Amino-terminal Truncation of Chemokines by CD26/Dipeptidyl-peptidase IV

CONVERSION OF RANTES INTO A POTENT INHIBITOR OF MONOCYTE CHEMOTAXIS AND HIV-1-INFECTION

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Chemokines are key players in inflammation and infection. Natural forms of the C-X-C chemokine granulocyte chemotactic protein-2 (GCP-2) and the C-C chemokine regulated on activation normal T cell expressed and secreted (RANTES), which miss two NH2-terminal residues, including a Pro in the penultimate position, have been isolated from leukocytes or tumor cells. In chemotaxis and intracellular calcium mobilization assays, the truncation caused a reduction in the specific activity of RANTES but not of GCP-2. The serine protease CD26/dipeptidyl-peptidase IV (CD26/DPP IV) could induce this observed NH2-terminal truncation of GCP-2 and RANTES but not that of the monocyte chemotactic proteins MCP-1, MCP-2 and MCP-3. No significant difference in neutrophil activation was detected between intact and CD26/DPP IV-truncated GCP-2. In contrast to intact natural RANTES(1–68), which still chemotactically monocytes at 10 ng/ml, CD26/DPP IV-truncated RANTES(3–68) was inactive at 300 ng/ml and behaved as a natural chemotaxis inhibitor. Compared with intact RANTES, only a 10-fold higher concentration of RANTES(3–68) induced a significant Ca2+ response. Furthermore, RANTES(3–68) inhibited infection of mononuclear cells by an M-tropic HIV-1 strain 5-fold more efficiently than intact RANTES. Thus, proteolytic processing of RANTES by CD26/DPP IV may constitute an important regulatory mechanism during anti-inflammatory and antiviral responses.

Chemokines constitute a family of small proinflammatory cytokines with leukocyte chemotactic and activating properties. Depending on the position of the first two Cys, the chemokine family can be divided in C-C, C-X-C, C, and C-X2-C chemokines (1–3). Many C-X-C chemokines, such as interleukin-8 (IL-8), are chemotactic for neutrophils, whereas C-C chemokines, such as monocyte chemotactic protein-3 (MCP-3), are active on a variety of leukocytes, including monocytes, lymphocytes, eosinophils, basophils, natural killer cells, and dendritic cells.

The NH2-terminal domain of chemokines is involved in receptor binding. NH2-terminal truncation can either activate chemokines or render chemokines completely inactive. The C-C chemokine platelet basic protein becomes a natural neutrophil chemotactic peptide (neutrophil activating peptide-2) only after the enzymatic removal of 24 NH2-terminal residues (4, 5). Proteolytic cleavage of up to eight NH2-terminal residues from IL-8 results in an enhanced chemotactic activity, but further deletion of the Glu-Leu-Arg motif, which is located in front of the first Cys in all neutrophil chemotactic C-X-C chemokines, causes complete inactivation (6). Similar NH2-terminal proteolysis (up to eight amino acids) of another C-X-C chemokine, granulocyte chemotactic protein-2 (GCP-2), has no effect on its neutrophil chemotactic activity (7). However, the NH2 terminus has been reported to be essential for MCPs to retain their biological activity. The synthetical C-C chemokines MCP-1, MCP-3, and RANTES missing the eight or nine NH2-terminal amino acids are inactive on monocytes and are useful as receptor inhibitors (8, 9). Extension of RANTES with one methionine results in complete inactivation of the molecule, and Met-RANTES behaves as an inhibitor for authentic RANTES (10).

In this report, we describe the physiological occurrence of natural forms of human GCP-2 and RANTES missing the first two amino acids, and we give direct evidence that dipeptidyl-peptidase IV (DPP IV; EC 3.4.14.5) is capable of cleaving these chemokines at their NH2 terminus. The exopeptidase DPP IV is present as a membrane-associated ectoenzyme on lymphocytes, epithelial cells, and endothelial cells and occurs in soluble form in body fluids, such as plasma, urine, and seminal fluid (11). In the hematopoietic system, DPP IV was identified as the activation antigen CD26. A subpopulation of memory (CD45RO+) T cells with a high surface density of CD26 is responsible for the proliferation in response to recall antigen in vitro (12). CD26/DPP IV is a highly specific aminopeptidase, cleaving off dipeptides from the NH2 terminus of peptides with a Pro, Hyp, or Ala at the penultimate position (11). A number of cytokines, and among these, several chemokines, share an Xaa-Pro sequence at their NH2 terminus (13). The NH2-terminal Xaa-Pro may not only contribute to the receptor binding and/or signaling function, but may also serve as a structural protection against nonspecific proteolytic degradation. Inhibitor-resistant RANTES, regulated on activation normal T cell expressed and secreted.
tion of the enzymatic activity of CD26/DPP IV has been reported to suppress T cell proliferation in vitro (14), to decrease antibody production in mice (15), and to prolong cardiac allograft survival in rat recipients (16). However, the natural substrates targeted by CD26/DPP IV in the immune system are unknown.

