β-Adrenergic agonist modulation of monocyte adhesion to airway epithelial cells in vitro

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Romberger, Debra J., Peggy Heires, Stephen I. Rennard, and Todd A. Wyatt. β-Adrenergic agonist modulation of monocyte adhesion to airway epithelial cells in vitro. Am. J. Physiol. Lung Cell. Mol. Physiol. 278: L139–L147, 2000.—β-Adrenergic agonists are commonly used in the treatment of obstructive airway diseases and are known to modulate cAMP-dependent processes of airway epithelial cells. However, little is known regarding the ability of cAMP-dependent mechanisms to influence cell-cell interactions within the airway. Thus we investigated the role of the β-adrenergic agonist isoproterenol in modulating the ability of human bronchial epithelial cells to support the adhesion of THP-1 cells, a monocyte/macrophage cell line, in vitro. We demonstrated that pretreatment of human bronchial epithelial cells (HBECs) with 10 µM isoproterenol or 100 µM salbutamol augments the adhesion of fluorescently labeled THP-1 cells to HBEC monolayers by ~40–60%. The increase in THP-1 cell adhesion occurred with 10 min of isoproterenol pretreatment of HBECs and gradually declined but persisted with up to 24 h of isoproterenol exposure. Exposure of THP-1 cells to isoproterenol or salbutamol before the adhesion assays did not result in an increase in adhesion to HBECs, suggesting that the isoproterenol modulation was primarily via changes in epithelial cells. A specific protein kinase A inhibitor, KT-5720, inhibited subsequent isoproterenol augmentation of THP-1 cell adhesion, further supporting the role of cAMP-dependent mechanisms in modulating THP-1 cell adhesion to HBECs.

MONOCYTES AND MACROPHAGES are important in immune and inflammatory processes that occur in the airways in response to infectious agents as well as noxious stimuli such as cigarette smoke. An increase in the number of cells of monocyte/macrophage phenotype is a feature of bronchial biopsies of smokers with airflow limitation (24). Mechanisms regulating interactions between monocytes and airway epithelial cells are not clearly defined, but airway epithelial cells are known to release chemotactic factors for monocytes and to support the adhesion of monocytes (19, 20, 29). Human airway epithelial cells have been shown to express several mediators capable of influencing monocyte/macrophage activity, including RANTES (regulated on activation, normal T cell expressed and presumably secreted), monocyte chemotactic protein-1, and macrophage inflammatory protein-1α (23). Furthermore, Robbins et al. (29) observed that stimulating bovine bronchial epithelial cells with bacterial lipopolysaccharide or cigarette smoke extract augmented the adherence of peripheral blood monocytes to epithelial cell monolayers in vitro. Thus it is likely that monocyte/macrophage interactions with epithelial cells of the airway are modulated by a variety of mediators.

In patients, the airway epithelium is frequently exposed to inhaled β-adrenergic agonists, which are capable of modulating epithelial cell cAMP-dependent pathways. Several airway epithelial cell functions are known to be influenced by cAMP, including ciliary beat frequency, cystic fibrosis transmembrane regulation, endotoxin-induced cytotoxicity, and nitric oxide release (19, 35, 37–39). The major cellular receptor for cAMP is cAMP-dependent protein kinase A (PKA). Wyatt et al. (43) recently demonstrated PKA, as well as protein kinase G (cGMP-dependent protein kinase), in bronchial epithelial cells and correlated cyclic nucleotide kinase activation with epithelial cell function, specifically ciliary beat frequency in vitro. However, little is known regarding PKA modulation of cell-cell interactions of the airway, such as epithelial cell-monocyte interactions. cAMP-dependent processes have been shown to influence other types of cell-cell interactions, although the influence of cAMP is dependent on the cell types involved (3, 17, 25).

In this work, we investigated the ability of two β-adrenergic agonists, isoproterenol and salbutamol, to influence adhesion of the human monocyte/macrophage cell line THP-1 to human bronchial epithelial cells (HBECs) in vitro. We observed that HBEC exposure to β-adrenergic agonists augments subsequent THP-1 cell adhesion to epithelial cells in a concentration- and time-dependent fashion. This augmentation of adhesion is inhibited by HBEC exposure to a specific PKA inhibitor, KT-5720, suggesting that monocyte adhesion to airway epithelial cells is, at least in part, a cAMP-dependent process.

