

Allergen-irritant interaction and the role of corticosteroids

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Studies of exposure to air pollutants, such as ozone and nitrogen dioxide (NO_2) ± sulphur dioxide (SO_2), have demonstrated that these agents, either individually or in combination, increase the airway response of both asthmatics and allergic rhinitics to inhaled allergen. Other studies have demonstrated that exposure to these pollutants significantly increased the levels of eosinophil cationic protein (ECP) in the nasal secretions of both asthmatics and allergic rhinitics, suggesting that pollutants may prime eosinophils for subsequent activation by allergen. More recently, our studies have demonstrated that treatment with inhaled corticosteroids, such as fluticasone propionate, significantly attenuated pollution + allergen-induced release of ECP in allergic rhinitics. Although the mechanisms underlying the potentiating effects of pollutants on allergen-induced changes in the airways of allergic individuals are not fully understood, *in vitro* studies have suggested that airway epithelial cells may play an important role, since they can synthesize a variety of cytokines and adhesion molecules which influence the activity of eosinophils and other inflammatory cells. Studies of nasal epithelial cells cultured from biopsies of atopic rhinitic and atopic non-rhinitic individuals have shown that they constitutively release significantly greater quantities of pro-inflammatory cytokines than nasal epithelial cells of non-atopic individuals, and that the release of these cytokines is greater from cells of atopic rhinitics during the pollen season. Furthermore, exposure of the cells of rhinitics to ozone led to an even greater release of these cytokines, and this effect was attenuated by treatment with fluticasone propionate and beclomethasone dipropionate.

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Introduction

Epidemiological studies have demonstrated that there is an association between episodes of air pollution and impaired respiratory function, as well as hospital admissions (1–3). Increases in the ambient concentration of ozone, in particular, have been shown to increase bronchial responsiveness in both asthmatic and non-asthmatic children (4–6). Laboratory based studies of asthmatics exposed to ozone, nitrogen dioxide (NO_2), and a combination of NO_2 and sulphur dioxide (SO_2), have indicated that these agents may increase the airway responsiveness to inhaled allergen in these individuals (7).

Effect of air pollutants on bronchial hyperreactivity

Molfino et al. (8) demonstrated that prior exposure of mild asthmatics for 1 h to 120 ppb ozone

increased the bronchial response of these subjects to inhaled ragweed allergen. They found that the mean provocation dose of allergen required to decrease the forced expiratory volume in 1 s (FEV_1) by 15% ($\text{PC}_{15}\text{FEV}_1$) after exposure to ozone was significantly reduced to approximately half the provocation dose required following pre-exposure to air. Jörres et al. (9) performed a more detailed study of the effect of exposure to ozone on bronchial responsiveness to inhaled allergen in allergic asthmatic and rhinitic individuals, and demonstrated that prior exposure for 3 h to 250 ppb ozone led to an increase in bronchial responsiveness to allergen in these subjects. In asthmatics, exposure to ozone significantly decreased both the methacholine $\text{PC}_{20}\text{FEV}_1$ and allergen $\text{PD}_{20}\text{FEV}_1$. In rhinitics, whereas the allergen-induced change in FEV_1 after exposure to filtered air was not significantly different from zero, the change after ozone exposure was significantly different compared with exposure to air. The effect

of exposure for 1 h to 100 ppb or 400 ppb NO₂ in mild asthmatics was investigated by Tunnicliffe et al. (10), who demonstrated that 400 ppb NO₂ significantly increased the airway response to inhaled house dust mite allergen during both the immediate and late phase. We have investigated the effect of exposure for 6 h to either air, 400 ppb NO₂, 200 ppb SO₂, or a combination of the two pollutants, on the airway response of non-exercising mild asthmatic volunteers to inhaled *Dermatophagoides pteronyssinus* allergen. It was found that exposure to the combination of the two pollutants, but not to the individual gases, caused a significant reduction in the mean allergen PD₂₀FEV₁, compared with exposure to air, without any significant effects on lung function (11) (Fig. 1a). We have also shown that the enhanced airway response to inhaled allergen in asthmatic individuals resulting from

exposure to the combination of 400 ppb NO₂+200 ppb SO₂, was shown to persist over a period of 24–48 h and was maximal by 24 h following exposure (12) (Fig. 1b).

