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Corticotropin-releasing factor inhibits antigen-induced plasma extravasation in airways

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Abstract

We investigated the potential of corticotropin-releasing factor (CRF) to reduce neurogenic plasma extravasation in sensitised guinea pig airways evoked by antigen challenge. Inhalation of 5% ovalbumin for 2 min in the presence of phosphoramidon (2.5 mg/kg, i.v.) increased extravasation of Evans blue dye in the trachea and main bronchi. The increase in plasma extravasation induced by antigen challenge was significantly reduced by pretreatment with CRF (30 nmol/kg, i.v.) (73% in the trachea and 42% in the main bronchi). The inhibition of plasma extravasation by CRF (30 nmol/kg, i.v.) alone was not different from the inhibition induced by the combination of CRF and the tachykinin NK_1 receptor antagonist, CP-99,994 (4 mg/kg, i.v.) (73% in the trachea and 38% in the main bronchi). CRF (30 nmol/kg, i.v.) inhibited by 32% in the trachea and by 43% in the main bronchi plasma extravasation induced by aerosolised bradykinin but did not reduce the plasma extravasation caused by aerosolised substance P in the presence of phosphoramidon. These findings suggest that CRF reduces ovalbumin-induced plasma extravasation in guinea pig airways by inhibiting the release of tachykinins from primary sensory nerves.

Keywords: CRF (corticotropin-releasing factor); CP 99,994; Plasma extravasation; Antigen challenge; Neurogenic inflammation, guinea pig; Substance P

1. Introduction

Release of peptide transmitters from sensory nerve endings results in a series of inflammatory responses, collectively referred to as neurogenic inflammation. In the airways these responses include plasma extravasation (Lundberg et al., 1983; Bertrand et al., 1993a,b), vasodilation (Piedimonte et al., 1992), adhesion of leukocytes to the vascular endothelium (Umeno et al., 1989) and bronchoconstriction (Lundberg et al., 1983; Ricciardolo et al., 1994). Tachykinin NK_1 and NK_2 receptors mediate the responses induced by tachykinins released from sensory nerves in the airways (Regoli et al., 1988, Maggi et al., 1991). In particular, tachykinin-evoked plasma extravasation in the guinea pig trachea and main bronchi is entirely mediated by activation of tachykinin NK_1 receptors (Abelli et al., 1991; Lei et al., 1992; Piedimonte et al., 1993). Neutral endopeptidase (NEP, E.C.3.4.24.11) cleaves tachykinins and inhibition of neutral endopeptidase causes an increase in neurogenic inflammatory responses (Nadel, 1992). Neurogenic inflammation has been shown to be involved in inflammatory responses in the airways induced by several stimuli. Recent studies have shown that plasma extravasation evoked by antigen challenge in the trachea of sensitised guinea pigs is largely mediated by tachykinin release from sensory nerve endings (Bertrand et al., 1993a; Nadel, 1994).

Tachykinin receptor antagonists may be used to reduce neurogenic inflammatory responses in the airways. Alternative strategies to obtain the same goal include the use of agents that inhibit the release of peptide transmitters from sensory nerve endings. Sensory neuropeptide release in the airways may be inhibited by various agents including opioids and ne-

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docromil sodium (Barnes, 1994). Corticotropin-releasing factor (CRF), a 41 amino acid peptide that controls the pituitary-adrenal axis, is co-localised with other neuropeptides in capsaicin-sensitive nerves in rat brain (Skofitsch et al., 1985). CRF has been found to inhibit neurogenic plasma extravasation in the paw skin and in the trachea of the rat (Wei et al., 1986; Wei and Kiang, 1987, Wei and Kiang, 1989). In the present studies we tested the possibility that CRF inhibits inflammatory responses in airways by the inhibition of sensory neuropeptide release. For this purpose, evaluation of plasma extravasation induced by ovalbumin challenge in sensitised guinea pigs was chosen because (a) the leakage of plasma proteins is an important feature of airway inflammation, (b) the anaphylactic response to ovalbumin is a relevant model of allergic asthma, and (c) in the trachea of guinea pigs pretreated with the neutral endopeptidase inhibitor, phosphoramidon, we observed that plasma extravasation induced by the ovalbumin was markedly reduced by a tachykinin NK_1 receptor antagonist, thus implicating tachykinins in the response (Bertrand et al., 1993a,b). The specific aim of the present study was two-fold. First, we tested whether CRF inhibits plasma extravasation in response to antigen in sensitised guinea pig airways. Second, we investigated whether the inhibitory action of CRF on antigen-induced plasma extravasation is due to the ability of this compound to inhibit tachykinin release in the guinea pig airways.