Recently, a role for both CD26/DPP IV and C-C chemokines, i.e. RANTES and the macrophage inflammatory proteins MIP-1α and MIP-1β, has been postulated during HIV-1 infection with macrophage-tropic (M-tropic) HIV-1 strains (17, 18). RANTES, MIP-1α, and MIP-1β inhibit HIV-1 infection by competing for the same seven transmembrane-spanning G protein-coupled C-C chemokine receptor 5 (CCR5) (19–21). The observation that CD26/DPP IV reduces the chemotactic efficacy of RANTES while increasing its antiviral potency brings new insights into the mechanisms underlying the role of CD26/DPP IV during HIV-1 infection and inflammation.

**EXPERIMENTAL PROCEDURES**

**Reagents**—Natural intact and truncated GCP-2 and RANTES were produced by cultured human sarcoma cells or freshly isolated human peripheral blood leukocytes (obtained from the blood transfusion centers of Antwerp and Leuven) and purified as described previously (22, 23). Intact MCP-2, MCP-3, and GCP-2 were synthesized by Fmoc chemistry (24, 25), recombinant human RANTES was obtained from Perpetech (Rocky Hill, NJ), and recombinant MCP-1 was a gift from Dr. J. J. Oppenheim (NCI, National Institutes of Health, Frederick, MD).

Human CD26/DPP IV was obtained from prostasomes (prostate-derived organelles), which occur freely in seminal plasma. The enzyme was purified to homogeneity as described before using ion exchange derived organelles, which occur freely in seminal plasma. The enzyme was purified to homogeneity as described previously (22, 23). CD26/DPP IV was incubated overnight at 37 °C with CD26/DPP IV in 100 mM Tris/HCl, pH 7.7. Chemokines were separated from CD26/DPP IV by SDS-polyacrylamide gel electrophoresis on a Tris/Triose (N-[2-hydroxy-1,1-bis(hydroxymethyl)ethyl] glycine) gel system as described previously (22). Proteins were electrophoretically separated on polyvinylidene difluoride membranes (Problott, Perkin-Elmer, Foster City, CA) and stained with Coomassie Brilliant Blue R250. After destaining, membranes were rinsed at least once with 0.5 M Tris (National Institute for Biological Standards & Control, Herts, United Kingdom). Peripheral blood mononuclear cells from healthy donors were isolated by density gradient centrifugation (5, 23) and stimulated

**Detection of Intracellular Ca$^{2+}$ Concentrations—**Intracellular Ca$^{2+}$ concentrations ([Ca$^{2+}$]) were measured as described previously (25). Briefly, purified cells were incubated with the fluorescent indicator fura-2 (**2.5 μM** fura-2/AM, Molecular Probes Europe BV, Leiden, The Netherlands) and 0.01% Pluronic F-127 (Sigma). After 30 min, cells were washed twice, resuspended in Hanks' buffered saline solution with 1 mM Ca$^{2+}$ and incubated for 10 min at 37 °C for 30 min. After 30 min, cells were lysed with 50 μM digitonin. Subsequently, the pH was adjusted to 8.5 with 20 mM Tris, and R$_{\text{max}}$ was obtained by addition of 10 mM EGTA to the lysed cells. The K$_{\text{d}}$ used for calibration was 224 nM.

For desensitization experiments, cells were first stimulated with buffer or chemokine at different concentrations. As a second stimulus, chemokines were added at a concentration inducing a significant increase in [Ca$^{2+}$], after prestimulation with buffer. The percentage inhibition of the [Ca$^{2+}$] increase in response to the second stimulus by prestimulation of the cells was calculated.