Mechanisms underlying air pollution-induced effects in the airways

Studies investigating the pathophysiological effects resulting from inhalation of ozone demonstrated that this agent leads to epithelial damage and an increased inflammatory response in the upper and lower airways. This is indicated by leakage of lactate dehydrogenase, albumin and total protein, and an increase in neutrophils, eosinophils, mononuclear cells, fibronectin, α -1-antitrypsin, interleukin (IL)-6, IL-8, granulocyte-macrophage colony stimulating factor (GM-CSF), and prostaglandin E₂, in nasal lavage (NAL), proximal airway lavage, and bronchoalveolar lavage (BAL) fluids (13–15). Similarly, studies investigating the effects resulting from inhalation of NO₂ in healthy non-smoking and lightly exercising individuals, demonstrated that the number of lymphocytes, lysozyme-positive alveolar macrophages, and mast cells were increased in BAL fluid following exposure (16). Most recently, Salvi et al. (17) randomly exposed non-smoking volunteers to diesel exhaust or air on two separate occasions for 1 h with intermittent periods of rest and exercise; bronchoscopy and endobronchial biopsy were performed 6 h after the end of exposure. A significant increase was found in the number of polymorphonuclear cells, CD3+, and CD4+ cells in both the epithelium and the submucosa, and the expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) in the epithelium, and lymphocyte functional antigen-1 in the epithelium and submucosa were also upregulated. Diaz-Sanchez et al. (18) investigated the effect of *in vivo* challenge of healthy volunteers with diesel exhaust particles (DEP) on nasal cytokine production and demonstrated that, although before challenge most subjects' nasal lavage cells had detectable levels of only interferon- γ (IFN- γ), IL-2 and IL-13 mRNA, after challenge the cells produced readily detectable mRNA for IL-2, IL-4, IL-5, IL-6, IL-10, IL-13 and IFN- γ . Enhanced IL-4 protein was also present in the post-challenge lavage fluid.

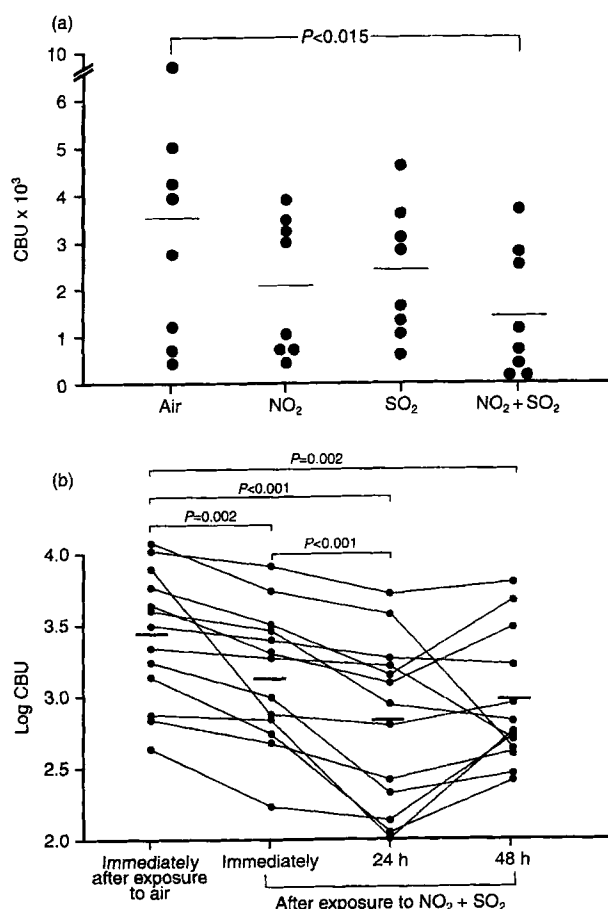


Fig. 1(a). The effect of 6 h exposure to 200 ppb SO₂ and/or 400 ppb NO₂ on inhaled allergen response in mild asthmatic subjects. Results are expressed as mean $\pm$ SEM. The level of significance was determined after log transformation of the data. (CBU=inhaled allergen expressed as cumulative breath units). (b). The effect of 6 h exposure to 400 ppb NO₂ plus 200 ppb SO₂ on the dose of inhaled allergen required to decrease the FEV₁ by 20% in mild asthmatic volunteers. Results are expressed as mean $\pm$ SEM. (CBU=dose of inhaled allergen expressed as cumulative breath units).