MATERIALS AND METHODS

Cells. THP-1 cells were obtained from American Type Culture Collection (Manassas, VA) and maintained in RPMI 1640 (Life Technologies, Grand Island, NY) with 2-mercaptoethanol (2 × 10⁻³ M) and 10% fetal bovine serum (Biofluids, Rockville, MD).
HBECS were obtained from one of three sources. We utilized bronchoscopy brushings (~6–8 brushes in 3–4 locations) of patients undergoing bronchoscopy for clinical reasons after we obtained informed consent and with the approval of the Institutional Review Board of the University of Nebraska Medical Center and the Human Studies Subcommittee of the Research and Development Committee of the Omaha Veterans Affairs Medical Center. Cells were processed using the technique of Kelsen et al. (15). Cells were passaged no more than seven times before use in experiments. By use of a cytokeratin stain, cells were found to be 95–98% epithelial. We also used HBECS obtained using an explant technique as previously described (1) from an autopsy specimen of a person without lung disease. Additionally, normal HBECS (NHBE 4263, Clonetics, San Diego, CA) were examined. HBECS from all sources were maintained in culture in serum-free medium at 37°C in 5% CO2-95% air. LHC-9-RPMI 1640 medium (1:1)

was used to support the growth of these cells as previously described (1, 2). LHC-9 medium contains LHC basal medium (Biofluids), 0.5 µM phosphoethanolamine or ethanolamine (Sigma, St. Louis, MO), 0.11 mM calcium (Fisher, Springfield, NJ), 50 U/ml penicillin and streptomycin (Life Technologies), 2 µg/ml amphotericin B (Fungizone, Life Technologies), trace elements, 5 µg/ml bovine insulin (Sigma), 5 ng/ml epidermal growth factor (Sigma), 10 µg/ml bovine transferrin (Sigma), 10 mM 3,3',5-triiodothyronine (Biofluids), bovine pituitary extract (50 µg protein/ml; Pel Freeze, Rogers, AR), 0.2 µM hydrocortisone (Biofluids), 0.5 µg/ml epinephrine (Sigma), and 0.1 µg/ml retinoic acid (Sigma). Epinephrine was removed from the medium immediately before HBECS were plated for use in the adhesion assays. During exposure to β-adrenergic agonists or the PKA inhibitor, HBECS were placed in LHC-D, a growth factor-deficient medium, which contains LHC basal medium, 0.5 µM phosphoethanolamine or ethanolamine, 0.11 mM calcium, penicillin and streptomycin, amphotericin B, and trace elements.

Cell adhesion assay. HBECS were grown to confluence in 96-well tissue culture plates, black with clear bottoms (Costar, Cambridge, MA). Medium was changed to growth-factor-deficient medium (1:1 LHC-D-RPMI 1640) with agents to be tested. HBECS monolayers were rinsed before initiation of the binding assay. THP-1 cells (0.6 × 10^6 cells/ml) that had been labeled with the fluorescent dye 2',7'-bis(2-carboxyethyl)-5(6)-carboxyfluorescein (Calbiochem, La Jolla, CA; 2 µg/ml for 15 min) were allowed to bind to the HBECS monolayers for 20 min. After incubation, wells were filled with RPMI 1640 medium, the plate was gently inverted, and nonadherent cells were sedimented. All wells were then gently washed with PBS. Attached cells were solubilized with 1% Triton X-100 in H2O. The cell lysates were evaluated by an automatic microfluorometer (Fluorolite 1000, Dynex Technologies, Chantilly, VA) at 490/530-nm excitation/emission wavelengths. In each experiment, HBECS without exposure to THP-1 cells were examined to evaluate autofluorescence of HBECS, and this value was subtracted from the fluorescence of THP-1 cells adherent to HBECS. A linear relationship existed between THP-1 cell number and amount of fluorescence measured when the number of THP-1 cells was 0.3 × 10^6 to 1.5 × 10^6 (data not shown).

To express the adhesion as percentage of THP-1 cells attached as opposed to mean fluorescence (see Fig. 5), we used the following formula: %adhesion = [fluorescence of experimental condition – background fluorescence (autofluorescence of HBECS)]/[fluorescence of THP-1 cells (same number used in the experimental conditions) in 1% Triton X-100 – background fluorescence] × 100.

