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Regulation of E-cadherin expression by dexamethasone and tumour necrosis factor-α in nasal epithelium

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ABSTRACT: Asthma and rhinitis often coexist and share many clinical features. The extent of epithelial alteration in nasal inflammation is controversial. Cell-cell adhesion plays an important role in tissue morphogenesis and homeostasis and is mediated by the cadherin family. In human bronchial epithelial cells the authors have shown that tumour necrosis factor (TNF)-α induced a significant decrease of E-cadherin and β-catenin expression. The addition of dexamethasone inhibited this decrease. The aim of the present study was to investigate the effect of TNF-α and dexamethasone on the regulation of E-cadherin, γ-catenin and β-catenin in human nasal epithelial cells (HNEC).

A primary culture of HNEC, obtained from human nasal turbinates after surgery, was used. The quantitative and qualitative modulation of E-cadherin, γ-catenin and β-catenin expression was assessed by Western blot and immunofluorescence analysis. In order to assess the TNF-α-induced activation of HNEC, interleukin-8 and RANTES (regulated on activation, normal T-cell expressed and secreted) release was assessed by enzyme-linked immunosorbent assay.

The results showed that TNF-α induced, a decrease in γ-catenin and β-catenin expression, but had no effect on E-cadherin expression. Immunofluorescence showed that TNF-α induced cytoplasmic localisation of E-cadherin, γ-catenin and β-catenin. Dexamethasone inhibited the effect of TNF-α and induced a three-fold increase in E-cadherin expression.

These results suggest that the difference in nasal and bronchial epithelial cohesion may be due to the differential effect of tumour necrosis factor-α and dexamethasone on E-cadherin expression.

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Asthma and rhinitis are now considered to be two ends of the same disease [1]. Indeed, they often coexist [2, 3] and share many clinical features such as intermittent symptoms, fluctuations in severity, inflammation and obstruction. Specific allergens elicit early and late phase reactions [4–6] in lungs and the nose. Bronchial epithelial damage is a common feature of asthma and bronchial epithelial cells of asthmatic patients are less viable than those from control subjects [7]. The extent of epithelial abnormalities in chronic rhinitis is controversial. Some studies have reported that epithelial damage is frequent [8, 9], whilst others have indicated that the nasal epithelium remains almost completely intact [10–12]. Previous studies from the current authors group have shown that nasal epithelium was not altered in allergic asthmatics with perennial rhinitis and that the epithelium alteration is greater in bronchial than in nasal mucosa of asthmatic patients with perennial rhinitis [10].

Cell-cell adhesion plays an important role in tissue morphogenesis and homeostasis [13] and is commonly mediated by cadherins, a family of Ca^{2+}-dependent transmembrane adhesion receptors. The cadherin family is involved in control of the cellular architecture. Cadherins form homophilic interactions with similar receptors on neighbouring cells whereas their cytoplasmic domain interacts with the cytoskeleton [14]. These interactions are mediated *via* β-catenin or γ-catenin (plakoglobin), that interact with microfilaments through α-actinin and α-catenin [15].

Topical corticosteroids are regarded as the most effective first-line treatment in allergic rhinitis. They are effective in relieving all symptoms of rhinitis and can be administered for long periods without risk of serious side-effects [16, 17]. The most striking effect of glucocorticoids is to inhibit the expression of multiple inflammatory genes (cytokines, enzymes, receptors and adhesions molecules). Moreover, glucocorticoids play a fundamental role in the function and maintenance of cell-cell contact in mammary epithelia by inducing tight junction formation [18].

The authors have shown previously, in human bronchial epithelial cells, that the pro-inflammatory mediator tumour necrosis factor (TNF)-α involved in the asthmatic process induced a significant decrease in

E-cadherin and β-catenin expression. The decrease in these adhesion molecules could be responsible for structural damage of the bronchial epithelium and may be involved in the loss of cohesion of this epithelium. This process could potentially be reversed by steroids, as shown by the addition of dexamethasone which inhibits the decrease of E-cadherin and β-catenin expression in cells [19]. KOBAYASHI and co-workers [20, 21] have shown that the expression of E-cadherin in cultured nasal epithelial cells was affected by transepithelial migration of inflammatory cells, especially eosinophils. They suggested that transepithelial migration of inflammatory cells can directly induce a decrease in epithelial E-cadherin expression.

