petersen LJ, Nielsen HJ, Skov PS. Codeine-induced histamine release in intact human skin monitored by skin microdialysis technique: comparison of intradermal injections with an atraumatic intraprobe drug delivery system. *Clin Exp Allergy* 1995;25:1045-52.
 29. Petersen LJ, Mosbech H, Skov PS. Allergen-induced histamine release in intact human skin in vivo assessed by skin microdialysis technique: Characterization of factors influencing histamine releasability. *J Allergy Clin Immunol* 1996;97:672-9.
 30. Petersen LJ, Church MK, Skov PS. Mapping of histamine release in the wheal and flare reaction by skin microdialysis technique [abstract]. *J Allergy Clin Immunol* 1995;95:225.
 31. Mosbech H, Skov PS. House dust mite-induced histamine release from washed blood cells: evaluation of effect parameters. *Allergy* 1987;42:553-5.
 32. Stahl Skov P, Norn S, Weeke B. A new method for detecting histamine release. *Agents Actions* 1984;14:414-6.
 33. Benyon RC, Lowman MA, Church MK. Human skin mast cells: their dispersion, purification, and secretory characterization. *J Immunol* 1987;138:861-7.
 34. Lawrence ID, Warner JA, Cohan VL, Hubbard WC, Kagey Sobotka A, Lichtenstein LM. Purification and characterization of human skin mast cells: evidence for human mast cell heterogeneity. *J Immunol* 1987;139:3062-9.
 35. Nakajima K, Hirai K, Yamaguchi M, Takaishi T, Ohta K, Morita Y, et al. Stem cell factor has histamine releasing activity in rat connective tissue-type mast cells. *Biochem Biophys Res Commun* 1992;183:1076-83.
 36. Taub D, Dastyh J, Inamura N, Upton J, Kelvin D, Metcalfe D, et al. Bone marrow-derived murine mast cells migrate, but do not degranulate, in response to chemokines. *J Immunol* 1995;154:2393-402.
 37. Nitschke M, Sohn K, Wolff HH, Amon U. Multiple chemokines do not influence human skin mast cell releasability [abstract]. *Allergy* 1995;50(Suppl 26):15.
 38. Longley BJJ, Morganroth GS, Tyrrell L, Ding TG, Anderson DM, Williams DE, et al. Altered metabolism of mast-cell growth factor (c-kit ligand) in cutaneous mastocytosis. *N Engl J Med* 1993;328:1302-7.