

Capsaicin pretreatment does not inhibit allergen-induced airway microvascular leakage in guinea pig

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We have studied the effects of tachykinin-depletion on airway microvascular leakage induced by allergen challenge in ovalbumin-sensitized guinea pigs. Tachykinin-depletion was obtained by capsaicin pretreatment 1 week before inhaled allergen challenge. Capsaicin pretreatment did not change airway microvascular permeability induced by allergen challenge. Thus, sensory neuropeptides may not be important in allergen-induced acute airway microvascular leakage in guinea pig *in vivo*.

Key words: allergen challenge; tachykinins; plasma leakage

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It has been suggested that tachykinins released from airway sensory nerves may be involved in the inflammation of asthmatic airways (2). Tachykinins are present in the airways of several species including man and guinea pig (7), and are found in close relation to the airway smooth muscle, beneath and within the epithelium, and around blood vessels in the airway submucosa (6). Exogenous administration of these tachykinins in experimental animals will produce several features of asthma, including airway smooth muscle contraction, mucus secretion and increased microvascular permeability (9, 11, 15, 16).

In guinea pigs, capsaicin has been shown to deplete airway sensory nerves of tachykinins (6, 9, 10), and to abolish the bronchoconstriction induced by endogenous tachykinins released *in vivo* by either vagal stimulation or capsaicin injection (6). We postulated that if sensory nerves are important in allergen-induced acute increases in microvascular permeability, then capsaicin pretreatment should in-

hibit this response. We therefore examined the effects of inhaled allergen challenge in capsaicin pretreated and sensitized guinea pigs.

METHODS

Male Dunkin-Hartley guinea pigs (250 g-300 g) were actively sensitized by a single intra-peritoneal injection of 0.5 ml normal saline containing 20 µg of chicken ovalbumin (OA, Grade V; Sigma, Dorset, UK) and 100 mg of aluminium hydroxide (Al(OH)₃; BDH Chemicals, Poole, Dorset, UK), or Al(OH)₃ alone as a control. Capsaicin pretreatment, previously described by Lundberg et al. (6), was performed 1 week before allergen challenge. Briefly, anaesthetized guinea pigs were protected by terbutaline and aminophylline before a single s.c. dose of 50 mg/kg of capsaicin. Control animals were injected with Tween 80 (Sigma, Poole, Dorset, UK), the vehicle for capsaicin. One week later, urethane-anaesthetized and mechanically ventilated animals were chal-

lenged with aerosolised OA (5 mg/ml, 30 breaths), generated by an ultrasonic nebuliser (Model 2511; PulmoSonic, DeVilbiss Co, PA, USA; particle size 4.2 μm , geometric SD of 1.2).

Airway microvascular leakage was measured as previously described (17), using Evans Blue dye (EB) as a marker for plasma albumin. Briefly, EB was injected 30 s before allergen challenge. Five minutes later, the vasculature was perfused through the aorta with 0.9%

saline. The lungs were dissected out, and the parenchyma carefully removed, and airways were then divided into central airways (lower trachea and main bronchi), and peripheral airways (intrapulmonary). Tissues were weighed, and Evans Blue dye was extracted in formamide and measured in a Philips spectrophotometer (Model PU 8630, Philips Cambridge, UK) at 620 nm.

Data are reported as mean $\pm$ SEM, and Kruskal-Wallis non-parametric test was used to evaluate significance among the groups.

RESULTS

Fig. 1 shows the mean Evans Blue dye measured in intrapulmonary airways. No significant increase in microvascular permeability was seen in proximal airways. Sensitized animals exposed to inhaled OA showed a significant increase of microvascular permeability in the intrapulmonary airways, as previously reported (4). Capsaicin pretreatment did not influence the increase in airway microvascular permeability after inhaled allergen challenge (Fig. 1). To evaluate whether capsaicin pretreatment was effective, two capsaicized animals were injected with capsaicin intravenously (12 $\mu\text{g/kg}$), and no increase in transpulmonary pressure was seen (data not shown).

DISCUSSION

We have previously demonstrated that increased microvascular permeability may be a contributory factor to airflow obstruction after allergen challenge (4), although the mechanism behind this increase in microvascular permeability is not known. As tachykinins have been shown to increase microvascular permeability *in vivo* in guinea pigs, they may have a role in allergen-induced leakage (2). We therefore investigated whether capsaicin pre-treatment, which has been shown to cause depletion of tachykinins in airway sensory nerves, would change the acute increase in microvascular permeability to allergen challenge. However,

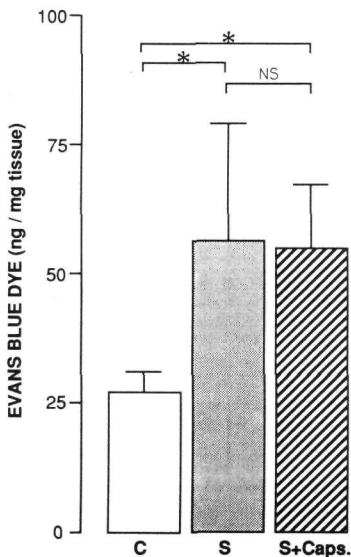


Fig. 1. Effect of capsaicin pretreatment on airway microvascular permeability in intrapulmonary airways induced by allergen aerosol challenge. C: ovalbumin challenge in non-sensitized animals ($n=7$), S: ovalbumin challenge in sensitized animals ($n=4$), S-Caps: ovalbumin challenge in sensitized and capsaicin pretreated animals ($n=4$). Capsaicin pretreatment did not inhibit the extravasation of Evans Blue dye after allergen challenge. Significant increase in leak induced by ovalbumin aerosol was seen in both sensitized groups ($*P<0.05$).

in this study we could not find any evidence that capsaicin pretreatment altered the acute increase in microvascular permeability induced by inhaled allergen challenge. This is consistent with a previous study (5), in which capsaicin pretreatment failed to reduce the bronchoconstrictor response to allergen challenge.

