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Nasal cytokines in common cold and allergic rhinitis

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Summary

Coronavirus-induced common cold and allergen-induced rhinitis are characterized by nasal mucosal exudation of bulk blood plasma. The mucosal exudation process involves 'flooding' of the lamina propria with plasma-derived binding proteins and it is possible that subepithelial inflammatory cytokines and mediators may be moved by the exudate to the mucosal surface. In this study, we have analysed cytokine levels in nasal lavage (NAL) fluids from non-allergic subjects inoculated with coronavirus ($n = 20$) and from subjects with allergic (birch pollen) rhinitis subjected to additional allergen challenge (samples were obtained 35 min post challenge) in the laboratory ($n = 10$). Ten of the 20 inoculated subjects developed common cold and 10 remained healthy. Interferon-γ (IFNγ), interleukin-1β (IL-1β), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-4, and IL-6 were analysed in unprocessed NAL fluids using immunoassays. The subjects who developed common cold had increased NAL fluid levels of IFNγ ($P < 0{\cdot}05$) that correlated well with the symptoms ($P < 0{\cdot}001$). IFNγ did not increase in subjects with allergic rhinitis. IL-1β levels were similar in NAL fluids obtained from all inoculated subjects. In the subjects with allergic rhinitis NAL fluid levels of both IL-1β and GM-CSF were increased ($P < 0{\cdot}05$). GM-CSF was not detected in common cold. IL-4 and IL-6 were not detectable in any of the NAL fluids. The present cytokines may not only emanate from superficial mucosal cells. By aiding plasma exudation subepithelial cytokines may potentially also be retrieved on the mucosal surface. Our study provides original *in vivo* data supporting the notion that a TH-1 profile of cytokines, notably IFNγ, is present in viral infection and further supporting the view that GM-CSF is an important cytokine in allergic airways disease.

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Introduction

We have previously demonstrated that there is a luminal entry of plasma including large binding proteins such as fibrinogen and α_2-macroglobulin [1,2] in common cold and allergic rhinitis which may bind and transport a variety of cytokines [3]. The mucosal exudation process is preceded by extravasation of plasma. This primary plasma exudate is flooding the lamina propria before it is cleared by non-injurious paracellular epithelial mechanisms into the airway lumen [4]. Hence, inflammatory factors emanating from epithelial and subepithelial airway cells may move to the mucosal surface particularly during the exudative phase of airways inflammation [5].

The inflammatory response to infection or allergen potentially involves the generation of a variety of cytokines. Interleukin-1 (IL-1) [6,7], IL-6 [8], and interferon-γ (IFNγ) [9] are pleiotropic cytokines with multiple effects in a series of immune, hematopoietic and other systems. A major biological activity of

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granulocyte-macrophage colony-stimulating factor (GM-CSF) is to induce proliferation and differentiation of granulocytic and monocytic stem cells [10]. IL-4 appears to be essential requirement for IgE production whereas IFNγ inhibits this effect [11]. The possibility that viral infection generates IFNγ is also of interest in view of the effect of this cytokine on T-helper (TH) cell properties. IFNγ may thus induce positive TH-1 immunity inhibiting the development of TH-2 dependent allergic responses [12]. On the other hand IFNγ may increase MHC class II expression on epithelial lining cells potentially abrogating an induced immune unresponsiveness [13]. Although there are numerous studies on cytokine generation by inflammatory cells and structural cells *in vitro* [14], little is known of the *in vivo* appearance of cytokines on the human airway mucosa in inflammatory airway diseases.

We have now analysed cytokines appearing on the nasal mucosal surface when plasma exudation is also known to occur at viral infection and at allergic disease. We have thus examined the cytokine profile in nasal lavage (NAL) fluids obtained in the morning at common cold [1,15] and after allergen challenge during seasonal allergic rhinitis [16].

