Available online at www.sciencedirect.com

SCIENCE DIRECT

European Journal of Pharmacology 518 (2005) 77 – 78

www.elsevier.com/locate/ejphar

Rapid communication

Capsazepine, a vanilloid receptor antagonist, inhibits allergen-induced tracheal contraction

Edwin van den Worm [a], Annick de Vries [b], Frans P. Nijkamp [a], Ferdi Engels [a,*]

[a] *Department of Pharmacology and Pathophysiology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, PO BOX 80082, 3508 TB Utrecht, The Netherlands*

[b] *Endocrinology Unit, Molecular Medicine Centre, Western General Hospital, Crewe Road, Edinburgh, EH4 2XU, United Kingdom*

Received 2 June 2005; accepted 7 June 2005

Abstract

To investigate the possible role of the vanilloid receptor-1 (TRPV1) in allergic airway responses, the effect of the specific TRPV1 receptor antagonist capsazepine was examined. Capsazepine significantly decreased the ovalbumin-induced contraction of isolated tracheal rings from ovalbumin-sensitized guinea pigs. This is the first report directly showing the involvement of the TRPV1 in experimental allergic airway responses.

Keywords: Allergic airway response; Capsazepine; Ovalbumin; TRPV1 (transient receptor potential vanilloid 1)

Allergen-induced airway narrowing, as well as airway hyperresponsiveness towards contractile stimuli, are often considered to be among the key features of allergic asthma. Recent data suggest that nerve growth factor (NGF) plays an important role in these symptoms of allergic asthma. Thus, we previously reported that airway constriction induced by allergen challenge could be inhibited by NGF antibodies (De Vries et al., 2002). In addition, NGF was shown to induce airway hyperresponsiveness in guinea pigs (De Vries et al., 1999). Its mode of action, however, has remained obscure. Initially, NGF was identified as a general growth factor that stimulates nerve growth and differentiation, but subsequently it was realized that NGF specifically interacts with sensory neurons (Lewin and Mendell, 1993). In agreement with this, we found that NGF-induced effects on airway responses were mediated by sensory nerves (De Vries et al., 1999, 2001).

Small diameter sensory neurons express the transient receptor potential vanilloid 1 (TRPV1), formerly known as vanilloid receptor-1 or the capsaicin receptor. TRPV1 is a cation channel of the transient receptor potential family and has been isolated and cloned in 1997 (Caterina et al., 1997). Heterologously expressed TRPV1 can not only be activated by vanilloid compounds, but also by low pH or noxious heat, two conditions frequently found in inflamed tissue. We hypothesized that airway symptoms in allergic asthma are caused by NGF influencing the TRPV1 on sensory nerves within the airways (Van den Worm et al., 2004). We now pursued this notion by investigating the effect of a specific TRPV1 receptor antagonist, capsazepine (Bevan et al., 1992), on allergen-induced contraction of isolated guinea pig trachea.

The animal studies were approved by the Animal Care Committee of the Utrecht University. Male Hartley guinea pigs were sensitized to ovalbumin as described previously (De Vries et al., 2002). Fourteen days after the sensitization, the animals were sacrificed and isolated tracheal rings were immediately placed in an isometric organ bath set-up as previously described (De Vries et al., 2001). After equilibration, the rings were incubated with either capsazepine (20 μM) or medium (control). After 5 min, the tracheal rings were challenged with ovalbumin (1 mg/ml) or saline

* Corresponding author. Tel.: +31 30 2537356; fax: +31 30 2537420.
E-mail address: G.M.H.Engels@pharm.uu.nl (F. Engels).

0014-2999/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2005.06.003

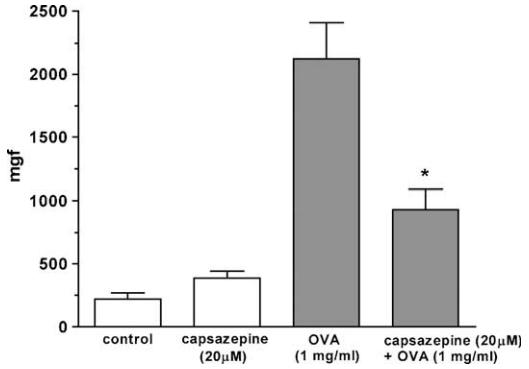

Fig. 1. Effect of capsazepine on allergen-induced tracheal contraction. All tracheal rings were isolated from ovalbumin (OVA)-sensitized guinea pigs ($n=3-6$). Subsequently the tracheal preparations were challenged with saline (open bars) or OVA (closed bars). Values are depicted as mean force (mgf) ± standard errors of the mean (S.E.M.). *Significantly different compared to non-capsazepine treated OVA-challenged tracheal rings ($P<0.01$; Student's t-test).

