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Evaluation of nasal barrier dysfunction at acute- and late-phase reactions in a guinea pig model of allergic rhinitis

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Abstract

Allergic rhinitis is a common disease characterized by the symptoms of pruritus, sneezing, hypersecretion and nasal blockage. Increased mucosal barrier permeability has been suggested to be an indicator for the severity of allergic rhinitis. This study investigates the passage of radiolabelled albumin from the nasal mucosal circulation into the lumen in guinea pigs intraperitoneally sensitized and intranasally challenged with antigen. In order to characterize the allergic rhinitis model, we evaluated a number of potential influencing factors in nasal plasma exudation, including antigen doses, volumes of antigen solution used, and animal position during the nasal lavage, and the conditions of nasal lavage. The number of eosinophils and levels of histamine and leukotriene B_4 in the nasal lavage and eosinophils in the nasal mucosa were determined at the early and late phases after antigen challenge. We also compared the effects of topical nasal treatments for allergic rhinitis on nasal inflammatory responses. Our results demonstrate that, in the guinea pig nasal mucosa, topical challenge with antigens induces plasma exudation and histamine release at the acute-phase reaction, and plasma exudation and eosinophil infiltration at the late-phase reaction. These changes are similar to those reported in human allergic rhinitis. Alterations of nasal plasma exudation, histamine release and eosinophil influx were dependent upon the concentrations and volumes of antigens. An antihistamine inhibited the acute-phase reaction partially, whereas budesonide inhibited effects at the late-phase reaction. We suggest that this model of guinea pig allergic rhinitis with the early and late responses may be useful for high-throughout screening of new drugs.

Keywords: Rhinitis; Plasma exudation; Early response; Late response; Histamine; Eosinophils

1. Introduction

Allergic rhinitis, with an incidence about 20% of the world's population, is characterized by the symptoms of pruritus, sneezing, hypersecretion and nasal blockage (Bellanti and Wallerstedt, 2000; Naclerio, 1991). The factors involved in the development and formation of nasal symptoms include eosinophil infiltration of the nasal mucosa and cavity (Terada et al., 1994), release of histamine (Gruber, 1994; Persson, 1990; Greiff et al., 2003; Howarth et al., 2000), and dysfunction of the nasal mucosal epithelial and endothelial barrier (Kaise et al., 1995; Persson, 1990). Extravasation of plasma protein from postcapillary venules can be employed as an accessible index reflecting the severity of the airway mucosal inflammation (Greiff et al., 2003). The contraction-like deformation of endothelial cells to inflammatory stimuli results in the increased permeability of subepithelial microvessels and plasma exudation into the nasal tissue. Leaked plasma molecules then passes through the mucosal epithelial tight junctions, dependent upon the basolateral hydrostatic pressure load on the epithelial surface cells (Persson, 1990).

In order to characterize the guinea pig allergic rhinitis model, we evaluated a number of potential influencing factors in nasal plasma exudation, a passage of radiolabelled human serum albumin (HSA) from the nasal mucosal circulation into the lumen, including antigen doses, volumes of antigen solution used, and animal position during the nasal lavage, and the conditions of nasal lavage in guinea pigs intraper-

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itoneally sensitized and intranasally challenged with antigen. We characterized the response to challenge by measurement of plasma exudation, eosinophil influx and levels of histamine and leukotriene B_4 in the nasal lavage and mucosa at the early and late phases after antigen challenge. Furthermore, the present study compares the effects of topical nasal treatments for allergic rhinitis, azalestine, levocabastine and budesonide, on nasal inflammatory responses.

2. Materials and methods

2.1. Animals

Dunkin–Hartley male guinea pigs, weighing 250–300 g, were purchased from Möllegaard Breeding Center, Ejby, Denmark and housed in plastic cages with aspen bedding (4 guinea pigs/cage). The animal room was maintained at 20 °C with a daily light–dark cycle (0600–1800 light). Animals were kept with food and water ad libitum. The study was approved by the Malmö/Lund ethical committee for animal experiments.

