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Tachykinin NK_2 receptor antagonists decrease eicosanoid release in lung anaphylaxis

Paolo Montuschi *, Diego Currò, Giovanni Ciabattoni

Department of Pharmacology, Faculty of Medicine, Catholic University of the Sacred Heart, Largo Francesco Vito 1, 00168 Roma, Italy

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Abstract

Two tachykinin NK_2 receptor antagonists, MEN 10.627 c(Met-Asp-Trp-Phe-Dap-Leu) and MEN 10.376 [(Tyr^5,Trp^{6,8,9},Lys^{10}]neurokinin A-(4–10), were used to investigate the role of tachykinins in in vitro guinea-pig lung anaphylaxis. Both antagonists dose-dependently decreased bronchoconstriction and the release of thromboxane and prostaglandin E_2 induced by antigen challenge in perfused sensitized lungs, but neither had any effect on the basal release of either eicosanoid. The findings indicated that tachykinins released by sensory nerve fibers may contribute to anaphylactic reactions by increasing arachidonic acid metabolite release.

Keywords: Tachykinin receptor antagonist; Eicosanoid; Anaphylaxis, lung

Tachykinins such as substance P and neurokinin A released from primary afferent nerve endings in the airways (Lundberg and Saria, 1987), are known to play important roles in antigen-induced bronchoconstriction in sensitized guinea-pig lungs (Ricciardolo et al., 1994). Current evidence suggests that both tachykinin NK_1 and NK_2 receptors are involved in the control of bronchial smooth muscle reactivity, although tachykinin NK_2 receptor activation seems to be primarily responsible for the allergic bronchoconstriction induced by ovalbumin (Bertrand et al., 1993).

In previous studies, we have shown that thromboxane A_2 is an important mediator of bronchospastic responses to sulfido-peptido-leukotrienes released in vitro by guinea-pig lung during anaphylaxis. Inhibitors of both cyclo-oxygenase and lipoxygenase pathways reduced the bronchoconstrictive response (Ciabattoni and Preziosi, 1985; Ciabattoni et al., 1993). Selective thromboxane synthase inhibitors decreased the release of thromboxane B_2 and ovalbumin-induced bronchoconstriction, but had no effect on the release of leukotrienes C_4 or B_4 (Preziosi and Ciabattoni, 1986).

In the present study, we used two new peptide tachykinin NK_2 receptor antagonists, MEN 10.627 c(Met-Asp-Trp-Phe-Dap-Leu) and MEN 10.376 [(Tyr^5,Trp^{6,8,9},Lys^{10}]neurokinin A-(4–10) (Maggi et al., 1991), to investigate the role of the cyclo-oxygenase pathway of arachidonic acid metabolism in tachykinin-mediated bronchoconstriction during in vitro anaphylaxis in guinea-pig lungs.

Guinea-pigs (400–500 g) were sensitized with 1% ovalbumin (Ciabattoni et al., 1993). 15–21 days later, the animals were killed and the lungs were removed separately. Each lung was perfused in a thermostated Perspex chamber at 37°C with Krebs-Ringer bicarbonate solution injected through the pulmonary artery. Air was pumped into and out of the sealed chamber to sequentially expand and collapse the lungs (Ciabattoni et al., 1993). A pressure transducer was attached to the trachea to measure pressure-volume variations in the system, which were recorded with a pen recorder. The lung perfusion solution was removed from the bottom of the chamber by a peristaltic pump connected to a fraction collector. Samples were collected every 2 min.

The lungs were allowed to equilibrate with tachykinin NK_2 receptor antagonists dissolved in the perfusion medium for at least 10 min before exposure to ovalbumin challenges. Perfusate levels of thromboxane B_2 and prostaglandin E_2 were measured as products of cyclo-oxygenation of arachidonate. Selective radioimmunoassays were used for the purpose (Ciabattoni et al., 1993).

Group means for all data were subjected to parametric analysis of variance for multiple comparisons and Student's *t*-test for single comparisons. All values are reported as

* Corresponding author. Tel.: +39 6 30154253; fax: +39 6 3050159.

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means ± S.E.M. and $P < 0.05$ was considered statistically significant.

In 45% of the sensitized lungs, ovalbumin challenge induced a bronchospastic response which did not resolve within the time course studied (30 min). In the control anaphylactic lungs (i.e. those not treated with tachykinin NK_2 receptor antagonists), there was a mean reduction of 88.6 ± 1.4% in the pressure-volume variation tracing accompanied by increases in the release of thromboxane B_2 (10.68 ± 1.33 vs. 2.55 ± 0.33 ng/min at baseline, $n = 8$) and prostaglandin E_2 (1.81 ± 0.31 vs. 0.48 ± 0.12 ng/min at baseline, $n = 8$). The lungs that did not undergo anaphylaxis did not show any increase in thromboxane B_2 (3.26 ± 0.57 vs. 3.31 ± 0.63 ng/min, $n = 5$) and prostaglandin E_2 (0.47 ± 0.09 vs. 0.49 ± 0.08 ng/min, $n = 5$).

