Asthma

PATHOPHYSIOLOGY

Asthmatic Bronchial Epithelial Cells Have a Deficient Innate Immune Response to Infection With Rhinovirus


PURPOSE OF THE STUDY. To determine if bronchial epithelial cells (BECs) from asthma patients have abnormal innate responses to rhinovirus infection.

STUDY POPULATION. BECs from 14 subjects with moderate persistent asthma treated with inhaled corticosteroids (ICSs), 10 subjects with mild intermittent asthma who were never treated with ICSs, and 10 healthy controls.

METHODS. BECs were cultured from bronchial brushings obtained by bronchoscopy. BECs were studied prerhinovirus and postrhinovirus infection treatment of BECs with exogenous IFN-β. Responses were both significantly greater in infected asthmatic subjects’ BECs were inhibited by postinfection treatment with IFN-β but were most inhibited by pretreatment with IFN-β. Responses were similar between ICS-treated and ICS-naive asthmatic subjects.

RESULTS. Rhinovirus-16 infection induced ICAM-1 (intercellular adhesion molecule-1), IL-6 (interleukin-6), and RANTES (regulated upon activation, normal T cells expressed and secreted) expression equally in BECs from asthmatic and healthy subjects. Viral RNA expression, lactate dehydrogenase activity, and virus titers all significantly increased in asthmatic versus healthy subjects’ BECs. The percentage of viable cells was 63% in asthmatic versus 80% in healthy subjects’ BECs, whereas apoptosis increased 1.4-fold in asthmatic versus healthy subjects’ BECs (P = .02). Caspase activity increased significantly more in the control versus asthmatic subjects’ BECs postinfection. Induction of apoptosis in the healthy controls was inhibited by treatment of BECs with ZVD-fmk, and in a similar experiment, viral titers increased in the control BECs posttreatment and closely approximated the titers seen in infected asthmatic subjects’ BECs. Induction of IFN-β messenger RNA and IFN-β production were both significantly greater in the control versus the asthmatic subjects’ BECs. The effect of IFN-β on induction of apoptosis was evaluated: although apoptosis increased with posttreatment, there was significantly greater (P = .02) induction of apoptosis with pretreatment. Likewise, viral titers in the supernatant of infected asthmatic subjects’ BECs were inhibited by postinfection treatment with IFN-β but were most inhibited by pretreatment with IFN-β. Responses were similar between ICS-treated and ICS-naive asthmatic subjects.

CONCLUSIONS. Examination of early innate immune responses revealed profound impairment of virus-induced IFN-β messenger RNA expression and IFN-β production from BECs of subjects with asthma. A novel use for type 1 interferons in the treatment or prevention of virus-induced asthma exacerbations is proposed.

REVIEWER COMMENTS. How a rhinovirus infection induces an asthma exacerbation remains largely speculative. Differences between the innate immune response to rhinovirus infection of asthmatic and healthy subjects are demonstrated by using this novel approach. Very interesting is the lack of difference seen in ICS-naive and ICS-treated asthmatic subjects, which may explain why controversy remains regarding the role of ICSs in prevention of viral-induced asthma exacerbations. These data suggest that impairment in IFN-β production may be important in the induction of immune responses resulting in an asthma exacerbation. The authors’ proposal that type 1 interferon use may treat or prevent viral-induced asthma exacerbations is intriguing.

IL-19 Induced Th2 Cytokines and Was Upregulated in Asthma Patients


PURPOSE OF THE STUDY. Interleukin-10 (IL-10) has been shown to inhibit allergen-induced airway hyperresponsiveness and inflammation. This study evaluates whether IL-19, a member of the IL-10 family, is associated with asthma.

STUDY POPULATION. The authors investigated IL-19 levels in 100 asthmatic patients, aged 3 to 12 years, as well as 50 healthy adults and 50 age-matched children. A dust mite–induced mouse model of asthma was also used to study the association of IL-19 with asthma.

METHODS. Cytokine levels were quantified by enzyme-linked immunosorbent assay. IL-19 levels were measured in all study subjects, but among asthmatic patients, the levels of IL-4 and IL-13 were analyzed in the 27 patients with the highest and 25 patients with the lowest IL-19 levels. By using a dust mite–sensitized murine...
Inflammatory Basis of Exercise-Induced Bronchoconstriction


PURPOSE OF THE STUDY. To establish whether epithelial cell and mast cell activation with release of inflammatory mediators occurs during exercise-induced bronchoconstriction (EIB) and how histamine and cysteinyl leukotriene antagonists alter the airway events occurring during EIB.

STUDY POPULATION. There were 25 patients aged 14 to 55 whose asthma was being treated only with a short-acting β2 agonist as needed and who experienced a fall in FEV1 of ≥15% after an exercise challenge.

METHODS. Induced sputum was obtained at baseline and 30 minutes after exercise challenge. In a randomized, double-blind crossover study, the cysteinyl leukotriene antagonist montelukast and antihistamine loratadine, or 2 matched placebos, were administered for 2 doses before exercise challenge.

RESULTS. The percentage of columnar epithelial cells in induced sputum at baseline was associated with the severity of EIB. After exercise challenge, histamine, tryptase, and cysteinyl leukotrienes significantly increased in the airways, and there was an increase in columnar epithelial cells in the sputum. The concentration of columnar epithelial cells was associated with the levels of histamine and cysteinyl leukotrienes. Treatment with montelukast and loratadine inhibited the release of cysteinyl leukotrienes and histamine but did not inhibit the release of columnar epithelial cells.

CONCLUSION. Epithelial cells, mast cell mediators, and eicosanoids are released into the airways during EIB, supporting an inflammatory basis for EIB.

REVIEWER COMMENTS. “Exercise-induced asthma” (EIA) is not a disease unto itself. As the authors point out, “[EIB] is a highly prevalent condition present in approximately half of patients with asthma.” Most such patients, if questioned carefully, will admit to symptoms under circumstances other than exercise, such as with upper respiratory infections or irritant or allergen exposures. It is better to consider EIB a very common phenomenon among patients with asthma. There are 2 competing hypotheses of the mechanism of EIB: (1) loss of heat leads to vascular engorgement as the airways rewarm after exercise, initiating bronchoconstriction; and (2) loss of water leads to a change in airway osmolarity that initiates epithelial cell and mast cell activation, leading to the release of inflammatory mediators in the airways that cause bronchoconstriction. These 2 theories are not necessarily mutually exclusive, and the former theory may apply more to the minority of patients who complain of symptoms only after they finish exercising (ie, when they stop breathing through an open mouth). If the number of desquamated epithelial cells before exercise is taken as an indication of the level of ongoing airway inflammation, this study would suggest that patients with worse baseline inflammation would have worse EIB. Also of note is that the combination of the cysteinyl leukotriene antagonist and antihistamine did not inhibit the desquamation. For patients in whom a short-acting β2 agonist does not prevent EIB or who have any abnormality on baseline spirometry, a truly and broadly antiinflammatory medication (ie, inhaled...
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