2.2. Sensitization and challenge

Guinea pigs were sensitized to OVA (OVA) by an intraperitoneal injection of 0.5 ml saline containing 100 mg Al $(OH)_3$ (F2200; Anachemia, Montreal, Canada) and 2 μg OVA (grade III; Sigma, St. Louis, MO, USA) (Erjefält et al., 1993). Three weeks after sensitization, animals were anaesthetized by intramuscular administration (1 ml/kg) of a 2:3 ratio of Xylazine (Rompun, 20 mg/kg; Bayer, Leverkusen, Germany) and Ketamine (Ketalar, 50 mg/kg; Park Davies, Detroit, MI, USA) and placed in a head-down supine position with an angle 25°. The exposure of the nasal cavity to allergen was performed by dropping OVA solution at different doses into bilateral nasal cavities. For the negative control, animals received either sensitization and challenge with saline or sensitization with saline and challenge with OVA.

2.3. Plasma exudation

The nasal mucosal barrier permeability was assessed by measuring the passage of ^{125}I-labeled human serum albumin

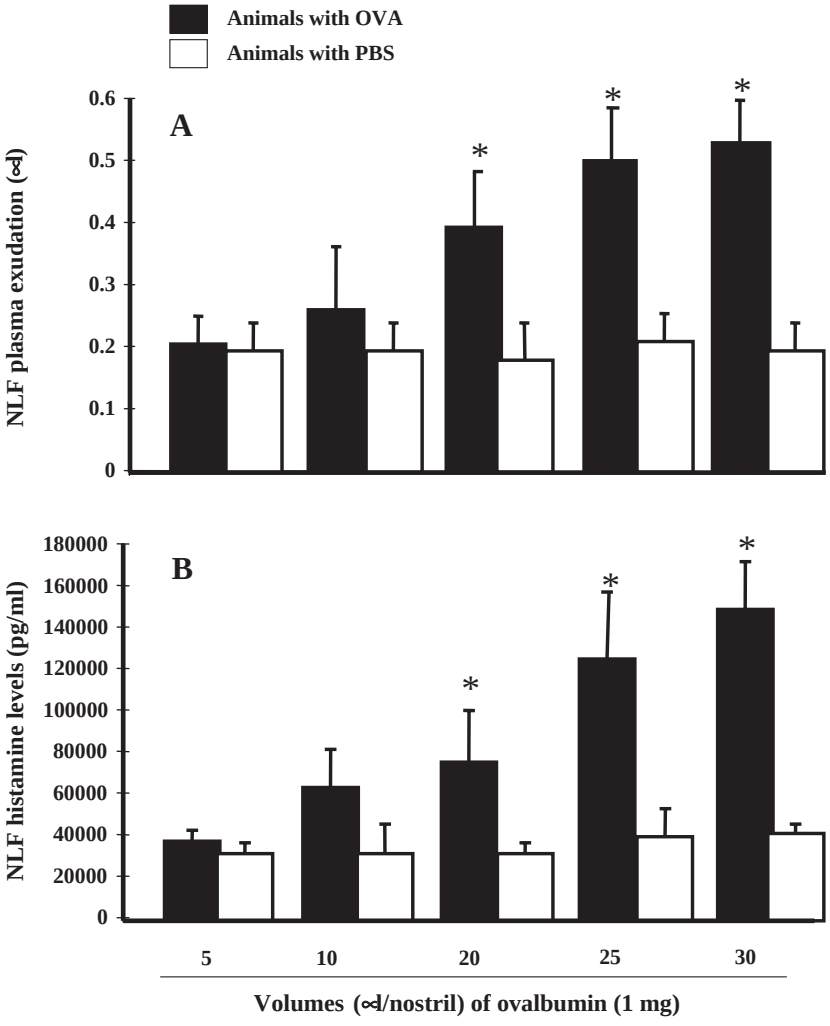

Fig. 1. Plasma exudation (A) and histamine release (B) in nasal lavage fluid harvested from OVA-sensitized guinea pigs intranasally challenged with PBS or OVA in different volumes with a fixed concentration. * Stands for p values less than 0.05, as compared with the respective group of OVA-sensitized guinea pigs intranasally challenged with PBS.