Methods

Subjects

Common cold Twenty male healthy (and non-allergic) volunteers (20–27 years) were isolated, in groups of four, for 9 days. After 2 days, during which all subjects remained healthy, they were inoculated with 100 TiCD50 (tissue culture infective dose 50, i.e. a dose producing infection in 50% of cultures) of human coronavirus 229E in the nose. Based on the outcome of a series of symptoms and clinical signs, recorded according to Beare and Reed [17], the subjects could be divided into two groups; those with common cold ($n = 10$) and those free of common cold ($n = 10$) (Fig. 1a). Details of the clinical course and the plasma exudation process have been reported elsewhere [1].

Allergic rhinitis Ten patients (nine males; 20–41 years) with allergic rhinitis (positive history and skin-prick test to birch pollen) were challenged in the right nasal cavity, first with diluent, and then with 100, 1000, and 10 000 SQ units of birth pollen allergen (Aquagen®, ALK, Copenhagen, Denmark) at the end of the Swedish birch pollen season of 1992. Diluent and allergen were administered as single actuactions (100 μl) with 10 min intervals using a spray device. Nasal symptoms experienced during the 10 min interval after each challenge were recorded; nasal itching, blockage, and secretion were scored from 0–3 (0 = no, 1 = mild, 2 = moderate, 3 = severe symptoms). Furthermore, the number of sneezes was counted and transformed into a score (0 = 0, 1 = 1–4, 2 = 5–9, 3 = 10 or more sneezes). A total symptom score was calculated by addition of the four scores (Fig. 1b).

All subjects gave their written informed consent to participate, and the study protocol had approval of the ethics committee.

Nasal lavage

Nasal lavages (NALs) were carried out with aid of a compressible 'nasal pool' device inserted into the right nostril [18]. Thus, 14 ml of saline was instilled and kept in the unilateral nasal cavity by compressing the accordion part of the device. Using this technique >90% of the lavage fluid is regularly recovered into the device after 2·5 min by releasing the pressure [18]. The lavage fluids were centrifuged for 10 min, at 325 × *g* and 4°C. Cell free NAL fluids were stored at −20°C.

Common cold In the coronavirus inoculated subjects morning (at 08.00 h) NALs were carried out 1 day prior to, and on day 1, 2, 4 and 5 after the inoculation.

Allergic rhinitis Two quick lavages were carried out before the diluent challenge to clear the nasal cavity from accumulated nasal secretions/exudations. Thereafter, NALs were carried out 10 min after challenge with diluent and each dose of allergen (100, 1000 and 10 000 SQ units). Cytokines were analysed in NAL fluids recovered after the diluent and the highest allergen dose challenge.

Cytokines

Cell free lavage supernatants were analysed for cytokines using specific immunoassays; interferon-gamma (IFNγ) ELISA [19], detection limit 0·078 IU/ml; interleukin-1β (IL-1β) ELISA (R&D Systems, Minneapolis, USA), detection limit 3·9 pg/ml; granulocyte-macrophage colony-stimulating factor (GM-CSF) ELISA (Genzyme, Boston, USA), detection limit 4 pg/ml; IL-4 ELISA (R&D Systems), detection limit 31·3 pg/ml; IL-6 ELISA (Genzyme), detection limit 35 pg/ml. In the present study, only kits with a variation coefficient for repeated measurements lower than 10% were accepted.

Statistic analysis

The results for each group are presented as mean±SEM or as individual values. Comparisons of variables within the