In the present study, a human nasal epithelial cell (HNEC) culture obtained from human nasal turbinates, was developed. First, on this epithelial cell culture, Western blot and immunofluorescence analysis was used to determine whether TNF-α and dexamethasone could modulate the E-cadherin, β- and γ-catenin expression and regulation. Finally, the release of the pro-inflammatory cytokines interleukin (IL)-8 and RANTES (regulated on activation, normal T-cell expressed and secreted), known to be regulated by TNF-α and dexamethasone [22, 23], were assessed, in order to check the inflammatory status of the epithelial cell culture.

Materials and methods

Cell culture

HNEC were obtained from turbinates after surgery with informed consent. The nasal turbinates were taken from patients without any macroscopic evidence of inflammation and weaned from steroid treatment for at least 2 months before surgery. After excision, the nasal turbinates were washed and incubated overnight at 4°C with 0.38 $mg \cdot mL^{-1}$ hyaluronidase, 0.75 $mg \cdot mL^{-1}$ collagenase, 1 $mg \cdot mL^{-1}$ protease and 0.3 $mg \cdot mL^{-1}$ deoxyribonuclease in Roswell Park Memorial Institute media (RPMI) 1640 (Gibco, Grand Island, NY, USA) and then filtered through a 100-μm mesh nylon cell strainer. Pieces of epithelium retained on the strainer were recovered with small airway cell growth medium (SAGM; Bio-Whittaker, Walkersville, MD, USA), and transferred into 12-well plates (Nunc Inc, Naperville, IL, USA).

Stimulation of human nasal epithelial cells

A TNF-α dose/response curve was performed on HNEC (0.1–100 $ng \cdot mL^{-1}$) for 48 h (R&D System, Abington, UK). In order to test the stimulation specificity, antibody against TNF-α (R&D System, Minneapolis, MN, USA), at 100 $ng \cdot mL^{-1}$ concentration, was added to the stimulated medium. Dexamethasone (1×10^{-7}M) was added at the same time to the stimulated medium.

Measurement of RANTES and interleukin-8 release from human nasal epithelial cells

IL-8 and RANTES were measured in cell-free supernatants of stimulated cells using commercial enzyme-linked immunosorbent assay (ELISA) kits (Quantikine, R&D System, Abington, UK). ELISAs were performed according to the manufacturer's instructions.

Western blot analysis

After stimulation, whole cells were washed with cold phosphate-buffered saline (PBS) and lysed in 10 mM Tris-HCl, pH 7.4, 50 mM NaCl, 5 mM ethylenediamine tetraacetic acid (EDTA), 1% Nonidet P-40, and 10 $\mu g \cdot mL^{-1}$ phenylmethylsulphonyl fluoride. Cell extracts were transferred into microcentrifuge tubes, mixed, and left on ice for 10 min. After one freeze/thaw cycle, they were centrifuged at 12,000×*g* for 5 min at 4°C. Supernatant samples were taken for protein estimation and the remainder adjusted with 4× Laemmli dissociation buffer. Ten μg of total protein was subjected to sodium dodecyl sulphate-polyacrylamide gel electrophoresis on 4–12% gradient gels (Novex, San Diego, CA, USA) and then blotted onto nitrocellulose membranes. Blots were blocked with PBS containing 3% bovine serum albumin, 0.1% Tween 20, and probed with anti-E-cadherin (1:2,500), β-catenin (1:500) and γ-catenin (1:2,000) monoclonal primary antibodies. After serial washes with PBS containing 0.1% Tween 20, membranes were incubated with peroxidase-conjugated goat anti-mouse antibody (Sigma, St. Louis, MO, USA) as secondary antibody at 1:3,000 dilution. The monoclonal antibody anti-β-actin 1:3,000 (Sigma) was used as a control. Revelation was performed using an enhanced chemiluminescence system (NEN, Boston, MA, USA) followed by autoradiography. Autoradiographical films were analysed by densitometric scanning using a monochrome CCD camera RS-170 (COHU) coupled to the National Institutes of Health (NIH) image analysis program.