Mechanism underlying air pollution and allergen interaction in the airways and the effect of fluticasone propionate

Peden et al. (19) have demonstrated that prior exposure of perennial allergic asthmatics to 400

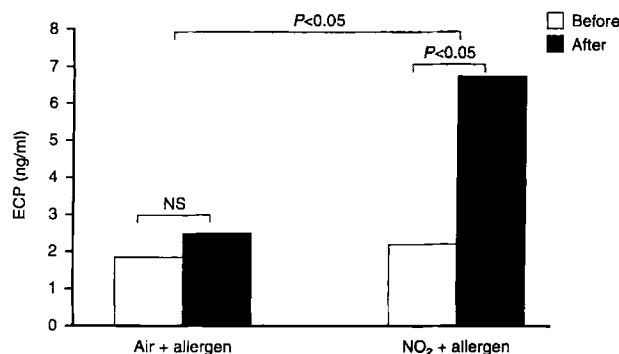


Fig. 2. The effect of 6 h exposure to air or 400 ppb NO₂±nasal allergen challenge on ECP concentration in nasal lavage fluid. Results are expressed as median values.

ppb ozone significantly increased the allergen-induced release of eosinophil cationic protein (ECP) in NAL fluid of these individuals, without significantly affecting the numbers of eosinophils, 4 h after allergen challenge. This suggests that exposure to ozone may 'prime' the eosinophils to subsequent activation by inhaled allergen. Similarly, we have exposed seasonal allergic rhinitics for 6 h to either 400 ppb NO₂ or air±allergen challenge, following 30 min after exposure, and have evaluated the changes in nasal airway resistance (NAR) and presence of inflammatory mediators in NAL. These studies demonstrated that while exposure to NO₂ alone did not significantly alter NAR or increase the concentration of ECP, tryptase or myeloperoxidase in NAL fluid, exposure to NO₂ prior to allergen challenge significantly increased the concentration of ECP, but not tryptase or myeloperoxidase, in NAL fluid, compared with exposure to air (Fig. 2). This suggests that acute exposure to NO₂ may also 'prime' the eosinophils for subsequent activation by allergen (20). In order to investigate whether treatment with fluticasone propionate aqueous nasal spray (FP) can alter the inflammatory response in the nasal airways under these conditions, another group of allergic rhinitic patients were randomized to receive either topical FP 200 µg once daily or matched placebo for 4 weeks. At the end of treatment, all individuals underwent nasal lavage followed by a 6 h exposure to 400 ppb NO₂. Following exposure, nasal allergen challenge was performed and nasal lavage repeated. After a 2-week wash-out period, the individuals were given the alternative treatment and tested as above. Analysis of the lavage samples obtained from placebo-treated patients revealed that ECP levels were significantly increased following exposure to NO₂+allergen. However, with FP pretreatment, there was a much smaller effect on ECP levels

after exposure to NO₂+allergen challenge (Fig. 3) (21). The difference in changes of ECP levels between placebo and FP treatment was significant ($P=0.003$), suggesting that FP may downgrade NO₂+allergen-induced eosinophil activation in allergic rhinitics.