**Inhibition of HIV-1 Infection—**The HIV-1 M-tropic strain BaL was obtained through the Medical Research Council AIDS reagent project (National Institute for Biological Standards & Control, Herts, United Kingdom). Peripheral blood mononuclear cells from healthy donors were isolated by density gradient centrifugation (5, 23) and stimulated...
Identification and Biological Characterization of Natural, NH$_2$-terminally Truncated GCP-2 and RANTES—During the isolation of natural C-X-C chemokines from conditioned media of MG-63 osteosarcoma cells, we previously purified different NH$_2$-terminally truncated forms of human GCP-2 (23). The least truncated GCP-2-form was cleaved beyond Pro at the penultimate position (GCP-2(3–77)). Using a similar standard purification procedure, the C-C chemokine RANTES was purified from peripheral blood leukocytes or sarcoma cells (22). In addition to full-length human RANTES, a truncated RANTES-variant missing the two NH$_2$-terminal residues (RANTES(3–68)) was consistently isolated.

GCP-2(3–77) and RANTES(3–68) were tested for chemotactic and/or intracellular Ca$^{2+}$-releasing activity, and their biological potency was compared with that of the respective intact chemokines. Natural intact GCP-2 and NH$_2$-terminally truncated GCP-2, when tested for their ability to enhance the [Ca$^{2+}$], in purified peripheral blood neutrophilic granulocytes (Fig. 1), were equally active, with a minimal effective concentration of 3 ng/ml. In contrast, NH$_2$-terminal deletion of two residues from RANTES resulted in considerably decreased monocyte chemotactic and Ca$^{2+}$-releasing activities (Fig. 2). Compared with intact natural RANTES (minimal effective dose of 3–10 ng/ml), natural RANTES(3–68) was totally inactive when tested at concentrations as high as 300 ng/ml in the Boyden microchamber (Fig. 2A). In addition, 10-fold higher concentrations of natural RANTES(3–68), compared with RANTES(1–68), were necessary to obtain a similar Ca$^{2+}$ response (Fig. 2B).

CD26/DPP IV Removes the NH$_2$-terminal Dipeptides of Chemokines—To investigate whether the aminopeptidase CD26/DPP IV could be responsible for the NH$_2$-terminal truncation of GCP-2 and RANTES, the intact chemokines were incubated overnight at 37 °C with CD26/DPP IV, blotted to polyvinylidene difluoride membranes, stained with Coomassie Blue, and subjected to automatic Edman degradation. CD26/DPP IV treatment of GCP-2 and RANTES resulted in the removal of the NH$_2$-terminal dipeptides. Parallel incubation of chemokines with buffer without CD26/DPP IV had no effect.

Because other chemokines contained the consensus sequence for CD26/DPP IV cleavage and because the NH$_2$ terminus of MCPs was shown to be crucial for biological activity (8, 9), MCP-1, MCP-2, and MCP-3 were also incubated with CD26/DPP IV. After treatment, MCPs were blotted on polyvinylidene difluoride membranes and stained with Coomassie Blue, and subjected to automatic Edman degradation. CD26/DPP IV treatment of GCP-2 and RANTES resulted in the removal of the NH$_2$-terminal dipeptides. Parallel incubation of chemokines with buffer without CD26/DPP IV had no effect.

Figure 2. NH$_2$-terminally truncated RANTES(3–68) has impaired chemotactic and intracellular Ca$^{2+}$-mobilizing effects. A, the chemotactic potencies of intact and NH$_2$-terminally truncated forms of natural or recombinant RANTES for monocytic THP-1 cells were compared in the Boyden microchamber assay. □, natural, intact RANTES(3–68); □, natural, truncated RANTES(3–68); ▲, intact recombinant RANTES(3–68); ■, CD26/DPP IV-cleaved recombinant RANTES(3–68). Results represent the mean chemotactic index ± S.E. of four or more independent experiments (the S.E. is not shown if it was smaller than the symbols used). B, effect of natural RANTES(3–68) (□), natural RANTES(1–68) (△), recombinant RANTES(1–68) (●), and recombinant CD26/DPP IV-treated RANTES(3–68) (■) on the [Ca$^{2+}$]i in THP-1 cells. Results represent the mean increase in [Ca$^{2+}$]i ± S.E. of three or more independent experiments.
RANTES Cleavage into a Chemotaxis and HIV-1 Inhibitor

TABLE I
Table I: RANTES(3–68) desensitizes monocyte chemotaxis induced by RANTES(1–68)

| Chemokine | Chemotactic response (CI)a | Inhibition mean ± S.E. |
|-----------|-----------------------------|------------------------|
|           | Lower well RANTES(1–68) | Upper well RANTES(3–68) |                   |
| 300 ng/ml | A 12.5 B 7.5 C 27.5 D 50.5 | 25 ± 10 | 67 ± 8 |
| 300 ng/ml | E 41.0 F 46.0 G 71.5 H 97.0 | 64 ± 13 | 31 ± 13 |
| 100 ng/ml | I 4.0 J 3.0 K 13.5 L 11.0 | 8 ± 3 | 82 ± 4 |
| 100 ng/ml | M 24.0 N 21.5 O 50.0 P 44.5 | 35 ± 7 | 0 |

a CI, chemotactic index.