Immunofluorescence

After specific stimulation, HNEC were obtained by cytocentrifugation. Cells were fixed in 4% paraformaldehyde and permeabilised for 4 min at 0°C using 0.5% (volume/volume) Triton X-100 in PBS. After blocking in PBS containing donkey serum, cells were incubated for 1 h at room temperature with the anti-E-cadherin, β-catenin and γ-catenin monoclonal antibodies (Transduction Laboratories Lexington, KY, USA) diluted 1:100 in the same buffer. In control experiments, the primary antibody was replace by an irrelevant antibody, mouse immunoglobulin (Ig)G1 (Dako, Golstrup, Denmark). Labelling was performed using a cy™ 3-conjugated AffinePure donkey anti-mouse IgG (Jackson ImmunoResearch Laboratories, Inc, West Grove, PA, USA). After extensive washing, cells were mounted and observed using a Nikon

Optiphot-2 fluorescence microscope (Nikon, Tokyo, Japan).

Statistical methods

Quantitative results are expressed as mean±SEM of three experiments performed in duplicate. All results were compared to basal values, except effect of anti-TNF-α and dexamethasone, which were compared to TNF-α 100 ng·mL^{-1}. The effect of cytokine and dexamethasone were analysed using a paired t-test and considered significant when p-values were <0.05.

Results

Quantitative regulation of cytokine expression in human nasal epithelial cells

In the supernatant of stimulated cells, IL-8 and RANTES levels were measured using ELISA. TNF-α increased the release of both IL-8 and RANTES in a dose-dependent manner with a maximal release at 100 ng·mL^{-1} concentration for both IL-8 (p=0.0001) and RANTES (p=0.03). Dexamethasone reversed this effect with 49% inhibition for IL-8 release (p=0.0001) and 72% for RANTES (p=0.03). Anti-TNF-α antibody induced a return to basal values for both cytokines at 100 ng·mL^{-1} concentration, p=0.0001 for IL-8 and p=0.03 for RANTES, compared to TNF-α alone (fig. 1).