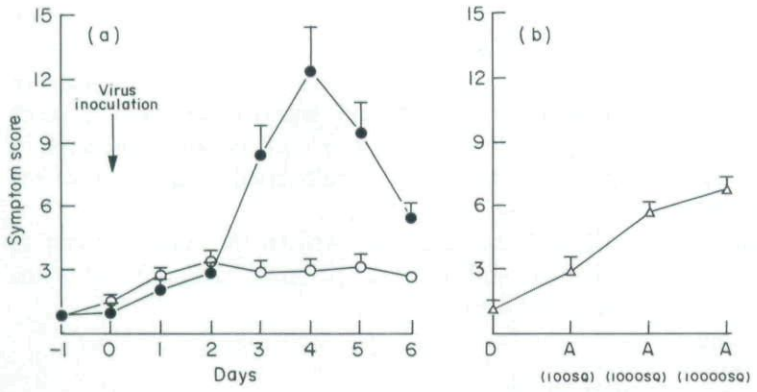

Fig. 1. Twenty non-allergic subjects were inoculated with coronavirus at day 0. Ten of these developed cold with significant symptoms (–●–), whereas 10 subjects remained healthy (–○–). (a) Total symptom scores in subjects with allergic rhinitis after challenge with diluent, and 100, 1000 and 10 000 SQ units birch pollen allergen (–△–) (b). Symptom scores: see Methods. The results are presented as mean±SEM.

groups were performed using Friedman test and Wilcoxon's sign rank test. Comparisons between the groups were performed using Mann–Whitney *U*-test. Correlations were tested by calculation of the Spearman correlation coefficients. Differences were considered significant at $P < 0{\cdot}05$.

Results

As reported elsewhere [1], half of the 20 coronavirus inoculated subjects developed symptoms of common cold, while the other half remained healthy (Fig. 1a). All subjects with seasonal allergic rhinitis developed symptoms after challenge with cumulative doses of birch pollen allergen (Fig. 1b).

NALs were performed before and during the exudative phase of inflammation caused either by virus infection in normal subjects [1] or by allergen challenge in allergic subjects [16]. In subjects who developed common cold after coronavirus inoculation NAL fluid levels of IFNγ increased significantly on day 4 (Friedman test: $P < 0{\cdot}01$; Wilcoxon's sign rank test: $P < 0{\cdot}05$ compared with the day before inoculation; Mann–Whitney *U*-test: $P < 0{\cdot}05$ compared with the asymptomatic group on day 4) (Fig. 2a, b). IFNγ did not increase in NAL obtained from the asymptomatic group (Friedman test and Wilcoxon's sign rank test: $P > 0{\cdot}05$). In subjects with allergic rhinitis allergen challenge did not cause any significant changes in NAL fluid levels of IFNγ (Fig. 2c).

IL-1β levels were similar ($P > 0{\cdot}05$) in NAL fluids obtained from the symptomatic and asymptomatic groups of the virus inoculated subjects (Fig. 3a, b). However, in the symptomatic group IL-1β was significantly higher on day 4 than prior to inoculation (Friedman test: $P < 0{\cdot}05$; Wilcoxon's sign rank test: $P < 0{\cdot}05$). Prior to allergen challenge IL-1β was not detectable (<3·9 pg/ml) but it was increased in NAL fluids obtained after allergen challenge in the subjects with allergic rhinitis (Wilcoxon's sign rank test: $P < 0{\cdot}05$; Fig. 3c).

The mean level of IL-1β in NAL fluids obtained during the exudative phase of the allergic rhinitis was about four times lower than those found in NAL fluids obtained during the exudative phase of common cold. However, since the IL-1β levels in allergic rhinitis group were analysed in NALs obtained after repeated prewashes, while the IL-1β levels in common cold group were analysed in NALs reflecting basal levels, a comparison of the absolute levels of lavage fluid cytokines between these groups is not appropriate.

Prior to allergen challenge GM-CSF was not detectable (<4 pg/ml), but in NAL fluids obtained after allergen challenge in subjects with allergic rhinitis it was clearly increased (Wilcoxon's sign rank test: $P < 0{\cdot}05$; Fig. 4). GM-CSF was not detectable in NALs obtained from the virus inoculated subjects. IL-4 and IL-6 could