Results in the top half represent the chemotactic index (CI) of four (A–D) independent experiments (including mean ± S.E.) and the percentage of inhibition (mean ± S.E.) of the chemotactic response towards recombinant RANTES(1–68) after preincubation of the THP-1 cells with inactive recombinant RANTES(3–68) or buffer. Results in the bottom half represent the CI of four (E–H) independent experiments (including mean ± S.E.) and the percentage of inhibition (mean ± S.E.) of the chemotactic response towards recombinant RANTES(1–68) when RANTES(3–68) was added simultaneously with intact RANTES to the lower well of the Boyden chamber.

In Ca2+ mobilization experiments with THP-1 cells (Fig. 3), 30 ng/ml of intact RANTES could desensitize for the effect of 30 ng/ml of intact RANTES for 39 ± 5%. About 10-fold higher concentrations of RANTES(3–68) were necessary to obtain the same amount of desensitization. However, at 300 ng/ml, RANTES(3–68) by itself gave a significant Ca2+ response. This Ca2+ response was comparable to the response obtained with 30 ng/ml of intact RANTES.

RANTES(3–68) Is a More Potent HIV-1 Inhibitor than RANTES(1–68)—RANTES(3–68) and RANTES(1–68) were compared for their ability to inhibit HIV-1 infection of peripheral blood mononuclear cells with the M-tropic BaL strain (Fig. 4). RANTES was added to the cultures at the time of infection, and p-24 Ag concentrations were determined in the culture supernatant 10 days after infection. Inhibition of HIV-1 infection by 40 ng/ml of RANTES(3–68) was significantly better (91% inhibition) than the inhibition obtained with an equal concentration of intact RANTES (60%) (p < 0.01 with a Student’s t test). In two out of four experiments, p-24 was still detected after treatment with 1 μg/ml of intact RANTES, whereas all peripheral blood mononuclear cell cultures remained uninfected when pretreated with 1 μg/ml of RANTES(3–68). In conclusion, although RANTES(3–68) was less efficient compared with intact RANTES in Ca2+ mobilization or chemotaxis assays, NH2-terminal truncation of RANTES by CD26/DPP IV significantly enhanced its anti-HIV-1 activity.

DISCUSSION

Limited NH2-terminal truncation of chemokines has different consequences for their biological potency resulting in either increased (C-X-C chemokines) or decreased (C-C chemokines) specific activity (4–10). During the purification of GCP-2 and RANTES from natural sources, we detected significant quan-
terminal Xaa-Pro motif as a target for CD26/DPP IV was observed several years ago, the failure of processing mature IL-1α, IL-1β, IL-2, and other cytokines by CD26/DPP IV indicated that peptides become less susceptible to cleavage by CD26/DPP IV with increasing length (11, 29). Indeed, the largest peptide (44 amino acids) reported to be sensitive to NH2-terminal truncation by CD26/DPP IV is growth hormone-releasing hormone (30).

In this study, two chemokines of about 70 residues with Pro at the penultimate NH2-terminal position, i.e. the C-X-C chemokine GCP-2 and the C-C chemokine RANTES, were processed by CD26/DPP IV, but the C-C chemokines MCP-1, MCP-2, and MCP-3 were resistant to degradation by the enzyme. Earlier observations that naturally truncated forms of MCP-1, MCP-2, or MCP-3, missing two NH2-terminal amino acids, were not isolated from various cellular sources (22) confirm the specificity of CD26/DPP IV. Resistance of MCP-2 to CD26/DPP IV is a consequence of the presence of the NH2-terminal pyroglutamic acid, because recombinant MCP-2 with an NH2-terminal Gln was cleaved by CD26/DPP IV (data not shown). The importance of the NH2-terminal residues has been illustrated by chemical synthesis of truncated MCP-1 and MCP-3, which are devoid of monocyte chemotactic activity (8, 9). Truncation of GCP-2 with CD26/DPP IV had no significant effect on the chemotactic and Ca2+-releasing capacity of the chemokine. In contrast, a 10–100-fold decreased monocyte chemotactic and intracellular Ca2+-releasing activity was detected with RANTES(3–68) processed by CD26/DPP IV. However, RANTES and RANTES(3–68) were reported to be equipotent eosinophil chemotactic proteins (31). Expression of different RANTES receptors, i.e. CCR3 on eosinophils compared with CCR1 and CCR5 on mononuclear cells (3, 19), may explain the different interaction of RANTES(3–68) with both cell types. In addition to monocytes, also memory type CD45RO+ T cells, which express CCR1, CCR5, and CD26, are important target cells for RANTES (32, 33). In view of these observations, a physical proximity between RANTES and CD26/DPP IV seems feasible, and therefore, the processing of RANTES by CD26/DPP IV is likely to be of biological significance.

