Stimulation of Monocyte Chemotaxis by Human Growth Hormone and Its Deactivation by Somatostatin

By Christian J. Wiedermann, Norbert Reinisch, and Herbert Braunsteiner

Monocyte infiltration occurs early in the course of inflammation and is a prerequisite for optimal repair of tissue damage. In this study, human recombinant growth hormone was shown to be a potent chemoattractant for human monocytes, inducing migration at picomolar concentrations of recombinant human growth hormone. Chemotaxis of monocytes was measured in vitro by a modified Boyden chamber assay using nitrocellulose micropore filters and measuring microscopically the migration depth of the leading front of monocytes. Somatostatin, which inhibits the release of growth hormone, and its long-acting analogue, octreotide, also stimulated chemotaxis of monocytes; however, the effective peptide concentration was in the micromolar range. When tested for chemotaxis in combination or in experiments using pretreatment with somatostatin and washing of treated cells, somatostatin significantly antagonized the chemotactic responses of monocytes to growth hormone. The inhibitory effect on growth hormone-stimulated chemotaxis was dose dependent and occurred at concentrations severalfold lower than the chemotactically active concentration of somatostatin. Combinations of growth hormone with interferon or substance P also deactivated the chemotactic responses. These observations suggest that human growth hormone may have a regulatory role in monocyte chemotaxis.

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THE PROCESS of inflammation and normal wound healing is characterized by an ordered progression of inflammatory cells, including platelets, neutrophils, monocytes, and lymphocytes, to sites of tissue injury. The recruitment of monocytes is a prerequisite for efficient repair of damage caused by various types of trauma, inflammation, and immune reactions. In the absence of localized tissue inflammation, migration of monocytes into different tissues seems to occur randomly. However, at sites of inflammation monocytes accumulate by migrating along gradients of chemoattractants released by damaged tissue. Specific receptors for chemotactic factors such as for (Met-Leu-Phenylalanine) or anaphylatoxin are present on the surface of monocytes. Receptors for these chemoattractants exhibit homology in their amino acid sequences and have the structure of a family of receptors for which seven putative membrane-spanning domains are characteristic and transduce ligand-mediated signals through interactions with G proteins. This type of receptor structure has also been reported for several other ligands, such as substance P (SP) and somatostatin (SS) both of which are neuropeptides.

Several factors that are known to have the property of promoting wound healing (eg, transforming growth factor-β) were found also markedly to stimulate migration and direct the recruitment of monocytes. Studies on activation of monocyte functions by growth hormone (GH) suggest that the effects of human (h) GH on monocytes may play a role in wound healing by GH. Moreover, GH activates monocytes and augments the respiratory burst of macrophages in vivo and this is functionally important because growth hormone protects rats against the otherwise lethal infection with Salmonella typhimurium. In our study it is demonstrated that hGH, which is known as neuroendocrine hormone and has recently been identified also as a lymphocyte product, possesses monocyte chemotactic activity.

MATERIALS AND METHODS

Mononuclear leukocyte (MNL) suspensions. MNL were isolated from heparinized blood of healthy volunteers or from buffy coats (Innsbruck University Hospital Blood Bank) by Ficoll-Paque (ICN Flow, Costa Mesa, CA) density gradient centrifugation and washed in Hank's balanced salt solution (HBSS) as described previously. The MNL preparations (>98% viability by trypan dye exclusion) were resuspended in RPMI 1640 medium containing 0.5% bovine serum albumin (BSA) (Sigma Chemical Co, St Louis, MO). Pretreatment of MNL with the monocyte-activating peptides was performed with 1 × 10⁶ cells/mL in RPMI 1640 containing 0.5% BSA and various concentrations of the chemoattractants under investigation; after incubating for up to 30 minutes at 37°C in a shaking water bath, cells were washed once and then resuspended for chemotaxis assays.

Chemotaxis. Chemotaxis through cellulose nitrate to gradients of test substances applied, alone or in combination, was measured, as described, using a 48-well microchemotaxis chamber (Neuroprobe, Bethesda, MD). A 5-μm pore cellulose nitrate filter separates the upper and lower chamber to allow only the actively migrating cells to get through the pores. The pore size of 5 μm allows only monocytes but not lymphocytes to enter the filter chemotactically. Cells (50,000/well) were placed in the upper compartment, and different concentrations of chemoattractant substances were put in the lower. After a 90-minute incubation at 37°C, the nitrocellulose filters were dehydrated, fixed, and stained with hematoxylin-eosin. Migration into the filter was quantitated by microscopically measuring the distance from the surface of the filter to the leading front of three monocytes. Data are expressed as “chemotaxis,” which is the difference between the distance of migration toward test attractants and that toward buffer alone. The migration depth of the leading front towards the buffer controls generally ranged from 80 to 90 μm.

