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Effect of stress on eotaxin and expression of adhesion molecules in a murine model of allergic airway inflammation

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Abstract

Recently we have shown that sound stress enhances allergic airway inflammation in a combined murine model. In the current study we investigated mediating factors and early kinetics of stress exacerbated allergic airway inflammation. Stress significantly increased allergen induced airway inflammation as identified by leukocyte numbers in BAL fluids. Eotaxin levels from stressed mice were significantly higher 24 h after stress. No differences were found for vascular or cellular adhesion molecule expression or cytokine levels. Our data indicate that the effect of stress on allergic airway inflammation might be mediated by the chemoattractant eotaxin, while Th2 cytokines and expression of adhesion molecules seem not to be differently regulated in stressed and non-stressed mice.

Keywords: Stress; Asthma model; Airway inflammation; Eotaxin; Adhesion molecules; Cytokine expression

1. Introduction

Stress has long been hypothesized to be associated with the exacerbation of asthma symptoms (Sandberg et al., 2004, 2000; Smyth et al., 1999; Wright et al., 2002). However, mechanisms linking stress to asthma are not well defined. One possible link might be the effect of stress on inflammatory processes. Liu et al. (2002) demonstrated that in asthmatic students stress increased the number of eosinophilic sputum cells after allergen challenge. In humans, acute stressors can enhance or reduce chemotaxis of peripheral blood mononuclear cells (PBMC) ex vivo, depending on the level of underlying chronic stress (Redwine et al., 2004, 2003). In mice, acute stress increases leukocyte infiltration in vivo and enhances chemokine- and cytokine-directed infiltration (Viswanathan and Dhabhar, 2005). Various investigators have demonstrated that the expression of adhesion molecules on peripheral leukocytes changes after stress exposure in humans and animals. Psychological stress decreases L-selectin and increases Lymphocyte Function-Associated Antigen-1 (LFA-1) and Mac-1 expression on human lymphocytes (Goebel and Mills, 2000; Mills and Dimsdale, 1996; Redwine et al., 2003). In mice, the expression of LFA-1 and very late antigen 4 (VLA-4) on $CD4^+$ cells was altered after a single period of restraint stress. However, the impact of stress on mechanisms of eosinophilic cell trafficking has not been investigated so far.

The accumulation of eosinophilic leukocytes in the airways is a main feature of allergic asthma, which in asthma patients correlates well with asthma severity (Bradley et al., 1991). A variety of molecules and different pathways contribute to eosinophil trafficking to the sites of allergic inflammation. Chemoattractants as well as adhesion molecules regulate eosinophilic inflammation. As shown in a study with eotaxin-deficient mice, eotaxin plays an important role in the early

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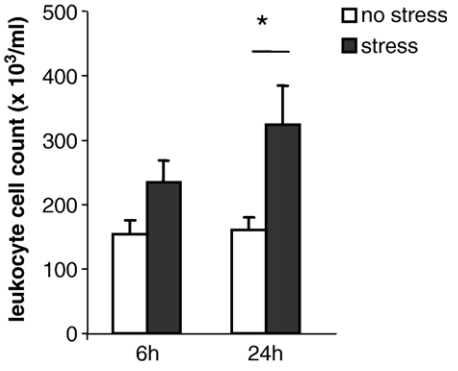

Fig. 1. Total leukocyte numbers in BAL fluid. BAL was performed 6 and 24 h after last allergen aerosol challenge. 24 h after the last challenge stressed mice showed significantly higher total cell numbers than non-stressed mice. ★$p<0.05$.

Fig. 3. Eotaxin concentration in BAL fluid. BAL was performed 6 and 24 h after the last allergen aerosol challenge and eotaxin protein concentration was determined by ELISA. 24 h after the last challenge stressed mice showed significantly higher eotaxin protein levels than non-stressed mice. ★$p<0.05$.

recruitment of eosinophils after allergen challenge (Rothenberg et al., 1997). Eotaxin is a chemokine binding to the CCR3 receptor, which is present on eosinophils, basophils, mast cells and Th2 cells (Daugherty et al., 1996; Gerber et al., 1997; Kitaura et al., 1996; Ponath et al., 1996; Romagnani et al., 1999; Sallusto et al., 1997; Uguccioni et al., 1997), and was characterized for the first time in the guinea pig in 1994 by Jose et al. (1994).

After being attracted to the target organ inflammatory cells enter the tissue with the assistance of adhesion molecules. Eosinophil cell surface adhesion receptors mediating rolling of eosinophils are P-selectin glycoprotein ligand-1 (PSGL-1) (Broide et al., 1998a; Symon et al., 1996), the α4β1 integrin and L-selectin (Sriramarao et al., 1994). Vascular P-selectin (Broide et al., 1998a; Symon et al., 1996) and vascular cell adhesion molecule 1(VCAM-1) (Sriramarao et al., 2000) mediate eosinophil rolling on endothelial cell surface while firm adhesion is mediated by VCAM-1 and intercellular adhesion molecule 1 (ICAM-1) (Broide et al., 1998a,b).

Recently, we demonstrated in a murine model of allergic airway inflammation that stress increases the number of eosinophils found in the broncho-alveolar lavage (BAL) fluid and enhances airway reactivity (Joachim et al., 2003, 2004). Given the important role of immune cell recruitment and cell migration in airway inflammation on one hand and the supposed role of stress in mediating leukocyte trafficking on the other hand, in the present study we aimed to investigate the mediating factors and early kinetics of eosinophilic allergic airway inflammation in response to stress.

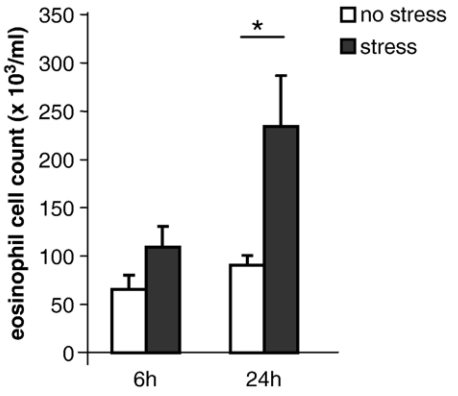

Fig. 2. Eosinophil numbers in BAL fluid. BAL was performed 6 and 24 h after the last allergen aerosol challenge. 24 h after the last challenge stressed mice showed significantly higher eosinophil cell numbers than non-stressed mice. ★$p<0.05$.

2. Methods

2.1. Animals

BALB/c mice were purchased from the Federal Institute for Health Protection of Consumers and Veterinary Medicine (BgVV, Berlin, Germany) and maintained on a 12-h light/dark cycle. 6 mice were housed per cage. Animal care and experimental procedures were followed according to institutional guidelines and conformed to requirement of the state authority for animal research conduct (LaGetSi, Berlin).

2.2. Protocol of sensitization and airway challenge

BALB/c mice were sensitized by intraperitoneal (i.p.) injection of 10 μg chicken ovalbumin (OVA, Sigma Chemie, Deisenhofen, Germany) emulsified in 1.5 mg $Al(OH)_3$ (Alum Imject Pierce, Rockford IL, USA) on day 0, 14 and 21. Mice were challenged twice with OVA aerosol (1% OVA diluted in phosphate buffered saline (PBS)) via the airways on day 26 and 27.

2.3. Stress exposure

After i.p. sensitization, mice were randomized in two experimental groups. Coinciding with the first OVA aerosol challenge, one group was exposed to sound stress for a single 24-h period ($n=12$), while the other group remained