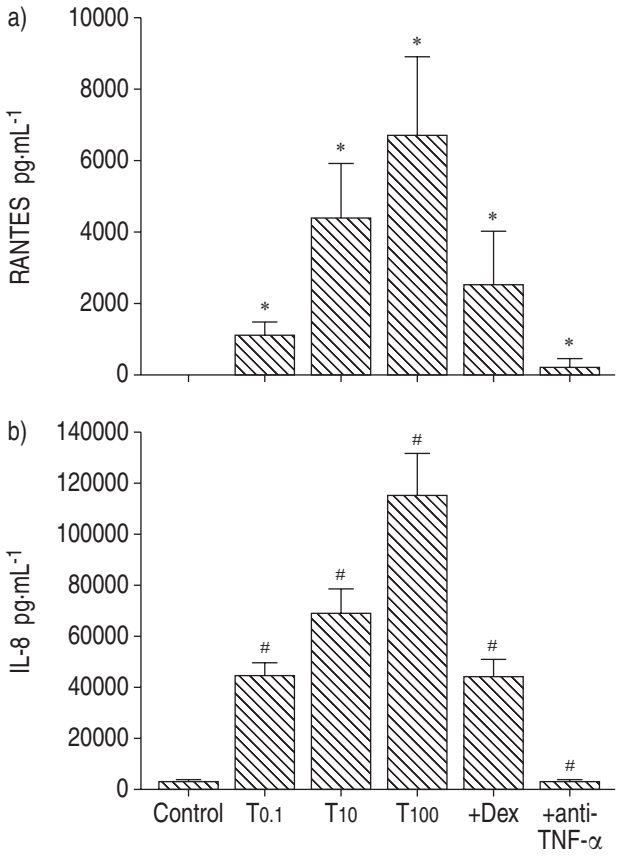

Fig. 1. – Effect of tumour necrosis factor (TNF)-α on a) RANTES (regulated on activation, normal T-cell expressed and secreted) and b) interleukin (IL)-8 release in human nasal epithelial cells after 48 h of stimulation with TNF-α±dexamethasone and anti-TNF-α antibody. The reported values are mean±SEM of three independent experiments, expressed as percentage of unstimulated control cells. $T_{0.1}$: TNF-α 0.1 ng·mL^{-1}; T_{10}: TNF-α 10 ng·mL^{-1}; T_{100}: TNF-α 100 ng·mL^{-1}; +Dex: TNF-α 100 ng·mL^{-1}+1×10^{-7} M dexamethasone; +anti-TNF-α: TNF-α 100 ng·mL^{-1}+anti-TNF-α antibody 100 ng·mL^{-1}. *: p<0.05; #: p<0.0005.

Quantitative regulation of E-cadherin, β-catenin and γ-catenin expression in human nasal epithelial cells

Western blot analysis showed that HNEC exhibited basal expression of E-cadherin, β and γ-catenin. TNF-α stimulation for 48 h significantly decreased the expression of β-catenin and γ-catenin but had no effect on E-cadherin expression (fig. 2). The maximal decrease in β-catenin expression was obtained at 10 ng·mL^{-1} concentration (71% of inhibition, p=0.008). For γ-catenin, the maximal decrease was obtained at 100 ng·mL^{-1} concentration (56% of inhibition, p=0.01).

When anti-TNF-α (100 ng·mL^{-1}) was added to the stimulated medium, the level of β-catenin and γ-catenin returned to the levels noted with unstimulated cells (fig. 3). When dexamethasone (1×10^{-7}M) was added to stimulated medium (100 ng·mL^{-1} of TNF-α), β-catenin (p=0.0002) and γ-catenin (p=0.04) expression returned to basal levels, while E-cadherin expression was increased three-fold relative to the basal level (p=0.03) and TNF-α alone at 100 ng·mL^{-1} concentration (p=0.005) (fig. 1a).

Qualitative regulation of E-cadherin, β-catenin and γ-catenin expression in human nasal epithelial cells

E-cadherin, β- and γ-catenin expression was assessed by immunofluorescence after 48 h of stimulation by TNF-α (100 ng·mL^{-1})±dexamethasone (1×10^{-7}M). In unstimulated cells, E-cadherin, β-catenin and γ-catenin expression was mainly restricted to the membrane of lateral cell walls with minimal cytoplasmic expression (fig. 4). In stimulated cells, immunoreactivity remained membranous for E-cadherin, β-catenin and γ-catenin, with an increase in cytoplasmic expression (fig. 4). When dexamethasone was added, E-cadherin, β-catenin and γ-catenin immunoreactivity became membranous again and the cytoplasmic expression was reduced (fig. 4).

Discussion

In this study, Western blot analysis showed a basal level of β-catenin, γ-catenin and E-cadherin expression in HNEC. TNF-α significantly decreased β-catenin and γ-catenin expression, but had no effect on E-cadherin expression. This decrease was specific since an antibody against TNF-α was able to reverse it. Moreover, the addition of dexamethasone reversed the effect of TNF-α on β-catenin and γ-catenin, and