When tested as a RANTES inhibitor, 1 μg/ml of inactive RANTES(3–68) was able to inhibit monocyte chemotaxis toward 100 ng/ml and 300 ng/ml of intact RANTES. In Ca2+-mobilization experiments, 300 ng/ml of RANTES(3–68) only partially desensitized for a response toward intact RANTES. These results suggest that RANTES(3–68) binds to at least one receptor and that the interaction of RANTES(3–68) with the receptor(s) is sufficient for partial signal transduction (increase of the [Ca2+]i) but not for chemotaxis.

Recently, chemokines, their receptors, and CD26/DPP IV have been linked to HIV-1-infection. Concerning the role of CD26/DPP IV in HIV-infection, contrasting reports have been published. A positive correlation between the level of CD26/DPP IV-expression and the susceptibility to infection with M-tropic HIV-1 viruses was found (17), whereas this correlation could not be detected for T-tropic viruses (34). Moreover, CD26/DPP IV was described as a cofactor for HIV entry in CD4+ T cells (35). In contrast, CD26/DPP IV+ cells were found to be less susceptible to HIV infection than CD26/DPP IV− cells (34). A specific decrease in CD26/DPP IV-expression was reported upon HIV-1 infection of cells with M-tropic, but not T-tropic viruses (17), and both the absolute number and the proportion of CD26+ T cells were decreased in HIV-infected persons (12).

Several chemokines, including RANTES, were identified as inhibitors of HIV-1 infection (18). The use of CCR5 as a coreceptor by M-tropic viruses explains the inhibitory effect of the C-C chemokines RANTES, MIP-1α, and MIP-1β on HIV-1 infection (19–21). Co-expression of CD26/DPP IV and CCR5 (32) could therefore explain the specific decrease of CD26+CD4+ cells during HIV infection. Recent reports on chemically synthesized RANTES(9–68), missing six extra NH2-terminal residues compared with RANTES(3–68), have shown a reduction of the anti-HIV activity of RANTES (36). RANTES(9–68) also functioned as a chemokine inhibitor, but about 10-fold higher amounts, compared with intact RANTES, were necessary to
obtain a comparable anti-HIV-1 activity. NH₂-terminally altered amino-oxypentane-RANTES also acts as a chemotaxis inhibitor and, in contrast to RANTES(9–68), was more efficient as an inhibitor of HIV-1 infection than intact RANTES (37). Thus, minor modifications of RANTES at the NH₂ terminus are detrimental to its chemotactic activity and alter its anti-HIV activity. Compared with intact RANTES, RANTES(3–68), generated by CD26/DPP IV cleavage, is a more efficient inhibitor of HIV-1 infection of peripheral blood mononuclear cells with M-tropic strains. At the same time, RANTES(3–68), which is a much weaker chemotaxis agonist compared with intact RANTES, can provide negative feedback to weaken the inflammatory response. Although it is at present impossible to discriminate between RANTES(1–68) and RANTES(3–68) in clinical samples, studies on the in vitro balance between both RANTES forms may provide interesting information on the (patho-)physiological role of RANTES(3–68).

In conclusion, we have isolated naturally occurring forms of the chemokines GCP-2 and RANTES, missing their NH₂-terminal Xaa-Pro motif. We demonstrated that CD26/DPP IV is able to cleave chemokines in vitro into these NH₂-terminally truncated forms. Although truncated and intact GCP-2 are equally active, RANTES(3–68) becomes a natural chemotaxis inhibitor and is a more potent inhibitor of HIV-1 infection than intact RANTES. RANTES is the first cytokine reported, of which the biological activity can be modified by CD26/DPP IV. This finding may lead to novel insights on the role of this specific peptidase not only in HIV-infection but also in inflammatory processes and immune responses.

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