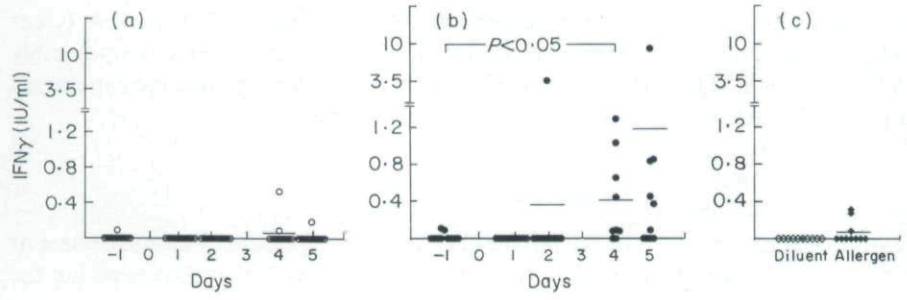

Fig. 2. IFNγ levels in NAL fluids obtained from asymptomatic (a) and symptomatic (b) groups of the virus inoculated (at day 0) non-allergic subjects. IFNγ levels in NAL fluids obtained before and 35 min after cumulative allergen challenge in the subjects with allergic rhinitis (c). The lower detection limit for IFNγ assay was 0·078 IU/ml.

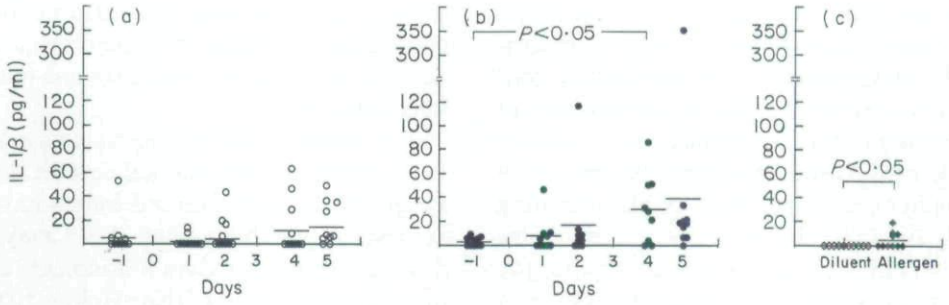

Fig. 3. IL-1β levels in NAL fluids obtained from asymptomatic (a) and symptomatic (b) groups of the virus inoculated (at day 0) non-allergic subjects. IL-1β levels in NAL fluids obtained before and 35 min after cumulative allergen challenge in the subjects with allergic rhinitis (c). The lower detection limit for IL-1β assay was 3·9 pg/ml.

not be detected in NAL fluids obtained from either group of subjects.

There was a positive correlation between IFNγ and total symptoms (Spearman's correlation coefficient $R = 0{\cdot}706$, $P < 0{\cdot}001$) in the coronavirus inoculated subjects on day 4 (Fig. 5), and between IL-1β and total symptoms ($R = 0{\cdot}573$, $P < 0{\cdot}05$). In the subjects with allergic rhinitis, the GM-CSF levels did not correlate with allergen-induced rhinitis symptoms.

Discussion

The present study demonstrates that coronavirus induced common cold is associated with increased luminal entry of IFNγ and IL-1β, but not GM-CSF. In contrast, allergen challenge in seasonal allergic rhinitis is associated with increased luminal entry of GM-CSF and IL-1β, but no increase in IFNγ. To our knowledge, this is the first *in vivo* study demonstrating that different pro-inflammatory stimuli may induce production of different cytokines in the human nasal airway mucosa.

The lumenal entry of bulk plasma that occurs in the common cold and the allergen challenge condition appears to be a non-injurious paracellular process that does not compromise the integrity of the epithelial lining as an absorption barrier [20–22]. The presently sampled

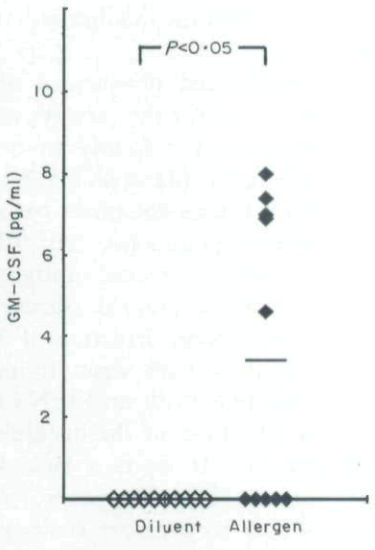

Fig. 4. GM-CSF levels in NAL fluids obtained before and 35 min after cumulative allergen challenge in the subjects with allergic rhinitis. The lower detection limit for GM-CSF assay was 4 pg/ml.