2. Materials and methods

2.1. Animals

Male Hartley guinea pigs (Simonsen Laboratories, Gilroy, CA) weighing 250–300 g at the time of housing, were used in this study. They were kept in a temperature-controlled environment with standard laboratory food and water freely available.

2.2. Sensitisation procedure

Animals were sensitised according to a protocol described previously (Ricciardolo et al., 1994; Dunn et al., 1988) that consisted of injection of 70 mg ovalbumin (Grade V) in 1.5 ml 0.9% NaCl intraperitoneally twice with a 1 week interval between injections. The animals were studied 2 weeks after the second injection.

2.3. Cardiovascular measurements

A polyethylene catheter (i.d. 0.8 mm, length 2.5 cm; Angiocath, Arrow International, Reading, PA) was inserted into the left carotid artery and then connected to a pressure transducer (model 1270A, Hewlett-Packard, Palo Alto, CA) for measurement of arterial blood pressure. The amplified signal from the transducer (module M2102B, Electronics for Medicine, Pleasantville, NY) and displayed continuously on a video monitor (model OM, Electronics for Medicine) and recorded using an oscillographic recorder (model DASH-8, Astro-Med, West Warwick, RI). Heart rate was derived from the pressure pulse signal by a cardiotachometer coupler.

2.4. Experimental design

On the day of the experiment, the animals (500–600 g) were anaesthetised with sodium pentobarbital (45 mg/kg i.p.; Anthony Product Corp., Arcadia, CA). A midline cervical incision was made to expose the larynx and upper trachea. The trachea was incised immediately below the larynx, and a cannula was inserted 4 mm into the trachea. The animals were then ventilated artificially at a frequency of 70 breaths/min with a tidal volume of 6 ml (Bertrand et al., 1993a). Pretreatment of CRF (30 nmol/kg, i.v.; Neurobiological Technologies, Richmond, CA) or vehicle was injected 15 min before the inhalation of ovalbumin (Rogers et al., 1993). The NK_1 tachykinin receptor antagonist, CP-99,994 (4 mg/kg, i.v.) or saline was injected along with phosphoramidon (2.5 mg/kg, i.v.; Peninsula Laboratories, Belmont, CA) dissolved in 0.9% NaCl (Piedimonte et al., 1993), into the jugular vein over a 10 s period 5 min before the inhalation of ovalbumin.

We used Evans blue dye (3% solution in 0.9% NaCl; Polysciences, Warrington, PA) to measure plasma extravasation. Immediately after the injection of the dye (30 mg/kg i.v. over 5 s) in the jugular vein, an aerosol of either 0.9% saline or 5% OVA, which has previously been shown to produce a nearly maximum amount of plasma extravasation (Bertrand et al., 1993a), was delivered to sensitised or control animals for 2 min via the tracheal cannula, using an ultrasonic nebuliser (Pulmo-Sonic model 25, De Vilbiss Co., Somerset, PA; aerosol delivery rate 0.2 ml/min).

The chest was opened 10 min after injection of the tracer, a cannula was inserted into the ascending aorta through the left ventricle, and the circulation was perfused for 3 min with a phosphate buffer of pH 5 at a pressure of 120 mmHg. The trachea was then removed, opened longitudinally along the ventral midline, blotted on bibulous paper, and weighed. Tissues were incubated in 3 ml of formamide (Fisher Scientific, Santa Clara, CA) at 50° C for 18 h to extract the extravasated Evans blue dye (Lundberg and Saria, 1983). These results were compared with those obtained from animals not treated with CRF.