The effect of prior exposure to ozone on allergen-induced inflammatory cell changes in the lower airways of mild asthmatics randomized to receive either inhaled FP 500 µg bd or matched placebo for 4 weeks has recently been investigated (22). Following treatment, individuals in both groups underwent randomized exposure for 1 h to either air or 120 ppb ozone. This was followed by bronchoscopy and saline challenge in the right upper lobe anterior segmental orifice, and allergen challenge in the right middle lobe medial segmental orifice. Bronchoscopy was repeated after 24 h and BAL and bronchial biopsies were obtained from the challenge sites. After a 4-week washout period, treatment with FP or placebo was repeated and BAL and biopsy samples were obtained after prior exposure for 1 h to the alternative atmosphere of air or 120 ppb ozone. Analysis of biopsy tissue demonstrated that prior exposure for 1 h to ozone did not significantly increase the number of either EG1/EG2-staining cells or neutrophils in biopsies, when compared with exposure to air. In patients pre-exposed to air, allergen challenge led to an increase in EG2 cells in the placebo-treated group. In contrast, in patients receiving FP, the number of EG2-staining cells was markedly reduced. Similarly, exposure to ozone followed by allergen challenge also led to an increase in EG2 cells in the placebo-treated group and this was significantly attenuated by treatment with FP ($P=0.017$) (Fig. 4).

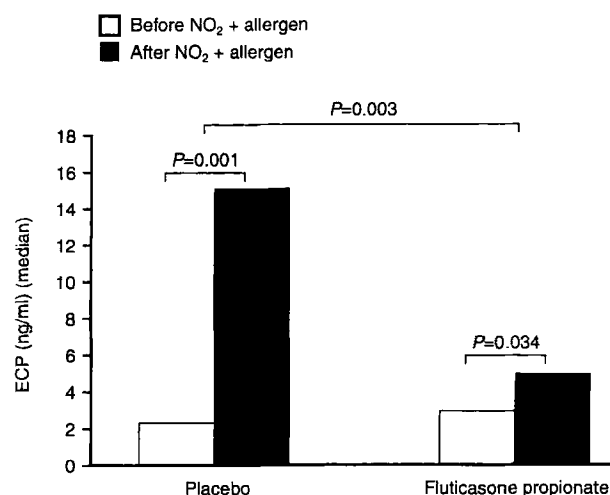


Fig. 3. Effect of fluticasone propionate on allergen-induced changes of ECP in nasal lavage fluid during the immediate phase following exposure to NO₂ ($n=16$).

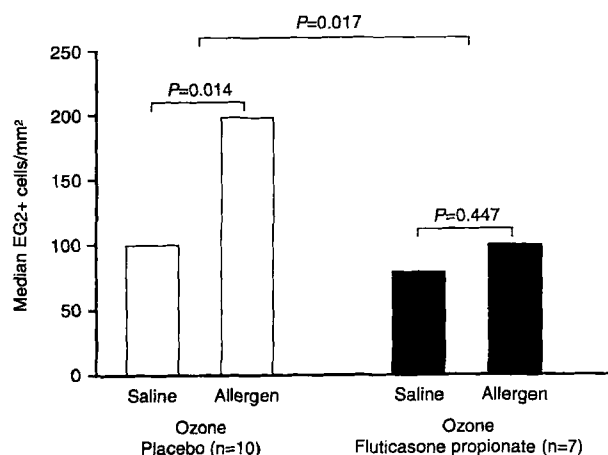


Fig. 4. Effect of placebo/fluticasone propionate (FP) on the number of EG2-staining cells in bronchial biopsies collected from mild asthmatic individuals, 24 h post-exposure for 1 h to 120 ppb ozone followed by allergen challenge.