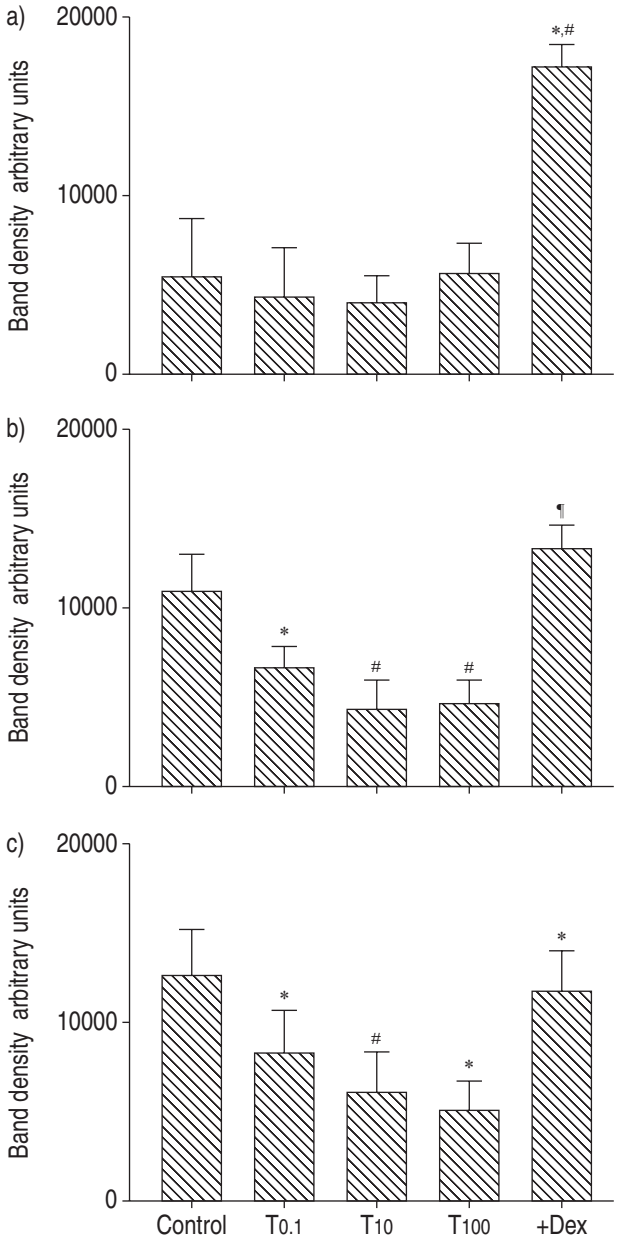

Fig. 2. – Effect of tumour necrosis factor (TNF)-α stimulation on a) E-cadherin, b) β-catenin and c) γ-catenin expression as determined by Western-blots on human nasal epithelial cells. The reported values are mean±SEM of three independent experiments. $T_{0.1}$: TNF-α 0.1 ng·mL^{-1}; T_{10}: TNF-α 10 ng·mL^{-1}; T_{100}: TNF-α 100 ng·mL^{-1}; +Dex: TNF-α 100 ng·mL^{-1}+1×10^{-7} M dexamethasone. *: $p<0.05$; #: $p<0.0005$; ¶: $p<0.0005$.

induced a three-fold increase in E-cadherin expression. Using immunofluorescence analysis, it was demonstrated that these adhesion molecules were mainly membranous. The addition of TNF-α delocalised adhesion molecules within the cytoplasm, which was reversed by the addition of dexamethasone. Moreover, it was observed that TNF-α induced IL-8 and RANTES release by HNEC and that addition of an anti-TNF-α antibody or dexamethasone inhibited this effect.

The respiratory epithelium depends on various

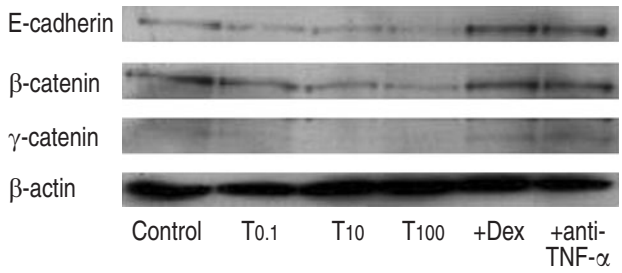

Fig. 3. – Representative Western blots of E-cadherin, β-catenin and γ-catenin expression in human nasal epithelial cells (HNEC) after 48 h stimulation with tumour necrosis factor (TNF)-α ±dexamethasone and anti-TNF-α antibody. Total proteins were isolated and Western blot analysis performed with anti-E-cadherin (120 Kd), β-catenin (92 Kd), γ-catenin (82 Kd) and a β-actin housekeeping gene (45 Kd). Lane 1: HNEC control expression; Lanes 2, 3, 4: HNEC 48 h after TNF-α stimulation; Lane 5: HNEC after TNF-α+dexamethasone stimulation. The β-actin signal was used as loading control. $T_{0.1}$: TNF-α 0.1 ng·mL^{-1}; T_{10}: TNF-α 10 ng·mL^{-1}; T_{100}: TNF-α 100 ng·mL^{-1}; +Dex: TNF-α 100 ng·mL^{-1}+1×10^{-7} M dexamethasone; +anti-TNF-α: TNF-α 100 ng·mL^{-1}+anti-TNF-α 100 ng·mL^{-1}.