2.5. Measurement of plasma extravasation

Extravasation of the dye-labelled macromolecules was assessed by measuring the optical density of the formamide extracts at a wavelength of 620 nm with a spectrophotometer (UV160U, Shimadzu, Columbia, MD). The amount of Evans blue dye extravasated from the tissue, expressed in ng/mg of wet weight, was interpolated from a standard curve of Evans blue dye concentrations.

2.6. Drugs

Ovalbumin was obtained from Sigma Chemical (St. Louis, MO). Phosphoramidon was purchased from Peninsula Laboratories (Belmont, CA). Rat/human amino acid sequence CRF was a kind gift from Neurobiological Technologies. CP-99,994 was kindly provided by Dr. J.A. Lowe (Pfizer Central Research Division, Groton, CT).

2.7. Statistical analysis

All data are expressed as means ± S.E.M. Statistical comparisons were performed using a one way analysis of variance and Dunnett's test or bilateral unpaired Students *t*-tests, when appropriate. In all cases, a P value of less than 0.05 was considered significant.

3. Results

3.1. Effects of CRF on vascular permeability

The extravasation of Evans blue dye in the trachea and main bronchi of sensitised guinea pigs after exposure to aerosolised vehicle of ovalbumin and in the presence of phosphoramidon (2.5 mg/kg, i.v.) was 26.5 ± 4.5 ng/mg ($n = 5$, Fig. 1, upper columns) and 18.7 ± 5.9 ng/mg ($n = 5$, Fig. 2, lower columns), respectively. Inhalation of 5% ovalbumin for 2 min in the presence of phosphoramidon (2.5 mg/kg, i.v.) increased the extravasation of the Evans blue dye significantly in both the trachea (78.5 ± 5.4 ng/mg, $n = 5$; Fig. 1, upper columns) and the main bronchi (109.0 ± 6.9 ng/mg, $n = 5$; Fig. 1, lower columns). Pretreatment with CRF (30 nmol/kg, i.v.) 15 min or CP-99,994 (8 μmol/kg, i.v.) 5 min before aerosol challenge, did not affect the extravasation of the Evans blue dye caused by the ovalbumin vehicle (data not shown). Pretreatment with CRF (30 nmol/kg) significantly reduced the plasma extravasation produced after ovalbumin challenge in the trachea (40.7 ± 2.4 ng/mg, $n = 5$; Fig. 1, upper columns) and in the main bronchi (71.0 ± 9.7 ng/mg, $n = 5$, Fig. 1, lower columns). Finally, pretreatment with a combination of CRF (30 nmol/kg, i.v.) and CP 99,994 (8 μmol/kg, i.v.) also reduced the plasma extravasation in the trachea (40.4 ± 3.8 ng/mg, $n = 5$; Fig. 1, upper columns) and main bronchi (74.7 ± 8.3 ng/mg, $n = 5$; Fig. 1, lower columns). Inhibition of ovalbumin-induced plasma extravasation caused by the combination of CRF and CP-99,994 was not significantly different from the inhibition caused by CRF alone either in the trachea or the bronchi.

CRF inhibited significantly the plasma extravasation caused by aerosolised bradykinin (100 μM, 2 min inhalation) in the guinea pig trachea (60.5 ± 4.1 ng/mg vs. 75.1 ± 4.2 ng/mg, $n = 5$; Fig. 2, upper columns) and