Modification of allergens by pollutants

It has also been suggested that air pollutants may promote sensitization and subsequent development of allergic disease, by modulating the allergenicity of airborne allergens. Behrendt et al. (23) demonstrated that pollen collected from roadsides with heavy traffic, and other areas with high levels of air pollution, are covered with large numbers of airborne particulates ($\leq 5 \mu\text{m}$ in size). Furthermore, incubation of pollen for 2–5 h in aqueous solutions prepared from these particulates led to morphological alterations in pollen and extravasation of allergens with altered antigenicity. More recently, Knox et al. (24) investigated the interactions between respirable DEP (30–60 nm diameter) and purified rye-grass pollen allergens Lol p1 and Lol p5, demonstrating that Lol p1 binds strongly to DEP. The authors suggest that DEP may act as an environmental asthma trigger, particularly during episodes of air pollution in the grass pollen season. Similarly, Thomas et al. (25) studied the effect of exposure for 4 h to 50–200 ppb NO_2 on viability, germination and protein release from freshly collected birch, rye, alder and hazel pollens. Exposure to 100 ppb NO_2 adversely affected the ability of all species of pollen to germinate, and this effect was most pronounced for alder pollen (reduction of 55%). The viability of alder and hazel pollens was also reduced, and the release of protein from the various pollens was enhanced, particularly after exposure to 100 ppb NO_2 . These results suggest that gaseous pollutants can modulate the allergenicity of pollen, and therefore influence the incidence of allergic airways disease.

Cytokine release from nasal epithelial cells and the effect of corticosteroids

A series of studies was established to investigate the cytokine profiles generated by nasal epithelial cells (NEC) from (i) non-atopic non-rhinitics, (ii) atopic non-rhinitics, and (iii) atopic rhinitics in (NECi) and outside (NECo) the pollen season. Although the epithelial cells from each group of individuals were capable of constitutively releasing IL-1 β , IL-8, GM-CSF, tumour necrosis factor- α (TNF α), and regulated on activation normal T-cell expressed and secreted (RANTES), the cells from both atopic non-rhinitics and atopic rhinitics released significantly greater amounts of IL-8, GM-CSF and TNF α than the cells from non-atopic non-rhinitics (26). Furthermore, nasal cells from atopic rhinitics released significantly greater amounts of these cytokines compared with cells from atopic non-rhinitics, and this was significantly increased during the pollen season, as compared with outside the pollen season.

Investigations of the effect of exposure to ozone on the release of these cytokines from NEC cultured from non-atopic non-rhinitics and atopic rhinitics, biopsied during and after the pollen season, showed that exposure to 0–100 ppb ozone for 6 h significantly increased the release of IL-8, GM-CSF, TNF α and RANTES in all groups (27). This increase was greater in the atopic rhinitic group compared with the non-atopic non-rhinitic group. Furthermore, the cells from the atopic rhinitics biopsied during the pollen season released significantly more IL-8, GM-CSF, TNF α and RANTES than cells from the same patients biopsied outside the pollen season in response to ozone exposure.

We have recently investigated the effect of FP and beclomethasone dipropionate (BDP) on release of IL-8 and RANTES from both NECi and NECo following exposure to air and 50 ppb ozone (27–28). Cultures were exposed for 6 h in the absence or presence of varying concentrations of either FP or BDP (10^{-8}M , 10^{-6}M and 10^{-4}M). Incubation of NECi and NECo in the presence of 10^{-4}M FP or 10^{-4}M BDP significantly attenuated the release of IL-8 from these cells after exposure to air. However, while 10^{-4}M FP attenuated release of RANTES from NECi and NECo, BDP had no effect on release of RANTES from NECi (Fig. 5).

Biological relevance of mediators released by airway epithelial cells

We have investigated the effect of culture medium collected from confluent bronchial epithelial cell cultures incubated for 24 h (conditioned medium) on eosinophil and neutrophil chemotaxis, and