Determination of cyclic nucleotide-dependent kinase activity. PKA activity was determined in diethylaminoethyl fractions as well as in crude whole cell fractions of bronchial epithelial cells. The assay is a modification of procedures previously described by Jiang et al. (12) using 130 µM PKA substrate heptapeptide (LRRASLG), 10 µM CAMP, 0.2 mM 3-isobutyl-1-methylxanthine, 20 mM magnesium acetate, and 0.2 mM [γ-32P]ATP in a 40 mM Tris–HCl buffer (pH 7.5). Negative controls consisted of similar assay samples without the appropriate substrate peptide or cyclic nucleotide. A positive control of 0.4 ng/ml purified catalytic subunit from type I bovine PKA (Promega) was included as a sample. Kinase activity was expressed in relationship to total cellular protein assayed and calculated in picomoles per minute per milligram. The absolute kinase activity of HBECS from different sources and at different passages is somewhat variable, as has been demonstrated with other HBECS components (22a, 42). Therefore, we have expressed the PKA data as magnitude activation over baseline (unstimulated HBECS).

Reagents. Isoproterenol, salbutamol, and dibutyryl cAMP (DBcAMP) were obtained from Sigma, and KT-5720 was obtained from Calbiochem.

Statistical evaluation. Values are means ± SE. Experimental values were compared using a one-way ANOVA for repeated measures.

RESULTS

THP-1 adherence to HBECS monolayers is augmented by HBECS exposure to β-adrenergic agonists and DBcAMP. To examine whether exposure of airway epithelial cells to β-adrenergic agonists influences subsequent monocyte binding to epithelial cells, HBECS were initially pretreated with various concentrations of isoproterenol (1 µM–1 mM) or salbutamol (10–100 µM) for 24 h before assessment of THP-1 cell adhesion to confluent HBECS monolayers. Media containing β-adrenergic agonists were removed, and HBECS were rinsed before fluorescently labeled THP-1 cells were allowed to adhere to the HBECS for 20 min. As shown in Fig. 1, pretreatment with isoproterenol (10 µM) or salbutamol (100 µM) for 24 h increased the subsequent binding of THP-1 cells to HBECS by ~40% (percent increase in adhesion compared with THP-1 adherence to unstimulated control HBECS = 100%: 137 ± 6.5% for 10 µM isoproterenol, 117 ± 6.5% for 100 µM isoproterenol, 127 ± 4.6% for 10 µM salbutamol, and 137 ± 2.5% for 100 µM salbutamol, means ± SE, n = 6, P < 0.005, by ANOVA, for 10 µM isoproterenol and 100 µM salbutamol). In repeat experiments with various HBECS, 10 µM isoproterenol and 100 µM salbutamol consistently demonstrated a maximal effect in terms of augmenting THP-1 cell adhesion to HBECS.

To ascertain that the β-agonist stimulation of THP-1 adhesion was due primarily to an effect on the epithelial cells as opposed to the THP-1 cells, THP-1 cells (before labeling) were placed in medium containing 10 µM isoproterenol or 100 µM salbutamol for 30 min before adhesion to unstimulated HBECS and compared with HBECS pretreated with isoproterenol or salbutamol for 1 h before the adhesion assay. There was again an ~35–40% increase in THP-1 binding when HBECS werepretreated with β-agonists (Fig. 2). However, there was no change in binding when only the THP-1
β-AGONISTS MODULATE MONOCYTE-EPITHELIAL CELL ADHESION

Fig. 1. THP-1 cell adhesion to cultured human bronchial epithelial cells (HBECs) pretreated with various concentrations of isoproterenol (Iso) or salbutamol (Sal). HBECs were plated on type I collagen in serum-free medium without epinephrine on 96-well plates. Confluent monolayers of HBECs were established by the following day. HBECs were then pretreated with 10 or 100 µM isoproterenol or salbutamol for 24 h in serum-free, growth factor-deficient medium. Medium was removed, and HBEC monolayers were rinsed. Labeled THP-1 cells were allowed to adhere to HBECs for 20 min. Nonadherent cells were removed, monolayers were rinsed with PBS, and attached cells were solubilized in 1% Triton X-100. Fluorescence was evaluated by automatic microfluorimeter at 490/530-nm excitation/emission wavelength. Results are from a single experiment, representative of triplicate experiments; n = 6 for each condition. Vertical axis, percent change in adhesion, as measured by fluorescence (mean ± SE), compared with unstimulated control HBECs (THP-1 adhesion to unstimulated control HBECs = 100%); horizontal axis, experimental conditions. *P < 0.005 by ANOVA.