Chemoattractants. Recombinant (r) preparations of hGH, produced for clinical use in the treatment of hypopituitary short stature (Serono, Vienna, Austria; Kabi Vitrum, Stockholm, Sweden; Eli Lilly, Giessen, Germany) were used in the present study. As sup...
applied by the manufacturers, the preparations are pyrogen tested, free of endotoxin, and of the highest purity. Preparations of rhGH were lyophilized and directly reconstituted into assay medium. Lyophilized human prolactin (Chemicon, Temecula, CA) was dissolved directly in assay medium to produce a stock solution of 10 \( \mu \text{mol/L} \). Lyophilized SS, atrial natriuretic peptide-28, epidermal chalone (ie, mitosis-inhibiting pentapeptide), and SP (Peninsula, Belmont, CA) were reconstituted to a stock concentration of 1 \( \mu \text{mol/L} \) in 0.02 N acetic acid (Sigma Chemical Co); this stock solution was stored at \(-80^\circ\text{C}\), and diluted to final concentrations in assay medium before use. Octreotide (OCT) (Sandoz, Basel, Switzerland) was stored at 4\(^\circ\text{C}\) at 0.5 mg/mL in 0.9\% NaCl containing 0.2\% sodium acetate-trihydrate. Thus, 0.9\% NaCl with 0.2\% sodium acetate-trihydrate was used for vehicle controls at corresponding dilutions. Interferon gamma (IFN-\(\gamma\)) (recombinant human; specific activity of \(2.5 \times 10^7\) U/mg protein) was from Genzyme (Cambridge, MA). FMLP (Sigma Chemical Co) was stored at \(-80^\circ\text{C}\) at 10 \( \mu \text{mol/L} \) in dimethyl sulfoxide (Merck, Darmstadt, Germany). FMLP and IFN-\(\gamma\) were tested in the monocyte chemotaxis assay. The results indicate that SS and OCT were used as described for peptides given above.

**RESULTS**

**Chemotaxis of monocytes to rhGH.** The effect of rhGH on migration of monocytes in vitro was tested using a modified Boyden chamber. On seven occasions when a wide range of concentrations of the rhGH preparations obtained from three different manufacturers were studied for effects on monocytes, significant migration of monocytes into micropore filters of Boyden chambers was seen. Maximal monocyte migration was consistently induced by concentrations of rhGH ranging from 1 pmol/L to 1 nmol/L. No significant difference in the activity of the three different preparations of rhGH was observed. The mean \( \pm \text{SEM} \) dose-response is presented in Fig 1A.

To find out whether rhGH induced migration of monocytes by acting as a chemokinetic or chemotactic agent, a Zigmund-Hirsch checkerboard analysis was performed. The rhGH potently induced migration of monocytes when it was present in excess in the lower compartment of the chemotaxis chambers, indicative of a chemotactic mechanism (Table 1). Addition of rhGH to the cells in the upper compartment of the chemotaxis chamber also augmented migration, indicative of chemokinesis (Table 1).

As studies on stimulation of neutrophils by rhGH showed that the effect of rhGH is mediated by activation of prolactin receptors, the effect of prolactin on monocyte migration was tested. In contrast to rhGH, prolactin did not stimulate monocyte migration over a wide range of concentrations tested (Fig 2).

The effect of rhGH on monocyte migration was compared with known chemoattractants. Of the chemoattrac-tants tested, FMLP, SP, and IFN-\(\gamma\) but not atrial natriuretic peptide or epidermal chalone exert a significant dose-dependent stimulatory effect on the migration of human monocytes in vitro. The dose-response curve for FMLP and SP was bell-shaped and similar to response curves observed with rhGH, whereas the IFN-\(\gamma\) response steadily increased over the concentration range tested (up to 1,000 U/mL).

Maximum effects occurred at about 10 nmol/L and 1 pmol/L of FMLP and SP, respectively (data not shown).

Migration of monocytes to GH release-inhibiting hormone. SS, which is the first of a family of somatostatin-related peptides to be identified, has a property of inhibiting GH release. Problems posed by limited availability and short duration of action and consequently limited clinical usefulness have been overcome with the development of OCT, a long-acting, synthetic analogue of the naturally occurring hormone. SS and OCT were tested in the monocyte chemotaxis assay. The results indicate that SS and OCT stimulate monocyte migration, significant effects being observed at 1 \( \mu \text{mol/L} \) and 10 nmol/L concentrations of SS, and at 1 \( \mu \text{mol/L} \) concentration of OCT (Fig 1B). SS and OCT, when compared with FMLP or rhGH, stimulated migration to an almost similar extent only at concentrations severalfold higher. The checkerboard analysis (Table 2) suggests that SS induces a true chemotactic response.