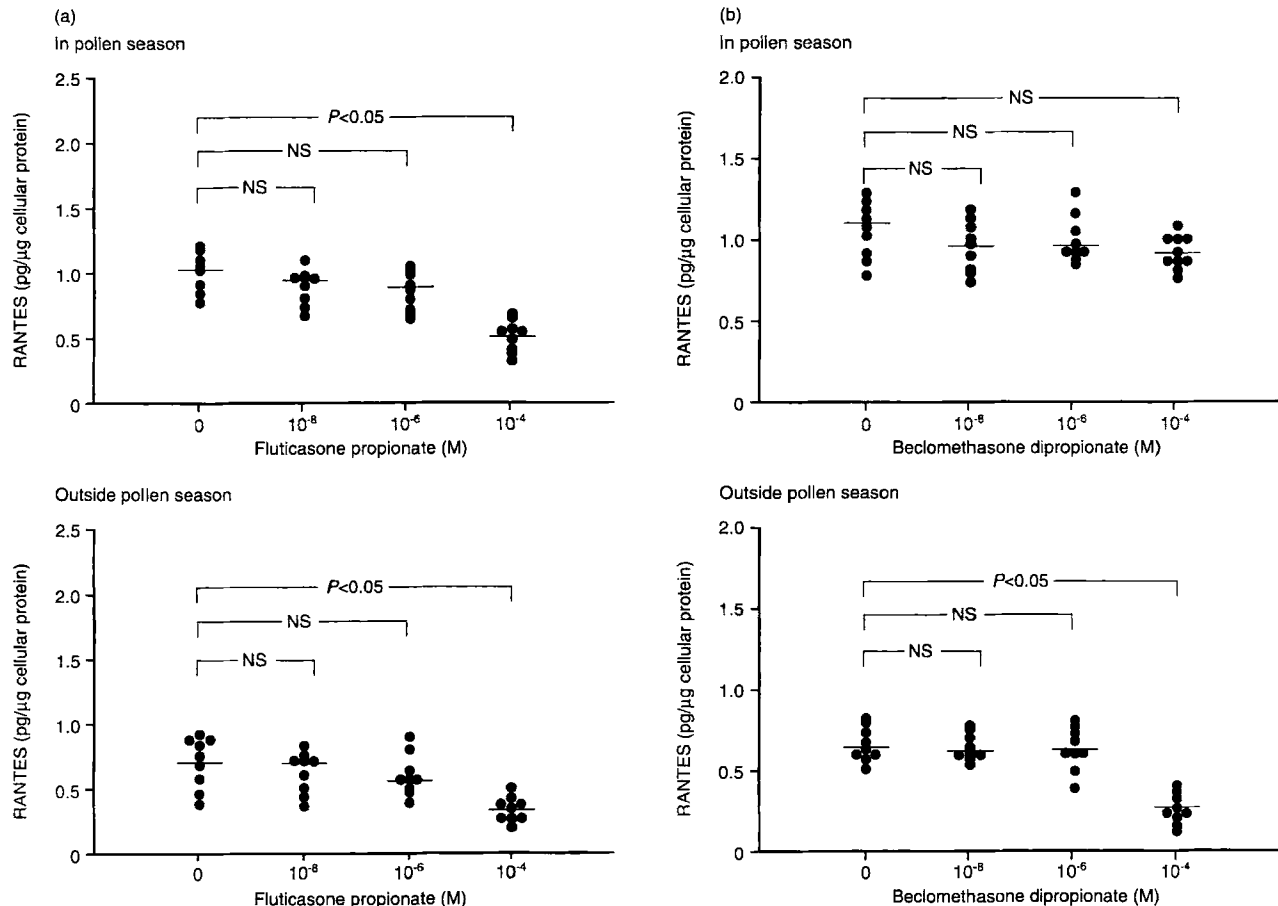


Fig. 5. Effect of fluticasone propionate (a) and beclomethasone dipropionate (b) on the release of RANTES from nasal epithelial cells cultured during and after the pollen season.

adhesion to human endothelial cells *in vitro*. These studies demonstrated that conditioned medium significantly increased the chemotaxis of both eosinophils and neutrophils, and that this effect was significantly attenuated by anti-GM-CSF, anti-IL-8 and anti-RANTES neutralizing monoclonal antibodies (29). Similarly, conditioned medium also significantly increased the percentage of eosinophils and neutrophils adhering to endothelial cells, an effect which was significantly attenuated by anti-human TNF α and anti-human IL-1 β neutralizing antibodies. While anti-GM-CSF and anti-IL-8 neutralizing monoclonal antibodies significantly attenuated the conditioned medium-induced chemotaxis of eosinophils and neutrophils, anti-RANTES neutralizing antibody significantly attenuated the chemotaxis of eosinophils alone. Treatment of endothelial cells with neutralizing antibodies against ICAM-1, E-selectin and VCAM-1 for 1 h prior to co-culture with eosinophils and neutrophils, also attenuated the adherence of eosinophils and neutrophils to the endothelial cells.