HBEC PKA activity was enhanced by isoproterenol exposure (Fig. 3B). Pretreatment with 10 µM isoproterenol resulted in a threefold increase in HBEC PKA activity at 10, 30, and 60 min (P ≤ 0.001 for each time point compared with unstimulated HBECs, by Student’s t-test).

β-Adrenergic agonists such as isoproterenol and salbutamol are known to influence a variety of intracellular signals including cAMP. To examine the role of cAMP, HBECs were pretreated with DBcAMP (10 pM–10 µM) for 10 min before THP-1 cells were allowed to adhere to HBEC monolayers. As shown in Fig. 4A, there was an approximately threefold increase in THP-1 adhesion to HBECs when HBECs were pretreated with 100 nM DBcAMP for 10 min (percent increase in adhesion compared with unstimulated control HBECs = 100%: 138 ± 3.5, 288 ± 10.5, 295 ± 10, 332 ± 7.6, and 279 ± 5.7% for 10 pM, 100 pM, 1 nM, 100 nM, and 10 µM DBcAMP pretreatment, respectively, n = 6, P < 0.0001, by ANOVA, for 100 pM, 1 nM, 100 nM, and 10 µM DBcAMP). Thus direct augmentation of HBEC cAMP activity with DBcAMP pretreatment was associated with a significant augmentation of THP-1 cell adhesion to bronchial epithelial cells. The fluorescence of THP-1 cells adherent to unstimulated HBEC monolayers was found to represent ~10–30% THP-1 cell adhesion depending on the various HBECs utilized. An example of actual percentage of THP-1 cells adherent to HBECs exposed to DBcAMP is shown in Fig. 5.
with a twofold increase in percent adherent THP-1 cells to HBECs pretreated with 100 nM DBcAMP for 10 min (10.7 ± 0.85% THP-1 cell adhesion for unstimulated control HBECs and 14.5 ± 0.76 and 21.7 ± 2.0% THP-1 cell adhesion for HBECs pretreated with 10 pM and 100 nM DBcAMP, respectively, P ≤ 0.002, by ANOVA).

Assay of the PKA activity of HBECs pretreated with DBcAMP demonstrated that the PKA activity increased with increasing concentrations of DBcAMP (Fig. 4B). Small increases in PKA activation (<2-fold) were observed between 10 pM and 1 nM, and maximal PKA activity levels were observed at 100 nM to 10 µM pretreatment.
Inhibition of isoproterenol-stimulated THP-1 adhesion to HBECs by PKA inhibitor KT-5720. To evaluate the role of bronchial epithelial cell cAMP-dependent PKA activity in modulating the ability of HBECs to support THP-1 adhesion, HBECs were pretreated with a selective and potent inhibitor of PKA, KT-5720, before adhesion studies were performed. Confluent monolayers of HBECs were pretreated with 10 µM KT-5720 for 2 h. HBECs were then exposed to 10 µM isoproterenol for 1 h. Media were removed, HBECs were rinsed, and adhesion assay was performed with fluorescently labeled THP-1 cells. As seen in Fig. 6A, HBECs treated with 10 µM isoproterenol alone (no KT-5720 pretreatment) supported THP-1 adhesion that was 170 ± 6% compared with that in unstimulated HBECs (THP-1 adhesion to unstimulated HBECs = 100%). Pretreatment of HBECs with 10 µM KT-5720 for 2 h before isoproterenol stimulation resulted in a reduction of THP-1 adhesion to 53 ± 9% of unstimulated cells. THP-1 adhesion to HBECs pretreated with 10 µM KT-5720 and then exposed to 10 µM isoproterenol was 71 ± 4% compared with adhesion to unstimulated HBECs (P < 0.0001 for both comparisons by ANOVA). Thus HBEC exposure to the PKA inhibitor KT-5720 reduced THP-1 cell adhesion to isoproterenol-stimulated bronchial epithelial cells. In addition, measurement of PKA activity of HBECs confirmed that exposure to 10 µM KT-5720 inhibits intracellular HBEC PKA activity (Fig. 6B).