We are confident that the capsaicin pretreatment was effective, since in a recent study using the same procedure, a high intravenous dose of capsaicin did not induce bronchoconstriction in pretreated animals, but only in controls (12). Further, this was also validated in the present study. The sensitisation procedure was effective, since there was a significant increase in Evans Blue dye extravasation in both the capsaicin and vehicle groups, compared to non-sensitised animals.

Neonatal treatment with capsaicin in rats has been shown, paradoxically, to enhance bronchial reactivity in immunized animals (1), and to influence the development of antibodies as detected in broncho-alveolar lavage fluid (14). Thus, capsaicin treatment could influence both the development of the acute reaction as well as the immunization process. Capsaicin pretreatment does not reduce microvascular permeability measured as a wheal reaction in the skin induced by allergen challenge in atopic patients (10, 13), in contrast to the flare reaction, which is reduced. In the present study, in which capsaicin was given after the immunization, we could not detect any influence on microvascular permeability. Therefore, we have not found any evidence to support the involvement of tachykinins in the acute increase in airway microvascular permeability in response to allergen challenge in actively sensitised guinea pigs. However, this does not preclude their involvement in more chronic responses to allergen.

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REFERENCES

- Ahlstedt S, Alving K, Hesselmar B, Olsson E. Enhancement of the bronchial reactivity in immunized rats by neonatal treatment with capsaicin. *Int Arch Allergy Appl Immunol* 80, 262-266, 1986.
- Barnes PJ. Asthma as an axon reflex. *Lancet* i, 242-245, 1986.
- Coles SJ, Neill KH, Reid LM. Potent stimulation of glycoprotein secretion in canine trachea by substance P. *J Appl Physiol* 57, 1323-1327, 1984.
- Hui KP, Lötvall JO, Rogers DF, Barnes PJ, Chung KF. Ovalbumin aerosol challenge in sensitized guinea-pigs. relationship between airway microvascular permeability and airflow obstruction. *Thorax* 84, 1989; 895P.
- Ingenito EP, Pliss LB, McCusker MT, Ingram RH. Assessment of the role of tachykinins in antigen-induced acute bronchoconstriction in the guinea pig. *Am Rev Respir Dis* 138, (Suppl 4), A229, 1989.
- Lundberg JM, Brodin E, Saria A. Effects and distribution of vagal capsaicin-sensitive substance P neurons with special reference to the trachea and lungs. *Acta Physiol Scand* 119, 243-252, 1983.
- Lundberg JM, Hökfelt T, Martling CR, Saria A, Cuello C. Substance P-immunoreactive sensory nerves in the lower respiratory tract of various mammals including man. *Cell Tissue Res* 235, 251-261, 1984.
- Lundberg JM, Martling CR, Saria A. Substance P and capsaicin-induced contraction of human bronchi. *Acta Physiol Scand* 119, 49-53, 1983.
- Lundberg JM, Saria A. Capsaicin-sensitive vagal neurons involved in control of vascular permeability in rat trachea. *Acta Physiol Scand* 115, 521-523, 1982.
- Lundblad L, Lundberg JM, Änggård A, Zetterström O. Capsaicin-sensitive nerves and the cutaneous allergy reaction in man. *Allergy* 42, 20-25, 1987.
- Lötvall JO, Hui KP, Lemen RJ, Barnes PJ, Chung KF. Effects of aerosolized substance P on lung resistance and compliance in guinea pig. contribution of airway microvascular leakage to bronchoconstriction. *Eur Respir J* 2 (Suppl. 8) 753s, 1989.
- Lötvall JO, Skoogh BE, Lemen RJ, Barnes PJ, Chung KF. Sodium metabisulfite induced bronchoconstriction in guinea pigs. Role of acetylcholine and tachykinin release. *Thorax*. (abstract; in press), 1989.
- McCusker MN, Chung KF, Roberts NM, Barnes PJ. Effect of topical capsaicin on the cutaneous responses to inflammatory mediators and antigen in man. *J. Allergy Clin Immunol* 83, 1118-1124, 1989.
- Nilsson G, Alving K, Lundberg JM, Ahlstedt S. Effect of neonatal or later capsaicin treatment on bronchial reactivity in sensitized rats. *Int Arch Allergy Appl Immunol* 88, 234-236, 1989.
- Nilsson G, Dahlberg K, Brodin E, Sundler F, Strandberg K. Distribution and constrictor effect of substance P in guinea-pig tracheobronchial tissue. In von Euler US, Pernow B (eds.). *Substance P*, pp. 57-61. Raven Press, New York, 1977.

16. Rogers DF, Belvisi M, Barnes PJ. Effects and interaction of sensory neuropeptides on airway microvascular leakage in guinea-pigs. *Br J Pharmacol* 95, 1109-1116, 1988.
17. Rogers DF, Boschetto P, Barnes PJ. Plasma exudation. correlation between Evans Blue dye and radiolabeled albumin in guinea pig airways *in vivo*. *J Pharmacol Methods* 21, 1-7, 1989.

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