To investigate the biological relevance of air pol-

lutant-induced release of cytokines in airway inflammation, we studied the effect of conditioned medium from human bronchial epithelial cell cultures exposed to 50 ppb ozone for 6 h. Ozone was found to significantly increase eosinophil chemotaxis and eosinophil adherence to human endothelial cells, compared with conditioned medium from cells exposed to air (Fig. 6). These results suggest that pollution-induced inflammation of the airways may be a consequence of increased synthesis and/or release of epithelial cell-derived mediators which influence the activity of inflammatory cells (30).

Summary

Taken together, the results described above provide evidence to suggest that atmospheric pollutants, such as ozone or the combination of NO₂ and SO₂, increase the bronchial response of mild asthmatic subjects to inhaled allergen, and that this may persist for a period of 24–48 h after exposure. Acute exposure to ozone or NO₂ 'primes' the eosinophils for subsequent activation by allergen, and pretreat-

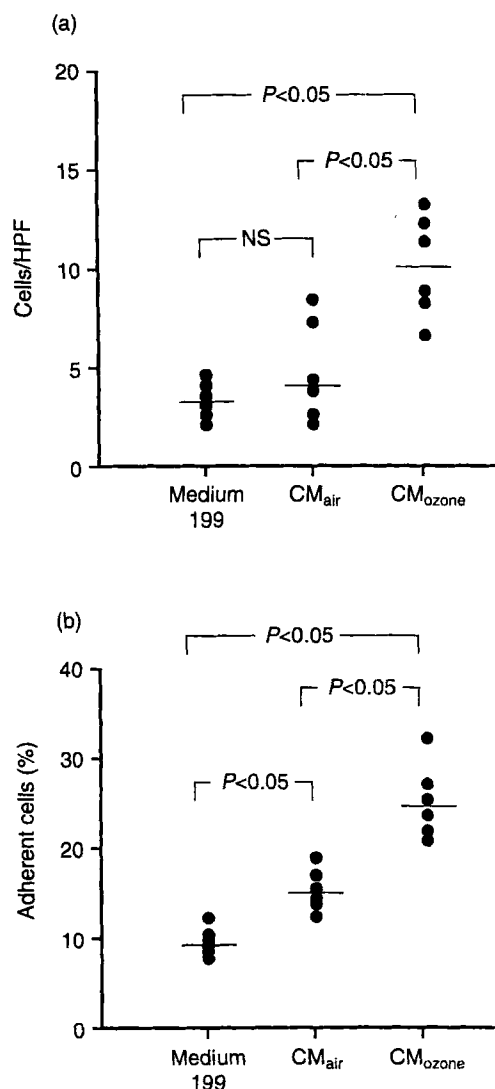


Fig. 6. Effect of conditioned medium from human bronchial epithelial cells exposed for 6 h to air (CM_{air}) or 50 ppb ozone (CM_{ozone}) on (a) eosinophil chemotaxis, and (b) eosinophil adhesion to human endothelial cells *in vitro*. Results are expressed as median and individual values ($n=6$ for each set of experiments).

ment with FP attenuates both the pollution-induced eosinophil priming and allergen-induced increase in the number of EG2-staining cells in the bronchial mucosa, suggesting that FP treatment may modulate airway inflammation by influencing the activity of eosinophils, and perhaps other inflammatory cell types.

At the cellular level, airway epithelial cells probably play an important role in the initiation and maintenance of airway inflammation, since these cells express and release pro-inflammatory mediators which influence the recruitment and activation of inflammatory cells, such as neutrophils and eosinophils, in the airways. Nasal epithelial cells from both atopic non-rhinitics and atopic rhin-

itics release significantly greater amounts of IL-8, GM-CSF and TNF α , than cells from non-atopic non-rhinitics. The cells of atopic rhinitics release significantly greater quantities of these cytokines during the pollen season, compared with outside of the pollen season, and exposure of these cells to ozone further enhances the release of these cytokines, an effect which can be attenuated by incubating the cells with FP or BDP.

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