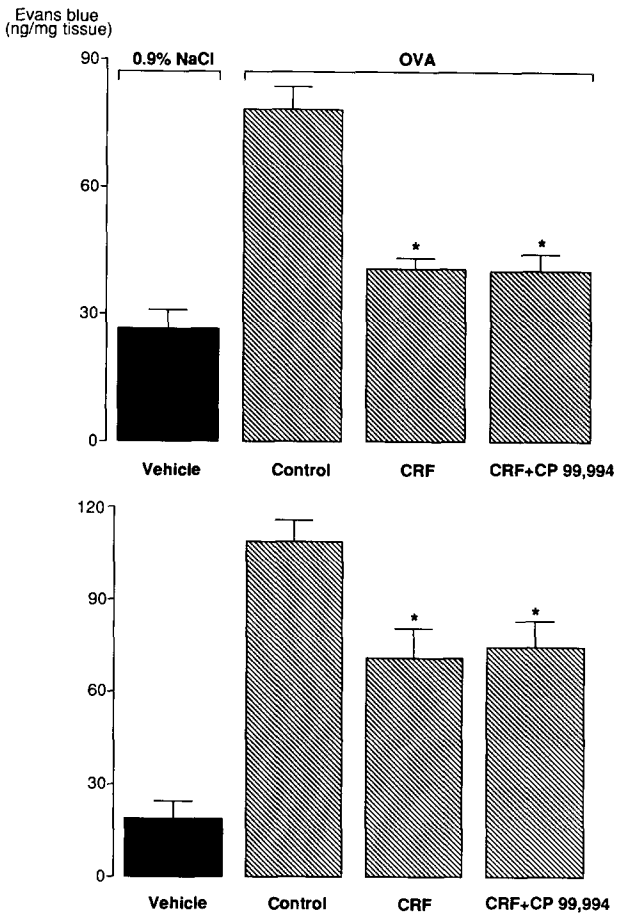

Fig. 1. Effect of corticotropin-releasing factor (CRF) alone (30 nmol/kg) or CRF and the tachykinin NK1 receptor antagonist CP-99,994 (4 mg/kg) on Evans blue extravasation in guinea pig trachea (upper columns) and main bronchi (lower columns) induced by inhalation of ovalbumin (OVA; 5% for 2 min) in presence of phosphoramidon (2.5 mg/kg, i.v., 5 min before the exposure to OVA). Vascular extravasation was evaluated by measuring the amount of Evans blue dye extravasated in the trachea after 10 min. Values are means ± SEM; $n = 5$ per group. * $P < 0.01$ vs. control (inhalation of 5% OVA in presence of phosphoramidon) in trachea and * $P < 0.05$ in main bronchi.

bronchi (58.5 ± 8.9 ng/mg vs. 85.9 ± 3.5 ng/mg, $n = 5$; Fig. 2, lower columns). However, CRF did not affect the plasma extravasation caused by aerosolisation of substance P (10 μM, 2 min inhalation) in the guinea pig trachea (75.2 ± 8.9 ng/mg vs. 74.1 ± 2.9 ng/mg, $n = 5$; Fig. 3, upper columns) and bronchi (80.6 ± 5.8 ng/mg vs. 83.8 ± 2.4 ng/mg, $n = 5$; Fig. 3, lower columns).

3.2. Cardiovascular parameters

In the animals treated with CRF (30 nmol/kg, i.v.) heart rate was not significantly different from the heart rate observed in animals pretreated with vehicle of CRF (179 ± 10 beats/min vs. 174 ± 9 beats/min, $n = 4$). Intravenous administration of CRF (30 nmol/kg, i.v.) increased mean arterial blood pressure as compared to the vehicle of CRF (88.75 ± 4.72 mmHg vs. 76.67 ± 5.77 mmHg; $n = 4$, $P < 0.05$).