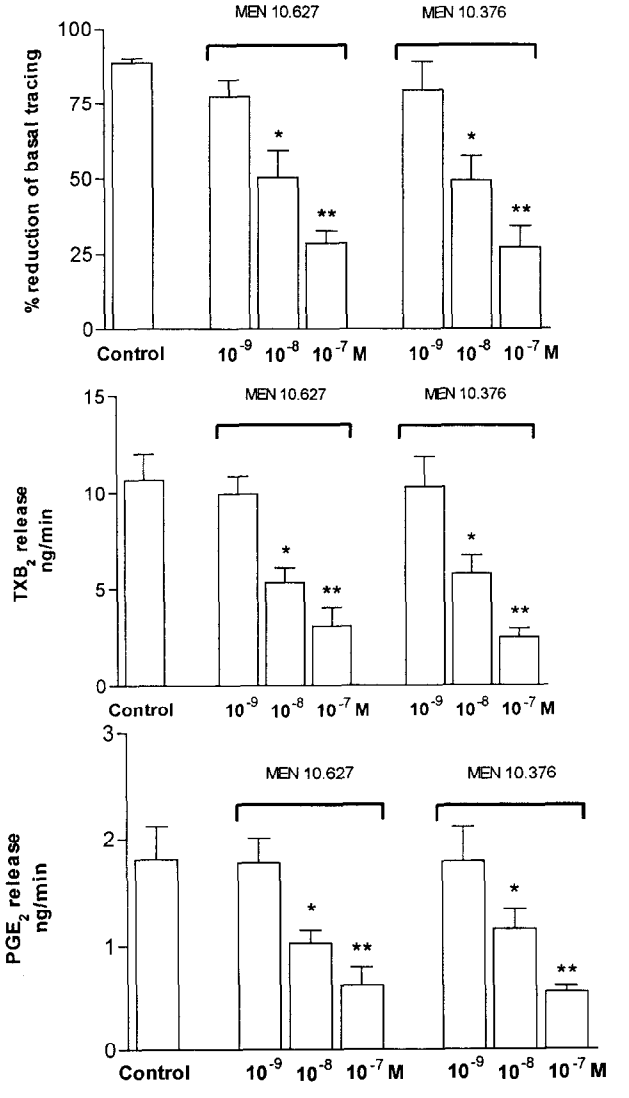

Fig. 1. Percentage reductions in the pressure-volume variation tracing (upper panel), and the release of thromboxane (TX) B_2 (middle panel) and prostaglandin (PG) E_2 (lower panel) induced in sensitized guinea-pig lungs by ovalbumin challenge. Arachidonic acid metabolite release was measured in 2-min fractions collected during bronchoconstriction. The effects of MEN 10.376 and MEN 10.627 are shown. * $P < 0.05$, ** $P < 0.01$ vs. control ($n = 5$).

Pre-treatment with MEN 10.627 and MEN 10.376 dose-dependently decreased bronchoconstriction and the peak of thromboxane B_2 and prostaglandin E_2 associated with the anaphylactic response (Fig. 1), with similar dose-response curves. Neither of the tachykinin NK_2 receptor antagonists had any effect on the basal release of thromboxane B_2 and prostaglandin E_2, which excludes the possibility of a direct inhibitory effect on cyclo-oxygenase.

The results of this study are compatible with a major role of tachykinin NK_2 receptors in the antigen-induced bronchoconstriction. The release of cyclo-oxygenase metabolites typically associated with guinea-pig lung anaphylaxis was also attenuated by the tachykinin NK_2 receptor antagonists. These findings suggest that tachykinins released from sensory nerve fibers contribute to anaphylactic bronchoconstriction, not only by direct activation of tachykinin NK_2 bronchial smooth muscle receptors, but also by stimulation of cyclo-oxygenation of arachidonic acid. Recent evidence from in vivo experiments indicates that substance P-mediated increases in histamine release are probably related to activation of tachykinin receptors on mast cells (Lilly et al., 1995), suggesting that the decreased release of thromboxane B_2 and prostaglandin E_2 caused by the antagonists in our study may have been due to reduced mast-cell activation. Further study is necessary: (1) to confirm this hypothesis using selective tachykinin NK_2 receptor agonists; (2) to determine whether other prostaglandins and/or lipoxygenase metabolites are also involved; and (3) to identify the cellular sources of the eicosanoids.

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