Inhibition of migration of monocytes by combinations of chemotactic agents. To test whether combinations of rhGH with known chemoattractants can affect monocyte chemotaxis, migration of monocytes to combinations of maximally chemoattractive concentrations of rhGH with FMLP or IFN-\(\gamma\) was tested. Figure 3 shows that rhGH deactivates monocyte migration to FMLP or IFN-\(\gamma\).

Figure 4 shows the effects of SS and SP on rhGH-induced migration of monocytes at a wide range of concentrations of rhGH. SS was present in the rhGH-containing lower compartment of the chemotaxis chamber during the assay. As seen with FMLP- and IFN-\(\gamma\)-induced chemotaxis of monocytes in the presence of rhGH, SS significantly deactivated the migratory response to rhGH. The inhibitory effect was present not only at the chemotactic, micromolar concentra-

**Respiratory burst assays.** The production of superoxide anion was assayed by measuring the superoxide dismutase (SOD) inhibitable reduction of cytochrome \(c\) by superoxide anion, the specificity of reduction being demonstrated via its inhibition by SOD. After the adherent MNL were preincubated for 24 hours in either 1 \( \mu \text{mol/L} \) of SS alone, or 1,000 U/mL of IFN-\(\gamma\) alone, or different concentrations of rhGH alone, or in a combination of 1 nmol/L of rhGH and 1 \( \mu \text{mol/L} \) of SS, they were immersed in 100 \( \mu \text{L} \) of a 160 \( \mu \text{mol/L} \) solution of cytochrome \(c\) (Sigma Chemical Co) in phenol-red-free HBSS containing 100 ng/mL of phorbol 12-myristate 13-acetate (PMA) (Sigma Chemical Co). To one vertical row, cytochrome \(c\) containing 300 \( \mu \text{L} \) of SOD (Sigma Chemical Co) was added, which served as a blank. The plates were covered with lids and placed in a 37\(^\circ\text{C}\) humidified incubator gassed with air-5\% CO\(_2\). At 10-minute intervals the plates were transferred to the enzyme-linked immunosorbent assay reader (Multiscan: Labsystems, Helsinki, Finland) and absorbances were read at 550 nm. The absorbance values can be converted to nanomoles of superoxide anion based on the extinction coefficient of (reduced minus oxidized) cytochrome \(c\): OD\(_{550nm} = 21 \times 10^3 \text{M}^{-1}\text{cm}^{-1}\). Because the vertical light path passing through 100 \( \mu \text{L} \) of cytochrome \(c\) was 3 mm, the calculation is \(\text{nmol superoxide anion per well} = \frac{\text{absorbance at } 550 \text{ nm} \times 15.87}{21 \times 10^3 \text{M}^{-1}\text{cm}^{-1}}\).

Calculations. The data are expressed as mean and standard error of the mean (SEM). Nonparametric analysis of variance was performed for independent samples according to Kruskal-Wallis. Differences were compared using the U-test or the two-tailed \(t\)-test for paired and unpaired samples, with \(P < .05\) being considered statistically significant. Statistical calculations were performed using the StatView5 12+ software package (Abacus, Berkeley, CA).
tions of SS, but also at concentrations as low as the picomolar range, at which SS did not induce monocyte migration. SP also exhibited a deactivation of rhGH-induced monocyte migration (Fig 4).

The time required for inhibition of rhGH-induced chemotaxis of monocytes by SS or SP was studied by pretreatment of cells with SS or SP and subsequent washing. Results are shown in Fig 5. Preincubation of MNL with medium containing 1 µmol/L of SS or SP followed by washing deactivated the chemotactic migration toward optimal concentration of rhGH. Half-maximal inhibition was reached within less than 2 minutes of preincubation. The observed inhibition of rhGH-induced chemotaxis, at 5 minutes of preincubation with SS, was dose dependent and significant at concentrations of SS as low as the nanomolar range (Table 3).

Effects of rhGH and SS on activation of monocyte respiratory burst. Stimulation of superoxide anion release from adherent MNL by pretreatment of the cells with rhGH and SS for 24 hours was also tested. Superoxide anion release was measured by SOD-inhibitable reduction of cytochrome c, which was triggered by PMA (100 ng/mL). The optical density at 550 nm of controls pretreated with vehicle was 0.118 ± 0.018 (n = 3). Compared with the known potent activation of macrophage respiratory burst activity by GH,27 pretreatment of adherent MNL with 1 µmol/L of SS did not affect respiration burst activity. Moreover, addition of 1 µmol/L of SS to 1 nmol/L of rhGH did not alter the rhGH-induced priming of adherent MNL.