adhesion mechanisms to maintain its epithelial structure [24, 25]. On the lateral border of epithelial cells, tight junctions, adherent junctions and desmosomes are amongst the structures which characterise the intercellular junctional complex of epithelium [26]. These cellular contacts are mediated by several kinds of adhesion molecules, including cadherins. E-cadherin is one of the best-characterised transmembrane glycoproteins expressed on many types of epithelial cell surfaces, including nasal epithelium [26–28]. E-cadherin has homophilic interactions with similar receptors on neighbouring cells, whereas their cytoplasmic domain interacts with the cytoskeleton [14]. Cell adhesion mechanisms most likely undergo pathological changes causing epithelial damage during inflammatory processes.

Airway epithelial cells are able to respond to such frequent environmental stresses by secreting pro-inflammatory mediators such as IL-8 and RANTES after TNF-α stimulation [22, 23, 29]. In the current study, TNF-α stimulation effectively led to a strong increase in IL-8 and RANTES release by HNEC. Without any stimulation, HNEC released a very low level of IL-8 and RANTES, confirming that the cells were initially in a quiescent state. In parallel with this induced inflammation, a decreased level and different cellular localisation of β-catenin and γ-catenin were observed. No effect of TNF-α on E-cadherin was observed, in contrast to the current authors' previous findings in human bronchial epithelial cells [19]. Moreover, the present findings differ from those in coeliac disease [30], and in Langherans cell-like dendritic cells [31]. In these two models and in the bronchial epithelial model, the decrease in E-cadherin expression may be associated with the loss of E-cadherin-mediated adhesion and furthermore may be related to the loss of epithelial cohesion.

β-catenin binds to the cytoplasmic domain of the E-cadherin structure and protects E-cadherin from proteolitic degradation [32]. The present results suggested that the cytoplasmic domain of E-cadherin