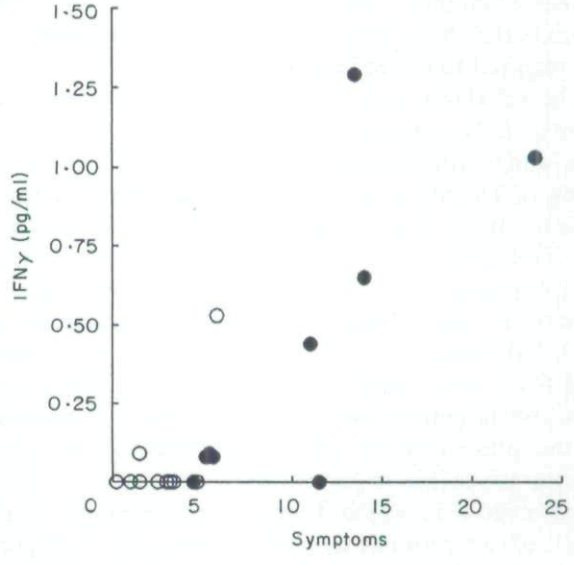

Fig. 5. There was a correlation between IFNγ and symptoms recorded on day 4 after inoculation with coronavirus in subjects who developed cold (–●–) and in subjects who remained healthy (–○–). $R = 0{\cdot}706$.

mucosal surface material, although it would contain large plasma proteins such as fibrinogen and α_2-macroglobulin [1,15,16], may, therefore, not necessarily contain mucosal injury-derived factors. In the absence of carrier proteins cytokines may not readily pass biological membranes/barriers [3]. However, plasma proteins such as α_2-macroglobulin have high efficient cytokine binding characteristics [3] and may thus promote lumenal entry of cytokines in exudative phases of airway diseases [4]. Hence the present cytokines may emanate both from superficial cells and lamina propria sources.

The present differences in cytokine profiles between viral infection and allergy have not been explained. However, they might be a consequence of activation of distinct subsets of T-helper cells (TH-1 and TH-2). Since TH-1 clones expressing mRNA for IL-2 and IFNγ have been associated with viral infection [23–25] it is gratifying to be able to record an increase in IFNγ output in the present study. TH-2 clones expressing mRNA for IL-4 and GM-CSF have been found in allergic inflammation [24,26]. The profile of cytokine mRNA (IL-3, IL-4, IL-5 and GM-CSF) in nasal mucosa biopsies observed by Durham *et al.* [27], along with findings on cytokine mRNA profiles in the lower airways [28,29], supports the possibility that activation of TH-2 type cells occurs after allergen challenge. However, in the present study we could only demonstrate a clear increase in GM-CSF in allergic rhinitis. Since we employed different subject populations we cannot exclude the possibility that our data in part reflect the presence of different responder cells in allergic and non-allergic nasal mucosa. Further studies examining effects on cytokine levels in allergic subjects that have been infected by common cold virus are required to further elucidate this point.