**DISCUSSION**

In this study we have shown that at concentrations ranging from 1 pmol/L to 1 nmol/L, rhGH is a potent chemotactic ligand for human peripheral blood monocytes. The rhGH chemotactic dose-response curve is bell-shaped, which is typical for peptide chemoattractants. In contrast to findings on neutrophils,26,29 activation of monocyte chemotaxis by rhGH does not seem to involve a monocyte prolactin receptor, as human prolactin was unable to elicit a migration of the maximally active concentration of 1 nmol/L of rhGH, the mean ± SEM stimulation was 116% ± 2.7% (n = 3). For comparison, IFN-γ at a concentration of 1,000 U/mL activated PMA-triggered respiration burst activity by 134% ± 3.5% (n = 3). Pretreatment of adherent MNL with 1 µmol/L of SS did not affect respiration burst activity. Moreover, addition of 1 µmol/L of SS to 1 nmol/L of rhGH did not alter the rhGH-induced priming of adherent MNL.

**Fig 1.** Dose-dependent stimulation of migration of human monocytes into nitrocellulose micropore filters. (A) RhGH, n = 7. (B) SS, n = 6; OCT, n = 6. Mean ± SEM of the difference between the distance of migration toward test attractants and that toward buffer alone after 90 minutes of incubation at 37°C.

**Table 1. Effect of Varying Concentration Gradients of rhGH on Monocyte Migration**

<table>
<thead>
<tr>
<th>rhGH (mol/L), Upper Chamber</th>
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<tr>
<td>Migration (µm, X ± SEM, n = 5)</td>
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<tr>
<td>0</td>
<td>0±0</td>
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Different concentrations of rhGH were added to the upper and/or lower compartment of chemotaxis chambers, and the distance of migration into the nitrocellulose filters was measured. Each value represents the mean ± SEM of the difference between the distance of migration toward test attractants and that toward buffer alone after 90 minutes of incubation at 37°C.

**Fig 2.** Migration of human monocytes into nitrocellulose micropore filters stimulated by rhGH or prolactin. Mean ± SEM of the difference between the distance of migration toward test attractants and that toward buffer alone after 90 minutes of incubation at 37°C. Prolactin, n = 5; rhGH, n = 4.
Table 2. Effect of Varying Concentration Gradients of SS on Monocyte Migration

<table>
<thead>
<tr>
<th>SOM 1-14 (mol/L), Upper Chamber</th>
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<th>SS 1-14 (mol/L), Lower Chamber</th>
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<tr>
<td>10^{-11}</td>
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Different concentrations of SS were added to the upper and/or lower compartment of chemotaxis chambers, and the distance of migration into the nitrocellulose filter was measured. Each value represents the difference between the distance of migration toward test attractants and that toward buffer alone after 90 minutes of incubation at 37°C.

tory response. Edwards et al have demonstrated that purified GH can prime for enhanced respiration burst activity of macrophages and stimulate production of tumor necrosis factor in vitro and in vivo. The data presented in this report on respiratory burst activity of circulating human monocytes show that the GH-induced activation of respiratory burst activity of circulating monocytes is a minor one and thus of doubtful biological significance.

We can confirm previous reports on the chemotactic effect of the neuropeptide SP for human monocytes. SS receptors have been identified on human monocytes and monocyte functions may be directly affected by SS.31,32 Stimulation by OCT but not by SS of a migratory response of human MNL was reported previously.33 In this study such a property is shown also for SS. However, the chemotactic effects of both OCT and SS were seen at concentrations well above the physiologically relevant ones. Atrial natriuretic peptide and epidermal chalone induced neither monocyte chemotaxis nor respiration burst activity (data not shown). Atrial natriuretic peptide was recently shown to prime human neutrophils. In the case of epidermal chalone, which inhibits proliferation of epidermal cells, no effect on cells of nonepidermal origin has been observed so far.35 In this

Fig 3. Inhibition of migration of human monocytes into nitrocellulose micropore filters by combinations of rhGH with FMLP or IFN-γ. rhGH (0.1 nmol/L), n = 8; FMLP (10 nmol/L), n = 20; FMLP (10 nmol/L) plus rhGH (0.1 nmol/L), n = 12; IFN-γ (1,000 U/mL), n = 16; IFN-γ (1,000 U/mL) plus rhGH (0.1 nmol/L), n = 9. Mean ± SEM of the difference between the distance of migration toward test attractants and that toward buffer alone after 90 minutes of incubation at 37°C.