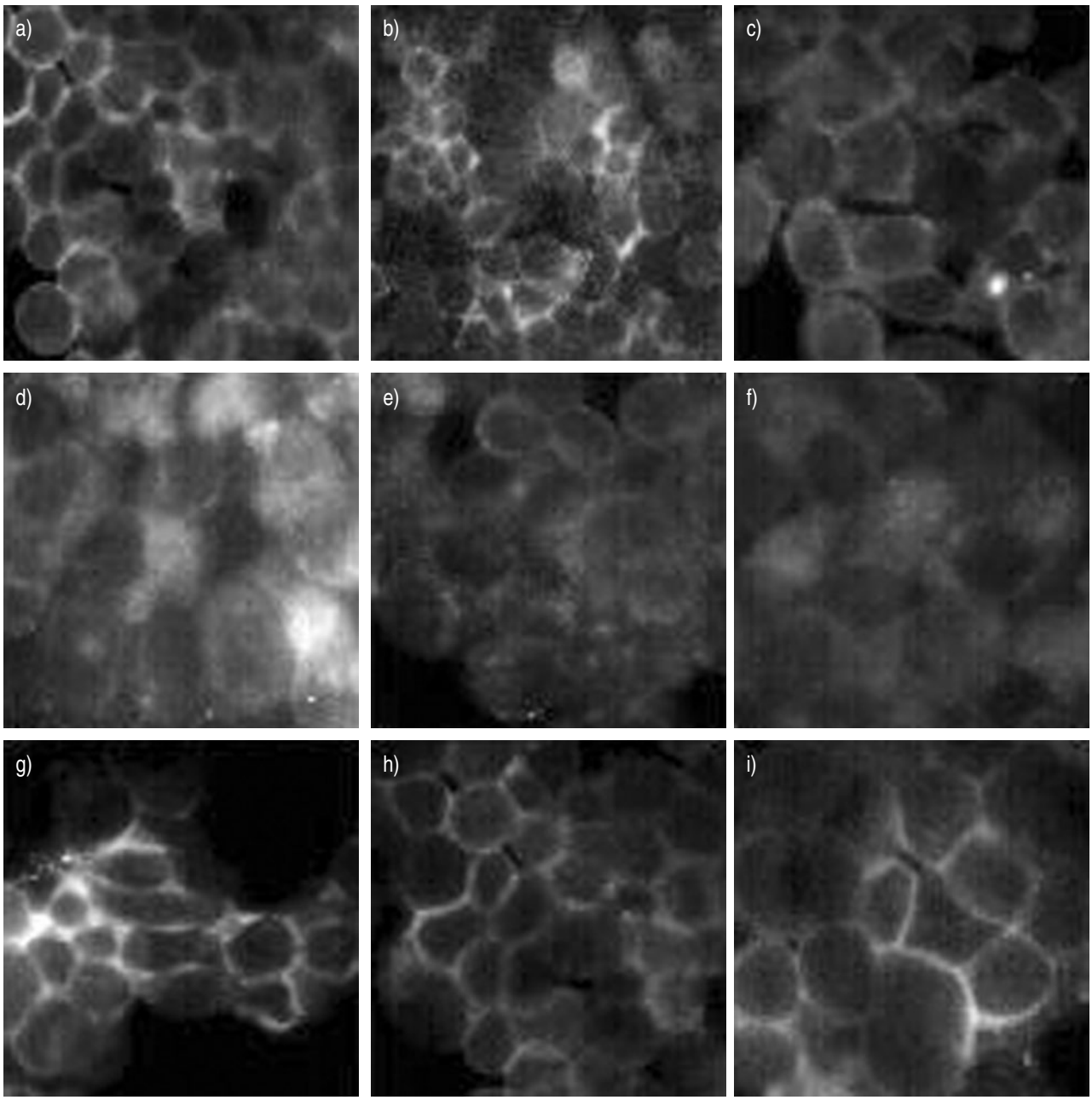

Fig. 4. – Subcellular distribution of E-cadherin (a, d and g), β-catenin (b, e and h) and γ-catenin (c, f and i) in human nasal epithelial cells (HNEC). a–c) Control. d–f) After 48 h of stimulation with tumour necrosis factor (TNF-α). g–h) After 48 h of stimulation with TNF-α+dexamethasone.

might be protected even in the absence of β-catenin binding. The inefficiency of TNF-α for inhibiting E-cadherin expression in nasal epithelium may be related to the lack of marked epithelial damage in nasal allergy, even in the presence of inflammation.

For many years, glucocorticoids have been shown to alleviate the symptoms of allergic diseases such as asthma and rhinitis when administrated orally or applied topically [33, 34].

In this study, it has been confirmed that dexamethasone effectively inhibits the TNF-α effect on IL-8 and RANTES release. Dexamethasone was also able to restore the level of β-catenin and γ-catenin expression and their membranous localisation. Moreover, dexamethasone induced a three-fold increase in E-cadherin expression and the immunoreactivity of E-cadherin again became membranous. In this study, it was shown that dexamethasone was able to strengthen epithelial cell-cell adhesion by induction of E-cadherin expression and restoration of catenin expression. The present results are in line with the suggestion of ZETTL *et al.* [18] that glucocorticoids could play a fundamental role in the function and maintenance of cell-cell contact in mammary epithelia by inducing tight junction formation. Moreover, FOTY *et al.* [35] showed that dexamethasone markedly

decreases the invasiveness of HT-1080 human fibrosarcoma cells. They hypothesised that this invasion-suppression by dexamethasone may therefore be at least partially due to an increase in cadherin-mediated cohesion.

The results presented here, obtained in nasal epithelial cells, highlight a major discrepancy in the regulation of E-cadherin by pro-inflammatory cytokines between nasal and bronchial epithelial cells. The different regulation of E-cadherin may explain the possible difference in epithelial alteration. The authors could thus conclude that E-cadherin may participate in enhancement of nasal epithelium cell-cell adhesion integrity despite persistent inflammation in chronic rhinitis.

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