HBEC isoproterenol exposure influences soluble mediators of subsequent THP-1 adhesion to bronchial epithelial cell monolayers. Exposure of HBECs to isoproterenol may influence a variety of epithelial cell processes, such as mediator release or cell surface changes, that could result in augmented THP-1 cell adhesion to bronchial epithelial cells. To assess whether isoproterenol-stimulated mediator release was involved, we used conditioned media from HBECs exposed to 10 µM isoproterenol for 10 min or 1 h to stimulate additional HBEC monolayers or THP-1 cells for 20 min before assessment of THP-1 adhesion to epithelial cells. As shown in Table 1, HBEC exposure to conditioned media from isoproterenol-stimulated HBECs resulted in sta-
Table 1. Effect of conditioned media from HBECs exposed to isoproterenol on subsequent THP-1 cell adhesion to HBECs

<table>
<thead>
<tr>
<th>HBEC Pretreatment</th>
<th>THP-1 Cell Pretreatment</th>
<th>Fluorescence, nm</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>593 ± 49</td>
</tr>
<tr>
<td>Iso CM (10 min)</td>
<td>None</td>
<td>495 ± 56</td>
</tr>
<tr>
<td>Iso CM (1 h)</td>
<td>None</td>
<td>903 ± 71*</td>
</tr>
<tr>
<td>None</td>
<td>Iso CM (10 min)</td>
<td>633 ± 89</td>
</tr>
<tr>
<td>None</td>
<td>Iso CM (1 h)</td>
<td>696 ± 59</td>
</tr>
<tr>
<td>None</td>
<td>10 µM Iso (10 min)</td>
<td>414 ± 29</td>
</tr>
<tr>
<td>None</td>
<td>10 µM Iso (1 h)</td>
<td>560 ± 58</td>
</tr>
</tbody>
</table>

Values are means ± SE, representative of duplicate experiments; n = 6 for each condition. Human bronchial epithelial cells (HBECs) were cultured to confluency in serum-free medium without epinephrine and then exposed to 10 µM isoproterenol (Iso) for 10 min or 1 h. Medium from these cultures (10 min) was harvested and used in adhesion assays to pretreat additional HBEC confluent monolayers for 20 min before adhesion assay with labeled THP-1 cells. In addition, in some wells of adhesion assay, THP-1 cells, and not HBECs, were pretreated with culture medium before adhesion assay. THP-1 cells were also pretreated with only 10 µM Iso for 10 min or 1 h before adhesion assay. *P < 0.003, by ANOVA.

Statistically significant THP-1 cell adhesion only when conditioned medium from HBECs exposed to isoproterenol for 1 h was utilized. Exposure of THP-1 cells only to conditioned medium from isoproterenol-stimulated HBECs did not augment THP-1 cell adhesion. Similar to our results in Fig. 2, exposure of THP-1 cells only to 10 µM isoproterenol for 10 min or 1 h did not influence THP-1 adhesion. This suggests that isoproterenol stimulation of HBECs for 1 h may influence soluble mediator(s) release capable of influencing adhesion of THP-1 cells, whereas the shorter isoproterenol exposure of 10 min did not cause enough change in the conditioned media and possible mediator release to influence THP-1 binding. However, 10 min of isoproterenol exposure directly to HBECs is sufficient to augment THP-1 adhesion (Fig. 3).

DISCUSSION

β-Adrenergic agonists are widely used in the treatment of obstructive lung diseases because of their ability to rapidly enhance bronchodilation. Airway epithelial cells are among the first cells of the airway to encounter inhaled β-adrenergic agonists, and it is increasingly recognized that a wide variety of epithelial cell functions may be modulated by these agents (8, 18, 30, 35, 37–39, 44). In this report, we have demonstrated that exposure to β-adrenergic agonists, specifically isoproterenol and salbutamol, augments the capacity of HBECs in vitro to support the adhesion of THP-1 cells, a monocyte/macrophage cell line. Furthermore, inhibition of HBEC PKA activity with KT-5720 blocked the isoproterenol augmentation of THP-1 cell adhesion, supporting the role of cAMP-dependent protein kinase activity in modulating monocyte/macrophage cell adhesion to airway epithelial cells.