Fig 4. Dose-dependent inhibition of rhGH (0.1 nmol/L)-induced migration of human monocytes into nitrocellulose micropore filters by combination with SS (n = 4) or SP (n = 3). Mean ± SEM of the difference between the distance of migration toward test attractants and that toward buffer alone after 90 minutes of incubation at 37°C. The asterisk indicates P < .05.

Fig 5. Time-dependent inhibition of rhGH (0.1 nmol/L)-induced migration of human monocytes into nitrocellulose micropore filters by pretreatment at 37°C with SS (n = 4) or SP (n = 5) followed by washing of the cells. Mean ± SEM of the difference between the distance of migration toward test attractant and that toward buffer alone after 90 minutes of incubation at 37°C.
study, both peptides served as negative controls. Because the receptors for SP and SS belong to a family with similar structural characteristics as typical leukocyte chemoattractant receptors, it is not surprising to find that these neuropeptide ligands function as chemoattractants.

The formylpeptide chemoattractant receptors are desensitized in the presence of an agonist (eg, FMLP). It has been suggested that such desensitization may result from alterations in the receptor-G-protein interaction. Exposure to agonist leads also to formylpeptide receptor internalization. In micropore filter chemotaxis assays with FMLP as attractant, typical bell-shaped dose-response curves were obtained, with reduced migration of cells at higher concentrations of FMLP presumably because of desensitization of chemotaxis receptors. Desensitization of GH receptors has been shown in IM-9 lymphocytes; exposure of cultured cells to GH results in a decrease in the number of binding sites for GH. The bell-shaped dose-response curves for rhGH in monocyte chemotaxis assays obtained in this study may thus be caused by desensitization by such receptor-mediated mechanisms.

Furthermore, we studied the chemotactic response of monocytes to combinations of peptide chemoattractants. Migration induced by FMLP or IFN-γ was deactivated by rhGH. Deactivation of rhGH-induced chemotaxis by SP or SS was tested at different concentrations of the neuropeptides. Interestingly, the range of concentrations of SP and SS, which were found to be inhibitory for rhGH-induced chemotaxis, was different from the concentrations at which SP and SS induced chemotaxis, but similar to concentrations of SS-related peptides that inhibit FMLP-triggered monocyte superoxide anion release. At micromolar concentrations of SP, which did not induce monocyte chemotaxis, significant antagonism to rhGH-induced chemotaxis was seen. On the other hand, SS, which was found to be chemotactic only at nonphysiologically high micromolar concentrations, desensitized monocyte chemotaxis to rhGH at concentrations as low as 10 fmol/L. Inhibition of rhGH-induced migration was observed after pretreatment of MNL with SS as well as SP and occurred within minutes of such treatment. Kinetics of the phenomenon based on the experiments that included washing steps can only be discussed in relation to the length of exposure necessary to achieve deactivation, which, in our experiments, occurred significantly enough within 2 minutes. Cotransfection and expression in human kidney cells of multiple cDNAs encoding chemoattractant receptors as reported in a previous study and studies on receptor cross-competition permit the conclusion that there are several distinct mechanisms of chemoattractant receptor desensitization all of which occur within minutes.

Monocyte recruitment and accumulation in inflamed and damaged tissue is pivotal in the process of inflammation and wound repair. In certain inflammatory diseases, such as rheumatoid arthritis, monocytes from inflamed tissue exhibit greatly diminished chemotactic response presumably because of their exposure to inflammatory mediators, including IFN-γ and granulocyte-macrophage colony-stimulating factor, which are potent monocyte activators. The conclusions of this report suggest that multiple interactions of monocyte activators, including the newly identified chemoattractant GH, may lead to deactivation of the chemotactic response. It may be that the deactivation provides a mechanism whereby activated monocyte-macrophages can persist within the inflamed tissue. Alteration of skin wound healing by rhGH in normal individuals has only recently been reported. Effects of GH on wound healing may include metabolic alterations as well as local effects on inflammatory cells and stromal elements. In this in vitro study potent chemoattractant activity of rhGH for normal human monocytes has been identified, and it can be assumed that sensory neuropeptides possibly play a modulatory role for monocytes as well as neutrophils. Moreover, our study on interactions of rhGH with endogenous mediators of inflammation and wound healing suggest that the responses of monocytes to chemoattractants are tightly regulated at different steps of recruitment and activation.

**ACKNOWLEDGMENT**

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