The cellular source of the present cytokines is not known. IFNγ production is attributed to activated T cells and natural killer cells [9]. In addition, a recent study of Dayton *et al.* [30] has demonstrated that the gene for IFNγ is also expressed by human B cells. IL-1 and IL-6 may be produced by a wide variety of cells [6,8]. It is also clear that cells other than T cells, such as mast cells, macrophages, eosinophils, fibroblasts and epithelial cells may produce cytokines, particularly GM-CSF, which may be relevant to the allergic process. Inflammatory cell populations were not examined in the present study but allergen-induced rhinitis is known to be accompanied by a cellular infiltrate in nasal mucosa in which T helper cells, eosinophils and mast cells are prominent [31,32]. Fraenkel *et al.* [33] have demonstrated that rhinovirus infection in humans may not increase inflammatory cells in nasal biopsies. Thus, other sources of mediators than increased cellularity in the airway mucosa may be responsible for nasal symptoms in common cold. It is also possible that mucosal endorgans, including the subepithelial microcirculation, develop an increased responsiveness to mediators at viral infections [34].

The present study demonstrated a correlation between IFNγ levels on the mucosal surface and the composite symptoms in virus-induced inflammation. This finding suggests a possibility that IFNγ may be a marker of disease severity, but does not indicate any specific, good or bad, contribution of this cytokine to the common cold processes. IFNγ exerts a series of pleiomorphic effects on immune cells, on myelomonocytic cells, and on other cell types; its anti-viral activity may not be its most important function [9]. Indeed, Higgins *et al.* [35] have recently reported that intranasal treatment with human recombinant IFNγ in an experimental rhinoviral infection in healthy subjects did not prevent rhinovirus infection or illness. On the contrary, this treatment enhanced the symptoms. There was also a correlation between mucosal IL-1β levels and common cold symptoms in the present study. The fact that IL-1β is better known for its immunomodulatory than antiviral effects [6,7], may suggest that it may be more important in modulating the inflammatory response to infection than directly interfering with viral replication, *per se*. Furthermore, both IFNγ and IL-1β may upregulate expression of intercellular adhesion molecule-1 (ICAM-1) on epithelial and endothelial cells [36]. ICAM-1, in addition to being an important adhesion molecule for inflammatory cells, is also the receptor for most of rhinoviruses and some coxsackie viruses [37]. Thus, it cannot be excluded that the release of mucosal IFNγ and IL-1β may amplify both the spread of infection and the inflammatory response in common cold.

A viral infection-induced production of cytokines, such as IFNγ and IL-1β, in the airways may serve to promote the inflammatory response to other inhaled factors including allergens. Ida *et al.* [38,39] have found that virus incubation causes enhanced basophil activation. Peripheral blood mononuclear cells (PBMC), containing basophils, have increased antigen-stimulated histamine release when evaluated during rhinovirus infections [40]. Furthermore, depletion of T-cells from PBMC before incubation with virus or incubation of virus-conditioned medium with anti-IFNγ monoclonal antibodies lead to inhibition of the histamine releasing activity, suggesting that IFNγ is a basophil function enhancing substance [41]. Moreover, recombinant IFNγ has been shown to promote eosinophil survival *in vitro* [42] and treatment of virus conditioned medium with anti-IFNγ monoclonal antibody has been demonstrated to inhibit the eosinophil survival enhancing activity of this medium [41]. There are also other

potentially important interactions between viral infection-induced cytokine generation and cellular mechanisms of the allergic disease process [12,13]. Although the role of viral infection in allergy and asthma attracts great interest [43,44], most of the information on the interaction mechanisms discussed above is based on *in vitro* observations with as yet only speculative relevance for the *in vivo* situation. We suggest that these interaction mechanisms may be studied *in vivo* with great advantage in the human nose. The nasal mucosa is not only very accessible to *in vivo* examinations. It is also potentially exhibiting mechanisms and functions that may be relevant to tracheobronchial airways as well [4].

In conclusion, the present results indicate that distinct cytokine mechanisms are expressed in common cold and allergic rhinitis, respectively. Different pro-inflammatory stimuli may thus lead to different manifestations of inflammation in the airway mucosa at the cytokine level. The present *in vivo* data on cytokine levels support the view that a TH-1 profile, notably IFNγ, of these agents is present in viral infection. Our data further support the view that GM-CSF may be a major cytokine in allergic airway disease.

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