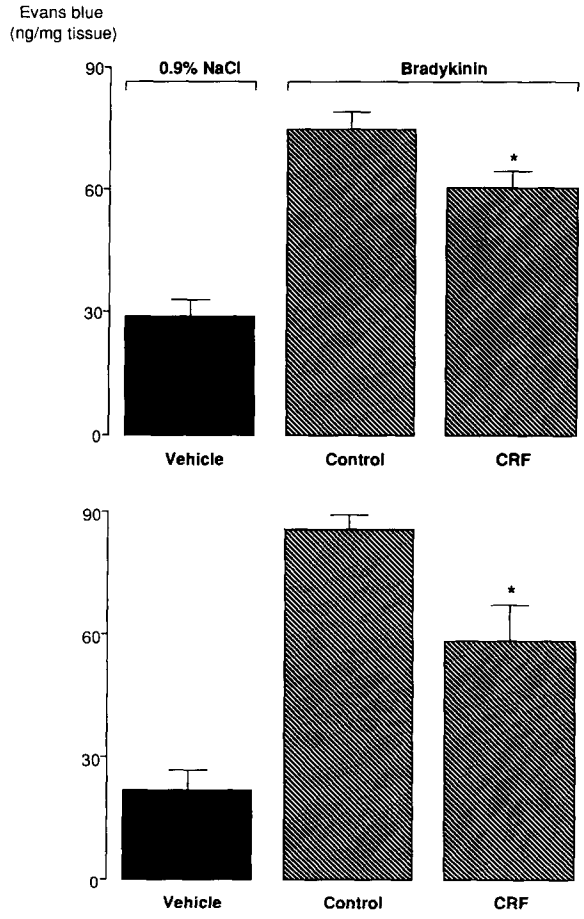

Fig. 2. Effect of corticotropin-releasing factor (CRF; 30 nmol/kg) on Evans blue extravasation in guinea pig trachea (upper columns) and main bronchi (lower columns) induced by inhalation of bradykinin (100 μM, 2 min) in presence of phosphoramidon (2.5 mg/kg, i.v., 5 min before exposure). Vascular extravasation was evaluated by measuring the amount of Evans blue dye extravasated in the trachea after 10 min. Values are means ± SEM; $n = 5$ per group. * $P < 0.05$ versus control (inhalation of bradykinin in presence of phosphoramidon) in both trachea and main bronchi.

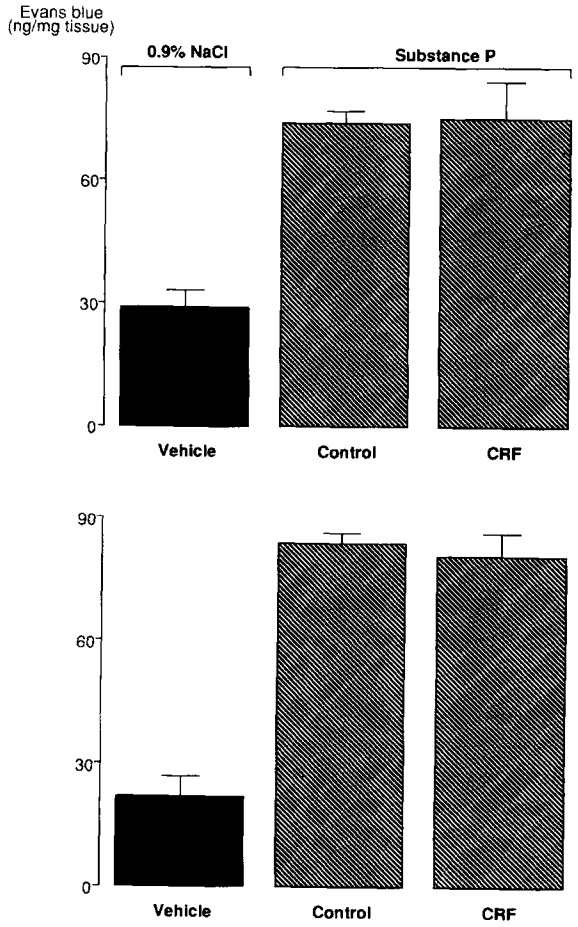

Fig. 3. Effect of corticotropin-releasing factor (CRF; 30 nmol/kg) on Evans blue extravasation in guinea pig trachea (upper columns) and main bronchi (lower columns) induced by inhalation of Substance P (10 μM, 2 min) in presence of phosphoramidon (2.5 mg/kg, i.v., 5 min before exposure). Vascular extravasation was evaluated by measuring the amount of Evans blue dye extravasated in the trachea after 10 min. Values are means ± SEM; n = 5 per group.

