Clinical studies of asthma phenotypes focusing on the role of the leukotrienes

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Abstract

Inflammation in the airways in connection to asthma is a complex phenomenon and the mechanisms underlying the associated clinical symptoms involve the interaction of many different kinds of cells and mediators, giving rise to different phenotypes. The aim of the present thesis was to investigate the molecular and cellular mechanisms that results in two of these phenotypes, i.e., aspirin-intolerant asthma and allergic asthma. The main focus was on leukotrienes and other eicosanoids, metabolites of arachidonic acid, and the major experimental approach employed was bronchial challenge.

Thirty-three subjects known to be suffering from aspirin-intolerant asthma were challenged with celecoxib a selective inhibitor of COX-2. Both escalating doses from 5-100 mg (administered in a blinded, placebo-controlled study) and an open label challenge with 200 + 200 mg celecoxib were tolerated well by these individuals. This finding indicates that the intolerance reaction leading to bronchoconstriction in patients with aspirin-intolerant asthma is due to inhibition of COX-1 and, furthermore, provides a scientific basis for administration of selective inhibitors of COX-2 to alleviate prostaglandin-mediated pain and inflammation in these patients.

With the ultimate objective of finding a marker that can be used to identify patients with leukotriene-associated asthma, the capacity to produce leukotrienes and responsiveness to inhaled leukotrienes was determined in 20 subjects with intermittent-to-mild asthma and 10 healthy control individuals. Neither group exhibited a correlation between the formation of LTB_4 by their whole blood in response to *ex vivo* stimulation or urinary levels of LTE_4 and airway responsiveness to LTD_4. In further attempts to predict which asthmatic patients will respond well to antileukotriene treatment, investigations on the capacity for leukotriene synthesis and responsiveness to these agents and expression of their specific receptor in the lungs are presently being performed.

When 8 individuals with allergic asthma were challenged repeatedly with low doses of allergen, the level of nitric oxide in the air they exhaled and their responsiveness to histamine rose significantly. At the same time, these subjects did not report any symptoms of asthma, required rescue by bronchodilator medication or display any change in the calibre of their airways. Accordingly monitoring of exhaled nitric oxide on a daily basis might allow for early detection of exacerbation in subjects with allergic asthma.

Thirteen patients with allergic asthma were subjected to bronchial challenges with methacholine and LTD_4 prior to and after administration of 500 µg fluticasone twice daily for two weeks, and their levels of exhaled nitric oxide and urinary LTE_4 was determined. Inhalation of glucocorticoid attenuated the responsiveness to methacholine and reduced the level of exhaled nitric oxide, but neither the responsiveness to LTD_4 nor urinary excretion of LTE_4 was affected. Thus, neither the release nor the actions of leukotrienes appear to be sensitive to inhaled glucocorticoids, strengthening the rationale for using a combination of glucocorticosteroids and antileukotrienes to treat allergic asthma.

In summary, we have shown the following here: 1) There is now a rationale basis for using selective inhibitors of COX-2 to alleviate prostaglandin mediated-pain and inflammation in individuals with aspirin-intolerant asthma. 2) The bronchial responsiveness of subjects with asthma cannot be predicted on the basis of the ability of their whole blood to produce LTB_4 in response to stimulation *ex vivo* or their urinary levels of LTE_4. 3) Regular monitoring of exhaled nitric oxide might allow early detection of exacerbation in subjects with allergic asthma. 4) There is a mechanistic rationale for combination treatment of allergic asthma with glucocorticosteroids and antileukotrienes.

Keywords: asthma, aspirin intolerance, leukotrienes, leukotriene D_4 responsiveness, methacholine responsiveness, exhaled nitric oxide