(control) and subsequently the contraction of the tracheal rings was measured.

Ovalbumin challenge of the sensitized tracheal preparations resulted in a contractile response, which was significantly decreased by capsazepine (Fig. 1). Capsazepine administration to control tracheas did not have any effect.

This novel finding clearly points to an important role for the TRPV1 in allergic airway disease. Indeed, recently it has been shown that the TRPV1 is present in the guinea pig respiratory system, localized on axons throughout the airways (Watanabe et al., 2005). Interestingly, asthmatic patients have been shown to display an enhanced sensitivity towards capsaicin (Doherty et al., 2000), also implicating a role for TRPV1 in asthma. Several lines of evidence suggest that NGF may be responsible for TRPV1 sensitization. For example, NGF treatment of dorsal root ganglia neurons increases TRPV1 mRNA expression (Winston et al., 2001). Further, NGF has been shown to regulate the sensitivity of dorsal root ganglia for capsaicin (Winter et al., 1988).

In summary, our present data provide direct evidence for the involvement of TRPV1 in allergic asthma. This finding may contribute to a better understanding of the enigmatic etiology of asthma and may eventually lead to new ways of treatment for this ever-growing disease.

Acknowledgement

Financial support of this study by the Netherlands Asthma Foundation (Grant: AF 3.2.01.50) is gratefully acknowledged.

References

Bevan, S., Hothi, S., Hughes, G., James, I.F., Rang, H.P., Shah, K., Walpole, C.S., Yeats, J.C., 1992. Capsazepine: a competitive antagonist of the sensory neurone excitant capsaicin. Br. J. Pharmacol. 107, 544–552.

Caterina, M.J., Schumacher, M.A., Tominaga, M., Rosen, T.A., Levine, J.D., Julius, D., 1997. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 389, 816–824.

De Vries, A., Dessing, M.C., Engels, F., Henricks, P.A.J., Nijkamp, F.P., 1999. Nerve growth factor induces a neurokinin-1 receptor-mediated airway hyperresponsiveness in guinea pigs. Am. J. Respir. Crit. Care. Med. 159, 1541–1544.

De Vries, A., Van Rijnsoever, C., Engels, F., Henricks, P.A.J., Nijkamp, F.P., 2001. The role of sensory nerve endings in nerve growth factor-induced airway hyperresponsiveness to histamine in guinea-pigs. Br. J. Pharmacol. 134, 771–776.

De Vries, A., Engels, F., Henricks, P.A.J., Leusink-Muis, T., Fischer, A., Nijkamp, F.P., 2002. Antibodies directed against nerve growth factor inhibit the acute bronchoconstriction due to allergen challenge in guinea-pigs. Clin. Exp. Allergy 32, 325–328.

Doherty, M., Mister, R., Pearson, M., Calverley, P., 2000. Capsaicin responsiveness and cough in asthma and chronic obstructive pulmonary disease. Thorax 55, 643–649.

Lewin, G.R., Mendell, L.M., 1993. Nerve growth factor and nociception. Trends Neurosci. 16, 353–359.

Van den Worm, E., Nijkamp, F.P., Engels, F., 2004. Nerve growth factor and the vanilloid receptor: partners in crime? Clin. Exp. Allergy 34, 996–1000.

Watanabe, N., Horie, S., Michael, G.J., Spina, D., Page, C.P., Priestley, J.V., 2005. Immunohistochemical localization of vanilloid receptor subtype 1 (TRPV1) in the guinea pig respiratory system. Pulm. Pharmacol. Ther. 18, 187–197.

Winston, J., Toma, H., Shenoy, M., Pasricha, P., 2001. Nerve growth factor regulates VR-1 mRNA levels in cultures of adult dorsal root ganglion neurons. Pain 89, 181–186.

Winter, J., Forbes, C.A., Sternberg, J., Lindsay, R.M., 1988. Nerve growth factor (NGF) regulates adult rat cultured dorsal root ganglion neuron responses to the excitotoxin capsaicin. Neuron 1, 973–981.