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In vivo PAF-induced airway eosinophil accumulation reduces bronchial responsiveness to inhaled histamine

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Abstract

Chronic eosinophilic bronchitis and bronchial hyperresponsiveness have been considered to be the fundamental features of bronchial asthma. However, the role of airway eosinophils in bronchial responsiveness in vivo has not been fully discussed. The aim of this study was to investigate the direct effect of airway eosinophil accumulation on bronchial responsiveness in vivo. Guinea pigs were transnasally treated with platelet activating factor (PAF) or vehicle twice a week for a total of 3 weeks. Anesthetized guinea pigs were surgically cannulated and artificially ventilated 48 h after the last administration of PAF or vehicle. Ten minutes after the installation of artificial ventilation, ascending doses of histamine were inhaled. In a subsequent study, selective inhibitors of diamine oxidase and histamine *N*-methyltransferase were intravenously administered before the histamine inhalation in the PAF-treated animals. Next study was conducted 20 min after treatment with indomethacin in this study line. Finally, ascending doses of methacholine were inhaled in our animal model. Proportion

Abbreviations: ANOVA, analysis of variance; BAL, bronchoalveolar lavage; cLTs, cysteinyl leukotrienes; DAO, diamine oxidase; ECP, eosinophil cationic protein; HMT, histamine *N*-methyltransferase; MBP, major basic protein; PAF, platelet activation factor; Pao, pressure of the airway opening

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of eosinophils and the number of nuclear segmentation in bronchoalveolar lavage fluid significantly increased in guinea pigs treated with PAF compared with vehicle and this finding was confirmed histologically. Nevertheless, bronchial responsiveness to inhaled histamine, but not methacholine, was significantly decreased by the PAF treatment. This bronchoprotective effect induced by PAF remained following aminoguanidine and histamine *N*-methyltransferase administration, but abolished by treatment of indomethacin. These results suggest that in vivo airway eosinophils may reduce non-specific bronchial responsiveness through production of inhibitory or bronchoprotective prostanoids, but not through histaminase production.

Keywords: PAF; Airway eosinophil accumulation; Bronchial responsiveness

1. Introduction

Bronchial asthma is a chronic airway inflammatory disease characterized by a reversible airflow limitation, bronchial hyperresponsiveness, and increases in eosinophils in sputum, bronchoalveolar lavage (BAL) and biopsied mucosal samples [1]. As eosinophils are known to produce and release many proinflammatory cytokines and mediators, they have been considered to play a critical role in the pathophysiology of asthma [2,3]. Several investigators [4–6] have reported the positive correlation between the bronchial hyperresponsiveness and the percentage of eosinophils in BAL fluid in asthmatics.

However, recent clinical studies on human allergic asthma have shown dissociation between airway inflammation, airway hyperresponsiveness, and the late asthmatic reaction [7,8]. On the other hand, previous investigators indicated that factors derived from eosinophils limit or possibly terminate allergic response via metabolizing the chemical mediators released by allergic reaction: for example, histaminase against histamine [9,10]. Vrugt et al. [11] also indicated that unstable severe corticosteroid-dependent asthmatics had decreased number of eosinophils in the airway mucosa compared with mild asthmatics. Moreover, a recent study demonstrated that airway hyperresponsiveness could not be observed in the late asthmatic reaction, despite there was an airway eosinophilic inflammation [12]. Furthermore, another recent clinical study using humanized anti-IL-5 antibody treatment in mild asthmatics failed to show any improvement in the early or late asthmatic reaction following an allergen challenge, while reduction of eosinophil levels was found in both peripheral blood and induced sputum [13]. Therefore, the exact role of eosinophils in the airways in vivo remains unknown.

We [14] previously studied the association between airway eosinophil accumulation induced by repeated transnasal administration of polymyxin-B and bronchial responsiveness to inhaled histamine in guinea-pigs. Though we found that airway eosinophilia coexisted with actual reduction in bronchial responsiveness, there were several problems to be resolved: polymyxin-B induces airway eosinophil accumulation in guinea pigs but not in other species, and it is unknown whether eosinophils accumulated by polymyxin-B is activated or not. This study was conducted to give light upon the role of eosinophils in the airways in vivo using platelet-activating factor (PAF). We studied influence of PAF-induced airway eosinophil accumulation and activation on bronchial responsiveness to inhaled histamine. In addition, we investigated the role of two different types of enzymes degrading