Human airway epithelial cells in vitro and in vivo express β-adrenergic receptors, which modulate intracellular cAMP (16, 36). The regulation of airway epithelial cell β-adrenergic receptors has been described (26). Utilizing a transformed human airway epithelial cell line, Kelsen et al. (14) recently observed that maintained exposure (24 h) to isoproterenol, forskolin, and DBCAMP results in desensitization of the cAMP response to isoproterenol, whereas only isoproterenol causes significant β-adrenergic receptor downregulation. In addition, HBECs obtained via a variety of techniques have been shown to synthesize cAMP in vitro, and this synthesis is modulated by inflammatory mediators such as interleukin-1β (4, 13, 27). Thus regulation of airway epithelial cell cAMP is complex, and cAMP-dependent cellular processes are modulated by a variety of endogenous as well as exogenous substances.

Using bronchial epithelial cells obtained from different sources, we observed an increase in THP-1 cell adhesion to isoproterenol-stimulated HBECs. Specifically, we utilized HBECs that we prepared from an autopsy specimen as well as cells obtained from brushings at bronchoscopies, as previously published (1, 30). In addition, we utilized commercially available normal primary HBECs. HBECs from all sources were passaged to obtain the number of cells required to perform multiple experiments. Despite different patient sources, techniques in obtaining cells, and number of passages, we routinely observed a 40–60% augmentation of THP-1 cell adhesion to isoproterenol-exposed HBECs.

Cells of the monocyte/macrophage phenotype are associated with airway inflammation and disease. Recently, O'Shaughnessy et al. (24) examined bronchial biopsies of normal nonsmoking subjects as well as patients with chronic bronchitis with and without airflow limitation and noted an increase in CD68+ (monocyte/macrophage phenotype)-staining cells in smokers with airflow limitation. Similarly, increases in the number of macrophages have also been observed in the bronchioles of smokers with airflow limitation (6). Saetta et al. (31) reported an increase in the number of macrophages in the bronchial glands of airway tissue from smokers with chronic bronchitis but not in the epithelium and submucosa. These observations support the importance of macrophages within the airway wall in participating in inflammatory processes that appear to lead to airflow remodeling and clinically significant airflow obstruction (10, 11). Macrophages within the airway epithelium may be derived directly from blood monocytes migrating into airway tissue or from monocytes migrating into alveolar tissue, which differentiate into alveolar macrophages and then migrate from the alveolar space to the airways. We utilized the monocyte THP-1 cell line in our studies because it provided a uniform population of monocyte/macrophage cells in which we could examine the ability to adhere to bronchial epithelial cells. THP-1 cells and peripheral blood monocytes have demonstrated several similar properties (22, 34).

We have demonstrated that epithelial cell PKA modulates the adhesion of THP-1 cells to HBECs in that stimulation of HBECs with isoproterenol and DBCAMP is associated with an augmentation of adhesion, and
while some analogs, such as benzoyl-cAMP, are only partially (not fully) specific for type II PKA.

HBECs are known to release and express a variety of molecules that may influence monocyte/macrophage adhesion to epithelial cells as soluble mediators or as receptors/ligands. However, relatively little is known regarding how PKA modulates airway epithelial cell expression of such molecules. For example, bronchial epithelial cells in vitro have been shown to release monocyte chemotactic activity, which is, at least in part, due to leukotriene B$_4$ (19, 20). More recently, human airway epithelial cells have been shown to express RANTES, monocyte chemotactic protein-1, and macrophage inflammatory protein-1α (23). Localized release of such chemokines may influence monocyte recruitment and subsequent adhesion to epithelial cells. In addition, airway epithelial cells express molecules such as intercellular adhesion molecule-1, which participates in epithelial cell adhesion to mononuclear cells (21, 40, 41). Depending on the type of cell involved, cAMP-dependent pathways have been shown to enhance and inhibit intercellular adhesion molecule-1 expression (3, 17, 25). We have not yet defined specific mediators or receptors/ligands that may be responsible for the PKA-mediated changes in THP-1 cell adhesion to HBECs.

In summary, we have demonstrated that monocyte adhesion to human airway epithelial cells in vitro is augmented via a cAMP-dependent pathway. This suggests that agents that target PKA within the airway epithelium may have potential utility in modulating monocyte/macrophage inflammatory responses, which may contribute to airway diseases such as chronic bronchitis.

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REFERENCES


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