4. Discussion

The major finding of the present study is that pretreatment with CRF significantly reduces ovalbumin-induced extravasation of Evans blue dye in the trachea and main bronchi of sensitised guinea pigs pretreated with the neutral endopeptidase inhibitor, phosphoramidon. In experimental conditions identical to those used in the present study, ovalbumin-evoked plasma extravasation in the trachea of sensitised guinea pigs was largely mediated by stimulation of sensory nerve endings and the release of tachykinins (Bertrand et al., 1993a,b). The present observation that inhibition in-

duced by CRF was not different from the inhibition induced by the combination of CRF and the tachykinin NK_1 receptor antagonist CP-99,994 indicates that CRF and CP-99,994 utilize a final common pathway to inhibit ovalbumin-induced plasma extravasation in the guinea pig airways. CP-99,994 is a potent antagonist of the tachykinin NK_1 receptors in guinea pigs, with minor calcium antagonist properties compared to its parent compound CP-96,345 (McLean et al., 1993), that was used in the previous study (Bertrand et al., 1993a). Therefore, it is possible that the inhibitory action of CP-99,994 on ovalbumin-evoked plasma extravasation is due to its antagonism of tachykinin NK_1 receptors. However, CRF did not inhibit substance P-induced extravasation, suggesting that CRF does not act by antagonizing tachykinin NK_1 receptors.

It is possible that CRF reduces ovalbumin-induced plasma extravasation by inhibiting the release of neuropeptide transmitters from sensory nerve endings. This hypothesis is compatible with the previous observation that CRF reduces neurogenic plasma extravasation in the skin and airways induced by antidromic stimulation of the vagus nerves (Wei et al., 1986; Wei and Kiang, 1987, Wei and Kiang, 1989).

To test this hypothesis further, we studied the effect of CRF on the plasma extravasation induced by aerosolised bradykinin or substance P in the guinea pig airways. Locally applied bradykinin increases vascular extravasation in rodent airways by two mechanisms: a major component that is due to stimulation of sensory nerves and, possibly via the activation of axon reflexes, with subsequent release of tachykinins, and a minor component that is probably due to the activation of bradykinin receptors on the venular endothelium (Saria et al., 1983; Lötvall et al., 1991; Geppetti, 1993). Plasma extravasation induced by aerosolised substance P is not neurally mediated but is due entirely to the direct stimulation of tachykinin NK_1 receptors in the postcapillary venules (Bertrand et al., 1993b). The present observation that CRF reduces the extravasation of the Evans blue dye induced by bradykinin but not the extravasation induced by substance P suggests that CRF reduces plasma extravasation by inhibiting sensory neuropeptide release.

Locally applied bradykinin increases plasma extravasation by a direct action on its receptors on endothelial cells or indirectly by stimulating the release of tachykinins from sensory nerve terminals (Saria et al., 1983; Ichinose et al., 1990). OVA-induced plasma extravasation is clearly due to indirect mechanisms, including sensory nerve stimulation (Bertrand et al. 1993a,b). The observation that CRF was more effective in reducing the plasma extravasation induced by OVA than the plasma extravasation induced by bradykinin suggests that CRF acts on additional indirect mechanisms which increase plasma leakage, different from sensory nerve activation. However, further experiments are required to clarify this point.

In the present study, CRF increased arterial blood pressure. An increase in arterial blood pressure may indicate peripheral vasoconstriction which may reduce plasma extravasation by reducing the flow to the leakage sites, but this is unlikely because CRF did not reduce plasma extravasation in response to aerosolized SP.

CRF releases corticosteroids indirectly from the adrenal glands. Corticosteroids inhibit vascular extravasation due to various stimuli, without showing any selectivity for neurogenic plasma extravasation. Therefore, it is unlikely that the inhibition by CRF of ovalbumin- and bradykinin-induced plasma extravasation is mediated by the release of corticosteroids. A recent preliminary study showed that CRF inhibits vagally induced bronchoconstriction but not bronchoconstriction caused by NKA (Rogers et al., 1993). Thus, the present findings support the conclusion that CRF inhibits neural transmission in sensory neurons. Microvascular leakage is an essential component of the inflammatory response to antigen in sensitised individuals and plays a critical role in asthma in producing edema and thickening of the bronchial mucosa which may underlie airway hyperresponsiveness (Rogers and Evans, 1992; Bertrand et al., 1993a,b; Yoshihara et al., 1995). The ability of CRF to reduce plasma extravasation through inhibition of sensory neuropeptide release suggests that this compound is a possible candidate in the therapy of asthma.

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